An investigation of the haemodynamic response and specific factors that impact intervention outcomes for young children on the autism spectrum

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An investigation of the haemodynamic response and specific factors that impact intervention outcomes for young children on the autism spectrum

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A thesis in fulfilment of the requirements for the degree of

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Autism spectrum disorder is a neurodevelopmental disorder where symptoms are often noticeable in infancy and continue across the life span. It is well established that children on the autism spectrum who receive early intervention have better social and communication outcomes. However, it is less known what factors might impact these outcomes. Moreover, while individuals on the autism spectrum show decreased brain activity in parts of the social brain network compared to typically developed individuals, less is known about how this decrease impacts social and communication outcomes. This thesis aimed to investigate the factors that impact intervention outcomes. Furthermore, the thesis aimed to examine differences in haemodynamic response amongst children on the autism spectrum and typically developing children using fNIRS.

Study one examined the impact of factors such as age, intensity and duration of intervention on intervention outcomes using the ESDM. The study utilised standardised measures that assessed adaptive behaviours, social and communication skills, fine motor and domestic skills. The findings showed that younger age at enrolment and a longer duration of intervention were associated with improvements in specific outcomes in language and communication skills.

Study two examined variations in initial language abilities of children on the autism spectrum, and how this impacts intervention outcomes. Utilising the same clinical measures, the study showed that differences in initial verbal ability had an impact on specific outcomes after children received the ESDM. Our results suggest that better initial verbal abilities might increase outcomes in language related areas

Study three explores the relationship between patterns of connectivity in parts of the social brain network and subsequent clinical presentations in measures focusing on social skills. The findings suggest that children on the autism spectrum have a different pattern of haemodynamic activity compared to typically developing children during social and non-social tasks. The findings also indicate that social and communication measures are related to haemodynamic outcomes within and between groups.

Together, this thesis provides important implications for future clinical practice and research by expanding our understanding of the factors that impact intervention outcomes and how children on the autism spectrum might be processing social information.

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Finally, thank you to the wonderful children and their parents who participated in the research. I appreciate the time and effort you put into being involved and without amazing people like you, discoveries, novel findings and an overall increase in knowledge would cease. Thank you!

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Contents

Chapter One:

General Introduction

Autism Spectrum Disorder

Autism spectrum disorder is a heterogeneous, neurodevelopmental disorder where symptoms are often noticeable in infancy (Dawson, 2008; Salomone et al., 2015), change with development, and continue across the life span (American Psychiatric Association, 2013; Dawson, 2008; Reichow, Barton, Boyd, & Hume, 2014; Salomone et al., 2015). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013), two symptom dimensions must be met, including social communication difficulties, as well as restricted and repetitive patterns of behaviour, activities or interests.

The first dimension, social communication and social interaction includes difficulties in social behaviours such as social-emotional reciprocity (e.g. initiation and maintenance of social interaction, affect or emotions), non-verbal communicative behaviours (e.g. facial expressions, gestures, body language, eye contact, language) and relationships (making and maintaining relationships, adjusting behaviour to suit different social contexts, imaginary play) (Frazier et al., 2012). In order to receive a diagnosis according, these difficulties must be persistent across multiple contexts (e.g. the same behaviour is present within different environments and around different people) (American Psychiatric Association, 2013; Lord & Bishop, 2015).

The second dimension includes four criteria, of which two must be met for a diagnosis of ASD (American Psychiatric Association, 2013; Frazier et al., 2012). These include stereotyped or repetitive use of speech, motor movements or use of objects (e.g. lining toys up, idiosyncratic phrases or echolalia), verbal and non-verbal rituals, inflexible adherence to routines, insistence on sameness (e.g. distress with routine changes, greeting rituals and rigid thinking patterns), intense or abnormal interests that

are restrictive and or repetitive. Recently included in the DSM-5, as part of the restricted and repetitive patterns of behaviour, is an assessment of hypo- or hyperactive sensory seeking input (e.g. adverse responses to textures/ sounds, excessive touching or smelling of objects, an indifference to pain or temperature, intense interest in lights or movement).

According to the DSM-5, symptoms must be present during early development but the DSM-5 acknowledges that some social impairment may not become evident until social demands surpass the child's social skills. Symptoms must also cause significant clinical impairments in functioning and are not better explained by an intellectual delay (Lord & Bishop, 2015). An autism severity level is assigned based on the level of impairment across social communication and restricted and repetitive patterns of behaviour (Lord & Bishop, 2015). These autism severity levels range from requiring support (level one), requiring substantial support (level 2) to requiring very substantial support (level 3) (Frazier et al., 2012). Clinicians often use clinical measures such as the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000; Lord & Bishop, 2015) comparison score to determine the severity scores.

Compared to the earliest epidemiologic studies in the 1960s and 1970s, which reported prevalence rates of five in 10,000, the global prevalence of ASD has increased thirtyfold (Christensen, 2016). Currently, prevalence estimates in the United States of America are 1 in 59 children (Baio et al., 2018). In the United Kingdom, prevalence rates are estimated to be around 1 in every 100 children (Brugha et al., 2016; Christensen, 2016). In Australia, approximately 164,000 individuals have ASD, which represents approximately 1 in 150 Australians (Hedley, 2018). There is a significant consensus amongst researchers that the increase in prevalence of ASD is likely related

to improved diagnostic practices and an increased awareness of symptoms characteristic of ASD (Christensen, 2016; Fombonne, 2018). Improved public awareness has also been linked to earlier diagnosis at two years or younger (Salomone et al., 2015).

ASD is more commonly reported in males than females, with initial ratios between 4:1 and 5:1 (Lai et al., 2017). However, more recent epidemiological findings have found a male to female ratio between 2:1 and 3:1 (Lai et al., 2017). This may be due to improved recognition of the unique set of clinical behaviours females display, as well as increased female participation in research (Alaerts, Swinnen, & Wenderoth, 2016). For instance, brain volumetric studies previously had a male to female ratio of 8:1, while task fMRI studies had a male to female ratio of 15:1 (Philip et al., 2012; Via et al., 2011). However, as a result of improved female identification and diagnosis, females have higher representation in ASD research (Lai et al., 2017). The increased participation of females in ASD research has led researchers to examine what gender disparities exist in behavioural presentation. Research has generally found differences on cognitive abilities, social and communication skills, and repetitive and restrictive behaviours between males and females with a diagnosis of Autism Spectrum Disorder (Lai et al., 2017). For example, research has shown that males may demonstrate greater cognitive abilities and repetitive behaviours, while females demonstrate greater social and communication skills (Coffman, Anderson, Naples, & McPartland, 2015; Halladay et al., 2015). However, research is lacking when it comes to exploring what associations might exist between brain function and the differences in behaviour between males and females (Lai et al., 2017).

Autism Spectrum Disorder (ASD) shows high comorbidities with developmental disorders, intellectual delay, neurological and psychiatric conditions (Zablotsky et al.,

2015). Furthermore, less than 10% of individuals with ASD spectrum have an identifiable genetic syndrome, such as Fragile X, Tourette Syndrome, etc (Fombonne, 2018; Zafeiriou, Ververi & Vargiami, 2007). The number of people diagnosed with ASD that have comorbidities varies between studies. For example, researchers have estimated that 25% of people diagnosed with ASD also have an intellectual disability (Fombonne, 2018) whereas other researchers have estimated that 70% have a comorbid diagnosis (Lord & Bishop, 2015). Similarly, researchers have estimated that 49% of people with ASD are also diagnosed with Attention Deficit and Hyperactivity Disorder (ADHD) (Pondé, Matos & de Oliveira, 2017), while other researchers have estimated that only 28% have a comorbid diagnosis with ADHD (Simonoff et al. 2008). Furthermore, it has been estimated that around 29 to 42% of individuals with ASD are diagnosed with anxiety disorders (Lenroot & Yeung, 2013). Additionally, a large portion of individuals with ASD have seizure disorders, dysregulated sleep, and gastrointestinal dysfunction (Lenroot & Yeung, 2013).

Researchers investigating these large variations in comorbidities have found a number of factors contributing to the current disparity in figures. Firstly, there is a lack of uniformity in the format of diagnosis. While some studies used standardised measures, others used single questionnaire items completed by parents, or a combination of both (Lord & Bishop, 2015; Frombone, 2018). Secondly, when clinical or standardised measures were utilised, there were large variations in the quality of the data used to score against the criteria (i.e. if and how the clinician was trained, the format of data collection and if the assessment was recorded or evaluated by a second clinician). Lastly, there were also disparities in scoring rules and cut offs when making decisions about comorbidities with other diagnoses. For instance, some researchers used an interpretive process, while others used strict cut-offs. This lack of consistency

amongst studies has led to the disparity in the prevalence figures for comorbid conditions in ASD. In addition to comorbidities, the presentation of symptoms can also vary widely between individuals with a diagnosis of ASD. The majority of these variations are found in cognition and language ability (Visser et al., 2017). For example, a portion of individuals with ASD are diagnosed with an intellectual disability whereas others are found to have average cognitive abilities (Arnett et al., 2018; Brookman-Frazee, Stadnick, Chlebowski, Baker-Ericzén, & Ganger, 2017). Similarly, 30 to 50% of children with ASD have significant language impairments with a portion of these individuals remaining non-verbal into adulthood (Arnett et al., 2018). Conversely, approximately 50% of people with ASD spectrum reach their language milestones during development and remain verbally fluent in adulthood (Howlin, Goode, Hutton, & Rutter, 2004; Visser et al., 2017). This vast difference in language abilities has been found to influence outcomes in therapy (Vivanti, Prior, Williams, & Dissanayake, 2014). It has been suggested that the interaction between genetic processing and environment effects during critical periods of development influences the variation in the presentation of ASD symptoms (Bick & Nelson, 2017; Wozniak, Leezenbaum, Northrup, West, & Iverson, 2017). However, attempts to establish the relationship between genes and behaviour has proven difficult with numerous environmental factors and genes impacting on neural development and subsequent function (Ferhat et al., 2017). Given the difficulties in examining the relationship between genes and behaviour, researchers have focused their efforts of the investigation of brain connectivity and subsequent behaviour (Bick & Nelson, 2017).

The aetiology of ASD has shifted drastically within the last sixty years. Initially, the development of ASD was attributed to the maternal parenting style. Specifically, the development of ASD was theorised to be a result of “emotionless mothers” (Joseph,

2018). Cognitive theories were then proposed which followed a phenotype and symptomatology approach where autism was thought to be a result of cognitive impairments alone (Boucher, 1989: Joseph, 2018). The most prominent of these approaches was the theory of mind hypothesis where individuals with ASD lack the ability to attribute mental states to oneself and others (Boucher, 1989). Another popular theory was the executive dysfunction hypothesis where repetitive behaviours were assumed to be a result of frontal lobe impairment (Joseph, 2018; Russell, 1997). However, parenting styles and cognitive theories alone were unsuccessful in explaining both the phenotypes and development of ASD. More recently, researchers have examined brain development in children with ASD (Inui, Kumagaya, & Myowa-Yamakoshi, 2017). Currently, the anabolic hypothesis has the most replicated findings. This hypothesis postulates that children with ASD have neuronal overgrowth resulting in increased brain growth followed by a period of normal development (Inui, Kumagaya, & Myowa-Yamakoshi, 2017; Joseph, 2018). Researchers have also consistently found imbalances in neurotransmitters (dopamine, serotonin, GABA and glutamate) brainstem dysfunction and decreased grey matter in the frontal cortex (Inui, Kumagaya, & Myowa-Yamakoshi, 2017; Joseph, 2018). Researchers examining the biological underpinnings on autism posit that the complex interactions between brain development and environment manifests in diverse phenotypes where deficits in social, communication and behaviour are found along a spectrum (Inui, Kumagaya, & Myowa-Yamakoshi, 2017). Overall, approaches to examining the aetiology of ASD has evolved from single cause theories to more wholistic approaches that include behavioural, cognitive, neurobiological explanations. However, approaches to examining the aetiology of ASD has evolved from single cause theories which do not adequately explain the aetiology of autism to more wholistic approaches that include behavioural, cognitive, neurobiological explanations. Given that autism is a

neurodevelopmental disorder, a focus on the neuro factors that may contribute to the causes of autism has increased.

Neurodevelopmental Theories

Derived from the research regarding the neurodevelopment of ASD is a plethora of theories attempting to explain these variations in brain connectivity. In this regard, it has been suggested that autism is more appropriately defined as "autisms" rather than one condition, due to the high variation in the presentation of symptoms (Ben-Itzchak & Zachor, 2007; Geschwind & Levitt, 2007). Geschwind and Levitt (2007) put forward a unifying model where they proposed that there may be a disconnection during development between areas of the brain, such as the frontal and temporal/parietal lobes. The authors went on to suggest that this model of disconnection could explain the neurobiological features, as well as the heterogeneity in behaviour and cognition seen in ASD (Geschwind & Levitt, 2007).

The social brain network alternatively suggests that multiple risk factors in early development could culminate in a failure to develop specialised functions in social communication (Pelphrey, Shultz, Hudac, & Vander Wyk, 2011). More specifically, this theory proposes that a lack of specialised neural networks within the posterior superior temporal sulcus may help to explain the impairments found in the perception of facial expressions and interpersonal interactions (Pelphrey et al., 2011). Further to the social brain network approach, Brock (2011) devised a complementary method to account for the heterogeneity of ASD. Brock (2011) highlighted that through examining both the brain and behaviour, meaningful subgroups could potentially be identified. This may assist with explaining the heterogeneity of ASD, as well as understanding how brain activity might impact behaviours differently. This concept shifts research

from simply examining specific brain regions, to exploring the relationship between decreased activity in these particular areas and any corresponding clinical presentations (Brock, 2011; Lenroot & Yeung, 2013).

Neurodevelopmental Techniques

Although the complex interactions between genes and environment are still unclear, there is consensus that ASD is accompanied by neurodevelopmental variations in brain connectivity, anatomy and functioning (Dajani & Uddin, 2016; Wozniak et al., 2017). To date, researchers have utilised a number of neuroimaging techniques to examine differences in structure and function in the brain of individuals with ASD. These neuroimaging techniques include functional magnetic resonance imaging (fMRI), electroencephalogram (EEG), magnetoencephalography (MEG) and more novel techniques such as function near-infrared spectroscopy (fNIRS). While all techniques have been utilised to examine brain function and connectivity across the life span with each having their own advantages and disadvantages, the majority of research has utilised fMRI (Wozniak et al., 2017). A number of meta-analyses now combine data from these fMRI studies to establish if potential biomarkers or mechanisms could illuminate the possible causes of ASD (Stanfield et al., 2008; Via, Radua, Cardoner, Happé, & Mataix-Cols, 2011). In turn, it is possible that an understanding of connectivity could lead to better early identification, prediction of developmental trajectories and treatment response (Stanfield et al., 2008).

A number of key findings have emerged from this research. Firstly, the most replicated findings in ASD populations are increases in total brain volume, cortical hemispheres, cerebellum and caudate (Stanfield et al., 2008). The age of participants within each study included in the meta-analysis ranged from two to 40 years of age.

Although this is a prominent finding, more recent meta-analyses have had smaller effect sizes and found no significant differences between the ASD and typically developing populations when specifically examining studies that were focused on the cerebellum. Their result suggested the presence of publication bias in a number of the studies included (Traut et al., 2017). Secondly, decreased volumes in brain areas have also been found in the corpus callosum, midbrain regions and parts of the cerebellar vermis (Stanfield et al., 2008; Via et al., 2011). Lastly, significantly smaller grey matter volume in the amygdala-hippocampus complex and medial parietal regions in individuals with ASD have also been identified (Via et al., 2011). Although this meta-analysis included an adult and adolescent population, no studies where children under the age of eight were included. Furthermore, the majority of studies examining adolescent populations, only sampled males. Therefore, it is unclear if adolescent females or children below the age of eight would demonstrate the same findings (Via et al., 2011). Furthermore, studies examining differences in brain connectivity between individuals with ASD and typically developing individuals during resting state have found decreased correlations among social brain regions (Hull, Jacokes, Torgerson, Irimia, & Van Horn, 2017; Olivito et al., 2017). While this study had participants ranging in age from two to 35, no age specific analysis was completed. Given that the brain is highly plastic during development, connectivity at an older age may not represent connectivity at a younger age. Therefore, a developmentally focused age comparison may have been beneficial in this study (Hull, Jacokes, Torgerson, Irimia, & Van Horn, 2017). Although there are some inconsistencies, collectively, findings indicate that ASD may result from abnormalities in specific brain areas due to atypical brain development (Stanfield et al., 2008).

More recently, researchers have begun to utilise fNIRS with clinical populations, including individuals with ASD. Similar to fMRI, fNIRS detects changes in the concentration of oxygenated (oxy-Hb) and deoxygenated haemoglobin (Deoxy-Hb) in blood and tissue throughout the outer cortex, reflecting changes in underlying neural activity (Lloyd-Fox et al., 2013). fNIRS has many advantages, including being a portable device which allows experimentation to be carried out in an environment familiar to the participant (Lloyd-Fox et al., 2013). Moreover, fNIRS has more capacity to measure where haemodynamic activity is occurring (spatial resolution) than EEG. fNIRS also has more capacity to measure when haemodynamic activity is occurring (temporal resolution) compared with fMRI. Therefore, fNIRS provides an ideal and novel way to examine haemodynamic activity with individuals with ASD(Lloyd-Fox et al., 2013).

A key area of this research has been in the study of haemodynamic connectivity associated with social information (Lloyd Fox et al., 2018). A number of studies utilising fNIRS have found a decreased haemodynamic response to social stimuli and sounds (e.g. voices) compared to non-social stimuli in the frontal and superior temporal regions of the social brain network, which is a network of brain regions that become activated during social tasks in individuals with ASD (Blasi et al., 2015; Grossmann, Oberecker, Koch, & Friederici, 2010; Lloyd-Fox et al., 2018). This is in contrast to the pattern of activity shown by typically developing children and adults, who display an enhanced response to social stimuli and sounds in the frontal and superior temporal regions of the social brain network (Belin & Grosbras, 2010; Grossmann et al., 2010; Raschle et al., 2014). Some researchers utilising fNIRS have also extended these findings by examining the relationship between these patterns of connectivity in the social brain network and subsequent clinical presentations. The findings from these

studies indicate that greater patterns of connectivity in the posterior superior temporal sulcus may be associated with greater outcomes in social skills and decreased autism severity (Dawson et al., 2010; Lloyd-Fox et al., 2013). Although the research is still emerging, a better understanding of these results could lead to knowledge of the different developmental trajectories for children withASD. This may subsequently lead to an understanding of subgroups based on neuroanatomical and clinical characteristics to develop more targeted interventions for children with ASD that are unique to the child's needs.

Brain Plasticity and Early Intervention

The social brain network suggests that a lack of specialisation in the brain may result from specific risk factors during development. One of these risk factors includes an absence of appropriate social experiences at specific points in time (sensitive periods) during a child's development (Bick & Nelson, 2017; Dawson, 2008). For instance, the development of social and linguistic brain circuitry and cortical organisation requires appropriate social interactions (e.g. reciprocal social interactions, engagement with a social partner) and language during particular times throughout development (Inguaggiato, Sgandurra, & Cioni, 2017; Samson, Zeffiro, Doyon, Benali, & Mottron, 2015). That is, the cortical organisation, circuitry and clinical presentation are a result of the complex interaction between the infant's brain and the social environment (Kuhl, Coffey-Corina, Padden & Dawson, 2005; Dawson, 2008).

Although typical development can occur in the absence of specific experiences, other risk factors may play a role (Bick & Nelson, 2017). As genes are considered to contribute to the development of ASD, it is possible that a child with ASDinteracts differently with their environment as a result of genetic risk factors (Dawson et al.,

2012). As a consequence, an infant's individual experiences can also alter their gene expression, which provides basic information regarding the establishment, growth and connectivity of neurons (Bick & Nelson, 2017). In other words, genes can impact a child's behaviour, and behaviour can also impact genetic expression. As a consequence, the course of brain development may be altered (Bick & Nelson, 2017). However, findings from animal studies show that epigenetic changes (non-genetic influences on gene expression) can occur with exposure to specific experiences (Weaver et al., 2004). For example, grooming and nursing behaviours performed on baby rats by their mothers produced changes in behaviour (i.e. stress, anxiousness, calmness), neurodevelopment and epigenetics (DNA methylation as well as chromatic structure) (Weaver et al., 2004). Collectively, this research demonstrates that environmental changes such as increased social interactions and intervention can have a positive impact on a child's social behaviours.

In general, the majority of neurodevelopmental changes are brought about by the brain's capacity to change. This phenomenon is known as brain plasticity, a term used to explain the malleability of neuronal circuitry and connectivity as a result of the interactions between a person's environment and genes (Power & Schlaggar, 2017). Brain plasticity is highly important, because it allows us to learn, remember and adapt to changing environments (Inguaggiato et al., 2017). Underlying physical changes occur at a cellular level and manifest as connectivity changes throughout the brain (Power & Schlaggar, 2017). Therefore, despite genetic risk factors, the brain has the potential to make new connections as a result of new environmental input throughout the life span (Bick & Nelson, 2017). This is because experience facilitates cortical specialisation (Bick & Nelson, 2017). For instance, increased attention to speech, facial expressions and gestures over time create specialised cortical areas that are more efficient in

processing social information (Bick & Nelson, 2017; Dawson, 2008). In the same way, these changes at the neural level can also be translated into observable behavioural changes (Cicchetti, 2015).

Although brain plasticity allows for changes in connectivity to occur throughout the lifespan, research shows that timing is crucial. In particular, sensitive periods are more prominent during child development (Inguaggiato et al., 2017). This is because neural circuitry during development has enhanced sensitivity for environmental input (Inguaggiato et al., 2017). This enhanced sensitivity may explain why younger children with ASD demonstrate greater improvements during intervention (Bick & Nelson, 2017; Dawson, 2008).

As appropriate input for the development of specific skills is known to be highly crucial during development, it is important that children with ASD receive early intervention (Inguaggiato et al., 2017). Through early intervention, children with ASD are able to gain additional access to a variety of social interactions and communication, allowing for increased cortical growth in specific regions of the brain (Bick & Nelson, 2017; Inguaggiato et al., 2017). For instance, reciprocal social interactions and social engagement during infancy are known to facilitate cortical specialisation in areas such as the superior temporal sulcus that are related to social and linguistic information processing (Dawson, 2008; Kuhl, 2007). Moreover, as other actions, such as attention and facial perception, are also required during social experiences, integration between different regions within the brain start to occur. For instance, attention requires dorsal lateral prefrontal activity, which becomes integrated with the fusiform gyrus for facial perception (Hernandez, Rudie, Green, Bookheimer, & Dapretto, 2015). Furthermore, both regions become integrated with the superior temporal sulcus during interpersonal

interactions (Braukmann et al., 2018). The integration of brain regions results in an increasingly complex social brain circuitry (Dawson, 2008; Kim et al., 2015; Kuhl, 2007; Tso, Rutherford, Fang, Angstadt, & Taylor, 2018). These new connections within the social brain circuitry support more complex behaviours such as joint attention and social imitation (Tso et al., 2018)

Early Intensive Behavioural Interventions

Early Intensive Behavioural Intervention (EIBI) is considered an exemplary practice for individuals with ASD (Landa., 2018). EIBI is based on a set of evidence-based procedures and principles derived from Applied Behaviour Analysis (ABA) (Rivard, Morin, Mello, Terroux & Mercier., 2018). These principles include positive reinforcement, prompting and fading, task analysis and generalisation (Lovaas, 1987; Landa, 2018). The approach is generally delivered one to one, and aims to build adaptive and functional skills, reduce autism symptoms and behaviours, as well as eating and sleeping difficulties (Landa, 2018). EIBI is considered the gold standard of support for children with ASD. A review examining the results of four large meta-analyses concluded that children who receive EIBI have greater outcomes in adaptive behavioural, social and communication skills compared to eclectic styles of intervention (a combination of intervention strategies from different approaches) (Reichow, 2011). Furthermore, studies focusing on ABA have found that increased intervention intensity is associated with better progress and learning outcomes for children with ASD(Granpeesheh, Tarbox, & Dixon, 2009). The authors also found that the earlier the child's intervention started, the better their outcomes were (Granpeesheh, Tarbox, et al., 2009; Zachor et al., 2017). Although most of these studies conducted randomised control trials, a number of studies included were quasi-randomised control trials, where

random assignment did not take place. Therefore, it is difficult to exclude the presence of confounding variables that may reduce the internal validity and overall generalisability of the results. Furthermore, as most EIBI programs are delivered one to one, researchers argue that this method is not readily available in a community setting. As a result, many children with ASD miss out on evidence-based intervention during their early and most critical preschool years (Eapen, Črnčec & Walter., 2013).

While there is consensus that early intervention is crucial, only a handful of interventions are specifically designed for toddlers with ASD (Waddington, van der Meer, & Sigafoos, 2016). An intervention approach that addresses the needs of infants and toddlers (12 to 60 months of age) with ASD is the Early Start Denver Model (ESDM) (Rogers & Dawson, 2010). The ESDM is a gold standard intervention that focuses on increasing social and communication skills. In order to accelerate the acquisition of these skills, the ESDM encourages naturalistic interactions to promote social attention and social reward (Ryberg, 2015). These factors make the ESDM an ideal intervention for exploring behavioural outcomes of younger children with ASD.

Although the ESDM is a widely utilised intervention that is practiced within a number of facilities globally, there remains a lack of research exploring how specific factors and initial abilities impact intervention outcomes. Firstly, given the heterogeneous expression of behaviours in ASD, there remains a lack of research into how these variations in initial behaviours alter children's responses to intervention. For instance, it is well known that language abilities can vary significantly amongst children with ASD (Visser et al., 2017). However, to date, it is largely unknown how a child's language abilities impacts their outcomes after receiving the ESDM. In a review by Zachor et al. (2017), baseline verbal abilities were associated with increased outcomes

in adaptive behaviour for children receiving EIBI interventions. However, there was no association between baseline verbal ability and other outcomes including visual spatial IQ, decreased autism severity and cognitive abilities (Zachor et al., 2017). In contrast, a meta-analysis comparing outcomes of children with ASD receiving behaviour analytic treatment or eclectic interventions found that baseline verbal ability was not correlated with outcomes in IQ or adaptive behaviour (Makrygianni & Reed, 2010). Although both reviews examined variables that impact intervention outcomes, there were inconsistencies amongst the measures used. For instance, communication skills were measured using the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2000), in some studies, while other studies used the Social Communication Questionnaire (SCQ) (Rutter, Bailey, & Lord, 2003). Given that the ADOS is administered by clinicians and the SCQ questionnaire is completed by parents, it is unlikely that both measures will provide the same information. Furthermore, while these reviews examined verbal abilities and outcomes, they did not investigate the impact of initial verbal abilities on treatment outcome for children receiving the ESDM. However, the examination of initial verbal abilities is especially important in this context, given that the ESDM specifically targets improvements in communication skills. Therefore, further research replicating and extending on Zachor et al (2017) findings is necessary to ascertain how variations in language abilities impacts or predicts intervention response within the ESDM framework.

In order to optimise children's outcomes in therapy and guide decisions that positively impact outcomes for children receiving the ESDM, an investigation into specific factors that might optimise the effectiveness of the ESDM is imperative (Ryberg, 2015; Virues-Ortega, Rodríguez, & Yu, 2013). The most consistently investigated characteristics amongst the general EIBI literature include age at

enrolment, intensity of intervention and intervention duration (Makrygianni & Reed, 2010; Vinen, Clark, Paynter, & Dissanayake, 2018; Virues-Ortega, Rodríguez, et al., 2013; Vivanti, Prior, et al., 2014; Zhou et al., 2018). Some studies examining the role of intervention duration and outcomes for an eclectic intervention found that duration did not impact outcomes (Howard, Stanislaw, Green, Sparkman, & Cohen, 2014; Virues-Ortega, Rodríguez, et al., 2013). However, others have indicated that children receiving more specialised EIBIs demonstrated marked developmental improvements after the first year of therapy (Cohen, Amerine-Dickens, & Smith, 2006; Howard et al., 2014). Similarly, the findings evaluating the impact of chronological age, treatment intensity and outcomes are also inconsistent. For instance, some research has shown no relationship between treatment intensity or chronological age and better outcomes for children receiving the ESDM (Vivanti, Prior, et al., 2014). However, others have found that younger age at enrolment was associated with improved outcomes (Eapen, 2016). However, it is possible that the variation in findings may be a result of other factors included in one study and not others. For instance, Vivanti, Prior, et al (2014) study had an increased teacher to child ratio compared to Eapen, (2016). Therefore, variation in the administration of the ESDM needs to be considered and controlled for. This will assist with guiding our understanding of how the ESDM intervention works, as well as optimising outcomes for children with ASD.

Aim of thesis

This thesis aimed to extend our understanding of the complex relationship between patterns of connectivity in the social brain network and subsequent social behaviours. This thesis also aimed to provide a greater understanding of the

mechanisms and factors that might influence outcomes in therapy for children with ASD.

In particular, this thesis aimed to determine the importance of the duration and intensity of early intervention on outcomes for children with ASD receiving the ESDM. Additionally, it examined the impact of age of entry into early intervention on outcomes. Given the ESDM specifically targets improvements in communication skills, as well as the variability in language skills amongst children with ASD, this thesis also aimed to determine the importance of initial language ability and changes following the ESDM. Moreover, while individuals with ASD show decreased haemodynamic activity in parts of the social brain network compared to typically developed individuals, less is known about how this decrease in haemodynamic activity impacts social and communication outcomes. In light of this, the thesis aimed to examine differences in haemodynamic response amongst children with ASD and typically developing children during social and non-social conditions using fNIRS. In addition, it explored the relationship between haemodynamic activity in parts of the social brain network and outcomes on social and communication measures.

The thesis consists of seven Chapters in the format of five manuscripts. Chapter Two provides a review of the literature of the ESDM, a therapy that is specifically designed for young children with ASD. Chapter Three then examines the impact of factors such as age, intensity and duration of intervention on intervention outcomes using the ESDM. Chapter Four utilised the same data from the outcome measures (VABS, SCQ and MSEL) as Chapter Two and examines variations in initial language abilities of children with ASD, and how this impacts intervention outcomes. The Fifth Chapter provides a review of the current research utilising fNIRS with individuals with

ASD, as well as emerging methodology for the analysis of fNIRS data. The Sixth Chapter then examines differences in haemodynamic activity amongst children with ASD and typically developing children during social and non-social conditions. Chapter Six also explores the relationship between patterns of connectivity in parts of the social brain network and subsequent clinical presentations in measures focusing on social skills. Together, these Chapters aim to investigate the relationship between social behaviours and patterns of connectivity in the social brain network and extend our understanding of the factors that might influence outcomes for children receiving therapy.

Chapter Two:

A Review of Studies examining the Early Start Denver Model

Introduction

Children diagnosed with ASD earlier in life, who are subsequently supported by early intervention, generally have better outcomes (Ryberg, 2015). Due to an increase in the availability of screening tools and improved accuracy in diagnosis, toddlers who show behavioural signs associated with the diagnostic criteria for ASD are now able to be assessed much earlier in life (Dawson & Bernier, 2013; Waddington et al., 2016). Earlier diagnoses, coupled with an increased prevalence rate for ASD (Waddington et al., 2016) means that an intervention model dominated by a one therapist to one child approach may not be feasible, practical or affordable. For instance, Early Intensive Behavioural Interventions (EIBI) requires a team of therapists to work with a child one on one for up to 40 hours per week (Peters & Scheffer 2011). This means that a number of trained therapists are required for each child, with the household income generally absorbing the majority of these costs (Ryberg, 2015). Additionally, if a diagnosis is made earlier in a child's life, there are very few interventions that are specifically designed for toddlers with ASD(Waddington et al., 2016). An intervention approach that addresses both of these concerns is the Early Start Denver Model (ESDM; Rogers & Dawson, 2010). Unlike other EIBI intervention models, that are expensive and require a large amount of one on one time between the therapist and child (Ryberg, 2015), the ESDM has the potential to be delivered within a one-to-one format, as well as a group based setting (Dawson & Bernier, 2013). Moreover, the ESDM approach is specifically developed for toddlers and young children with ASD from 12 to 60 months of age. As the ESDM is becoming more established as a group based intervention approach, the uptake of the ESDM model is increasing among community service providers and within preschool settings (Dawson et al., 2010).

The ESDM intervention methods, curriculum and goals are a combination of principles derived from other therapies including; The Denver model (Rogers & Pennington, 1991), Pivotal Response Training (Peirce & Schreibman, 1995), ABA (Lovaas; 1987; Lovaas & Koegel, 1974), Social Motivation Hypothesis (Rogers, Herbison, Lewis, Pantone, & Reis, 1986) and Rogers's and Pennington's Model for Early Intervention (Rogers & Pennington, 1991). Each of these models aims to increase social and communication skills among young children with ASD. Firstly, in order to accelerate the acquisition of communication and social skills, these therapies encourage naturalistic interactions to promote social attention and social reward. The ESDM's focus on verbal and non-verbal communication stems from the Denver Model, which emphasises the imitation and reciprocation of gestures, facial expressions and movements through interpersonal engagement between the child, their parents and therapists (Rogers & Pennington, 1991; Waddington et al., 2016). Rogers and Pennington (1991) hypothesised that children with ASD are unable to gain others' perspective or share emotions due to a deficit in imitation skills. The ESDM also uses social motivation to increase learning experiences that focus on communication, facial expressions, emotion and language development (Dawson, 2004). Finally, behavioural practices (the use of various reinforcements to control or manage behaviours) are incorporated from ABA and Pivotal Response Training (PRT). This allows children to engage in repeated learning opportunities, with techniques such as response prompting, reinforcement and shaping (Hayward, Gale, & Eikeseth, 2009; Koegel, Koegel, Harrower, & Carter, 1999).

Although the ESDM is classified as an early intensive behavioural intervention (EIBI), it also incorporates more naturalistic teaching strategies, making the therapy a naturalistic developmental behavioural intervention (Ryberg, 2015; Waddington et al.,

2016). While the ESDM approach integrates the principles of ABA, its design is much more child-directed and naturalistic. This means that the child engages in meaningful, naturally occurring social activities which include a mixture of structured daily routines and self-directed play (Ryberg, 2015). Behavioural teachings (the application of ABA and PRT principles) are structured around these activities in order to increase the child's responsiveness in a more generalised manner (Rogers & Dawson, 2009a; Ryberg, 2015). The use of a more naturalistic approach means that the ESDM intervention is versatile in its method of delivery. For instance, the ESDM intervention is implemented in group and preschool settings, which often creates opportunities for incidental learning to occur (Dawson et al., 2010; Ryberg, 2015).

In order to assess baseline skills and progression throughout the intervention, the ESDM *Curriculum* is used to measure each child's abilities across four levels. This includes moving from basics at level one to more complex integrated abilities at level four, and multiple developmental domains. Developmental domains include: social skills, expressive communication, gross motor, fine motor, receptive communication, play skills and adaptive behaviour. Within each of these domains two or three individualised short term learning objectives are identified and taught over 12 weeks. Throughout the 12 weeks, the teaching targets are modified based on data the teacher takes throughout the sessions. At the end of the 12 weeks, a new checklist assessment is conducted to re-assess learning objectives. New objectives are also developed or old objectives are revised. From each objective, therapists then develop a sequence of steps which serve as teaching targets. In particular, the therapist focuses on teaching new skills (acquisition) and practicing skills that have been mastered immediately after acquisition (maintenance). Each child's performance is entered into a daily data sheet in order to track each child's learning. An adapted version of the ESDM has also been

developed, where parents are able to learn the ESDM approach and therapy techniques and deliver the intervention to their children in the home (Estes et al., 2014; Vismara, Colombi, & Rogers, 2009). In this model, parents are able to utilise the behavioural teachings of the ESDM within the child's home environment during daily routines and play (Estes et al., 2014). Although the evidence for parent delivered ESDM is still emerging, theory, practice and research all emphasise the importance of parent delivered therapy (Rogers et al., 2012). Parent delivered therapy has the potential to increase generalisation as well as spontaneity of responses as the delivery of therapy is not constrained to a particular environment and can be used in addition to traditional therapy (Rogers et al, 2012).

While the number of studies examining the effectiveness of the ESDM approach is steadily increasing, there are a number of similarities and differences between the methodologies used in this research. Most studies utilise the same standardised assessments at both baseline and follow up to examine the effectiveness of the ESDM. This allows the results and outcomes from each of these studies to be compared. Although most of the studies delivered the whole ESDM curriculum, a few studies have modified the ESDM program or utilised only a small portion of the curriculum. For instance, Jouen et al. (2017) delivered the components of the ESDM that focused on joint attention and imitation. While the study evaluates a broad range of standardised outcomes, it only delivered a subsection of the ESDM. Furthermore, there are differences between the design and methodology of these studies. While some include a comparison group, others only assess children receiving the ESDM. Finally, perhaps the most distinct difference amongst the studies is the significant variation in the amount of time children spend in the ESDM therapy in each of the studies.

To date, studies examining intervention outcomes from the implementation of the ESDM curriculum contain an intervention duration ranging from 3 to 24 months. Although the amount of time a child with ASD receives intervention is important, it remains unclear as to why there in large variation between studies. It is possible that there is a lack of people trained in the ESDM intervention or that the intervention is too expensive for some families and therefore, a three month intervention is more appropriate. There are a number of factors that play a role in the effectiveness of the ESDM including the intensity of the intervention, family involvement, additional therapies, age at enrolment, as well as differences in the individual's functioning (high or low functioning) (Makrygianni et al., 2010). However, the amount of time the children spend in therapy is likely to impact their outcomes differently (Reichow et al., 2014). For example, children may demonstrate greater outcomes on a number of assessments, or a particular subset of assessments, after receiving 24 months of ESDM therapy compared to children who receive three months of ESDM therapy (Reichow et al., 2014). Additionally, while two years of ESDM therapy is recommended for improvements to occur in IQ, language, adaptive behaviours and social skills (Ryberg, 2015), the majority of studies examining outcomes of children receiving the ESDM therapy have been shorter than a year (Waddington et al., 2016).

In order to guide research and practice, it is important to ascertain how differences in the amount of time spent in therapy impacts outcomes. Moreover, given that the majority of studies utilising the ESDM approach have examined outcomes for children who have received less than 12 months of therapy, it is important to establish how effective the ESDM approach is when timeframes are utilised that are less than the recommendations for EIBI intervention. This paper will provide a review and comparison of the outcomes from studies that evaluated the ESDM delivered for

different periods of time, including 24 months, 10-12 months six months and three months duration.

Length of Treatment: 24 months

Researchers suggest that the most favourable outcomes for children with ASD occur when therapy commences early in life, and is sustained for two or more years (Vismara & Rogers, 2010). Meta analyses focusing on EIBI have indicated that future studies should look at increasing the efficacy, methodological rigor and evidence of outcomes (Dawson et al., 2010). In an attempt to resolve these issues, Dawson et al. (2010) conducted a randomised controlled trial using the ESDM intervention. This study included gold standard diagnostic criteria, and comprehensive outcome measures administered by examiners blind to the study outcomes. Aditionally, measures of fidelity were recorded regarding the way in which the manualised therapy was implemented by trained therapists and parents (Dawson et al., 2010). Utilising these standardised methods, the study formed the first and only randomised clinical trial to date assessing outcomes of the ESDM.

The study was conducted over a two year period with 45 children aged between 18 and 30 months of age with ASD. Upon entry, each child was assessed using a number of standardised assessments, including the Autism Diagnostic Interview-Revised (ADI-R) (Lord et al, 1994) , Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2000), Vineland Adaptive Behaviour Scales (VABS-II) (Sparrow, Chicchetti & Balla, 2005), Mullen Scales of Early Learning (MSEL) (Mullen, 1995) and the Repetitive Behaviour Scale (RBS) (Moss & Oliver 2008). These assessments were also administered again after the children completed 12 months of therapy, and

upon exit at two years (Dawson et al., 2010). Children were randomly assigned to two different groups: the ESDM intervention (n = 24) or the community group, where the intervention that was most commonly available in their community was used (n = 21) (Dawson et al., 2010). The children in the ESDM group received two hours of therapy by trained therapists and their parents, twice per day, five days a week. Similarly, the children in the community group received one on one therapy (average 9.1 hours per week) and group therapy (average 9.3 hours per week) (Dawson et al., 2010). The two groups did not differ at baseline (P > .10 on all measures) in chronological age (conrol M = 23.1 months, ESDM M = 23.9 months, d = .02), severity of symptoms (conrol M = 6.9, ESDM M = 7.2 d = *.17*), or adaptive behaviours (conrol M = 69.9, ESDM M = 69.5 d = .06). Furthermore, children were only included if they demonstrated an IQ above 35 as measured by the visual reception and fine motor subscales of the MSEL. As both the control and ESDM average visual reception and fine motor subscales scores were 35, both groups were defined as relatively low functioning. Given that the effect sizes were all below .2, group differences are considered to be minimal.

The results of the study showed that, after one year of intervention, the ESDM group demonstrated significantly more change on the visual reception MSEL subscale compared to the community group, with other MSEL subscales and IQ also approaching significance in a similar trend (see Table 1). By the second year, the ESDM group showed significant increases across a number of subscales on the MSEL including the expressive and recepetive language subscales. This suggests that the ESDM group's communicative abilities were improving as a result of the ESDM focus on face to face communication (Dawson et al., 2010).

The ESDM group also displayed similar standard scores at at both first and second year outcomes on the VABS-II adaptive behaviours indicating no change in score.(Dawson et al., 2010). This is in contrast to the community group that showed a decline in VABS-II adaptive behaviours including socialisation, daily living skills and motor skills. Interestingly, the groups did not differ on ADOS severity scores or RBS total scores after one or two years of intervention (Dawson et al., 2010). Moreover, based on diagnostic criteria from the DSM-IV, the diagnosis of seven children in the ESDM groups changed from autistic disorder to pervasive developmental disorder after the first year of therapy. Collectively, these results demonstrate that the toddlers who received the ESDM intervention over two years displayed greater changes in IQ, adaptive and cognitive abilities compared to children in the community group (Dawson et al., 2010). The results of the randomised control trial support the use of ESDM for children with ASD as an EIBI.

Using the same cohort, the researchers also examined brain activity, compared to typically developing children, after children with ASD received either the ESDM approach or community intervention (Dawson et al., 2012; Kuhl et al., 2013). Electroencephalogram (EEG) activity was measured while children viewed a series of faces and objects (Dawson et al., 2012). At the end of the two year intervention, children who received the ESDM approach had EEG measurements that were similar to typically developing children. Children who received ESDM and typically developing children also showed greater cognitive and attentional resources and a faster neural response (shorter Nc latency) when viewing faces. This is in contrast to children in the community group, who showed shorter Nc latency for objects. The authors concluded that these increases in activity towards social stimuli were due to the social-communicative focus of the ESDM therapy (Dawson et al., 2012). Although this study

was the first to provide insight into the neurological changes that may occur due to the type of therapy undertaken, the EEG measurements were only taken following intervention. Consequently, a lack of comparable baseline measurements makes it difficult to draw conclusions about brain activity over time.

Length of Treatment: 10-12 months

Although the Dawson et al. (2010) study was the only randomised controlled trial to assess outcomes of children receiving the ESDM intervention after two years, other studies have evaluated the outcomes of young children receiving the ESDM within shorter timeframes. Four studies have assessed various outcomes over a 10 to 12 month period, as well as assessed the effectiveness of the ESDM delivered within a community based day care setting (see Table 1). In the first of these studies, Eapen, Črnčec, and Walter (2013) evaluated the effectiveness of 10 months of the ESDM in a preshool, with children with ASD from two to six years. The MSEL (Mullen, 1995), Social Communication Questionnaire (SCQ) (Rutter, Bailey, & Lord, 2003) and VABS-II (Sparrow et al., 1989) were used to assess outcomes. Results showed that overall intellectual functioning of the children increased significantly from pre to post assessments (Dawson et al, 2010). This finding showed a significant change in developmental quotients, a numerical indicator expressing a child's growth and maturity across a range of assessments). Similar to Dawson et al. (2010), significant improvements were also found on MSEL subscales including visual reception, receptive language and expressive language. Based on standardised scores and developmental quotients (DQs) (the child's age equivalent score divided by their chronological age at the time of testing and then multiplied by 100) derived from MSEL

subscale raw scores, these gains were found to be over and above expected child development and maturation, indicating that the increases were a result of the intervention. As the ESDM heavily targets overall language skills, this finding indicates that children may be more likely to make changes in areas related to the objectives of the ESDM therapy.

Further examination of assessment outcomes revealed significant increases on the VABS-II from pre to post intervention (Eapen et al. (2013). These included sub domains such as receptive communication and gross motor skills, as well as the overall motor skills domain. However, without the addition of a control group where DQs could have been compared, it is difficult to differentiate between developmental maturation and those changes that occurred as a direct result of therapy (Eapen et al., 2013). The authors found overall decreases in reciprocal social interaction, language and communication and stereotyped patterns of behaviour, suggesting that there was a decrease in the children's autism specific features. Moreover, after the time two post assessment, 42% of children scored below the clinical cut-off on the SCQ, compared with 21% at pre-assessment, indicating a reduction in the number of ASD symptoms they presented with. Overall, this study provided evidence of significant improvements in children with ASD receiving ESDM therapy over a 10 month period. However, the effect size for the ESDM group (d =.47) was less than the effect found in Dawson et al. (2010) study (d = .87). It is important to note that the decrease in effect size may be a result of the average enrolment age of the children. While children in Dawson et al. (2010) study started at 23.9 months, children in Eapen et al. (2013) study started at 49.6 months old. This means that age may have played a role in the effect size difference. Moreover, any comparisons between these studies need to be interpreted with caution given the differing designs of the two projects. Despite this, these findings suggest that

the ESDM is effective in both an intensive one on one design, as well as a less intensive group setting.

Fulton, Eapen, Črnčec, Walter, and Rogers (2014) examined the effectiveness of the ESDM intervention in reducing maladaptive behaviours over an 11 month period. They found increases in MSEL sub scales including Visual Reception, Receptive Language, Expressive Language, and overall DQs). In contrast to Eapen et al. (2013), no significant changes over time were found on the SCQ or the VABS-II. The authors argued that this was due to the VABS-II and SCQ being parent based questionnaires. Furthermore, the addition of a parent ESDM approach may have allowed for generalisation of these skills at the child's home. The authors suggest that this may have resulted in an improvement in outcomes on these questionnaires (Fulton et al., 2014). Further analysis revealed that children with less severe symptoms and higher adaptive functioning skills at entry were more likely to display improvements in their level of maladaptive behaviours. Interestingly, 68% of children who displayed a reduction in maladaptive behaviours showed this decrease in the first 12 weeks of therapy (Fulton et al. (2014). This indicates that there may be a sub-group of children who respond rapidly to the ESDM therapy which may be predicted based on their symptom severity and adaptive functioning level at entry (Fulton et al., 2014). In other words, children with specific clinical presentations may achieve greater outcomes in therapy in a shorter amount of time. This highlights the importance of searching for subgroups of children that may or may not respond to intervention programs. These promising findings need to be replicated with the addition of a control group in order to consolidate and further confirm these results.

Researchers have also explored predictors of treatment outcome in young children with ASD receiving ESDM therapy over a 10 month period. A subsequent study by Eapen et al. (2013) found a relationship between less severe autism symptoms at entry and greater improvements on visual reception, expressive language and overall developmental skills on the MSEL. Furthermore, a decrease in autism symptoms was shown on the restricted social interaction subscale of the ADOS, as well as reported by parents on the SCQ. This is consistent with previous research showing that lower autism symptom scores were associated with better outcomes in EIBI (Eapen et al. (2013). Interestingly, maternal efficacy, measured by the parenting sense of competence scale (measuring satisfaction, interest and efficacy as well as a total score) was found to be a predictor (Eapen et al. (2013). This implies that greater perceived maternal self-efficacy at baseline was related to lower autism severity. Chronological age at entry was also associated with improved autism symptoms over the course of therapy (Eapen et al. (2013). That is, children who started therapy at a younger age showed greater improvements. Additionally, the researchers found that children with better play skills showed overall increases in adaptive behaviour. Considering the ESDM is a play-based therapy, children initially having a set of play skills may also be a predictor to treatment response. Collectively, these findings indicate that improvements in autism severity, language and social skills can be observed within 10 months of ESDM intervention.

Vivanti, Paynter, et al. (2014) were the first to examine the effectiveness of the ESDM approach in a community day care setting, compared to children receiving an eclectic style of community intervention. Similar to the previous studies, the ESDM was delivered by one teacher to three students. Results showed that both groups made significant increases over a 12 month period on the ADOS social affect scale, the VABS-II communication domain and MSEL scales and subscales. This is with the

exception of the Receptive Language subscale on the MSEL, where the ESDM group demonstrated larger gains compared to the community group (Vivanti, Paynter, et al. (2014) . These results replicate some of the findings from the Dawson et al. (2010) study, and provide further evidence that the ESDM can achieve significant outcomes when delivered in a group based setting.

Overall, research examining the outcomes of children receiving the ESDM for a period of 10 to 12 months has demonstrated increases in a number of areas. These include increases in visual reception, receptive language, expressive language and receptive communication, as well as motor skills and overall intellectual functioning. Furthermore, decreases were found in ASD specific features and maladaptive behaviours following 10 to 12 months of the ESDM intervention. Although only one study provided a comparison group, the findings from these studies do provide further evidence that the ESDM therapy can be successfully delivered within a 10 to 12 month period.

Length of Treatment: 6 months

One study has evaluated outcomes within a six month period by utilising a set of computer games focusing on joint attention and imitation (Jouen et al., 2017). The authors reasoned that imitation and joint attention are crucial to the development of social skills and communication, and as a result, they targeted these two specific areas of the ESDM (see Table 1). Additionally, to address the issue of heterogeneity amongst children with ASD, the authors created the video games to be adjusted by the parent based on the child's strengths and difficulties, as well as their developmental age. An age, sex and IQ matched control group who received treatment as usual (treatment as

usual was defined as all therapeutic interventions a child would normally receive within their local area). were also included in the study. The children in the ESDM group received five 30-minute computer sessions, as well as one session per week at the hospital, in addition to receiving treatment as usual.

Both groups demonstrated a faster response times and significant increases over time on the ADOS, VABS-II socialisation score, the CBCL sub scales of internalising, externalising and total problems. This indicates that the intervention provided to both groups was positive. Although overall increases were observed after six months of therapy in both groups, there were no significant differences between the two groups on any of the clinical assessments used (ADOS, VABS-II, WPPSI III/ WISC IV, CBCL, SCQ and PSI) (Jouen et al. (2017). While faster response times to perform the joint attention and imitation games were observed, improved abilities obtained throughout the gaming context may not have generalised to the assessment environment. A major limitation of this study was the age of the participants in the experimental group. Jouen et al. (2017) recruited children between five and eight years old. However, the ESDM approach is designed for young children with ASD between one to four years (Dawson et al., 2010). Therefore, it is difficult to draw conclusions about this study given the age range of participants is outside the age for which the ESDM was developed. Furthermore, more research analysing the effects of the ESDM when the entire curriculum is applied, as opposed to a sub section (i.e. imitation and joint attention), needs to be undertaken. The study also does not mention how or if fidelity was measured, thus the extent to which the delivery of the ESDM adheres to the criteria is unclear

Length of Treatment: 3 months

To date, only three studies have examined the effectiveness of the ESDM over a 12 week period (see Table 1). In all of these studies, the ESDM was delivered by parents of children with ASD. In the first study, eight children aged between 12 months and 3 years received one hour of intervention per week for 12 weeks (Estes et al., 2014). Although all eight parents completed the ESDM training program, only seven parents mastered the ESDM techniques. In addition to the ESDM checklist, the MSEL and ADOS assessments, this study also incorporated a 10 minute sample of child-parent, as well as child -therapist play session that was recorded at baseline and at follow up. In addition to increases in social communication behaviours, the researchers found an increase in functional verbal responses, spontaneous vocalisations and imitation during the 10-minute parent–child and therapist–child interactions (Estes et al., 2014). Similar to previous research reviewed here, this study indicates that improved social and language outcomes are also found when the ESDM is delivered by parents.

A case study has also examined the outcomes of parent delivered ESDM for one and half hours a week over 12 weeks, as well as four additional follow-up sessions (Vismara et al., 2009). The participant (aged 9 months) demonstrated an increase in spontaneous utterances and imitative behaviours during play sessions with the therapist and parent. Moreover, the participant attended to and initiated more social behaviours with their parent compared to baseline scores. This increase was also sustained during play sessions conducted during the follow up sessions rated by clinicians after the completion of the 12 week intervention (Vismara et al., 2009). Although these increases occurred during both the child-parent and child-therapist play sessions, higher scores

were demonstrated during the child-parent interactions (Vismara et al., 2009). The studies provide some evidence that an hour of ESDM therapy over 12 weeks can improve rates of skill acquisition provided that ongoing parent training of the ESDM techniques occurs. However, It should be noted that these two studies did not utilise a control group and they did provide a measure of fidelity between assessors. Therefore, it is possible that the ESDM and outcome measures may have been delivered differently between assessors.

Another study that evaluated ESDM over three months compared outcomes between the parent-ESDM intervention and a treatment as usual group with a younger cohort, aged between 14 and 24 months (Rogers et al., 2012). Results demonstrated that although 95% of children still met ADOS criteria for ASD, over the 12-week period, both groups significantly improved in social and verbal abilities. When the researchers combined the two groups, they found two main factors predicted these improvements: the age of the child and the number of hours they attended therapy (Rogers et al., 2012). This indicates that children who spent more hours in therapy displayed reductions in restrictive and repetitive behaviours and increases in communication skills, vocabulary, comprehension, overall DQ, as well as a reduction in the number of ASDsymptoms reported. Similar to Eapen et al. (2013) findings, children who were older (closer to 24 months) displayed smaller increases in developmental rates (Rogers et al., 2012). Collectively, these findings indicate that age may play a role in intervention outcomes. Specifically, children who started intervention at a younger age displayed improved outcomes in adaptive functioning and social outcomes. Although, the researchers were unable to show that the ESDM was more effective than a generic intervention approach within this timeframe, the study does provide further evidence for the notion that early intensive intervention is imperative.

Collectively, studies evaluating the ESDM delivered over three months show improved outcomes in social and language skills. Furthermore, two of the studies examined outcomes when parents delivered the ESDM techniques. These studies provided some evidence that a parent delivered ESDM over 3 months can improve outcomes in social skills and vocalisations from baseline scores. Furthermore, the research by (Rogers et al., 2012) highlights the relationship between age and duration and their impact on outcomes. The results indicate that even within three months of intervention, younger children and children who spent more hours in therapy were displaying improved outcomes.

Follow up Studies

One study has investigated the outcomes of children with ASD two years after receiving either the ESDM or community intervention (Estes et al., 2015) (see Table 1). Utilising the cohort from the Dawson et al. (2010) RCT, the researchers examined whether the children in this study, at the age of six years, maintained the improvements made during therapy at age 18 to 30 months. Results indicated that the ESDM group had significantly higher standard scores on the VABS-II composite and socialisation scores, as well as lower ADOS total and Restrictive Behaviours scores compared to the community intervention group (Estes et al., 2015). This demonstrates that after two years, children in the ESDM group maintained the improvements made during the ESDM intervention in areas including ASD symptoms, challenging behaviours, intellectual ability and adaptive behaviours. Additionally, two children in the ESDM group no longer met diagnostic criteria for ASD at six years of age, according to two clinicians who were blind to which intervention group the children were placed in. Although this finding may indicate that the children's symptoms improved and that they

no longer met specific criteria, this finding may also demonstrate the lack of reliability between clinicians assessing children. Future research should aim to include a measure of reliability to rule out subjectiveness between assessors.

It should be noted that, on conclusion of the RCT, children in the ESDM group went on to receive significantly less therapy hours per week, with more of these hours being spent in a group setting compared to children in the community intervention group. This implies that the less restrictive and more naturalistic environment of the ESDM is crucial to learning and generalising skills and behaviours (Estes et al., 2015).

Additionally, some assessments at the two year follow up also showed lasting improvements in both groups. Children in the ESDM and community intervention groups continued to make improvements in adaptive and intellectual functioning as evidenced by increases in all adaptive function and IQ domains. The finding that neither group declined or regressed in skills is important, as it denotes that in general, early intervention has the capacity to have long lasting outcomes for children with ASD. Nevertheless, the ESDM approach showed a higher amount of significant improvements, even with a reduction in therapy hours and less one on one therapy, relative to the community intervention. Even though some domains fell short of significance with respect to group differences, the ESDM group still demonstrated higher scores. For instance, nonverbal IQ scores were 10 points higher on average in the ESDM group as was verbal IQ scores, averaging 6.4 points higher than the community intervention group (Estes et al., 2015). Therefore, it is clear from this study that the ESDM approach plays a crucial role in altering the long term developmental trajectory of children with ASD (Estes et al., 2015).

Study Aims	Duration of Therapy	Authors	Child Age	N	Assessments Used	Comparison Groups,	Firdelit and Effect Size	Results
Investigated the impact of P-ESDM on parenting-related stress and sense of competence.	3 months	(Estes et al.)	12 – 24 months	98 49 PESDM 49 community	QRS PSOC MSEL DAS ADOS CHARGE LES	P-ESDM, Community	ESDM Parent Fidelity Tool - two coders independently rate 10 minutes of the recordings Average Fidelity score 4.47 (s.d. =.24) measured on the 14-item fidelity tool with scores ranging from 1–5. P-ESDM group effect size (.57) community group's effect size (.37)	- No increase in paren compared to commu - No# of negative life a significant predicto parenting stress. - Parent coaching inte may help parental ad after diagnosis.
Parent acquisition of intervention skills and, possible developmental gains and reduced core autism symptoms.	3 months	(Sally J. Rogers et al., 2012)	14-24 months	7 P-ESDM 7 matched cases	ITC AOSI Infant start parent /Thaerapist fidelity measure Parent satisfaction rating Working Alliance Scale for Interventions with Children The Carolina Curriculum for Infants and Toddlers with Special Needs, ESDM checklist ADOS MSEL	1 treatment 4 COMPARISON GROUPS Declined referral High risk Low risk Autism outcome	ESDM Parent Fidelity Tool - two coders independently rate 10 minutes of the recordings Average Fidelity score 4.47 (s.d. =.24) measured on the 14-item fidelity tool with scores ranging from 1–5. P-ESDM group effect size (.57) community group's effect size (.37)	- No group difference between families in and community treat - No group differences outcome variables pa receiving ESDM coa stronger working alli primary therapist tha community intervent

Effectiveness of one hour of ESDM intervention over 12 weeks.	3 months	(Vismara et al., 2009)	12 months to 3 yrs	8	ADOS MULLENS 10 mins play session (child/parent) 10 mins play session (child/therapist)	No control group	Fidelity of Implementation measure - two coders independently rate 25 percent of the tapes. .85 inter-rater agreement.	- Increases in social communication beha Increase in functiona responses, spontaneo vocalisations and im during 10-min paren therapist–child intera
Study aims	Duration of therapy	Authors	Child age	N	Assessments used	Comparison groups		Results
Evaluate Intervention outcomes for an infant identified at 9 months of age.	3 months	(Vismara & Rogers, 2008)	9-24 months	1	ADOS MULLENS 10 minute play session (child/parent) Child social communicative behaviours. Child Behaviour Rating Scale 10 minute play session (child/therapist)	No control group	No measure of fidelity / effect sizes	- Increase in productio spontaneous utteranc imitative behaviours sessions with therapi father.
Evaluate outcomes of an automated serious gaming platform with 11 games to deliver intervention at home.	6 months	(Jouen et al., 2017)	5-8 years	14	ADOS VABS II WPPSI III/ WISC IV CBCL SCQ PSI	age and sex matched children receiving treatment as usual.	No measure of fidelity/effect size	- Participants trained v GOLIAH improved t perform the task in n games and imitation most imitation game intervention did not a Parental Stress Index significant improven ADOS, Vineland soc score, PSI total score CBCL internalizing, externalizing in both

Evaluated effectiveness of the ESDM. using a group-based intervention in a community child care setting.	10 months	(Eapen et al., 2013)	Between 2-6 yrs old average 49.6	26	MSEL SCQ VABS two parent-report questionnaires	No comparison groups	No Fidelity measures Effect sizes: Visual reception .63. Receptive Language .48 Expressive Language .40, Receptive communication .49, Motor skills .87.	- Significant post-inter improvements on vis reception, receptive l and expressive langu domains of the MSE significant increases receptive communica motor skills on VAB significant decrease i specific features on S
Study aims	Duration of therapy	Authors	Child age	N	Assessments used	Comparison groups		Results
Predictors of treatment outcome in a cohort of preschool - aged children with ASD. receiving a group Early Start Denver Model (ESDM) intervention.	10 months	(Eapen, Crncec & Walter, 2016)	Average 52 months	49	MSEL VABS ADOS SCQ DASS 21	No comparison groups	Fidelity- therapists were required to achieve: (1) a fidelity rate of 80% or more with the ESDM trainer on each of the 13 ESDM teaching principles Effect size: Visual Reception -0.47, receptive language -.40, expressive language -.38. Motor skills .19	- > MSEL domains of reception, receptive a expressive language overall intellectual fu >receptive communi motor skills on VAB report.< in autism-sp features on the SCQ.
Explore if ESDM treatment approach reduced maladaptive behaviours in a community-based long day care setting.	11.8 months	(Fulton et al., 2014)	2-6 yrs old Av 52.2 months	38	VABS SCQ MSEL	No comparison groups	Fidelity- therapists were required to achieve: (1) a fidelity rate of 80% or more with the ESDM trainer on each of the 13 ESDM teaching principles Effect Size: MSEL -0.41.	- Significant reduction children's maladapti behaviours on exit. Improvement in chil overall developmenta MSEL. No sig differ VABS II or SCQ.
Investigated effectiveness/ feasibility of ESDM in a long-day care community service, with child-staff ratio of 1:3 .	12 months	(Vivanti, Paynter, et al., 2014)	2.5 to 6 yrs	27	ESDM checklist VABS	ESDM Community long day care centre	Fidelity: staff submitted a series of videos that were reviewed by independent certified ESDM	- Children in both grou gains in cognitive, ac social skills. ESDM

					PLS MSEL SCQ ADOS		trainers. Average score achieved on the 5 point ranking system was 4.34. Effect size: Receptive Language .09, developmental rate .07	gains in developmen receptive language.
Evaluate the efficacy of the ESDM with a secondary outcome measurement, EEG activity.	2 years	(Dawson et al., 2012)	18 to 30 months	48	Faces v objects	Age matched typical children ESDM group Community intervention group	Therapists required to demonstrate/ maintain a fidelity of 85% of maximum scores on the fidelity instrument Effect Size: Autism severity 1.6, expressive language .61, adaptive/social behaviours .50	- ESDM Increased in symptoms, language and social behaviour to community group TD shorter latency a increased cortical ac when viewing faces. Community interven opposite effect - Increased cortical ac associated with impr behaviour.
Study aims	Duration of therapy	Authors	Child age	N	Assessments used	Comparison groups		Results
randomized, controlled trial to evaluate the efficacy of the ESDM.	2 years	(Dawson et al., 2010)	Between 18 and 30 months	48 total 24 ESDM 21 community intervention	MSEL ADOS ADI VABS RBS	randomly assigned to 1 of 2 groups: ESDM or intervention commonly available inthe community.	Therapists required to demonstrate/ maintain a fidelity of 85% of maximum scores on the fidelity instrument Effect Size: Autism severity 1.6, expressive language .61, adaptive/social behaviours .50	- ESDM group > impr IQ, adaptive behavio diagnosis. ESDM gr improved 17.6 stand points compared wit in community group baseline scores. ESD maintained rate of g adaptive behaviour c with TD children wh community group sh delays in adaptive be
Examined evidence for the sustained effects of early intervention based on a follow up study of children with ASD who began participation in a randomized clinical trial.	Follow up 2 years after therapy	(Estes et al., 2015)	Six years old	48 total 24 Post- ESDM group 24 Post- Community Intervention group	IQ VABS II	Post- ESDM group, Post-Community Intervention group	No fidelity measures Effect size: Adaptive behaviour .177, symptom severity .05,	- ESDM group mainta made in overall intel ability, adaptive beha symptom severity an challenging behaviou group demonstrated core autism sympton

					Aberrant behaviour checklist RBS ADOS ADI-R		repetitive behaviours .062	adaptive behaviour c community-group. B did not differ on inte functioning.

Table 1. Overview of studies included in Chapter Two.

Discussion

The aim of this review was to evaluate and compare the outcomes from studies that delivered the ESDM for different periods of time, including 24 months, 10-12 months, six months and three months duration. Several studies presented in this review have provided evidence of the effectiveness of the ESDM delivered across various time frames.

All studies reporting the ESDM that was implemented from10 to 24 months reported significant improvements. Although a variety of improvements were found across a number of assessments, the most consistent changes were identified in communication, as well as expressive and receptive language. Furthermore, in the two studies that included a comparison group, improvements in expressive and receptive language were found to be significant in the ESDM group only (Vivanti et al., 2014; Vismara et al., 2009). This demonstrates that these significant improvements are likely due to the ESDM, rather than general intervention practices for ASD. This highlights that the social communicative focus of the ESDM may have a specific positive impact on language skills. Furthermore, given that parent scores of various clinical measures and questionnaires improved over time, this suggests that children receiving ESDM therapy are able to generalise these skills outside of the therapy environment. Of note, studies with shorter timeframes (three to six months) were unable to detect greater improvements in expressive and receptive language in the ESDM group when compared to a control group. Although Fulton et al. (2014) findings suggested that there may be a sub-group of children who respond rapidly to the ESDM therapy (within the first three months), it may be the case that, in general, some children respond rapidly regardless of the therapy type. This is evidenced by the consistent improvements found in both

studies conducted within six and three month timeframes. Overall, the findings from these studies indicate that children benefit from being in the ESDM therapy for longer. However, further research is needed, with the inclusion of control groups, to increase our knowledge about what role duration plays with respect to outcomes.

Another consistent finding amongst the research reviewed here is the relationship between age at enrolment and improved outcomes. More specifically, children who started therapy at a younger age were more likely to display improved outcomes over the course of the intervention. This relationship between age and improved outcomes was associated with improvements in social and communication skills, restrictive and repetitive behaviours, cognitive abilities and autism severity (Eapen et al., 2013; Rogers et al., 2012). These widespread improvements across various assessments signify the importance of starting intervention as early as possible. In particular, Rogers et al. (2012) reported that children approaching 24 months, the average age children are being enrolled into therapy (Rogers & Pennington, 1991; Waddington et al., 2016), had smaller increases in developmental rates compared to children who started therapy at 14 months of age. These findings highlight the need for children to start intervention earlier. Indeed, much remains to be learned about characteristics that have the potential to impact an individual's response to intervention. While more research is needed, this research indicates that early intervention is key to better outcomes for children with Autism.

Another relevant and emerging theme from the studies reviewed here is the effectiveness of the naturalistic and less restrictive environments that the ESDM is delivered within. In these studies, the ESDM was mostly delivered in a group setting, or within a preschool environment. While children also received a certain amount of one

on one therapy, the majority of the children's time was spent in a group of three and four children to one therapist. Although the ESDM utilises ABA principles, and both therapies show equivalent outcomes, the environment in which these principles are carried out are distinctly different (Waddington et al., 2016). While EIBI models are predominantly taught one on one and within the child's home, the ESDM is often delivered within a group setting, with a small part of the day dedicated to one on one therapy (Vismara & Rogers, 2010). Given the play-based nature of the ESDM, delivery of this method within a group or preschool appears to be ideal (Eapen et al., 2013). Additionally, with fewer one on one hours and more widespread reach, the ESDM appears to be more practical in terms of wider community access to therapy. As a result, the costs associated with the ESDM are lower.

Lastly, while the improved outcomes of participants in many of these studies are promising, it is important to acknowledge that the majority of the research did not include a control group. While this research showed significant improvements over the duration of the studies, caution still needs to be taken when interpreting these results. Without a control group, it may be difficult to ascertain what improvements were due to the therapy, and which were the result of maturational development (Eapen et al., 2013). However, given that ASD symptoms and IQ (Begovac, Begovac, Majić, and Vidović (2009) are generally stable over time; it is likely that these changes in assessment scores can be attributed to the ESDM intervention. However, future research should include comparison groups where possible.

Limitations and Future Directions

Of the 12 studies reviewed here, 10 focused on the effectiveness of the ESDM therapy by measuring outcomes from standardised assessments. While one study

examined only a small portion of the ESDM therapy in a computer-based game, the researchers still utilised assessments that were widely known to assess change over time in various cognitive and social domains. The remaining two studies did not utilise any standardised assessments. Instead, one study focused on parental stress (Estes et al.), while the other compared brain activity over time (Dawson et al., 2012; Estes et al., 2014). Collectively this demonstrates two points. Firstly, research into the efficacy of the ESDM includes small scale research, such as case studies and small sample sizes, as well as large scale studies and randomised controlled trials (Dawson et al., 2010; Eapen et al., 2013; Fulton et al., 2014; Vivanti, Paynter, et al., 2014). Although many researchers argue that the ESDM is already empirically supported, more large scale studies focusing on outcomes are necessary in order for the ESDM to be further recognised as an empirically supported intervention for young children with ASD (Vismara, Young, Stahmer, Griffith, & Rogers, 2009; Vismara et al., 2009; Waddington et al., 2016). Moreover, in order to identify what improvements are functions of the implementation of the ESDM, more studies need to include a control group or a comparison group. Secondly, only two published studies have incorporated neuroimaging (to potentially understand biomarkers and measure other responses to therapy) (Dawson et al., 2012), as well as the use of technology assisted therapy (Dawson et al., 2012). Further extensions of these studies are important. This is particularly the case for neuroimaging, where the findings have the potential to complement ESDM efficacy studies by showing that changes in brain activity over time are associated with the ESDM. Although research examining the brain activity and behavioural outcomes before and after intervention shows promising findings, more research examining the relationship between brain activity and behavioural outcomes is required. Collectively this additional research will provide a comprehensive

understanding of the factors impacting both clinical and neurological outcomes and as a result complement ESDM efficacy.

Conclusion

The current review offers insights into the effectiveness of the ESDM delivered across various timeframes. In general, the findings are promising across a number of domains, specifically in areas targeted by the ESDM, such as receptive and expressive language. This indicates that the social communicative focus of the ESDM may result in an increase in various language skills. These skills may also be generalised outside of the intervention environment. In studies evaluating intervention outcomes from 10 months to 24 months in duration, greater outcomes were found. This indicates that children who receive a longer period of the ESDM make more improvements across a variety of outcomes including maladaptive behaviours, social and communication skills, cognitive and adaptive behaviours and motor skills. This highlights that there may be an optimal time that children should stay in therapy. Similarly, another consistent finding within the review was that better outcomes were demonstrated when children start therapy at a younger age. Although two studies examined age at enrolment and outcomes, further investigation of these specific factors in more detail is important as it will help to optimise children's outcomes in therapy, and guide decisions in the field of early intervention.

Chapter Three:

The Impact of Age, Duration and Intensity on Outcomes for Children Receiving the ESDM

Introduction

The rising prevalence of children diagnosed as having ASD has led to a substantial increase in research focusing on the effectiveness of early interventions. In general, there is a consensus amongst studies examining the outcomes of interventions that early intensive behavioural intervention (EIBI) results in improved outcomes in developmental functioning, as well as a reduction in symptom severity and maladaptive behaviours for children with ASD (Reichow et al., 2014; Reichow, Barton, Boyd, & Hume, 2012). Moreover, follow up studies have shown that these outcomes have a lasting effect, where some individuals with ASD are able to achieve a level of independence later in life (Estes et al., 2015; Reichow et al., 2014).

Despite the plethora of studies investigating outcomes from a variety of EIBIs, an understanding of what characteristics and factors might optimise the effectiveness of intervention is not conclusive (Makrygianni & Reed, 2010). Research investigating the relationship between factors and overall treatment gains is scarce within the EIBI literature. Given the diversity in the biological underpinnings of ASD (Brambilla et al., 2003), a variety of factors could potentially impact outcomes in therapy. Furthermore, it is important to examine specific factors in order to optimise children's outcomes in therapy, and guide decisions in the field of early intervention (Virues-Ortega, Rodríguez, et al., 2013). The most consistently investigated characteristics within the literature include age at enrolment, intensity of intervention and intervention duration (Virues-Ortega, Rodríguez, et al., 2013; Vivanti, Prior, et al., 2014). Intensity, duration and age at enrolment have also been shown to be distinguishing factors that are important for the efficacy of EIBI (Makrygianni & Reed, 2010).

While these factors have been identified as important for outcomes in EIBI, an examination of the research in this area yields somewhat mixed results. In terms of intervention duration, some studies examining the role of duration and outcomes for an eclectic intervention found that duration did not impact outcomes (Howard et al., 2014; Virues-Ortega, Rodríguez, et al., 2013). In contrast, others have indicated that children receiving more specialised EIBIs demonstrated marked developmental improvements after the first year of therapy (Cohen et al., 2006; Howard et al., 2014; Virues-Ortega, Julio, & Pastor-Barriuso, 2013; Vivanti, Prior, et al., 2014). It is argued that specialised interventions are generally focused on building foundational skills within the first year, while the second year helps to further develop and solidify these skills (Howard et al., 2014). Therefore, it is possible that the type of intervention (specialised compared to eclectic) may explain the difference in duration and outcomes found in this research.

Similarly, the findings evaluating the impact of chronological age and treatment intensity on outcomes are also inconsistent. For instance, some research has shown no relationship between treatment intensity or chronological age and better outcomes for children with ASD receiving the Early Start Denver Model (ESDM) (a specialised therapy specifically tailored to young children with ASD (Vivanti, Prior et al.,2014). However, younger age at enrolment was found to be associated with greater reductions in autism severity in another study also evaluating the ESDM (Eapen, 2016). Although these studies examined the same intervention (ESDM), the exclusion criteria differed between the research. While both studies excluded children with medical conditions, Vivanti, Prior et al. (2014) also excluded children with an IQ less than 50. Therefore, it is possible that the results reflect the predictors that might be optimal for a homogenous sample defined by IQ. Studies focusing on Applied Behaviour Analysis (ABA) (a therapy based on learning principles and techniques to improve adaptive functioning

and behaviour) have found that increased intervention intensity was related to better progress and learning outcomes for children with ASD (Granpeesheh, Tarbox, et al., 2009). The authors also found that the earlier the child's intervention started, the better their outcomes were (Granpeesheh, Tarbox, et al., 2009; Zachor et al., 2017). Moreover, meta-analysis of EIBIs has indicated a significant relationship between increased intervention intensity, duration of intervention and age at enrolment and better outcomes for children on the spectrum (Makrygianni & Reed, 2010).

The ESDM (Rogers & Dawson 2009) is the only specialised EIBI for young children with ASD delivered by a team of trained therapists that focuses on social learning, language and independence by incorporating behavioural, relational and developmental approaches (Vivanti, Paynter, et al., 2014). While studies have validated the ESDM by demonstrating better outcomes in cognition, adaptive functioning and social and communication skills, other research has found that these outcomes are impacted by age at enrolment (Eapen, 2016; Cohen et al., 2006; Howard et al., 2014; Virues-Ortega, Julio, et al., 2013; Vivanti, Prior, et al., 2014). Although the impact of age, duration and intensity on outcomes has been examined for EIBI, it is important to establish how these factors impact outcomes in a specialised intervention such as the ESDM in order to optimise the effectiveness of intervention. So far, research has found that children enrolled at a younger age into the ESDM had greater reductions in autism severity (Eapen, 2016). However, to date, no studies have specifically examined intensity or duration and outcomes for the ESDM. Furthermore, Chapter Two highlighted that there are a range of intervention durations (3 to 24 months) in the ESDM literature. Therefore, an investigation of these factors and how they specifically relate to outcomes for children receiving the ESDM is necessary. This will help to optimise children's outcomes in therapy, and guide decisions in the field of early

intervention. This study aimed to investigate the relationship between duration of intervention, age at enrolment and intensity of intervention and outcomes including social and communication, adaptive behaviour and motor skills for children with ASD who received the ESDM

Method

Participants

Participants comprised 47 children who attended an Autism Specific Early Learning and Care Centre (ASELCC) in Sydney, Australia. The ASELCC provides early intervention for pre-school aged children with ASD. All participating children were diagnosed using the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) (American Psychiatric Association, 2013) criteria by a community-based physician. All of these children would have met DSM-5 criteria for a diagnosis of Autism Spectrum Disorder, with the exception of one child who was diagnosed with Asperger's Disorder and four children diagnosed with Pervasive Developmental Disorder Not Otherwise specified. Diagnosis was also confirmed prior to children commencing ESDM intervention (between 2011 and 2017) by trained researchers and clinicians using the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000). Exclusion criteria included known neurodevelopmental (e.g., Fragile X Syndrome) or neurological (e.g., epilepsy) disorders, and significant vision, hearing, motor or physical problems. Demographic information is provided in Table 1.

Table 1. Characteristics of the Study Sample

Characteristics

Average Age at Enrolment (months)	49
Sex (Male)	86%
English Spoken at Home	72%
Cultural Background (other than Australian)	65%
Aboriginal or Torres Strait Islander background	2.1%
Children Living with Both Parents	85%

Procedure

ESDM Intervention

The ESDM treatment approach is specifically designed for preschool settings and children with ASD aged between 12 to 48 months (Rogers & Dawson, 2009b; Steiner, 2013; Warren et al., 2011). The ESDM incorporates a flexible curriculum providing opportunities for teachers and parents to teach skills at any given time (Dade, 2013). The main objectives of the program are to increase social-communicative learning by strengthening children's preference and active attention to social information, including faces, voices, gestures, and speech. This is obtained through increased adult-child interactions that promote joint attention, social play and imitation (Dade, 2013; Rogers & Dawson, 2009b). All therapists delivering the ESDM were previously trained in the ESDM theory and practical application by accredited trainers. Therapists delivered ESDM therapy one on one to participants for two half-hour sessions per week. The participants also received 15-to-20 hours of group ESDM intervention while they attended the centre. Treatment plans were individualised to the child's needs and included a range of objectives dependent on the child's level of functioning and the ESDM curriculum.

The ESDM curriculum is broken into several domains: receptive communication, expressive communication, social skills, joint attention, fine motor, gross motor, imitation, cognition, play skills, behaviour and personal independence (eating, dressing, grooming, chores) (Rogers & Dawson, 2009). Each domain has a list of particular skills with four levels (four being the highest skill level). A curriculum checklist is initially used when the children commence therapy in order to establish the child's current level of abilities in each of these domains.

Learning activities were completed in small groups where each child's individual objectives were targeted in structured group learning experiences. The therapist designed joint activity routines using ESDM-based instructions. For example, the therapist would create natural play routines where the therapist became a play partner and children were encouraged to model and imitate, share materials with the therapist and others, point to objects and name them. During group activities, children were encouraged to use communication, sound, gestures, other body language or eye contact to signify their intent and take turns. Therapists supported communication by using both verbal and visual-auditory cues, supporting temporal sequencing, reducing unwanted behaviours and reducing competing stimuli (Waddington et al., 2016). Participants were evaluated at the beginning of the intervention program, and followed up every 12 months until they exited the preschool. Assessments were conducted at the preschool by individuals trained to administer the diagnostic assessments. All assessors completed ESDM training and received substantial practice alongside an experienced team member in other assessments. Therapists were required to achieve a fidelity rate of 80% or more across sessions delivered and each ESDM teaching principle in order to be certified in direct delivery. All individuals completing assessments were independent from the delivery of the intervention.

Measures

The Autism Diagnostic Observation Schedule

The Autism Diagnostic Observation Schedule (ADOS-2; Lord et al., 2000) was used to confirm whether children met the DSM-5 (American Psychiatric Association, 2013) criteria for autism spectrum disorder. The ADOS-2 is a semi-structured; clinician administered standardised diagnostic assessment of communication, social interaction, repetitive behaviours and play to evaluate the diagnostic criteria for autism. Research has demonstrated that the ADOS-2 has strong inter-rater and test-re-test reliability ranging from 81% to 93% as well as internal consistency for all domains and modules ranging from 47% to 94% (Gotham, Pickles & Lord, 2009). The ADOS-2 was administered at baseline only by a trained researcher.

The Mullen Scales of Early learning

The Mullen Scales of Early Learning (MSEL; Mullen,1995) is a standardised developmental assessment for children from birth to 68 months of age. The scales provide an overall index of cognitive and motor ability and assess the child's weaknesses and strengths. The MSEL consists of five subtests including gross motor, visual reception, expressive language, fine motor, and receptive language. Internal consistency for the MSEL is above 0.80 for all five of the subscales while test-retest reliability ranged between 0.80 and 0.70. The age equivalent scores from each scale were used and higher scores were indicative of higher functioning. The MSEL was administered to all participants by a trained researcher at baseline and follow up.

Vineland Adaptive Behaviour Scales

The Vineland Adaptive Behaviour Scales 2 (VABS; Sparrow, Chicchetti & Balla, 2005) evaluate a child's level of adaptive behaviour across a number of domains including communication, socialisation, motor skills and daily living skills. The standard scores for each domain are as follows: communication 65, Daily living 79, Socialisation 57 and motor skills 85. The VABS is a parent completed measure that provides age equivalent and standard scores across each domain of adaptive functioning. Test re-test reliability ranged between .74 and .98 across domains, subdomains, and ages while inter-rater reliability ranged between .71 to .81 across domains and subdomains. The VABS was completed by parents independently at baseline and follow up. V Scale scores were used for each domain. V-scale score (mean:15, SD:3), higher scores were indicative of better functioning.

Social Communication Questionnaire

The Social Communication Questionnaire (SCQ; Rutter, Bailey & Lord, 2003) is a 40-item, parent report measure evaluating communication skills and social functioning. Items are scored on a dichotomous (yes/no) scale, with higher scores indicating the presence of more autistic traits. The SCQ has strong internal consistency at .90 as well as sensitivity/specificity ranging between .80 and .95. The SCQ was completed by parents independently at baseline and follow up. Total raw scores were used for each subscale and higher scores were indicative of higher functioning.

Statistical Analyses

The difference between entry and exit scores were calculated for the MSEL, SCQ and VABS subscales (see Table 2). Therefore, only participants with entry and exit data on these measures were included in the analysis. This meant that the number of participants in the correlation and regression analysis varied for different subscales. The data from the MSEL, SCQ and VABS subscales were utilised in both Chapter Three and Four. To check the assumption of normality, a normal Q-Q plot was utilised. Based on a visual inspection of the Q-Q plots, the assumption was not violated. The data were normally distributed, as the data points fell close to the diagonal line and did not appear to have a non-linear pattern. No multicollinearity was found between the independent variables.

Table 2. Pre-to post-intervention scores in a cohort of preschoolers receiving the ESDM

	Pre intervention		Post Intervention		Difference score	*N*	*d*
	Mean	**SD**	**Mean**	**SD**			
Vineland Adaptive Behaviour Scales							
Receptive Communication	7.92	3.174	9.26	3.306	1.34	47	0.40
Expressive Communication	6.96	2.352	7.32	2.793	0.36	47	0.15
Written Communication	12.47	3.815	11.70	4.039	-0.77	47	0.22
Communication Domain	29.47	22.05	28.29	8.419	-1.18	47	0.06
Personal Skills	8.72	2.468	8.41	2.313	-0.31	47	0.13
Domestic Skills	10.9	2.772	10.63	3.118	-0.27	47	0.10
Community Skills	9.81	2.662	8.31	3.373	-1.5	47	0.50
Daily Living Skills	29.57	6.765	28.98	12.359	-0.59	47	0.06
Interpersonal Relationship Skills	8.02	2.233	8.3	2.628	0.28	47	0.11
Play and Leisure Skills	8.36	2.007	7.4	2.12	-0.96	47	0.43
Coping Skills	10.9	2.696	10.37	3.029	-0.53	47	0.21
Socialisation Domain	27.38	6.174	26.42	7.722	-0.96	47	0.12
Gross Motor skills	10.78	2.594	11.25	2.914	0.47	47	0.18
Fine Motor Skills	9.93	3.114	9.86	2.871	-0.07	47	0.03
Internalising	19.89	2.603	19.91	2.703	0.02	47	0.03
Externalising	16.61	2.582	16.64	2.504	0.03	47	0.01
Maladaptive Bahaviour	19.26	1.817	19.28	1.981	0.02	47	0.01
Mullen Scales of Early Learning							
Visual Reception	21.01	13.38	29.99	16.23	8.98	47	0.60
Fine Motor	23.18	12.58	30.93	15.61	7.75	47	1.07
Receptive Language	14.52	11.26	24.25	20.39	9.73	47	0.59
Expressive Language	15.92	10.23	24.15	14.5	8.23	47	
Social Communication Questionaire							
Total Score	18.36	6.301	16.13	6.881	-2.23	47	0.65
Communication	6.05	5.412	4.93	2.373	-1.12	47	0.38
Reciprocal Social Interaction	7.08	3.484	6.13	3.708	-0.95	47	0.26
Repetitive Behaviour	4.4	2.271	4.13	2.262	-0.27	47	0.12

For VABS, SCQ and MSEL measures, higher scores are indicative of better functioning.
For MSEL, age equivalent scores from each scale were used.
For VABS, V Scale scores were used for each domain. V-scale score (mean:15, SD:3)
For the SCQ, total raw scores were used for each subscale.
No significant differences among pre-intervention outcomes measures were found.
Standard score (mean: 100, SD: 15)

Correlations were calculated between duration of the intervention (number of months each participant received the ESDM), intensity of intervention (how many days a week the child received the intervention) and the age of the child at enrolment and the outcome variables. Significant correlations were then subsequently analysed using multiple linear regression. Table 3 displays the indeendent variables that were included in the study; duration of intervention, intensity of intervention and the age of the child at enrolment. The dependant variables included the change in primary outcome measures and subscales of the MSEL, VABS and SCQ. Correlations were also calculated to

examine the relationship between months in therapy, intensity of therapy and age at enrolment. Significant correlations were then analysed using multiple linear regression.

Table 3. Characteristics of the Intervention

Factors	***N***	***M***	***SD***
Age at enrolment (months	47	4.1	0.5
Intensity of Intervention (days attended per week)	47	2.6	0.9
Duration (months)	47	12.8	6.8

Results

Duration of Intervention

The results of the correlation analyses are provided in Table 4. There was a significant correlation between months spent in therapy and the MSEL subscale Reciprocal Language score (see table 5). Regression analysis also indicated a significant relationship between months spent in therapy and MSEL subscale Reciprocal Language score ($F(2,62) = 5.756$, $p < .005$) (beta= -.025, $R^2 = .141$), after controlling for baseline scores. Children who stayed longer in the ESDM therapy showed greater improvements in reciprocal language (see Figure 1).

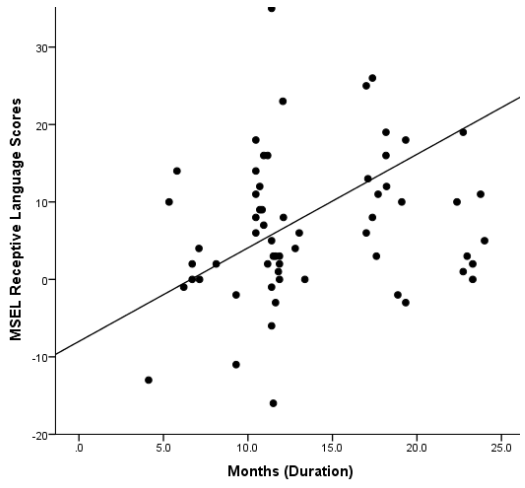

Figure 1. *Relationship between duration and change scores on the MSEL Receptive Language scale after controlling for pre-test scores.*

Age at Enrolment

The results of the correlation analyses for age at enrolment are provided in Table 4. There was a significant correlation between age at enrolment and VABS primary communication domain score, the VABS subdomain score of receptive communication and MSEL fine motor subscale (see Table 5). Multiple linear regression analysis also revealed a significant relationship between age at enrolment and VABS primary communication domain ($F(2,43) = 3.056$, $p < .019$) (beta= -.317, $R^2 = .272$), as well as the VABS subdomain of receptive communication ($F(2,44) = 2.854$, $p < .034$) (beta= -.306, $R^2 = .158$). Additionally, a significant relationship between age at enrolment and the MSEL fine motor subscale was found ($F(2,94) = 2.706$, $p < .025$) (beta= .225, $R^2 = .081$) (see Figure 2).

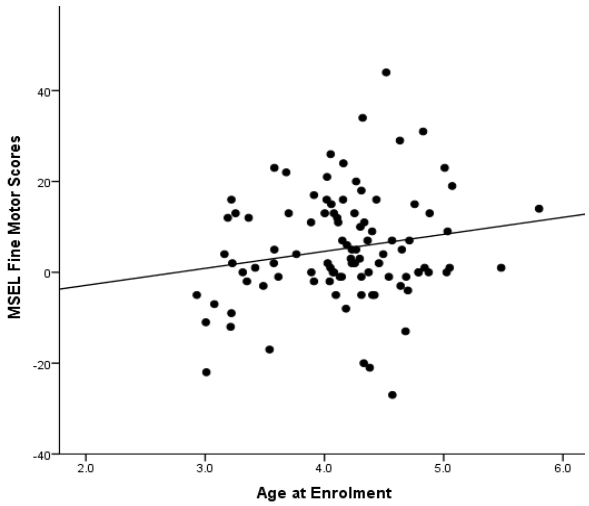

Figure 2. Relationship between Age at Enrolment and change scores on the MSEL Fine Motor scale after controlling for pre-test scores.

Intensity of Intervention

The results of the correlation analyses for intensity of intervention are provided in Table 4. No significant relationships were found between any of the outcome measures and intensity of intervention.

Table 4. Correlations Between Factors and Clinical Assessments

	Age at Enrolment	Duration	Intensity
Vineland Adaptive Behaviour Scales			
Receptive Communication	**-.34**	.30	-.27
Expressive Communication	-.09	-.19	-.10
Written Communication	-.19	-.09	.21
Communication Domain	**-.34**	.12	-.91
Personal Skills	.18	-.12	-.10
Domestic Skills	-.14	.20	-.28
Community Skills	.14	-.21	-.35
Daily Living Skills	.09	-.03	-.36
Interpersonal Relationship Skills	-.26	.08	-.03
Play and Leisure Skills	.05	-.33	-.01
Coping Skills	-.13	.06	-.20
Socialisation Domain	-.19	-.10	-.23
Gross Motor skills	.12	-.01	.27
Fine Motor Skills	**.25**	-.38	.06
Internalising	.25	-.03	-.57
Externalising	.19	.14	.01
Maladaptive Bahaviour	.18	-.17	.07
Mullen Scales of Early Learning			
Visual Reception	.11	.10	.00
Fine Motor	.23	-.06	-.03
Receptive Language	-.02	**.37**	.02
Expressive Language	.13	-.19	-.07
Social Communication Questionnaire			
Total Score	.16	-.18	.21
Communication	-.09	.11	.29
Reciprocal Social Interaction	.22	-.34	.10
Repetitive Behaviour	-.10	.16	-.07

Significant correlations are noted in bold in Table 4

Table 5. Significant Relationships Between Clinical Measures and Factors

Scales	Beta	R2	Pearson's r	F	n	*P*
Duration						
MSEL Receptive Language	-0.025	0.141	0.298	5.756	47	0.005
Age at Enrolment						
VABS Communication	-0.317	0.272	-0.342	3.056	47	0.019
VABS Receptive Communication	-0.306	0.158	-0.335	2.853	47	0.034
MSEL Fine Motor	0.225	0.081	0.233	2.706	47	0.025

Predictor Variables

The relationship between months in therapy (duration), intensity of therapy and age at enrolment was also examined. Significant relationships emerged between duration and age at enrolment ($F(1,124) = 18.716$, $p < .000$) (see Figure 3) as well as duration and intensity of therapy which remained significant when age at enrolment was accounted for in the multiple regression analysis ($F(2,79) = 8.940$, $p < .000$) (See Figure 4).

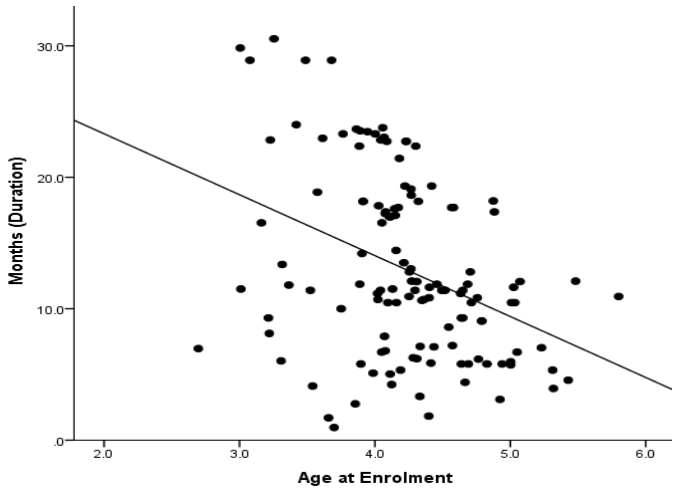

Figure 3. Relationship between duration and age at enrolment.

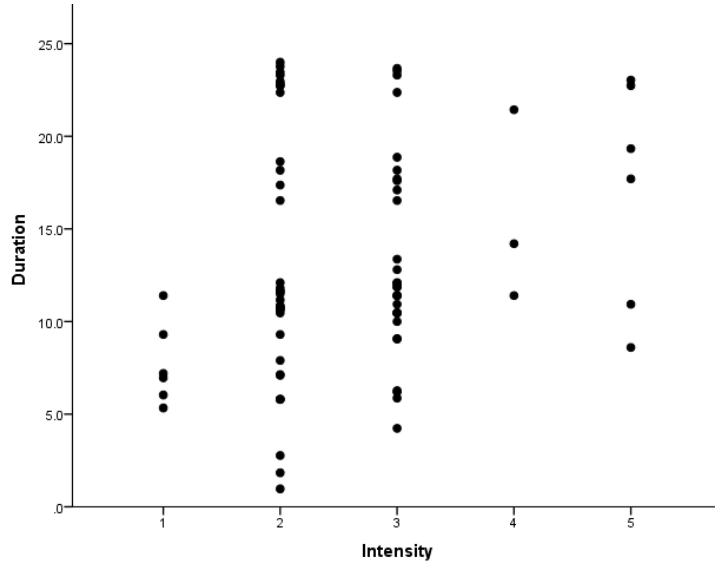

Figure 4. Relationship between duration and intensity.

Discussion

The current study examined the impact of specific factors on outcomes for children with ASD receiving the ESDM intervention. The findings demonstrate that certain factors may optimise the effectiveness of the ESDM. For example, both age at enrolment and the duration of the intervention were associated with improved outcomes. More specifically, both of these factors were found to be related to significant changes in communication, language and fine motor skills, which are skills specifically targeted by the ESDM curriculum. The finding that children who stayed longer in intervention demonstrated better outcomes is novel. This indicates that, unlike eclectic interventions, duration may play a role in outcomes for children receiving a more specialised intervention such as the ESDM (Granpeesheh, Dixon, et al., 2009). Furthermore, the results regarding age at enrolment are in line with previous studies showing that children who started intervention at a younger age demonstrated improved intervention outcomes after receiving the ESDM (Eapen, 2016). The results remained significant after accounting for potential moderators and baseline scores. These findings add to the growing literature examining what factors impact treatment response for

broader EIBI and within the ESDM. Furthermore, these findings emphasise the importance of both receiving intervention at an earlier age, as well as for a longer period of time. This has important implications for social policy and funding.

When examining the relationship between duration and outcomes, greater improvements were shown in reciprocal language. The results indicated that children who stayed in the ESDM for a longer amount of time were more likely to show improvements in reciprocal language. This may be due to the overall target of the ESDM. That is, the ESDM focuses on teaching specific social communicative skills aimed to enhance social attention, communication abilities, joint attention and affect sharing (Eapen et al., 2013).

Similarly, age at enrolment was associated with significant changes in communication skills. After accounting for baseline scores, the overall communication domain and receptive communication subdomain on the VABS was found to be associated with age at enrolment. In other words, children who started therapy at a younger age were more likely to demonstrate improved outcomes in communication. In contrast to these findings, older children demonstrated improvements in fine motor skills on the MSEL. While maturation of skills may have played a role, this was not reflected in a difference in baseline scores on fine motor abilities. This is consistent with previous research, outlining a relationship between age at enrolment and language abilities, but no other factors across EIBI studies (Makrygianni & Reed, 2010).

Previous research has found an association between intensity (amount of days a child spent in intervention per week) of therapy and improved outcomes in ABA (Granpeesheh, Tarbox, et al., 2009). However, this was not replicated in the current study. While intensity of intervention is one of the most heavily investigated

characteristics in the literature, most studies only find gains in adaptive behaviours and intellectual abilities with more intensive therapy (Vivanti, Prior, et al., 2014; Zachor et al., 2017). In contrast, Makrygianni and Reed (2010) found no relationship between intensity and improvements in children's language abilities across studies. It is possible that no significant relationships were found with intensity in this study as the ESDM is focused on language and communication skills, rather than adaptive behaviour and IQ. Further research examining intensity and outcomes is required to assess if this finding is unique to the ESDM.

A novel finding from this study was the relationship between duration and age at enrolment, as well as the relationship between duration and intensity. Children who enrolled into therapy at an older age received a higher intensity of the ESDM, but received the intervention for a shorter duration. This makes sense, given that older children enrolled in therapy may only receive a short period of ESDM before moving onto a variety of primary school options. It should be noted that this finding may also reflect multicollinearity as duration and intensity are independent variables. This can result in inflated p values, as factors may become more sensitive to change in the model. However, given that only one correlation was found between the independent variables, this is considered to be moderate multicollinearity, which is acceptable in a multiple regression model (Graham, 2003). Although further research is needed, this study provides evidence that, in general, early intervention improves outcomes in communication skills for children with ASD (Granpeesheh, Tarbox, et al., 2009; Makrygianni & Reed, 2010).

Interestingly, a more recent meta-analysis by Zachor et al. (2017) found that children's initial verbal skills were strongly related to better outcomes in adaptive behaviour. Given that the ESDM focuses on social skills and communication, initial

verbal skills may have been an important characteristic that contributed to outcomes and potentially moderated other relationships found within this study. Future studies should include characteristics that are more closely related to the focus of the therapy, such as the child's initial verbal skills.

Limitations

There were a number of limitations within the current study. Although the factors utilised in this study were derived from previous research outlining factors that influence EIBI (Makrygianni & Reed, 2010), it is possible that there are other factors that may influence outcomes in the ESDM that were not included in this study. For instance, support or therapy received in addition to the ESDM may have impacted outcomes. Furthermore, it is possible that maternal and paternal education and age may have influenced outcomes as well. Although, a control group was not included, the study explores previously identified factors including duration and age that were identified in Chapter Two as potentially impacting intervention outcomes. It is also possible that there was a lack of variation in intensity amongst the participants in the current study. Lastly, the assessors were not blind to the research question which may have inadvertently created differences in scores. To further build on these current findings, the inclusion of a comparison group (children with ASD who received a different therapy) and assessors who are blind to the study would help to evaluate whether these outcomes are unique to children receiving the ESDM or apply to other EIBI models.

Conclusion

This study aimed to better understand the relationship between duration, intensity of intervention and age at enrolment and outcomes using the ESDM. The findings suggest that younger age at enrolment and a longer duration are associated with improvements in specific outcomes in language and communication skills. Interestingly, these changes closely map those specific skills targeted by the ESDM of intervention. Although further research is needed, this study supports the idea that specific factors and characteristics can influence outcomes for children with ASD who receive early intensive behavioural intervention.

Chapter Four:

The Importance of Language Skills and Outcomes in Early Start Denver Model

Introduction

A number of studies have investigated intervention outcomes of children with ASD, and it is now well established through practice and theory that early intensive behavioural intervention (EIBI) achieves the most successful outcomes (Reichow et al., 2014; Rogers et al., 2012). Although findings have shown that EIBI improves communication, social, adaptive and cognitive functioning of children with ASD, individual differences in response to treatment are also found (Howlin, Magiati, & Charman, 2009; Makrygianni & Reed, 2010; Zachor et al., 2017). Vivanti, Paynter, et al. (2014) have suggested that children's outcomes fall into one of three groups: moderate gains, minimal gains or no gains. This variation in outcomes is suggested to stem from the heterogeneity of ASD at the phenotypic level (behavioural characteristics) (Lord, Bishop, & Anderson, 2015). These variations in behavioural and clinical characteristics have been shown to be related to underlying neurophysiological mechanisms and numerous genes (Vivanti, Prior, et al., 2014; Zachor et al., 2017).

In line with this, numerous studies have examined how specific factors influence outcomes of EIBI. To date, the most commonly examined factors have been chronological age, intensity of intervention, duration of intervention and pre intervention IQ (Makrygianni & Reed, 2010; Vivanti, Prior, et al., 2014; Zachor et al., 2017). There are several conflicting findings among these studies (Zachor et al., 2017). For instance, while some researchers have found that children who start intervention at a younger age have better outcomes in therapy, other studies have found no differences in outcomes when age was considered (Granpeesheh, Dixon, Tarbox, Kaplan, & Wilke, 2009; Makrygianni & Reed, 2010). Similar results have been found for intensity of intervention, duration and children's initial verbal abilities. While some researchers

found better progress and learning outcomes for children receiving ABA for intensity (Granpeesheh, Dixon, et al., 2009), this finding was not observed for children receiving the ESDM (Vivanti, Paynter, et al., 2014). On the other hand, duration of intervention was found to impact outcomes for children receiving the ESDM but not children receiving eclectic therapy (Granpeesheh, Dixon, et al., 2009, Eapen, 2016). Chapter Three of this thesis indicated that longer intervention duration was associated with improvements in specific outcomes in language and communication skills. This supports the idea that broad factors such as age and duration may influence outcomes in social and communication for children receiving the ESDM.

Autism is characterised by a delay and impairment in the development of verbal and nonverbal social interactions and communication (American Psychiatric Association, 2013). As a number of individuals with ASD have difficulties in social and communication abilities, a variety of therapies aim to improve these skills (Reichow et al., 2012). However, to date, there are very few studies examining initial verbal abilities and how they impact outcomes in therapy. Furthermore, there is also a lack of consistency amongst these research findings examining baseline verbal ability and intervention outcomes for children with ASD. A review by Zachor et al. (2017) found that baseline verbal abilities were associated with increased outcomes in adaptive behaviour for children receiving EIBI interventions. However, they found no association between baseline verbal ability and other outcomes including visual spatial IQ, decreased autism severity and cognitive abilities (Zachor et al., 2017). The authors concluded that future research should investigate more specific subgroups of baseline verbal ability which would be a more accurate representation of the children's language at intake. In contrast, baseline verbal ability was not correlated with outcomes in IQ or adaptive behaviour in a meta-analysis investigating behavioural interventions studies

evaluating behaviour analytic treatment and early behavioural treatment (Makrygianni & Reed, 2010).

Although a lack of consistency exists amongst the literature, these large reviews only take into account broad behavioural interventions. However, there is reason to believe that verbal abilities will be predictive in the context of the ESDM intervention, given that the ESDM specifically targets language and communication. To date, no research has examined initial verbal abilities and outcomes for children receiving the ESDM. Therefore, the present study aims to examine the ESDM and language. More specifically, the present study will categorise children based on their initial verbal ability and examine how these differences impact outcomes in social and communication, adaptive functioning and cognitive abilities after receiving the ESDM.

Method

Participants

Participants comprised 47 children who attended an Autism Specific Early Learning and Care Centre (ASELCC) in Sydney, Australia. The preschool provides early intervention for pre-school aged children with ASD. All participating children were diagnosed using the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV-TR) criteria. Diagnosis was confirmed with the Autism Diagnostic Observation schedule – 2 (ADOS-2) (Lord et al., 2000). Exclusion criteria included known neurodevelopmental (e.g., Fragile X Syndrome) or neurological (e.g., epilepsy) disorders, and significant vision, hearing, motor or physical problems. Demographic information is provided in Table 1.

Table 1. Characteristics of the Study Sample

Characteristics	
Average Age at Enrolment (months)	49
Sex (Male)	86%
English Spoken at Home	72%
Cultural Background (other than Australian)	65%
Aboriginal or Torres Strait Islander background	2.1%
Children Living with Both Parents	85%

ESDM Intervention

The ESDM is a treatment approach specifically designed for children with ASD aged between 12 to 48 months (Rogers & Dawson, 2009b; Steiner, 2013; Warren et al., 2011). The curriculum focuses on increasing social-communicative learning. This is done by reinforcing a child's preference and active attention to social information, including faces, voices, gestures, and speech. The ESDM is delivered in a preschool setting and incorporates a adaptable curriculum where teachers and parents are able to teach skills at any given time (Dade, 2013).

These adult-child interactions promote joint attention, social play and imitation (Dade, 2013; Rogers & Dawson, 2009b). Children in the present study received treatment plans individualised to their needs, and included a range of objectives dependent on their level of functioning and the ESDM curriculum. Further details regarding the ESDM curriculum can be found in the methods section of Chapter Three.

Measures

The Autism Diagnostic Observation Schedule

The Autism Diagnostic Observation Schedule (ADOS-2; Lord et al., 2000) was administered by a trained researcher at baseline to confirm whether children met the DSM-5 (American Psychiatric Association, 2013) criteria for autism spectrum disorder. The ADOS-2 is a semi-structured, clinician-administered standardised diagnostic assessment of communication, social interaction, repetitive behaviours and play to assess whether diagnostic criteria for ASD are met. Research has demonstrated that the ADOS-2 has strong inter-rater and test-re-test reliability, as well as internal consistency among individual items (Gotham, Pickles, & Lord, 2009).

The Mullen Scales of Early Learning

The Mullen Scales of Early Learning (MSEL; Mullen, 1995) is a standardised developmental assessment for children from birth to 68 months of age. The MSEL consists of five subtests including gross motor, visual reception, expressive language, fine motor, and receptive language. The MSEL also provides an overall index of cognitive and motor ability. The MSEL was administered to all participants by a trained researcher at baseline and follow up. Age equivalent scores from each scale were used, higher scores are indicative of better functioning.

Vineland Adaptive Behaviour Scales

The Vineland Adaptive Behaviour Scales 2 (VABS II; Sparrow, Chicchetti & Balla 2005) evaluate a child's level of adaptive behaviour across a number of domains including communication, socialisation, motor skills and daily living skills. The VABS is a parent-completed measure that provides age equivalent and standard scores across each domain of adaptive functioning. The VABS was completed by parents

independently at baseline and follow up. V Scale scores were used for each domain. V-scale score (mean:15, SD:3), higher scores are indicative of better functioning.

Social Communication Questionnaire

The Social Communication Questionnaire (SCQ; Rutter, Bailey & Lord, 2003) (Rutter et al., 2003) is a 40-item, parent-report measure evaluating communication skills and social functioning. Items are scored on a dichotomous (yes/no) scale, with higher scores indicating the presence of more traits of ASD. The SCQ was completed by parents independently at baseline and follow up. For the SCQ, total raw scores were used for each subscale. Higher scores were indicative for better functioning.

Verbal Ability

Initial verbal abilities were calculated using the A1 item on the ADOS-2 assessment. The A1 item measured the overall level of non-echoed spoken language produced during the ADOS-2 assessment. Language was coded between zero and four; zero: regular use of utterances with two or more words, one: occasional phrases (mostly single words), two: recognisable single words (at least five), three: at least one word or word approximation, four: no words or word approximations. These categories were used to establish each child's initial verbal abilities in the present study. No participants in the sample obtained a score of zero or four. There were therefore only three language groups included in the study. Characteristics of each group are provided in Table 2. No significant differences were found between sex, age at enrolment, intensity of intervention or duration and initial verbal ability groups.

Table 2. Characteristics of each Verbal Group

	Phrase Speech		Single Words		Word Approximations		
	Mean	SD	Mean	SD	Mean	SD	*d*
Sex (male)	76%		78%		79%		
Age at Enrolment	4.17	0.503	4.13	0.52	4.17	0.58	0.03
Intensity of Intervention	2.55	0.82	2.74	0.955	2.71	0.85	0.09
Duration of intervention	12.82	5.09	14.9	6.4	12.82	6.3	0.40

Statistical Analyses

Difference scores were calculated for scales and subscales by subtracting the exit score from the entry score. Only participants with entry and exit data on the MSEL, SCQ and VABS subscales were included in the analysis. This meant that the number of participants in the analysis varied for different subscales (see Table 3).

A one-way ANCOVA was employed to analyse differences in mean scores for children with varying verbal abilities. Change scores between pre- and post-treatment were evaluated for the MSEL, VABS and SCQ. The data from the MSEL, SCQ and VABS subscales were utilised in both Chapter Three and Four. The analysis also controlled for age at enrolment and duration of the intervention. VABS and SCQ scores at post-treatment were not available for a number of participants, resulting in slightly different numbers of participants for these analyses.

To check the assumption of normality, a normal Q-Q plot was utilised. Based on a visual inspection of the Q-Q plots, the data were normally distributed, as the data points fell close to the diagonal line and did not appear to have a non-linear pattern. Furthermore, the independent variables were not highly correlated with each other, indicating no multicollinearity.

Results

A significant difference between initial verbal abilities and outcomes on the VABS domestic skills change score was obtained after controlling for duration and age at enrolment ($F(2,45)= 3.765$, $p = 0.031$). A Tukey post hoc analysis revealed that significant differences in domestic skills outcomes were found between the phrase speech group (M= -1.86, SD= 3.33) and the single words group (M= .93, SD= 2.319, $p < 0.05$). This indicates that children with single, recognisable words demonstrated better outcomes than children with phrase speech.

A significant difference between initial verbal abilities and outcomes in the MSEL Visual Reception change score was found (see Figure 1) after controlling for duration and age at enrolment ($F(2,87)= 8.641$, $p = 0.000$). A Tukey post hoc analysis revealed that significant differences in the visual reception change score were found between group one (M= 20.00, SD = 11.22) and group two (M = 6.15, SD = 14.147, $p < 0.05$). A significant difference was also found between occasional phrase group (M= 20.00, SD = 11.22) and word approximation group (M=1.48, SD= 8.94) (see Figure 1). This indicates that children with occasional phrase speech demonstrated better outcomes on the Visual reception subscale compared to children with single words and children who spoke one word or word approximation. See Table 3 for all pre and post intervention scores.

Table 3. Displays pre and post intervention scores between the three groups.

Table 3. Pre-to post-intervention scores in a cohort of preschoolers receiving the ESDM

	Phrase Speech Group				Single Word Group				Word Approximations						
	Pre Intervention		Post Intervention		Pre interventio		Post Intervention		Pre intervention		Post Intervention		*P*	*d* Pre Intervention	*d* Post Intervention
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD			
Vineland Adaptive Behaviour Scales															
Receptive Communication	17.6	3	9	3.2	17.7	3	9.1	3.2	17.4	2.8	8.9	3.4	0.95	0.07	0.05
Expressive Communication	8.2	3.8	7.7	3	8.2	3.7	7.7	2.9	8	3.6	7.6	3	0.30	0.05	0.03
Written Communication	15.5	7.5	12.7	5.6	15.2	7.3	12.8	5.5	15.1	7.1	12.8	5.7	0.84	0.06	2.01
Communication Domain	50.6	26.6	58.7	24.6	52.2	26	59.3	24.3	50.3	25.8	57.5	25.2	0.77	1.63	1.56
Personal Skills	9.8	2.4	8.6	2.4	9	2.4	8.6	2.3	8.9	2.4	8.7	2.5	0.17	0.26	0.34
Domestic Skills	10.5	2.8	10.4	3.1	10.6	2.8	10.4	3.1	10.4	2.8	10.1	3.1	**0.03**	0.38	0.43
Community Skills	13.6	8.2	9.9	6.1	13.3	8	9.8	6	13.2	8.1	10	6.4	0.21	0.06	0.08
Daily Living Skills	37	16.4	31.9	15.2	36.4	16	31.8	15	36.3	16.2	32.2	16	0.10	0.05	0.07
Interpersonal Relationship Skil	8.1	2.1	83.3	2.5	8.1	2.1	8.3	2.5	7.9	2.1	8.2	2.4	0.46	0.03	22.5
Play and Leisure Skills	8.8	2.2	7.6	2.2	8.7	2.1	7.6	2.2	8.5	2	7.6	2.3	0.06	2.03	0.01
Coping Skills	14.2	7.3	11.7	5.2	13.9	7	11.6	5.2	13.7	7	11.8	5.4	0.88	0.07	0.20
Socialisation Domain	54.4	25.5	58.4	21.8	55.8	25	58.4	21.4	54	24.4	57.3	22.8	0.47	0.15	0.11
Gross Motor skills	10.6	2.4	10.6	3.5	10.7	2.5	10.6	3.5	10.8	2.4	10.8	3.6	0.96	0.05	0.04
Fine Motor Skills	12.4	5.8	11.1	2.9	12.2	5.6	11.1	2.8	12.2	5.9	11	2.9	0.26	0.04	0.03
Internalising	19.3	2.7	19.6	2.8	19.4	2.7	19.7	2.8	19.4	2.8	19.7	2.9	0.97	0.028	0.028
Externalising	17.2	2.7	16.8	2.7	17.2	2.7	16.9	2.6	7.2	2.8	17	2.6	0.98	2.85	0.05
Maladaptive Bahaviour	18.6	3.1	17.8	5.5	18.7	3.1	17.8	5.4	18.6	3.2	17.7	5.8	0.55	0.026	0.052
Mullen Scales of Early Learning															
Visual Reception	21.3	11.7	29.7	15.6	21.6	12	29.9	15.5	21.1	12.1	29.3	15.9	**0.00**	0.05	0.06
Fine Motor	21.3	11.3	28.9	15.2	21.7	12	29.2	15.2	21.2	11.8	28.7	15.6	**0.03**	0.06	0.05
Receptive Language	14.7	10.5	23.4	19.1	14.7	11	23.4	18.9	14.5	10.6	21.6	13.6	0.28	0.02	0.21
Expressive Language	15.8	10	25.3	17.5	16.1	10	25.5	17.3	15.7	10.3	25.2	17.9	**0.00**	0.05	0.04
Social Communication Questionaire															
Total Score	18.4	5.9	16.3	6.8	18.4	6.1	16.4	6.7	18.4	6.1	16.4	6.8	0.90	0.05	0.04
Communication	5.9	4.9	4.8	2.4	5.9	4.9	4.9	2.4	5.9	5.2	4.9	2.4	0.53	0.01	0.026
Reciprocal Social Interaction	7.2	3.5	6	3.6	7.2	3.5	6.2	3.5	7.3	3.5	6.1	3.6	0.47	0.02	0.04
Repetitive Behaviour	4.3	2.1	4.4	2.3	4.3	2.1	4.3	2.3	4.3	2.1	4.3	2.4	0.43	0.01	0.03

Significant differences between the groups are noted in bold.

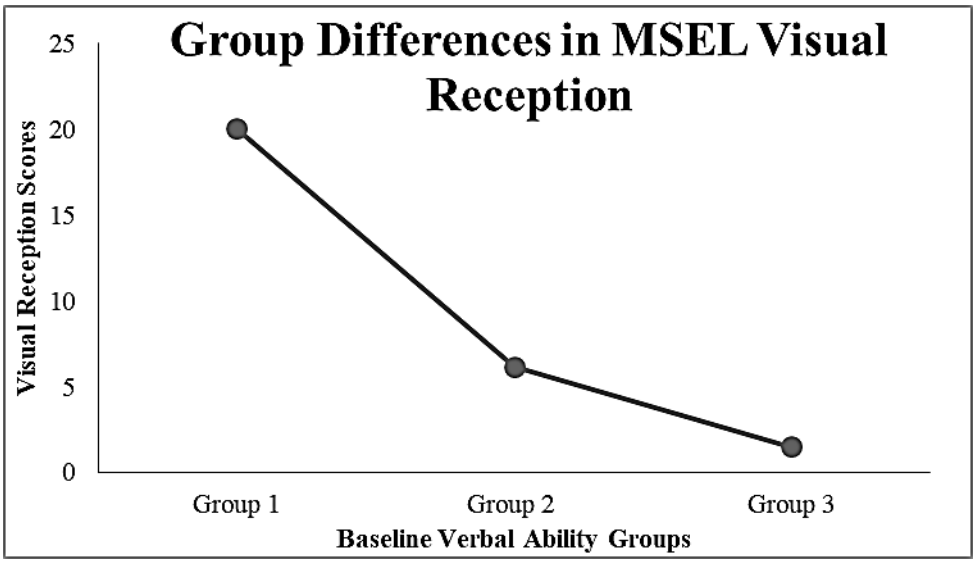

Figure 1. *Differences between baseline verbal groups in MSEL Visual Reception Subscale scores*

A significant difference between initial verbal abilities and outcomes on the MSEL Expressive Language change score (see Figure 2) was found ($F(2,56)= 9.631$, $p = 0.000$) after controlling for age at enrolment and duration of intervention. A post hoc

analysis revealed that significant differences on the Expressive language change score between the phrase speech group (M =13.64, SD= 10.856) and the word approximation group (M=3.00, SD= 5.05, p <0.05). A significant difference was also found between the single word group (M=8.88, SD= 6.09) and the word approximation group (M= 3.00, SD= 5.05, p <0.05). Therefore, children who had initial phrase speech and children with recognisable single words showed higher scores on the expressive language subscale compared to children with single words or word approximations (see Figure 2).

Although a significant difference between initial verbal abilities and outcomes in the MSEL fine motor subscale was initially found, after including duration of intervention as a covariate, the model was no longer significant.

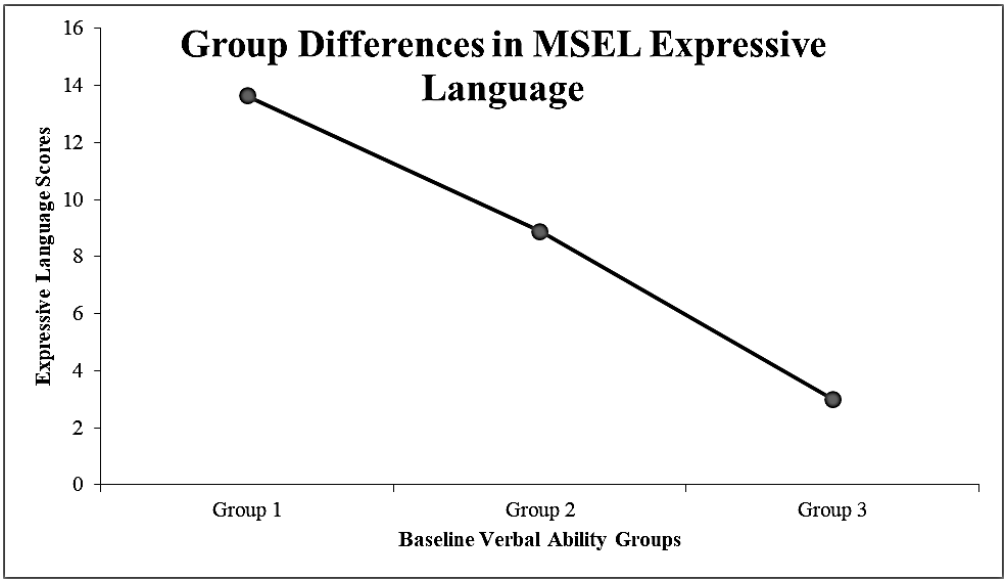

Figure 2. *Differences between baseline verbal groups in MSEL Expressive Language*

Discussion

The current study examined what impact initial verbal ability had on outcomes after children received the ESDM. More specifically, this study categorised children

based on their initial verbal ability and examined how these differences impacted outcomes in social and communication, adaptive functioning and cognitive abilities after receiving the ESDM. Results demonstrated that children receiving the ESDM showed significant differences between their outcome scores on VABS and MSEL assessments and initial verbal abilities. More specifically, significant differences were found between initial verbal abilities and expressive language, receptive language MSEL subscales, as well as the domestic subscale on the VABS. These results were all still observed when age at enrolment and duration of intervention were taken into account. This indicates that initial verbal abilities had an impact on specific outcomes for children with ASD receiving the ESDM. The results are consistent with previous research findings showing an association between baseline verbal abilities and outcomes in therapy (Zachor et al., 2017). Our findings indicate that examining variables that are more closely related to the target of the intervention allows for a better understanding of the relationship between initial skills and subsequent outcomes.

Interestingly, greater outcomes in domestic skills on the VABS were found when children's initial verbal abilities were taken into account. In particular, children with single recognisable words (more than five) had increased outcomes in domestic skills compared to children with phrase speech and children with a single word or word approximations. The domestic subscale is part of the daily living domain which assesses a child's ability to dress, eat, bathe, understand personal safety, and perform household chores. This finding demonstrates that children with single recognisable words had better outcomes compared to other groups. This indicates that higher initial verbal abilities may not be required for better outcomes in a variety of domestic skills. This is a novel finding that is in line with previous research, where greater baseline verbal abilities were related to greater outcomes in adaptive functioning (Zachor et al., 2017).

However, given that previous research only assessed broader EIBI supports, it is possible that this finding is unique to children receiving the ESDM. Consequently, this may indicate that children with better verbal abilities are able to understand and converse with others, allowing for greater learning opportunities for domestic and adaptive skills.

Significant differences were also observed between initial verbal abilities and outcomes on the expressive language subscale, after controlling for age at enrolment and duration of intervention. More specifically, children who could initially speak in phrases, and children with recognisable single words (five or more), displayed higher scores on the MSEL expressive language subscale compared to children with single words or word approximations. This suggests that baseline verbal ability, specifically increased single words or phrase speech, may predict outcomes in expressive language. Similarly, differences in outcomes were also found on the receptive language MSEL subscale based on children's initial verbal abilities. In particular, children who were able to speak in phrases prior to starting intervention demonstrated better outcomes in receptive language, compared to children with single words and children who spoke one word or word approximations. The results from this study indicate that greater gains in receptive language are made by children who spoke in phrases. It should also be noted that previous meta-analyses did not report a relationship between baseline verbal ability and greater language outcomes (Makrygianni & Reed, 2010). A reason for the difference in findings may be due to more specific subgroups of baseline verbal ability being utilised in the present research. It is possible that a more accurate representation of the children's language at intake allowed for the detection of more subtle outcomes specific to the baseline subgroup. Given that communication skills are one of the main targets of the ESDM, it is not surprising that differences were found between initial

verbal abilities and increased outcomes in language related areas. Furthermore, the results of this study demonstrate that children with better initial verbal abilities were more responsive to the therapy, showing better outcomes in expressive and receptive language. Future research should compare outcomes for children with lower verbal abilities when they receive a more targeted intervention for language skills compared to children who receive the ESDM. In this way, we can better understand what intervention style is more beneficial based on the child's needs.

Although a limitation of this study was that it did not examine other cognitive variables, the findings are in line with Vivanti, Prior, et al. (2014) suggestion that children with specific cognitive and learning profiles might be more responsive to a particular therapy or teaching approach. To further validate this notion, future research should compare mediating variables across different interventions. This will increase our understanding of which variables and characteristics work best for different interventions and teaching styles. In this way, based on a child's cognitive and learning profile, an intervention can be specifically tailored to meet the child's individual needs.

Limitations

A possible limitation of this study is that there was a lack of variation in verbal ability amongst children in this cohort. While there are five categories within the ADOS-2 A1 item, children in this study only fell into one of three categories for verbal abilities. This means that there were no groups of children in the study with regular use of utterances (the highest categorised group). It is possible that further differences would have been detected if there was greater variability in the verbal abilities of the sample. Future research examining a wider spectrum on verbal abilities would allow for

a deeper investigation of differences in initial verbal abilities and their impact on various outcome measures.

Conclusions

The present study showed that differences in initial verbal ability had an impact on specific outcomes after children with ASD received the ESDM. Higher levels of initial verbal skills were associated with changes in receptive and expressive language. It is possible baseline verbal ability, specifically increased single words or phrase speech, may predict outcomes in language related areas. Conversely, children with lower initial verbal abilities demonstrated increased outcomes on domestic skills. This finding suggests that higher initial verbal abilities may not be required for better outcomes in a variety of domestic skills. Future research is needed to ascertain if children with better initial verbal abilities are more responsive to interventions that focus on communication and language.

Chapter Five:

The Promise of Functional Near-Infrared Spectroscopy in Autism Research: What Do We Know and Where Do We Go?

Introduction

Autism Spectrum Disorder is a heterogeneous, neurodevelopmental condition with an international prevalence rate estimated at 1% (Dawson, 2008; Reichow et al., 2014; Salomone et al., 2015). ASD is characterised by delay and impairments in the development of verbal and nonverbal social interactions and communication, as well as restricted or stereotyped patterns of behaviour (American Psychiatric Association, 2013; Reichow et al., 2012). These characteristics are often noticeable from around the age of two, and may be accompanied by developmental differences in brain anatomy, function, and connectivity that continues across the life span (Ecker, Bookheimer, & Murphy, 2015).

To date, most studies examining differences in human brain activity have utilised functional Magnetic Resonance Imaging (fMRI), which measures the blood oxygen level-dependent response from local concentration changes in neural activity, and electroencephalography (EEG), which primarily measures electrical activity reflecting the synchronous activation of neurons in response to external stimulation (Cui, Bray, Bryant, Glover, & Reiss, 2011; Wallois, Mahmoudzadeh, Patil, & Grebe, 2012). Although both fMRI and EEG are effective tools for examining different aspects of brain function, the use of these technologies with clinical populations can be challenging. This is largely due to their susceptibility to motion artefact as well as experimental setting constraints (e.g. being enclosed within a long tube during scanning, or sitting still in an unfamiliar laboratory environment) (Lloyd-Fox, 2010). This is also impacted by the unique challenges faced by children with ASD during fMRI procedures (Fox, 2012; Higuchi, Narita, & Sakatani, 2012; Lloyd-Fox et al., 2013; Lloyd-Fox, Blasi, & Elwell, 2010). This may include sensitivities to the fMRI sounds that occur

during scanning, as well as having to remain still in a confined space for a long period of time. A relatively new method that offers greater tolerance of these factors is functional near-infrared spectroscopy (fNIRS).

fNIRS detects changes in the concentration of oxygenated and deoxygenated haemoglobin in blood and tissue throughout the outer cortex, reflecting changes in underlying neural activity (Lloyd-Fox et al., 2013; Lloyd-Fox et al., 2010). This change in the concentration of blood oxygenation can be detected using near-infrared light (Gervain, 2011). Typically, this entails light sources positioned in a head cap that emit near infrared wavelengths of light between 650nm and 950nm. These wavelengths penetrate the scalp, skull and underlying tissues into the outer cortex of the brain. Some of this light is differentially absorbed by oxygenated and deoxygenated blood, due to physical properties of the biological tissue within the cortex, and the remainder is scattered. The returned scattered light, which is also affected by the metabolic processes within the brain, is detected by the fNIRS sensors on the scalp. Through this method, fNIRS provides an indirect measure of brain haemodynamic activity based on changes in blood oxygenation.

Similar to fMRI, fNIRS measures cortical activity through measuring changes in regional cortical blood flow. In the context of an experiment, the onset of a stimulus presentation elicits an increase in oxygen rich blood which is known as oxy-haemoglobin (oxy-Hb) lasting three to eight seconds long. This is followed by a lesser decrease in deoxy- haemoglobin (deoxy-Hb) before slowly returning to baseline. This is known as the haemodynamic response function (HRF). As oxy-Hb and deoxy-Hb are interrelated, it is important that both are reported (Tachtsidis, 2016). This is because an increase in oxy- Hb and a decrease in deoxy- Hb are both required to make a functional

activation. Therefore, reporting both oxy-Hb and deoxy-Hb allows for a more accurate physiological interpretation of the results (Tachtsidis, 2016). These physiological measurements are used to answer questions about particular spatial and temporal localisation of a signal (Lloyd-Fox et al., 2010). By measuring changes in regional cortical blood flow, questions regarding the spatial location of the activation across the cortex can be addressed. Furthermore, examining the latency of oxy-Hb and deoxy-Hb and how they vary within and among different regions of the brain allows for a temporal measurement of the haemodynamic response to neural activity (Li, Potter, Huang & Zhang, 2017; Li et al., 2017). Overall, fNIRS ability to analyse both temporal and spatial signals allows researchers to capture a more precise understanding of the neuroanatomy of ASD.

In order to accurately define and assess functional activation in relation to underlying anatomical structures, fNIRS caps typically utilise the EEG standard international 10–20 system of electrode positioning (Tsuzuki & Dan, 2014). This system ensures that optode spacing is equal and proportional to skull size and shape. Scalp locations are defined within this system using relative distances between primary landmarks (nasion, inion, right and left preauricular points) (Tsuzuki & Dan, 2014). The 10–20 system then sets points across the scalp at 10% or 20% distances. Overall, this system reduces the variability between studies examining brain activity and allows for comparisons to be made between various neuroimaging techniques (Tsuzuki & Dan, 2014). As a result of the 10-20 system, research utilising fNIRS to examine the neuroanatomy of ASD is consistent in terms of cortex locations with other neuroimaging techniques and therefore comparable (Tsuzuki & Dan, 2014).

fNIRS has both strengths and weaknesses in comparison with other neuroimaging technologies. Studies testing fMRI and fNIRS concurrently have found correlations ranging between .71 and .94 in a variety of tasks including resting state, cognitive and motor tasks, supporting the comparability of results obtained using the two methods (Cui et al., 2011). Advantages of fNIRS in regards to fMRI include portability, not requiring exposure to strong magnetic fields or a potentially aversive MRI environment, and greater motion tolerance. This makes it particularly valuable for studies of populations such as individual's with ASD, who are often excluded from other types of neuroimaging studies because they are unable to remain still or tolerate loud noises during recording (Yamasaki et al., 2013). In addition, although both fNIRS and fMRI measure brain activity through the relatively slow haemodynamic response, fNIRS has a much more rapid temporal sampling rate (.01 sec) than fMRI, which may allow more precise characterisation of the haemodynamic response (Wilcox, 2015). Drawbacks of fNIRS compared to fMRI include poorer signal to noise and lower spatial resolution though methodological improvements such as increasing optode density are improving this (Brigadoi, 2014), and allowing for a more stable signal over repeated measurements (Cui et al., 2011).

fNIRS measurements are dependent on light penetration and reflection, and so can only be used for examining brain activity in the outer cortex to a depth of about two to three centimetres. This means that deeper cortical and sub cortical areas cannot be investigated using fNIRS. Other factors that affect the penetration of light into the cortex, and therefore can impact on measurements, also need to be taken into account, such as hair colour, skull thickness and age. For instance, newborns have thinner surface tissue and shallower sulci than adults, resulting in an increase in penetration into the cortex (3-5mm to 10-15mm) (Gervain, 2011; Vanderwert, 2014). The sensitivity of

fNIRS to characteristics of tissues between the cerebrum and optodes, such as blood flow in skin and muscles of the head, also makes the fNIRS signal more susceptible to artefacts arising from changes in extra-cerebral blood flow rather than brain activation. Finally, the level of spatial resolution available with fNIRS, about 1 cm^3, is significantly lower than what is available with fMRI, limiting the ability to do finely-grained mapping of brain activity.

Similar to EEG, fNIRS equipment can be portable, allowing the study of brain activity in more naturalistic settings, such as social interactions. This means that fNIRS equipment can more accurately explore social and communication skills which are among the core deficits in ASD (Lloyd-Fox, 2010). Although fNIRS lacks the ability to track rapid changes in neural activity possible with EEG, fNIRS has higher spatial resolution, allowing for more accuracy in the investigation of the specific brain regions being activated (Vanderwert, 2014). fNIRS is also less sensitive to motion-related artefact than EEG, as motion-induced change and the inherently low electrical conductivity of the skull contribute to degradation of the EEG signal (Cui, 2010; Lloyd-Fox et al., 2010). Several motion correction techniques have been developed for fNIRS, with the most commonly used at present being principle component analysis, wavelet filtering and correlation-based signal improvement (Brigadoi, 2014). Collectively, these features allow fNIRS technology to have advantages where motion and vocalisations are unavoidable without sedation or restraint (Kawakubo et al., 2009; Lloyd-Fox et al., 2010), such as in specific clinical populations, or in infants and young children. The growing interest in fNIRS to study clinical populations such as ASD has led to a number of fNIRS studies, which have evaluated aspects of brain function including resting state, inhibition, facial and emotional processing, working memory, joint

attention and auditory tasks (see Table 1). The current review will be the first we are aware of to provide a comprehensive evaluation of fNIRS research to date.

Table 1. Displays Studies Evaluated Within This Review That Utilised fNIRS to Examine Haemodynamic Activity.

Task type	Paper	Participant Age range	N	Participant type	Task	measurement	Region of Interest	Results
Resting state	(Zhu, Fan, Guo, Huang, & He, 2014; Huilin Zhu et al., 2015)	Average ASD: 9.0 yrs CONTROLS: 8.9 yrs	20 ASD: 10 Control: 10	ASD/control	Resting state: eyes closed, sitting still for 8 minutes	oxy-Hb deoxy-Hb HbT	inferior frontal cortices and temporal cortices	• ASD < interhemispheric functional connectivity in temporal cortex • HbO: < local • connectivity in right temporal cortex and lower interhemispheric connectivity between bilateral temporal cortex in ASD • No effect size reported
	(Mitsuru Kikuchi et al., 2013)	ASD and CONTROL: 3-7 years	30 ASD: 15 Control: 15	ASD/control	Resting state (Participants viewed a narrated picture show)	Oxy-Hb/ Deoxy-Hb HbT	BA10 Bilateral Anterior PFC	• ASD < inter-hemispheric coherence Oxy-Hb compared to TD in the 0.02-Hz frequency. *d* = .06 • Positive correlation between inter-hemispheric coherence in the 0.02-Hz frequency and social deficit for ASD group.
Executive Function	(Xiao et al., 2012)	HFA ADHD CONTROL: 8 to 14 yrs	51 HFA: 19 ADHD:16 Control: 16	HFA/AHDH/control	Go/ No Go task Stroop task	Oxy-Hb	bilateral prefrontal cortex	• HFA< Oxy-Hb in right PFC in No-Go blocks compared to controls. *d = .02* • HFA/ADHD > Oxy-Hb in right PFC during No-go blocks *d = .03* • HFA/ADHD < Oxy-Hb in left inferior PFC than TD during inhibitory tasks. *d= .49*
	(Yasumura et al., 2014)	Average age ASD ADHD CONTROL: 9.72 yrs	36 ASD: 11 ADHD:10 Control: 15	ASD/ADHD/control	Stroop/ reverse stroop task	Oxy-Hb	Prefrontal cortex	• ASD demonstrated no deficit in inhibition in Stroop and reverse stroop. • ASD > activity in right hemisphere

	(Akira et al., 2012)	ASD and CONTROL: 7 to 12 years	34 ASD: 14 CONTROL: 20	ASD/control	**Baseline Task:** indicate if circle is on left/right of screen. **DCCS task:** matched cards according to shape or colour	Oxy-Hb	bilateral prefrontal cortex	• < activity in channels 4 and 5 (right lateral prefrontal cortex) during DCCS task for ASD
dFacial Emotional stimuli (static)	(Mori et al., 2015)	Mean ASD: 11.5 CONTROL: 11.8	20 ASD:10 CONTROL:10	ASD/ control	**Pre test/ post task:** stared at asterisk on screen while static emotional facial expressions presented **Training:** imitate emotional facial expressions presented.	Oxy-Hb	Bilateral frontal regions	• Pretest: < Oxy-Hb in pars opercularis of the inferior frontal gyrus for ASD • Post test: Sig increase in Oxy-Hb in pars opercularis after training.
	(Hosokawa, Nakadoi, Watanabe, Sumitani, & Ohmori, 2015)	Average 24.4 yrs	38 MALE:20 FEMALE:18	Autism tendency	48 static images of 8 facial expressions	Oxy-Hb	bilateral frontal cortex regions	• Autistic tendency < activation in prefrontal cortex for fear, contempt, sadness and disgust. • Significant negative correlation between AQ scores and Oxy-Hb change in right PFC fear, contempt, sadness, anger and disgust.
	(Nakadoi et al., 2012)	PDD: 31.6 yrs CONTROL: 31.5 yrs	28 PDD: 14 CONTROL:14	PDD/control	Static emotional expression stimuli (fearful & neutral stimuli 100% intensity) Pre/post- neutral faces presented **Task phase**- fearful faces presented. Participants indicated whether face was M/F	Oxy-Hb Deoxy-Hb	Frontal region	• PPD < oxy-Hb concentration than TD during task phase • Sig correlation between Oxy-Hb change and FSIQ/ VIQ in PDD participants
	(Kita et al., 2011)	ASD: 10.2 yrs Adult control: 21.9 yrs	34 ASD: 10 Adult control: 11	ASD/ Adult control/child control	Facial images (self-face, familiar face, unfamiliar face)	Oxy-Hb	right inferior frontal gyrus/ left inferior frontal gyrus	• Oxy-Hb activity in IFG dependent on ASD severity • Increased ASD severity < Oxy-Hb activity in the IFG

		Child control: 10.9 yrs	Child control: 13		Participants indicated when sex of image had changed to opposite sex			when looking at self-recognition *d*=.38
Facial emotional stimuli (Dynamic)	(Fox, Wagner, Shrock, Tager-Flusberg, & Nelson, 2013)	HRA: 5-7 months LRC: 5-7 months	25 HRA: 10 LRC: 15	High risk ASD (HRA) (Older sibling diagnosed with ASD) Low risk group (No family history)	Videos of participant's mother's answering questions with a neutral face or a smiling face.	Oxy-Hb Deoxy-Hb	PFC and right lateral region	• Increased Oxy-Hb activity in lateral regions for LRC compared to HRA *d* .28 • Greater deoxy-Hb activity in frontal channels for HRA compared to LRC *d*=.06 • Greater deoxy-Hb response to mother's face compared to stranger face within HRA in frontal and lateral regions *d=.31*
Facial stimuli (Dynamic)	(Lloyd-Fox et al., 2013)	HRA and LRC: 4-6 months old	34 HRA: 18 LRC: 16	High risk ASD (HRA) (Older sibling diagnosed with ASD) Low risk group (No family history)	Videos of females who moved their eyes L/R or performed hand games (peek-a-boo) Auditory stimuli Vocal/non-vocal stimuli presented at onset of 2 of every 3 videos	Oxy-Hb HbT	Frontal and temporal lobes	• HRA < Oxy-Hb response to visual social stimuli compared to LRA in posterior temporal cortex • HRA < Oxy-Hb response to visual vocal stimuli compared to LRA in right-mid posterior STS
Joint attention/ imitation tasks	(Zhu et al., 2015)	Average ASD: 8.75 yrs CONTROL: 8.09 yrs	41 ASD: 21 CONTROL: 20	ASD/control	Joint attention/ non-joint attention videos Female's eyes followed a ball moving around (joint attention) or moved around independently of the ball (non-joint attention)	Oxy-Hb	Prefrontal Cortex	• ASD< activity and atypical functional connectivity in bilateral PFC during joint attention. *d=.34*
	(Iwanaga et al., 2013)	Average ASD: 11.5 yrs CONTROL: 11.4 yrs	32 ASD: 16 CONTROL:16	ASD/control	**MS task**- 3 pictures of eyes. Participants commented on mental state of eyes in picture **OC task** 3 pictures of objects. Participants expressed mental state of a person or	Oxy-Hb	central frontal area/ rosteral frontal cortex/ dorsal medial prefrontal cortex (Brodmann areas 9, 10)	• ASD < bilaterally activation during MS task compared to controls. *d=.07*

					described objects characteristics **Pre/post task baseline-** Participants repeat vowels			
	(Tamura, Kitamura, Endo, Abe, & Someya, 2012)	Average ASD: 10.2 yrs CONTROL: 9.5 yrs	40 ASD: 20 CONTROL:20	ASD/control	**Imitation:** match own hands to monitor. **Mirror-image imitation:** mirror position of own hands to models	Oxy-Hb Deoxy-Hb	PFC, rostral part of the superior or middle frontal gyrus (BA 10)	• No sig difference between ASD and Control AI and MI task • < left lateralization in Rostral PFC *d=.48*
Auditory/ linguistic tasks	(Keehn, Wagner, Tager-Flusberg, & Nelson, 2013)	3/6/9/12 months	76 HRA:27 LRC:37	High risk/ Low risk	**Linguistic stimuli** (trisyllabic sequences presented in either an ABB (e.g., "ba-lo-lo") or ABC (e.g., "ba-lo-ti") continuous video of different moving shapes	oxy-Hb	left anterior, left posterior, right anterior, right posterior	• HRA at 3 months> overall functional connectivity compared to LRC infants in left anterior, right posterior and left anterior, left posterior. • LRA at 12 months > interhemispheric connectivity compared to HRA in left anterior and left posterior
	(Kawakubo et al., 2009)	Average ASD: 12.7 yrs SIBLINGS: 11.1 yrs CONTROL: 10.6 yrs	78 ASD:27 SIBLINGS:24 CONTROL:27	ASD/unaffected siblings/control Subgroups: Adult /children	**Letter fluency task:** generate words that began with a syllable/s	Oxy-Hb Deoxy-Hb	prefrontal regions Brodmann's areas 10 (BA10)	• Adult: ASD < activation in BA10; frontopolar regions (anterior prefrontal cortex) (Oxy-Hb only) *d=1.03*
	(Funabiki, Murai, & Toichi, 2012)	Average ASD: 16.8 yrs CONTROL: 14.2 yrs	23 ASD:11 CONTROL:12	ASD/control	**Auditory stimuli:** pure tones, vowels, meaningless syllables/ simple story (each played twice/ participants listened in one and ignored in the other) Recall post-test after simple story.	Oxy-Hb	prefrontal cortex/ temporal cortex	• ASD < laterality when attending to auditory stimuli • ASD > recall during ignore phase of simple story
	(Minagawa-Kawai et al., 2009)	ASD: 9.2yrs CONTROL: 7.3 yrs	22 ASD:13 CONTROL:9	ASD	Phonemic and prosodic cue decoding task	Oxy-Hb	L/R temporal	• Control > left-dominant and right-dominant responses to phonemic and prosodic differences. ASD functional

	Three different forms of the Japanese verb	asymmetry for phonemic changes weak *d*=.075

Resting state

Resting state functional connectivity is a commonly used measure of the correlation of activity between different brain regions while an individual is not performing any specific task. (Lu et al., 2010; Sasai et al., 2012). In general, findings from fMRI studies in children and adults with ASD have shown reduced bilateral connectivity, increased local coherence and altered functional connectivity in the frontal and temporal regions of the brain (Fox & Greicius, 2010; Iidaka, 2015). To date, there have been two studies that have examined resting state functional connectivity in participants with ASD using fNIRS.

In the first study, Kikuchi et al. (2013) compared children aged three to seven with ASD and typically developing children to evaluate haemodynamic functional connectivity between the left and right anterior prefrontal cortex (aPFC) while passively watching a narrated picture-card show (see Table 1). fNIRS was used to monitor oxy-Hb and deoxy-Hb for each participant for a total of 600 ms. Coherence analysis of oxy-Hb data showed that, relative to typically developing children, children with ASD had higher interhemispheric connectivity indicated by 0.02 Hz fluctuations in haemodynamic activity at the left and right aPFC. Additionally, they found a significant positive relationship between social deficit and higher activity for oxy-Hb bilaterally. In other words, lower social ability in the ASD group was related to increased functional connectivity bilaterally in the aPFC.

Zhu et al. (2014) evaluated brain activity in the inferior frontal and temporal cortices while nine year old children sat still with their eyes closed for eight minutes (see table 1). The oxy-Hb results showed that children with ASD displayed reduced connectivity in the right temporal cortex and overall decreased interhemispheric

connectivity between the left and right temporal cortices compared to typically developing children. Similarly, when looking at deoxy-Hb, findings showed reduced local connectivity in the left temporal cortex and lower connectivity from bilateral superior temporal gyrus to left inferior frontal gyrus. These results imply that a differential trajectory of development of the temporal cortex may be apparent during resting state tasks between children with ASD and typically developing children.

While the results found by Zhu et al. (2014) are in line with previous fMRI findings, it is worth noting that both fNIRS studies only measured brain activity from the frontal and temporal lobes due to choice of optode placement on the scalp. While brain activity seen within these areas implies that they play a functional role, further research using fNIRS is needed to establish if there is a clear pattern of differential resting-state activity between clinical and control groups.

Executive function

Executive functions include cognitive activities such as the selection of appropriate behaviours or suppression of irrelevant or interfering information and impulses (Reineberg, Andrews-Hanna, Depue, Friedman, & Banich, 2015), and the manipulation of information for problem solving, planning and language processing (Akira et al., 2012; Narita et al., 2012). Executive function is generally divided into six domains, including working memory, inhibition, shifting, sentence memory, planning and fluency (Reineberg et al. 2015). Executive function in individuals with ASD has been widely researched using a variety of tasks. In general, most research has shown that scores on executive function tasks are lower for individuals with ASD compared to typically developed individuals (Narita et al., 2012). Moreover, studies using fMRI have shown that this difference in scores corresponds to decreased brain activity in the dorsal

lateral prefrontal cortex (DLPFC) in individuals with ASD (Narita et al., 2012), an area associated with executive function. As the DLPFC and surrounding frontal regions have been found to be active during executive function tasks, the fNIRS studies observing these domains have focused on the prefrontal cortex.

Most fNIRS studies examining the executive function abilities of individuals with ASD have focused on inhibition and task switching. To examine inhibitory control, Xiao et al. (2012) measured changes in oxy-Hb to compare the brain activity of high functioning children with ASD to children with Attention Deficit Hyperactivity Disorder (ADHD) and typically developing children while they performed inhibitory tasks (Go/No-go and Stroop tasks) (see table 1). Results indicated reduced oxy-Hb activation in the right prefrontal cortex in children with ASD and children with ADHD (Xiao et al., 2012). This suggests that inhibitory dysfunction is a shared feature of both high functioning children with ASD and children with ADHD. In contrast, Yasumura et al. (2014) found a modest tendency for increased right hemisphere activity in children with ASD compared to children with ADHD when they performed inhibitory tasks (Stroop/ reverse stroop task).

Further, a study examining task switching also found similar patterns of results to Xiao et al. (2012) where children on with ASD and typically developing children aged between seven and 12 years performed the dimensional card sorting task where participants were asked to sort cards according to one (e.g. colour) dimension or another (e.g. shape) (see table 1) (Akira et al., 2012). Children with ASD showed reduced oxy-Hb activity in the right lateral prefrontal cortex (PFC) compared to typically developing children during this task. Further analysis revealed that children with ASD displayed greater activity in only three of the 16 channels while children in the control group

displayed greater activity in 10 of the 16 channels (Akira et al., 2012). Thus it appears that this fNIRS method of comparing which channels are active allows for a more in-depth understanding of the region of the brain that is impaired. Taken together, there is some evidence to suggest the possibility of a reduction in brain activity in the right PFC in individuals with ASD during tasks assessing executive function. However, more research should be undertaken to determine if this decreased pattern in the right PFC is unique to inhibition and task switching or extends to other domains of executive function.

Facial Emotional Processing

Previous research suggests that individuals with ASD often have difficulty processing social information from faces, such as eye gaze, facial expression and facial speech (Hosokawa et al., 2015). Processing and understanding this information is important for social interaction (Lloyd-Fox et al., 2013). Although face perception initially activates occipitotemporal regions, this perceptual information is then passed on to the amygdala and PFC where emotional significance of the stimuli is appraised before social decisions and behaviours are actioned (Lloyd-Fox et al., 2013). fMRI studies have shown impaired function in the frontal cortex including the superior frontal gyrus and the medial frontal gyrus, the orbitofrontal cortex, the middle frontal gyrus and the inferior frontal gyrus in individuals with ASD during facial emotional processing tasks (Nakadoi et al., 2012; Ogai et al., 2003; Pelphrey, Morris, McCarthy, & LaBar, 2007). This atypical pattern of activity may be due to disruptions in areas of the cortex that make up the social brain network early in development, altering the child's developmental trajectory for social interactions (Lloyd-Fox et al., 2013).

fNIRS has also been used to determine the cortical activity of individuals with ASD in relation to processing facial emotional stimuli. Using 48 static facial images with eight varying expressions, Hosokawa et al. (2015) observed that adults with higher levels of autistic traits showed less oxy-Hb activation in the PFC for fear, contempt, sadness and disgust (see table 1). Nakadoi et al. (2012) found similar results while examining both oxy and deoxy-Hb data. They found that adults with ASD displayed reduced oxy-Hb concentration in the PFC compared to typically developed individuals when viewing fearful static faces compared to neutral expressions. In a pre- and -post study design, children with ASD and typically developing children were asked to imitate emotional facial expressions before and after a training phase (Mori et al., 2013). During the training phase participants imitated emotional facial expressions twice a week for 30 minutes. Analysis of the post- test results showed that children with ASD displayed decreased Oxy-Hb in the pars opercularis of the inferior frontal gyrus compared to typically developing children. However, a significant increase in Oxy-Hb was observed in the same area in the post-training phase compared to their pre-training phase levels (Mori et al., 2013). While the results here are consistent with previous fMRI studies indicating that individuals with ASD show disrupted prefrontal cortical activity when processing facial emotional stimuli, Mori et al. (2013) was the first to implement a training phase. The implementation of a training phase was an important factor and the results imply that repeated imitation of emotional stimuli helps to increase prefrontal activity, an area associated with learning and higher executive function.

The impairment in facial processing extends beyond static stimuli and facial expression tasks. Kita et al. (2011) used oxy-Hb data to demonstrate that children with ASD showed less activation in the left and right inferior frontal gyrus when looking at

their own faces compared to typically developing children (see table 1). Severity of symptoms was negatively correlated with cortical activity, indicating that more severe symptoms of ASD were associated with decreased brain activity in areas associated with facial recognition as evidenced by oxy-Hb data. Two studies have also utilised dynamic stimuli (videos) to investigate differences in facial processing between infants classified as high risk for ASD (i.e. babies whose siblings are on the autism spectrum) and typically developing children. Fox et al. (2013) assessed both oxy-Hb and deoxy-Hb while participants watched videos of their mothers answering questions with a neutral or smiling face (see table 1). The researchers found that high risk group displayed decreased oxy-Hb in the right lateral regions of the brain and increased deoxy-Hb concentrations in the frontal channels compared to low risk controls. Interestingly, the researchers also found greater deoxy-Hb concentrations for infants in the high-risk group when looking at their mothers compared to strangers in both frontal and lateral regions (Fox et al. 2013). However, only infants in the low risk group showed increased oxy-Hb in the orbital frontal cortex in response to smiling faces. While the changes in deoxy-Hb seen in the high risk group indicate that some level of discrimination between mother and stranger is occurring, it is unclear why there were differences in activation. In a similar study, Lloyd-Fox et al. (2013) measured brain activity in the frontal and temporal regions of high-risk infants and low-risk infants. The participants watched videos of females moving their eyes left to right and playing hand games (peek-a-boo) (see table 1). Additionally, vocal and non-vocal sounds were presented at the onset of two out of the three videos shown. High risk infants were found to have a reduced oxy-Hb response in the posterior temporal cortex to visual stimuli compared to low risk infants (Fox et al., 2013). Moreover, a decreased oxy-Hb response was also found to vocal stimuli in the right mid posterior part of the superior

temporal sulcus. On the whole, these findings suggest a link between decreased activity in the cortical areas of the brain associated with the social brain network for tasks using facial emotional stimuli.

Joint attention/ Imitation Tasks

Findings from a number of fMRI studies suggest that the PFC is also involved in processing tasks that assess theory of mind, joint attention and imitation (Castelli, Frith, Happé, & Frith, 2002; Iwanaga et al., 2013; Zhu & Godavarty, 2013). While fNIRS may be ideal for examining PFC activity during these specific tasks, very little research has been conducted in this area of the brain in individuals with ASD. To date, one study has used fNIRS to assess brain activity in children with ASD during a joint attention task (Zhu & Godavarty, 2013). In this study, participants watched two videos where a female either followed a ball moving around with her eyes (joint attention task) or looked in other locations from where the ball was moving (non-joint attention task) (see table 1). In this study children with ASD showed reduced oxy-Hb bilaterally in the PFC during the joint attention task compared to typically developing children. While typically developing children also exhibited distinct lateralisation towards the left hemisphere of the PFC during the joint attention task, no distinct interhemispheric changes were observed in children with ASD (Zhu & Godavarty, 2013). The researchers concluded that the social information within each task may influence the cortical organisation of the PFC of typically developing children, but not for children with ASD (Zhu & Godavarty, 2013). Reduced activity in the PFC, as indicated by a decrease in oxy-Hb, was also observed by Iwanaga et al. (2013) in children with ASD using a mental state task requiring participants to identify emotions by viewing the eyes alone. Further analysis revealed that this decrease reflected regions such as the Brodmann 10 area and the medial PFC, which have previously been associated with theory of mind

(the ability to attribute mental states to oneself and others) (Iwanaga et al., 2013; Schulte-Rüther et al., 2011; Schulte-Rüther et al., 2014).

As some fNIRS devices are portable, participants in Tamura et al. (2012) study were able to move their hands freely to imitate actions displayed on screen or a video of a model (see table 1). Children with ASD displayed reduced oxy-Hb activity in the left rostral PFC during the imitation tasks compared with typically developing children. There was no difference in deoxy-Hb between the two groups (Tamura et al. (2012). Overall, these studies indicated a reduction in oxy-Hb activity over the PFC during imitation, joint attention and related mental state tasks with a pattern of decreased activity occurring at the left PFC. Taken together, these studies may imply that individuals with ASD rely more on the right PFC and other regions to process information about joint attention and imitation tasks.

Auditory/linguistic tasks

Recently, several authors have utilised fNIRS in the study of language and auditory processing. This research suggests that individuals with ASD display decreased activation and an atypical pattern of lateralisation (Boddaert et al., 2004; Funabiki et al., 2012; Gervais et al., 2004; Minagawa-Kawai et al., 2009). The research undertaken in this area using fNIRS has revealed a pattern of results similar to fMRI studies. For instance, when Funabiki et al. (2012) analysed oxy-Hb data, they found that adolescents with ASD showed decreased laterality in the temporal cortex compared with typically developing adolescents when instructed to ignore various forward and backward speech intervals (see table 1). Conversely, no differences were detected between the two groups when they were asked to pay attention to the auditory stimuli (Funabiki et al., 2012). Minagawa-Kawai et al. (2009) evaluated phonemic and prosodic cues while children

with ASD and typically developing children listened to three different types of Japanese verbs. After analysing oxy-Hb data, results showed that typically developing children had increased left hemisphere dominance for phonemic cues and increased right hemisphere dominance in the auditory cortex for prosodic cues Minagawa-Kawai et al. (2009). Children with ASD displayed less localisation to the left hemisphere, indicating less-specialised left hemisphere brain functions (Minagawa-Kawai et al., 2009). This finding is consistent with previous studies, which also indicate a pattern of reduced left hemisphere activity that may impair their ability to effectively process language (Belin, 2010). In a novel extension to these findings, Keehn et al. (2013) explored oxy-Hb and deoxy-Hb data of high risk infants at three and 12 months of age (see table 1). The results showed that three month old high risk infants displayed increased overall functional connectivity compared to low risk infants in the left and right posterior and left anterior temporal regions of each hemisphere when listening to auditory stimuli. However, at 12 months of age, low risk infants showed elevated interhemispheric connectivity and greater activity in the left anterior and posterior temporal regions of each hemisphere compared to high risk infants. This study suggests that there may be differences early in development in brain connectivity in children with a family history of ASD. This has the potential to be identified as a possible early indicator of ASD. Collectively, these studies assessing brain activity during auditory and linguistic tasks demonstrate a consistent pattern of atypical interhemispheric connectivity and localisation.

Discussion

There were a number of preliminary findings identified through the review of the fNIRS literature concerning ASD. Firstly, despite the challenges of obtaining neuroimaging data from individuals with ASD, particularly younger participants, fNIRS

has demonstrated the ability to measure functional cortical activity associated with specific tasks involving visual, auditory and linguistic stimuli. Secondly, fNIRS studies were able to show that individuals with ASD were likely to have patterns of atypical and altered activity compared to typically developed individuals in tasks ranging from resting state to executive function and joint attention. Findings included reduction in haemodynamic activity within specific brain regions, differences bilaterally across parts of the cortex and a lack of cortical specialisation in certain areas of the brain.

One of the potential advantages of fNIRS over fMRI due to its relative tolerability and low cost is being able to obtain repeated measurements over time. The studies reviewed above suggest that fNIRS is able to detect longitudinal changes in brain activity in challenging populations such as in individuals with ASD. An essential factor to support such work is establishing the reliability of test-retest measurements using fNIRS. Preliminary studies have shown intersession reliability of fNIRS measures of brain connectivity (Blasi, Lloyd-Fox, Johnson, & Elwell., 2014) and response to auditory stimuli (Wiggins, Anderson, Kitterick & Hartley, 2016). However, much work still needs to be done to establish the reliability of test-retest measurements using fNIRS, and what methodological considerations need to be taken into account for specific tasks and populations. In addition to technical considerations, fNIRS, as other neuroimaging techniques, is susceptible to group differences in characteristics such as motion during scanning being misinterpreted as differences in brain activity. For example, in the studies above, it is unclear if individuals with ASD made movements during the testing session that were different to those of typically developed individuals which could potentially affect intersession reliability (Blasi, Lloyd-Fox, Johnson, & Elwell., 2014). Although the relative motion-tolerance of fNIRS may be an advantage

here, measurements of intersession reliability would be a valuable addition to longitudinal fNIRS studies with clinical populations.

Overall, these findings demonstrate that fNIRS is able to measure differences in brain activity in young children with ASD and infants at increased genetic risk who are often difficult to image using other methods. Although the use of fNIRS in the understanding of ASD is still an emerging area, there have been some promising initial results. For instance, when looking at the findings from the six studies assessing facial emotional processing, a reduction in oxy-Hb activity in the prefrontal cortex emerges as a consistent finding. Similarly, all three studies assessing joint attention and imitation showed a decrease in oxy-Hb in the left PFC, while the three studies looking at executive function generally found relative reductions in oxy-Hb activity in the right PFC. An overall reduction in activity and atypical lateralisation in the temporal cortex was the main finding from the four studies focusing on auditory and linguistic processing. Lastly, the two studies measuring resting state functional connectivity found abnormalities in individuals with ASD, with one study showing a decrease in activity in the temporal cortex and the other study showing an increase in activity that was linked to increased autism severity (Blasi, Lloyd-Fox, Johnson, & Elwell., 2014; Wiggins et al, 2016).

Limitations

While the differential patterns of brain activity evident in individuals with ASD may reflect a decrease in effective processing of information, there are some methodological issues to consider. Firstly, unlike fMRI, fNIRS is only able to address the external portion of the cortex, and many of the studies described above only obtained measurements from specific cortical regions such as the prefrontal cortex.

Thus, it is possible that relevant activity was occurring in regions not sampled due to optode placement or in sub cortical structures not accessible to fNIRS (Lloyd-Fox et al., 2013; Wilcox & Biondi, 2015)).

Secondly, the majority of studies reviewed here only reported oxy-Hb as a measurement of brain activity. Although this has been common practice, emerging research is now showing that oxy-Hb and deoxy-Hb both need to be reported in order to accurately interpret findings (Tachtsidis, 2016). fNIRS, like fMRI, infers changes in brain activity based on differences in blood oxygenation levels due to the presence of neurovascular coupling. Both fNIRS and fMRI are susceptible to confounding changes in oxy-Hb due to local brain activity with vascular changes arising from other sources, including systemic intra-cerebral and/or extra-cerebral changes related to factors such as respiration, heartrate, and autonomic activity. Several measures can be taken in fNIRS studies to account for this, as reviewed by Tachtsidis et al (2016). One key aspect, however, is analysis of both oxy-Hb and deoxy-HB signals, as the simultaneous increase or decrease in both is a strong suggestion that it may be due to systemic or extra cerebral factors (Tachtsidis, 2016; Cui, 2010).

Lastly, although most studies removed motion artifact prior to analysis, artifacts can have different shapes, timing and frequency, and if the optimal method is not utilised, true signal can be removed along with motion artifact (Brigadoi, 2014). While fNIRS is a suitable neuroimaging option for individuals with ASD, it remains a challenge to utilise this equipment with such individuals, especially over relatively long periods of time. This often results in designs where the number of trials in fNIRS studies is limited, which reduces the signal to noise ratio (Vanderwert, 2014). Removing whole trials due to motion or eliminating signal from noise using methods borrowed

from other neuroimaging techniques such as EEG and fMRI may not be ideal. In turn, this may lead to an incomplete understanding of the true activity occurring in the brain, resulting in inaccurate conclusions being made (Brigadoi, 2014). However, emerging research focusing on motion artifact correction in fNIRS has shown that methods such as wavelet filtering can be effective with various forms of motion artifact, maximising the amount of usable data (Brigadoi, 2014). It is hoped that future studies will utilise improved correction methods that work best with fNIRS data.

Future Directions

The studies described in this review have hinted at the potential of fNIRS in the study of ASD, but there is clearly much more to do. Multi-modal imaging studies are being explored as a way to combine the relative strengths of different methods; for example combining the temporal specificity of EEG with the spatial localization made possible by fNIRS. As alluded to above, the tolerability and relatively low cost of fNIRS makes longitudinal imaging increasingly feasible, either in regards to intervention or to map trajectories of brain development at closer intervals than is usually feasible with MRI. The capacity of fNIRS to measure brain activity associated with large-scale physical motion such as walking has opened up a means to better understand how these differences in motor function often present in individuals with ASD may relate to other aspects of function.

One of the most intriguing capacities of fNIRS may be its ability to look at brain activity associated with the difficulties with real-world social interactions that lie at the core of ASD. Although the majority of studies in this review examined different aspects of social skills, including joint attention, facial and emotional processing, and language, this was done with individuals in isolation, using passive tasks on a monitor

or from a speaker (Rolison, Naples & McPartland, 2015). While this approach has methodological advantages, such as repeatability of stimuli, it cannot capture brain differences associated with actual interpersonal interactions where individuals with ASD are most likely to have difficulties. (Rolison, Naples & McPartland, 2015). One of the greatest potential advantages of fNIRS above other imaging techniques is its combination of portability and relative robustness to motion, making it possible to obtain imaging data while individuals are engaged in real-world social activities. Hyperscanning, or obtaining measures of brain activity from two or more individuals simultaneously during an interaction, has been done using fMRI and EEG, but may be particularly amenable to fNIRS. Initial studies in healthy individuals have demonstrated aspects of brain activity to synchronize during coordinated activity (Cui et al, 2017, suggesting that hyperscanning may eventually provide a window into how brain activity may differ in individuals with ASD during language development and other reciprocal activities (Rolison, Naples & McPartland, 2015).

Conclusion

This review brings to light the versatility of fNIRS, and its capacity to obtain brain imaging data in individuals with ASD of varying ages, in different contexts and across a wide range of tasks. fNIRS has specific strengths such as being portable, quiet, and relatively tolerant to motion that give specific advantages to working with individuals with ASD. It also has specific weaknesses such as spatial resolution, limitation to superficial cortical structures, and signal strength, although technical and methodological improvements are ongoing rapidly. fNIRS appears a promising technique that is a practical and feasible option for working with individuals with ASD.

The continued use of fNIRS technology will allow researchers to further elucidate how brain function in children on the spectrum may differ or change over time.

Chapter Six

The Relationship between Haemodynamic Response and Social Stimuli: A comparison Study of Children with ASD and Typically Developing Children

Introduction

Understanding how neurobiological features of ASD are related to behaviour and cognition has long been the focus of researchers and clinicians (Geschwind & Levitt, 2007). Separately, neuroimaging and clinical studies can offer valuable insights into multiple aspects of ASD (Ecker & Murphy, 2014). Neuroimaging studies typically aim to understand the underlying brain structure and function, while clinical studies tend to focus on symptom severity, intervention outcomes and factors related to behaviours (Ecker & Murphy, 2014). However, as ASD is a neurodevelopmental disorder that manifests in a spectrum of behavioural symptoms, the need for research in both fields is equally important in providing a framework for better understanding the phenotypic characteristics including communication, social skills and behaviours as well as the underlying neural basis for these characteristics (Hernandez et al., 2015).

As deficits in social skills and communication are among the most prominent features of ASD, both clinical and neuroimaging researchers have focused their investigations on these phenotypic characteristics (Lloyd-Fox et al., 2013). In fact, impairment of key social behaviours (i.e., eye contact, joint attention, orientating to name, verbal and non-verbal communication) in infancy are often the first indicators of ASD (Lloyd-Fox et al., 2013). Given the importance of complex social interaction in everyday life, a number of researchers have examined brain networks that may be involved in the social impairments observed in ASD.

The social brain network is defined as a network of regions that process social information. In typical adults, these regions include the inferior frontal gyrus, orbitofrontal cortex, amygdala, anterior temporal lobe regions and posterior superior temporal sulcus (temporoparietal region). Findings have consistently demonstrated

patterns of atypical brain response to visual and auditory social stimuli in individuals with ASD. More specifically, converging evidence indicates that temporal regions, specifically the superior temporal sulcus, are involved in processing social information (Eyler, Pierce, & Courchesne, 2012; Gervain et al., 2011; Lloyd-Fox et al., 2018; Pelphrey et al., 2011; Zhu et al., 2015). It has been suggested that specific interactions between genes, the brain, and behaviour during early development culminate in a failure to develop specialised functions in the brain circuitry involved in social communication (Pelphrey et al., 2011). As a result, the typical development of the social brain network may be disrupted, which may lead to different neural responses towards facial features and expressions (Pelphrey et al., 2011). Specifically, Pelphrey et al. (2011) postulated that impaired perception of facial expressions and difficulties in interpersonal interactions apparent in ASDmay be explained by a lack of specialised neural networks within the posterior superior temporal sulcus (Pelphrey et al., 2011). A number of researchers have found anatomical and functional connectivity and atypicalities in these areas for individuals with ASDcompared to typically developing children (Lenroot & Yeung, 2013). These atypicalities include reduced connectivity between brain regions and reduced activity in areas dedicated to processing social information (Allison et al., 2000; Pelphrey et al., 2005a; Van Overwalle & Baetens, 2009).

A number of studies have found relatively greater activation in the frontal and superior temporal regions of the social brain network in typically developing infants and children (six months to seven years) to dynamic social stimuli (e.g., people singing nursery rhymes) (Grossmann et al., 2008, 2013; Lloyd-Fox et al., 2009, 2011, 2014a; Farroni et al., 2013). This pattern of activity in the frontal and superior temporal regions of the social brain network is also observed in studies examining static social and non-social stimuli and older children and fMRI studies with adults (Allison et al., 2000;

Pelphrey et al., 2005a; Lotze et al., 2006; Van Overwalle & Baetens, 2009). Researchers have also utilised functional near-infrared spectroscopy (fNIRS) in the study of brain function associated with social information (Lloyd Fox et al., 2018). fNIRS studies examining social sounds (e.g., vocalisations) have also found greater activity in the middle and superior temporal gyri and sulci in typically developing children, compared to non-social sounds like cars and environmental sounds (Grossmann et al., 2010; Minagawa-Kawai et al., 2011; Lloyd-Fox et al., 2012, 2014a,b, 2015). Overall, these studies demonstrate that an enhanced response to social stimuli is found in the frontal and superior temporal regions of the social brain network compared to non-social stimuli in typically developing infants, children and adults. Collectively, these studies indicate that there may be a developmental pathway of specialisation to social stimuli and sounds and speech, relative to non-social stimuli and sounds.

In contrast to the patterns of activity shown by typically developing children and adults to social stimuli, research examining children and adults with ASD has found atypical patterns of activation to social stimuli. Some studies utilising either fMRI or fNIRS have demonstrated atypical patterns of connectivity and decreased haemodynamic activity within temporal regions such as the superior temporal sulcus (STS), in children and adults with ASD (Boddaert et al., 2014). More specifically, studies have shown that high risk infants have a reduced response in the posterior temporal cortex (specifically the STS) to dynamic social stimuli (Fox et al., 2013; Lloyd-Fox et al., 2013). A decreased oxy-Hb response was also found to social auditory stimuli in the right mid posterior part of the STS (Fox et al., 2013). Research examining children with ASD aged one to four years using fMRI also found a relative decrease in activity in the left hemisphere when listening to language, compared to typically developing children (Eyler et al., 2012). Taken together, these studies indicate that

children and adults with ASDmay have atypical activity in temporal regions, specifically reduced activity in the STS (Lloyd-Fox et al., 2018).

Recently, researchers have begun to use both fNIRS and clinical measures to examine the relationship between haemodynamic activity and behaviour. In one study, researchers used fNIRS and the Pervasive Developmental Disorders Japan Rating Scale (Tachimori, Osada, & Kurita, 2003) to assess the relationship between cortical activity and autism severity, as well as self-consciousness, during a self-face recognition task (Kita et al., 2011). The researchers found that decreased activity in the inferior frontal gyrus was related to increased autism severity (Kita et al., 2011). This research indicates that dysregulation of neuroanatomic structures might play a role in autism severity. Furthermore, Dawson et al. (2012) used EEG during a passive task where children with ASD viewed static social stimuli consisting of faces and objects. The results showed a relationship between greater cortical activation, fewer social pragmatic problems (social interactions and social conventions) and better social communication (Dawson et al., 2012). In a similar study using fNIRS, high risk infants (infants with diagnosed siblings) watched videos of females moving their eyes left to right and playing hand games (peek-a-boo) (Lloyd-Fox et al., 2013). The results showed a relationship between autism severity and decreased activity in the posterior superior temporal sulcus in high risk infants (Lloyd-Fox et al., 2013). Specifically, children with ASD with increased symptom severity were found to have weaker patterns of activation. The authors concluded that further research using social and non-social stimuli to understand the relationship between patterns of brain activity and social outcomes could lead to a greater understanding of differing developmental trajectories of children with ASD given that ASD is a neurodevelopmental condition characterised by social and communication impairments, further research examining the relationship between brain

activity and social outcomes may serve to identify potential early biomarkers for ASD. This information may bring about a better understanding of the possible developmental trajectories, and in turn, more targeted interventions based on the specific impairments demonstrated by the child.

It is well known that children with ASD have difficulties with social interactions. Furthermore, previous findings indicate that difficulties in processing social information, specifically facial emotional stimuli, may be linked to a relative decrease in activity in the social brain network. Therefore, it is crucial that further research examining the extent of this decrease in activity compared to typically developing children is undertaken. Furthermore, given that previous research suggests that a relationship exists between brain activity and social outcomes, a preliminary examination of which social behaviours are likely to impact the haemodynamic response is necessary.

Therefore, the present study aims to examine potential differences in brain haemodynamic activity across the temporo-parietal region between children with ASD and typically developing children using fNIRS. More specifically, the study aims to examine differences between dynamic social (e.g., women singing nursery rhymes) and non-social (spinning toy with a ball dropping periodically) stimuli. The study also aims to extend previous findings by Dawson et al. (2012) by providing a preliminary investigation of the relationship between the temporo-parietal region and social measures for both children with ASD and neurotypically developing children.

Method

Participants

Written informed consent was obtained from the child's parent. Participants comprised 7 children with ASD who attended one of two KU Autism Specific Early Learning and Care Centre (ASELCC) in Sydney, Australia: KU Campbelltown (N = 5) KU or KU Liverpool (N = 2) and 12 typically developing (TD) children recruited from the UNSW preschools. The ASELCC provides early intervention for pre-school aged children with ASD . A total of nine children with ASD were excluded from the study as they were unable to tolerate the procedures or they were inattentive. A table of all participants who were included and excluded can be found in appendix B. All participating children were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) (American Psychiatric Association, 2013) criteria by a community-based physician. The average age of children at the time of study commencement was four years and four months (See Table 1). The percentage of males in the study was 47.3% (See Table 1). All assessments were completed in English.

Inclusion/Exclusion criteria

Exclusion criteria included known neurodevelopmental (e.g., Fragile X Syndrome) or neurological disorders (e.g., epilepsy), and significant vision, hearing, motor or physical problems. All children were initially screened for their ability to tolerate the fNIRS procedure and the experimental task. This took place via discussion with parents and/or preschool staff in the case of the children with ASD

Table 1. Characteristics of the Study Sample		
Characteristics	**Autism**	**TD**
Age (years)	4.4	4.5
Sex (M/F)	4:3	5:7
N	7	12

Clinical Measures

The Autism Diagnostic Observation Schedule

The Autism Diagnostic Observation Schedule (ADOS-2; Lord et al., 2000) was used to confirm whether children met the DSM-5 (American Psychiatric Association, 2013) criteria for ASD. The ADOS-2 is a semi-structured, clinician administered standardised diagnostic assessment of communication, social interaction, repetitive behaviours and play to evaluate the diagnostic criteria for ASD. Research has demonstrated that the ADOS-2 has strong inter-rater and test-re-test reliability ranging from 81% to 93% as well as internal consistency for all domains and modules ranging from 47% to 94%((Gotham, Pickles & Lord, 2009). The ADOS-2 was administered at baseline only.

The Mullen Scales of Early learning

The Mullen Scales of Early Learning (MSEL; Mullen, 1995) is a standardised developmental assessment for children from birth to 68 months of age. The scales provide an overall index of cognitive and motor ability and assess the child's weaknesses and strengths. The MSEL consists of five subtests including gross motor, visual reception, expressive language, fine motor, and receptive language. Internal consistency for the MSEL is above 0.80 for all five of the subscales while test-retest reliability ranged between 0.80 and 0.70.The MSEL was administered to all participants at baseline and follow up.

Social Communication Questionnaire

The Social Communication Questionnaire (SCQ; Rutter, Bailey & Lord, 2003) is a 40-item, parent report measure evaluating communication skills and social functioning. Items are scored on a dichotomous (yes/no) scale, with higher scores indicating the presence of more autistic traits. The SCQ has strong internal consistency at .90 as well as sensitivity/specificity ranging between .80 and .95. The SCQ was completed by parents at baseline and follow up.

Clinical Procedure

Children were evaluated with the aforementioned clinical assessments before the fNIRS sessions were conducted. All assessments were completed in clinic rooms at the child's preschool or at Neuroscience Research Australia. The parents were invited to sit in the room during the clinical assessments. The assessments were completed by trained post-graduate students or clinical psychologists. If this was not possible, one examiner was present with the addition of external cameras monitoring the room for later behavioural examination.

Stimuli

A passive task was used which included dynamic social and non-social stimuli. The social stimuli included videos of female actors singing nursery rhymes, while the non-social stimuli included videos of moving toys. Each social and non-social stimulus varied between 8 and 15 seconds in duration. The stimuli were presented 5 times each in 5 separate blocks. The order of the stimuli being presented was in a fixed alternating order of social > non-social or non-social > social, randomised between blocks. Each video was immediately preceded by an inter stimulus interval (ISI) of grey screen with a

black fixation cross (used as a temporal baseline for each video). This was jittered, which involved the randomisation of the interval between successive stimulus events, by one second to minimise habituation effects. A 10 second baseline also occurred at the start and end of each block. The durations of the stimuli were implemented in order to be long enough to allow a haemodynamic response function to develop and decline. There was no established precedent for the number of repeated trials necessary to elicit a robust mean haemodynamic response function. However, it was attempted to maximise the number of trials available in a 15-minute timeframe. This was to make the tasks likely to be tolerable to preschool aged children.

fNIRS Equipment

Measures of brain haemodynamic activity were obtained using a portable NIRx NIRSport device (NIRX, Germany) with NIRStar (15.0) fNIRS data acquisition software. The fNIRS caps contained eight pairs of source/detector optodes located bilaterally over the temporoparietal region according to a pre-designed montage based on universal 10/10 system positioning. Specific combinations of these source-detector pairs generated 20 channels of fNIRS data. A topographical layout of the precise optode and diode positioning and channel locations across the temporo-parietal regions can be seen in Figure 1. Each optode was spaced approximately 3cm apart and held at a constant distance using embedded plastic joints.

The fNIRS assessment was recorded using a Logitech C922 Pro Stream webcam in order to help identify motion-related artefact and lapses in participant attention to the task. Presentation software running on a separate laptop was used to control stimulus presentation on a 22-inch monitor.

fNIRS acquisition Procedure

The fNIRS session was usually completed on a different day to the clinical assessments or following a rest break in order to increase engagement during the fNIRS session. Prior to the fNIRS session, the participant's head circumference was measured for correct fNIRS cap size selection. The protocol for the study can be found in Appendix A.

During the session, participants were either seated on their parent's laps or next to their parent in front of a monitor at a distance of approximately 80 cm. Once the participant was seated, the correct sized fNIRS cap was placed on the child's head. The midpoint of the head was measured to determine the Cz location using standard procedures. Two investigators were always present in order to expedite fNIRS cap fitting and other set-up procedures. The children were able to take breaks or stop the session, as required.

Before the test paradigm started, lights were dimmed to reduce the risk of ambient light contamination of the fNIRS signal. A calibration was then completed using NIRSLAB (NIRx Medical Technologies, Berlin, Germany) to check signal quality, gain, level and dark noise (ambient light contamination). Participants were then instructed to watch and the stimulus paradigm on the screen and the fNIRS recording commenced. NIRSLAB (NIRx Medical Technologies, Berlin, Germany) was used to record brain activity from the NIRSport device and save the data for pre-processing and later statistical analysis.

Pilot Testing

Before children with ASD completed the session, a number of pilot sessions were recorded with adults and typically developing children. This allowed for the testing of the equipment, the recording devices, stimuli, and optode positioning. This also allowed for preliminary data analysis of the recordings collected. Pilot testing was also completed in order to ensure that the sessions with children were efficient and precise. Further to pilot testing, children with ASD who were unable to tolerate the cap were provided with another opportunity to become familiar with the fNIRS cap.

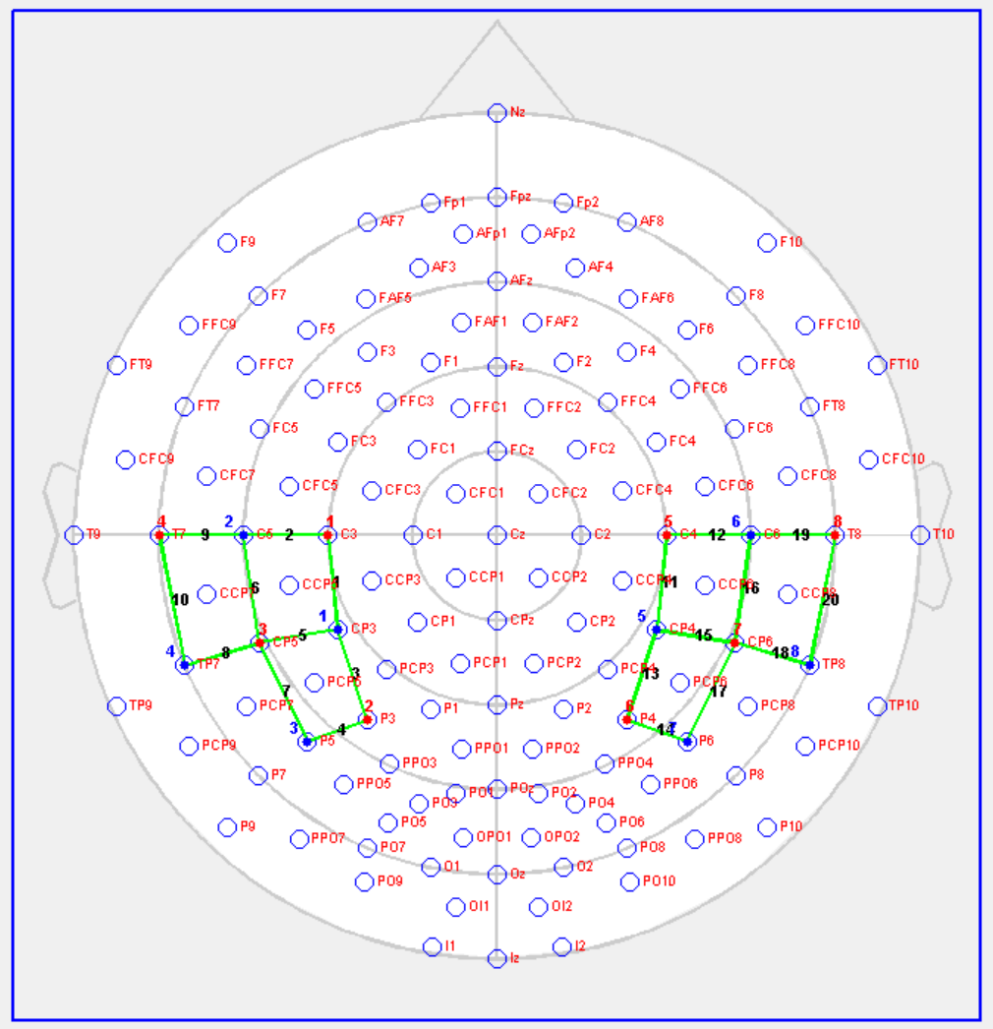

Figure 1. Indicates channel locations across the temporo-parietal region, marked as green lines.

fNIRS Preprocessing and Computation of Haemodynamic Response Function

fNIRS data was pre-processed using the NIRSlab 2017 version 6 analysis package (NIRx Medical Technologies, Berlin, Germany). The quality of the raw data was examined for each channel and any channels with poor signal quality (e.g. excessive motion artefact) were flagged and excluded from further processing and later analysis. As some children were only able to tolerate the fNIRS cap for small amounts of time, this resulted in missing data, which was also excluded from further processing and later analysis. The remaining channels were subject to additional pre-processing steps. Extraneous data prior to the start of the first stimulus and after the end of the last stimulus were truncated. Excessive spike recording activity was selected and removed. A band pass filter was then applied (low cut-off of 0.01 Hz and a high cut-off of 0.2 Hz) (Koenraadt, Roelofsen, Duysens, & Keijsers, 2014) to ensure removal of drifts in signals caused by respiratory and cardiac rhythm. The haemodynamic parameters were set to 760 and 850 nm wavelengths, with a separation distance of 3 cm between source/detector pairs before computing the haemodynamic states, where the optical density data were converted into relative concentrations of oxygenated (oxy-Hb) and deoxygenated haemoglobin (Deoxy-Hb) by applying the modified Beer-Lambert Law (Cope et al., 1988). These computed oxy-Hb and deoxy-Hb values for each condition (social, non-social, fixation and baseline) for each participant were then exported as plain text for later analysis in conjunction with the behavioural data.

Statistical Analysis

All analyses were completed using the IBM SPSS Statistics for Windows, (Version 21.0) (IBM Corp., Armonk, NY, USA)

Clinical data

Independent t-tests were then used to compare mean SCQ social and communication as well as MSEL expressive language and receptive language scores between the ASDand TD groups. Only participants with full scores on all subscales were included in the analyses. This meant that the number of participants in each analysis varied for the different scales and subscales because of missing data.

fNIRS Statistical Analysis

Linear regression models with the backward elimination procedure were used to model potential predictors of haemodynamic activity in each of the 20 channels. FDR corrections were then utilised in order to control for multiple comparisons. Predictor variables consisted of diagnostic group, gender and social clinical measures taken from the MSEL (i.e., receptive language and expressive language) and the SCQ (i.e., communication and social). Missing data for both clinical measures (incomplete measures) and fNIRS (head movements, ceiling effects, probe movement) resulting in slightly different numbers of participants for these analyses. The analysis did not have enough power to support the exploration of variables such as age at enrolment in the backward regression. The criterion for backward elimination was $F \geq 0.1$. Although underpowered, due to a small sample size, an exploratory follow up group analysis was conducted using univariate ANCOVA to primitively explore group differences for predictors that were significant in the backward regression. In the follow up analysis, SCQ Social and communication scores as well as MSEL receptive language and expressive language scores were analysed as covariates.

Results

Independent T-Tests were initially conducted to examine group differences of clinical assessments. A significant difference was found on the SCQ Total score t(17) = .605, p=.004 where the ASD group demonstrated increased scores on the SCQ total (M = 53.4, SD = 7.61) compared to the TD group (M = 52.0, SD =.2.55). The ASD group also displayed significantly increased SCQ communication scores (M= 18.8, sd = 4.18) compared to the TD (M=16.4, sd=1.16) t(17)= 1.933, p=.002. The ASD group also showed increased SCQ Social scores (m= 18.8, sd = 1.95) compared to the TD group (M=16.0, sd=.66) t(17)= 4.563, p=.002 (See Table 2).

Table 2. Clinical Measure outcomes for Autism and TD

	ASD		TD		*N*	*t*	*Df*	*P*	*d*
	Mean	**SD**	**Mean**	**SD**					
Autism Diagnostic Observation Schedule -2									
Social Affect	11.14	2.854			7				0.0
Repetitive and Restrictive Behviour	2.14	2.116			7				0.0
Social Affect+Repetitive/Restrictive Behviour	13.29	2.928			7				0.1
Comparison Score	5.29	0.951			7				0.1
Mullen Scales of Early Learning									
Visual Reception	34.67	12.741	50.92	12.094	19	-2.064	13	0.773	1.3
Fine Motor	27.33	7.024	58.67	13.159	19	-3.91	13	0.245	3.0
Receptive Language	33.67	14.012	57.42	7.716	19	-4.099	13	0.304	2.1
Expressive Language	31.67	10.693	60.67	11.765	19	0.796	13	0.796	2.5
Social Communication Questionnaire									
Total	53.43	7.613	52	2.558	19	0.605	17	0.04	0.3
Communication	18.86	4.18	16.42	1.165	19	1.933	17	0.02	0.8
Social	18.86	1.952	16.08	0.669	19	4.563	17	0.02	1.9
Restrictive and Repetitive Behaviour	11	1.732	15.08	1.73	19	-4.961	17	0.89	2.4

Table 3 displays all channels found to be significant in the backward regression analysis. Only significant group effects are reported in Table 3.

Table 3 Signficant Channels Identified in Backward Regression *Model*

Channel	*Location*	*Brain Region*	*Condition*	*Oxy/dexoy*	*R*	*Adjusted R^2 (SE)*	*f^2*	*Predictors*	*% Variance*	*Std Beta Coef*	*p*	*FDR*
1 (D1-S1)	C3-CP3	L Inferior Parietal & Postcentral Gyrus	Social	Oxy Hb	0.85	.600 (.0123)	5.6	SCQ Social	23%	1.028	0.024	0.034
								MSEL Expressive Language	34%	-1.605	0.009	0.020
								Diagnosis	64%	1.516	0.001	0.004
6 (D2-S3)	C5-CP5	L Superior Temporal & Supramarginal Gyrus	Non-Social	Deoxy-Hb	0.817	.556 (.0343)	4.4	Diagnosis	31%	-0.832	0.018	0.030
								SCQ Social	49%	-1.159	0.005	0.016
								SCQ Communication	49%	0.813	0.005	0.015
			Non-Social	Oxy Hb	0.91	0.771(.0956)	10.1	SCQ Social	19%	0.716	0.012	0.022
								SCQ Communication	39%	-0.725	0.001	0.002
								Diagnosis	52%	1.08	0.001	0.001
8 (D4-S3)	CP5-TP7	L Middle & Superior Temporal Gyrus	Non-Social	Oxy Hb	0.925	0.766 (.0122)	12.33	SCQ Social	9%	-0.791	0.027	0.038
								Gender	23%	-0.44	0.024	0.034
								MSEL Receptive Language	14%	-1.307	0.024	0.033
								Diagnosis	26%	-1.005	0.005	0.012
								MSEL Expressive Language	54%	2.043	0.001	0.003
15 (D5-S7)	CP6-CP4	R Inferior Parietal & Supramarginal Gyrus	Social	Deoxy-Hb	0.758	.458 (.0430)	3.1	Diagnosis	50%	-1.1	0.004	0.010
								MSEL Expressive Language	48%	1.104	0.005	0.014
			Social	Oxy Hb	0.748	.439 (.0780)	2.96	Diagnosis	31%	0.707	0.018	0.030
								MSEL Expressive Language	36%	-0.96	0.012	0.020
								Gender	40%	0.685	0.009	0.021
16 (D6-S7)	CP6-C6	R Superior Temporal & Supramarginal Gyrus	Social	Oxy Hb	0.778	.487 (.0903)	3.5	Diagnosis	24%	0.867	0.034	0.044
								SCQ Communication	38%	0.902	0.011	0.020
18 (D8-S7)	CP6-TP8	R Middle & Superior Temporal Gyrus	Social	Deoxy-Hb	0.726	.410 (.0483)	0.264	Gender	22%	-0.514	0.037	0.045
								Diagnosis	40%	-1.044	0.008	0.019
								MSEL Expressive Language	47%	1.136	0.005	0.014
			Non-Social	Deoxy-Hb	0.637	.257 (.0762)	1.75	Diagnosis	22%	0.772	0.058	0.050
								Gender	27%	-0.906	0.038	0.045
								MSEL Expressive Language	30%	0.571	0.03	0.043

We then conducted a backwards regression for the specified predictor variables at each site. This analysis revealed three significant predictors of oxy-Hb concentration at the left Inferior Parietal and Postcentral Gyrus (Channel 1) during the social condition (see Table 3). Specifically, diagnostic group accounted for the largest percentage of variance (64%), followed by MSEL expressive language (34%) and SCQ social (23%). A robust negative relationship between oxy-Hb and expressive language was found, suggesting that expressive language performance was inversely related to oxy-Hb overall.

A follow-up ANCOVA analysis was then conducted as a preliminary exploration of these significant differences. The analysis showed a significant difference between groups ($F(1, 10) = 14.584$, $p = .003$), as the children with ASD displayed a relative decrease in oxy-Hb ($M = -.0472$ SD = .022) at Channel 1, compared to a slight relative increase (M= .0165, SD = .018) for typically developing children. MSEL

expressive language performance was also found to be a significant covariate (F (1, 10) = 8.599, p = .015).

For the non-social condition, two significant predictors of deoxy-Hb concentration at the left Superior Temporal and Supramarginal Gyrus (Channel 6) (see Table 3) were also identified. SCQ social and SCQ communication accounted for the largest percentage of variance (49%), followed by diagnostic group (31%).

ANCOVA analysis showed a significant difference between groups at channel six (F (1, 11) = 12.426, p = .005). Children with ASD displayed a relative increase in deoxy-Hb (*M* = 6.528 *SD* = .021) at Channel 6, compared to a relative decrease (*M* = -4.44 *SD* = .056) for typically developing children. SCQ social performance (F (1, 11) = 14.849, p =.003) and SCQ communication performance were found to be significant covariates (F (1, 10) = 18.654, p = .001).

Diagnostic group, SCQ communication and SCQ Social were found to significantly predict oxy-Hb concentration at Channel 6 during the non-social condition (see Table 3). The largest percentage of variance was accounted for by diagnostic group (52%), followed by the SCQ Communication (39%) and SCQ Social (19%) subscales. A positive relationship where increased SCQ social performance for the TD group was associated with increased oxy-Hb. In contrast, a negative relationship for the ASD group where decreased social performance was associated with decreased oxy-Hb was found for the ASD group. Decreased communication performance on the SCQ was also related to decreasing oxy-Hb for both groups.

Significant differences between groups was found (F (1, 11) = 23.182, p = .001). Specifically, children with ASD displayed a relative decrease in oxy-Hb (*M* = -3.43; *SD*

= .013) at Channel 6, compared to a relative increase (*M* = 0.013 *SD* = .015) for typically developing children. Both SCQ Social (F (1, 11) = 9.421, p =.011) and SCQ Communication (F (1, 10) = 16.622, p = .002) were significant covariates.

Significant predictors of oxy-Hb concentration at the left Middle and Superior Temporal Gyrus (Channel 8) during the non-social condition were found (see Table 3). MSEL expressive language accounted for the largest percentage of variance (54%), followed by group (26%), MSEL receptive language (14%) and SCQ social (9%). Decreasing social performance was related to increasing oxy-Hb for the ASD group compared to the TD group. Furthermore, increasing receptive language performance was related to increasing oxy-Hb in the TD and control group. Increasing expressive language performance was also related to increasing oxy-Hb in the TD and control group.

Further analysis revealed a significant difference between groups (F (1, 9) = 5.449, p = .044). Children with ASD displayed a relatively larger increase in oxy-Hb (*M* = .025 *SD* = .015) at Channel 8, compared to typically developing children (*M* = .021 *SD* = .027). SCQ Social (F (1, 9) = 5.840, p = .039). MSEL receptive language (F (1, 9) = 9.768, p = .012) and MSEL expressive language (F (1, 9) = 19.675, p = .002) were all found to be significant covariates.

Two significant predictors of deoxy-Hb concentration at the right Inferior Parietal and Supramarginal Gyrus (Channel 15) during the social condition were identified. The largest percentage of variance was accounted for by Diagnostic group (50%), followed by MSEL expressive language (48%). Increased expressive language performance was found to be associated with increasing deoxy-Hb for the TD and ASD group.

Significant group differences were found (F (1, 12) = 7.098, p = .021), where children with ASD displayed a relative increase in deoxy-Hb (*M* = .011 *SD* = .036) at Channel 15, compared to a relative decrease (*M* = -6.1 *SD* = .061) for typically developing children. Significant covariates included MSEL expressive language performance (F (1, 11) = 9.421, p =.011).

Backward regression analysis also identified three significant predictors of oxy-Hb concentration at the right Inferior Parietal and Supramarginal Gyrus (Channel 15) and at the right Superior Temporal and Supramarginal Gyrus (Channel 16) during the social condition (see Table 3). Similarly, significant predictors of deoxy-Hb concentration at the right Middle and Superior Temporal Gyrus (Channel 18) during the non-social condition and at the right Middle and Superior Temporal Gyrus (Channel 18) during the social condition were found (see Table 3). However, no significant differences between diagnostic groups were evident after a follow-up analysis was conducted.

Discussion

The current study examined and explored differences in brain activity across the temporo-parietal region between children with ASD and typically developing children using fNIRS. Overall our findings demonstrate that there are differences in the haemodynamic response between children with ASD and typically developing children that may be linked to social and communication abilities. Furthermore, the difference in haemodynamic activity between the ASD and typically developing group was evident during both the social and non-social conditions. Collectively, this differential

haemodynamic response between the groups may indicate that children on the autism spectrum are underutilising brain regions involved in processing social information.

Significant differences in oxy-Hb concentration were found between groups in the left inferior parietal/postcentral gyrus (Channel one) during the social condition. More specifically, the typically developing group displayed greater haemodynamic activity compared to the ASD group. This finding is in line with previous research which has also shown that children with ASD have a decresed haemodynamic response in inferior parietal/postcentral gyrus while viewing social stimuli (Fox et al., 2013; Lloyd-Fox et al., 2013). The results indicate that there may be a link between relatively decreased activity in the left Inferior Parietal and Postcentral Gyrus, during tasks utilising dynamic social stimuli for children with ASD. As the inferior parietal and postcentral gyrus are responsible for the perception of emotions in facial stimuli (Braukmann et al., 2018), it is possible that children with ASD may not processing facial information in the same regions of the brain as typically developing children. In the current study, this relationship was also moderated by expressive language scores. Specifically, lower expressive language scores were associated with greater oxy-Hb concentration overall. This finding is in contrast to previous research showing that increased autism severity is related to decreased, rather than an increase, in brain activity during social processing (Dawson et al. 2012; Lloyd Fox et al. 2013; Kita et al. 2011). It is possible that, in general, children with lower expressive language scores may be utilising different brain regions such as the Inferior Parietal and Postcentral Gyrus that are primarily involved in facial emotional processing and not traditionally related to language.

A significant difference in deoxy-Hb concentration was also found between the groups in the right inferior parietal and supramarginal gyrus (channel 15) during the social condition. In particular, children with ASD displayed greater deoxy-Hb concentration than typically developing children. This finding is in contrast to previous research indicating that both children and adults with ASD displayed decreased activity in temporal regions, specifically the STS (Fox et al., 2013; Lloyd-Fox et al., 2013; Lloyd-Fox et al., 2018). The right inferior parietal and supramarginal Gyrus have been found to be associated with general social and language processing (Bzdok et al., 2016). Collectively these findings may indicate that children with ASD are underutilising areas that process emotions and facial stimuli, such as the inferior parietal and postcentral gyrus (channel one). In contrast, they may be utilising more generalised social and language regions to process social information. This relationship between the right Inferior Parietal and Supramarginal Gyrus and social stimuli was also moderated by expressive language, where increased scores were related to increased deoxy-Hb across both groups. This finding is consistent with previous research where greater cortical activation was related to better social communication whilst viewing static social stimuli (Dawson et al., 2012) . The current research also extends on this previous research by utilising dynamic social stimuli. Therefore, our findings suggest that children with ASD with higher expressive language abilities may also be demonstrating greater deoxy-Hb concentration when viewing social information. Given that this relationship between increased expressive language abilities and increased haemodynamic response was only present in some children and not others, this suggests that there may be subgroups. Specifically these subgroups may be based on expressive language that moderates brain connectivity for social information. Further research examining this relationship will help to establish what developmental trajectories

children with ASD might have based on differences in expressive language. In turn, this may lead to more targeted supports that are specific to the child's needs.

A significant difference in oxy-Hb and deoxy-Hb were found between the groups in the left superior temporal and supramarginal gyrus (Channel six) during the non-social condition. Although the opposite results were found between oxy-Hb and deoxy-Hb across channel six, these findings actually demonstrate an archetypal haemodynamic response function (HRF) (Tachtsidis, 2016). As oxy-Hb and deoxy-Hb are interrelated, an increase in one and a decrease in the other concentration (e.g. increase in oxy-Hb and decrease in deoxy-Hb) is the most accurate inference of changes in brain activity. Overall, these results indicate that typically developing children showed greater oxy-Hb concentration than children with ASD. This finding implies that children with ASD may also be processing non-social information to a lesser extent in the left superior temporal and supramarginal gyrus compared to typically developing children or processing non-social information in other areas of the cortex. Furthermore, these results were moderated by SCQ communication and social scores. In particular, increased social scores for the typically developing group was associated with increased oxy-Hb and decreased SCQ social scores was associated with decreased oxy-Hb for the ASD group. Moreover, decreased SCQ communication scores were related to decreased oxy-Hb for both groups. Previous research has shown that children with ASD have reduced orienting to audio-visual information (Falck-Ytter et al. 2018). Furthermore, the left superior temporal and supramarginal gyrus is also involved in the integration of audio-visual information (Vander Wyk et al. 2010). Therefore, it may also be case that children with ASD may have a reduced response to the type of stimuli (social and non-social) and the integration of audio-visual stimuli.

Another significant difference in oxy-Hb was found between the groups in the left Middle and Superior Temporal Gyrus (Channel eight) during the non-social condition. In particular, children with ASD displayed greater oxy-Hb concentration than typically developing children. This finding indicates that children with ASD are processing non-social information in the left Middle and Superior Temporal Gyrus, an area involved in processing social information (Pelphrey et al., 2011). In line with the social brain network, these findings suggest that children with ASD may have impaired specialised functions in the brain circuitry involved in social communication (Pelphrey et al., 2011). This impairment may lead to different neural responses towards social and non-social stimuli (Pelphrey et al., 2011). This relationship was also moderated by scores on receptive language, expressive language and social scores. Interestingly, in both groups, increased scores on receptive language and expressive language were related to increases in oxy-Hb. However, in the ASD group, increased social scores were related to decreased oxy-Hb. Collectively, these findings further suggests that children with ASD may be processing social information outside of the regions that are typically involved in social processing.

Limitations

There were a number of limitations that need to be addressed in the present study. Firstly, the number of children in the ASD group was small. Although a substantial number of children had consented to the study, many of the participants were unable to tolerate wearing the fNIRS cap. Although attempts were made to re-test these children, they still found this challenging. As the children who were unable to tolerate the fNIRS cap generally reported sensory issues specific to their head (i.e. difficulties with haircuts and wearing hats), our power to detect group differences in

haemodynamic activity was impaired. Therefore, the use of different neuroimaging techniques (fMRI and fNIRS) is advantageous to ensure all children (regardless of their symptoms) are included. This will increase our overall understanding of where activity is occurring and if this is different based on symptomatology. Secondly, the fNIRS cap only measured specific parts of the cortex and was not able to address sub cortical areas. It is also possible that activity is occurring in sub cortical areas of the brain that are not accessible to fNIRS (Lloyd-Fox et al., 2013; Wilcox & Biondi, 2015). This means that there may be activity occurring during the social non-social conditions that are being missed during the study that would be detected with the use of fMRI (Hernandez et al., 2015). However, findings from Chapter Five (review of fNIRS studies) indicated that there is an underconnectivity in regions that process social information. Therefore, it is uncertain if children with ASD in this study were showing decreased haemodynamic activity or were instead using atypical haemodynamic activity elsewhere in the brain (Lloyd-Fox et al., 2018).

Another potential limitation of the current research was that sound and visual stimuli were played concurrently to participants during fNIRS recording. While both sounds and stimuli can indicate social and non-social conditions, we were unable to differentiate if the children were perhaps preferencing sound over stimuli, or visual stimuli over sound. Previous studies have examined this by playing sounds in separate blocks or intermittently with stimuli. This allows sound and voice trials to be separately analysed and compared. Future research would benefit from a similar approach.

Future Research

Further research is needed to ascertain how differences on social outcomes between individuals with ASD impact haemodynamic activity. Given that these findings

indicate that social and communication scores impacts haemodynamic activity, the incorporation of more specific strategies and supports based around the child's social and communication needs may in turn lead to a greater haemodynamic response

Future research would also benefit from incorporating both fNIRS and fMRI paradigms in order to ascertain if individuals with ASD simply show a decrease in activity or if they are utilising different networks to process social information. This would further validate the findings of the present study, as well as allow for subcortical structures to be analysed. Consequently, this would increase our ability to detect differences between groups and further explore potential subgroups associated with social information processing in ASD. Longitudinal research is also important in order to allow for a more thorough examination of neurodevelopmental trajectories over time.

Conclusion

The present study investigated differences in brain activity across the temporo-parietal region between children with ASD and typically developing children using fNIRS. The findings suggest that typically developing children and children with ASD display different patterns of haemodynamic activity during the social and non-social conditions. Although preliminary, this suggests that children with ASD may potentially be underutilising brain regions typically involved in processing social information.

Furthermore, our findings showed that social and communication performance measures are related to haemodynamic outcomes. This indicates that a child's social and communication abilities may modulate their level of haemodynamic response to social stimuli. Furthermore, the current findings indicate that social and communication scores differentially impact haemodynamic activity for both children with ASD and typically

developing children. Therefore, these results highlight the need to further examine if these findings are in fact potential subgroups based on social and communication outcomes. With further research, this knowledge could lead to more specific approaches based on the understanding that social and communication outcomes may impact neurodevelopment differently.

Chapter Seven:

General Discussion

Overview of Findings

This thesis examined the impact of age, duration and intensity of treatment on ESDM intervention outcomes. It also investigated how children's initial language abilities impacted their outcomes after receiving the ESDM. In addition, the thesis sought to determine the differences in haemodynamic activity amongst children with ASD and typically developing children during social and non-social conditions. Additionally, the relationship between patterns of connectivity in parts of the social brain network and social and communication scores were explored. This thesis consists of five Chapters in the form of manuscripts.

Given that appropriate environmental input is highly critical for the development of specific skills during development, emphasis has been placed on early intervention for children with ASD . Through early intervention, children with ASD are able to gain additional access to a variety of social interactions and communication, allowing for increased cortical growth in specific regions of the brain (Bick & Nelson, 2017). The ESDM is an intervention approach that addresses the needs of infants and toddlers, aged between 12 and 60 months with ASD , and focuses on the acquisition and maintenance of social and communication skills (Jouen et al., 2017). The review in Chapter Two offer insights into the effectiveness of the ESDM and the specific outcomes that were found amongst studies utilising different durations. The studies reviewed ranged in duration from 10 to 24 months Another consistent finding was that children who started intervention at a younger age demonstrated better outcomes in social and communication skills, restrictive and repetitive behaviours, cognitive abilities and autism severity. This finding emphasises the importance of early diagnosis and early intervention. In general, the findings are promising in areas targeted by the therapy,

such as receptive and expressive language. This indicates that the social communicative focus of the ESDM is improving language abilities.

Chapter Three extended on this review by specifically examining the relationship between duration, intensity of intervention and age at enrolment and outcomes using the ESDM. The study utilised standardised measures that assessed adaptive behaviours, social and communication skills, fine motor and domestic skills. The findings of this study were consistent with the review, showing that younger age at enrolment and a longer duration of intervention were associated with improvements in specific outcomes in language and communication skills. In line with the review, most changes were shown in communication and language skills, closely mapping specific skills targeted by the ESDM. Interestingly, intensity of intervention was not associated with any outcomes in this study. Overall, this study supports the idea that specific factors and characteristics can influence outcomes for children with ASD who receive early intensive behavioural intervention.

Chapter Four examined initial verbal abilities and outcomes using the same dataset of outcome measures as Chapter Three. Utilising the same clinical measures as Chapter Three, the analysis showed that differences in initial verbal ability had an impact on specific outcomes after children received the ESDM. Our results suggest that better initial verbal abilities might increase outcomes in receptive and expressive language. Chapter Four provided evidence that children with better initial verbal abilities made increased gains in language related areas as they might be more responsive to a therapy style such as the ESDM that focuses on social interactions and communication. More specifically, these results suggest that having foundational language skills facilitates greater uptake of social and communication skills.

Chapter Five evaluated key fNIRS studies that examined brain function of individuals with ASD across a variety of tasks. These tasks included executive function, facial/emotional processing, joint attention and auditory/linguistic tasks. A number of preliminary findings were identified throughout the review. Firstly, fNIRS is able to measure differences in brain activity in young children with ASD and infants at increased genetic risk who have not yet developed full clinical symptoms. Secondly, the review demonstrated that fNIRS has the ability to measure functional cortical activity associated with specific tasks involving visual, auditory and linguistic stimuli. Thirdly, fNIRS studies were able to show that individuals with ASD were likely to have patterns of atypical and altered activity compared to typically developing children in tasks ranging from resting state to executive function and joint attention. Findings included reduction in haemodynamic activity within specific brain regions, differences bilaterally across parts of the cortex and a lack of cortical specialisation in certain areas of the brain.

Chapter Six extended on this review by investigating differences in the haemodynamic response across the temporo-parietal region between children with ASD and typically developing children using fNIRS. This Chapter also explored the relationship between the haemodynamic response and clinical measures assessing social outcomes. The findings suggest that children with ASD have a different pattern of haemodynamic activity compared to typically developing children during social and non-social tasks. The findings also indicate that social and communication measures are related to haemodynamic outcomes within and between groups. The research indicates that individuals with ASD with similar social and communication scores might have distinct neurodevelopmental trajectories which may be particularly helpful in predicting long-term outcomes and differing responses to intervention.

This thesis provides an in depth examination of the factors that are likely to influence intervention outcomes. For example, it was found that greater duration of intervention resulted in better outcomes in social skills. The same results were also found when children were enrolled at a younger age and when children started therapy with higher initial verbal abilities. This thesis also provided a comparison of the haemodynamic response to social stimuli and explored the relationships between the haemodynamic response and social and communication skills. The results of this thesis indicated that children with ASD may be underutilising areas that are typically used for processing social information. There was also evidence that social and communication scores differentially impacted haemodynamic activity of individuals with ASD . The findings bring to light the importance of understanding how specific factors can impact developmental trajectories and intervention outcomes as well as the important contribution this could have on the structure and delivery of therapy.

Predictors of intervention outcomes

A number of Chapters within this thesis provided evidence for the existence of specific factors that have an impact on intervention outcomes. Chapters Three and Four indicated that increased intervention duration, younger age of initiation of intervention and greater initial verbal ability led to better outcomes in the social domain. While there is a wealth of research indicating that early intervention leads to better outcomes for children with ASD , there is limited research examining how intervention duration and initial verbal abilities impact outcomes.

While the limited research examining duration of intervention on outcomes has found mixed results, the study outlined in Chapter Two found evidence in support of better outcomes with increased duration. In particular, the findings suggest that the

optimal duration of intervention is between 10 and 24 months for increased outcomes in various language skills such as expressive and receptive language. Furthermore, the research outlined in Chapter Three found that children who stayed in the ESDM for a longer amount of time were more likely to show improvements in specific outcomes in language and communication skills, specifically reciprocal language. In line with the review in Chapter Two, most changes were shown in communication and language skills, closely mapping specific skills targeted by the ESDM.

Collectively, these findings suggest that while duration improves overall outcomes, the specific target areas of the ESDM intervention resulted in specific gains. In particular, teaching specific social communicative skills aimed to enhance social attention, communication, joint attention and affect sharing (Eapen et al., 2013) resulted in gains within the communication domain. Specifically, this was evidenced by the reciprocal language subscale on the MSEL. Consequently, these Chapters contribute to the current knowledge base by demonstrating that there may be an optimal time that children with ASD should stay in therapy.

This has important implications for funding and social policies based around the recommended amount of time for which children with ASD should receive intervention. Findings in Chapter Four of the thesis indicate that initial verbal abilities are associated with better outcomes in expressive and receptive language. While there is lack of consistency in the literature regarding verbal abilities and outcomes, this may at least be partly due to the fact that behavioural interventions being examined are rather broad as opposed to specific, targeted intervention. However, the research detailed in Chapter Four involving children receiving the ESDM, a specialised intervention focusing on the acquisition and maintenance of social and communication skills, suggests that initial

verbal abilities may play a significant role in outcomes. Specifically, children with greater initial verbal abilities demonstrated increased outcomes in language related areas. Similar to the previous findings in Chapters Two and three, better outcomes were found across expressive and receptive language following ESDM intervention probably aided by the specific social and communicative focus of the ESDM.

Autism and the Social Brain Network

This thesis provided evidence for the atypical development of the social brain network, a subset of areas known to process social information, including the superior temporal sulcus (Johnson et al., 2005), in children with ASD. Chapter Six indicated that children with ASD showed decreased haemodynamic activity in the left Inferior Parietal and Postcentral Gyrus during the social condition. This research is in line with previous studies that consistently find an atypical brain response to visual and auditory social stimuli in individuals with ASD (Eyler et al., 2012; Gervain et al., 2011; Lloyd-Fox et al., 2018; Pelphrey et al., 2011; Zhu et al., 2015). Although an infant's experiences can alter their gene expression, which provides information regarding the growth and connectivity of neurons (Bick & Nelson, 2017), Chapter Six indicates that children with ASD might be utilising other more general language and social brain regions. In particular, Chapter Six found that children with ASD had a greater haemodynamic response to social stimuli in areas less specialised to language and social skills such as the right Inferior Parietal and Supramarginal Gyrus. This indicates that children with ASD may not be developing specialised functions in the brain circuitry specifically involved in social communication (Johnson et al., 2005). Although typical growth and connectivity may be disrupted, it is perhaps the case that children with ASD are able to

make new and unique connections as a result of new experiences brought about by therapy.

Emerging research indicates that social and communication scores may impact brain activity in parts of the social brain network. In particular, Dawson et al. (2012) found a relationship between greater cortical activation and fewer social pragmatic problems (social interactions and social conventions) and better social communication in children with ASD while viewing static social stimuli. Similarly, our research indicated that children with ASD with lower expressive language abilities showed increased oxy-Hb in the left Inferior Parietal and Postcentral Gyrus. Furthermore, children with ASD with increased expressive language scores also showed increased deoxy-Hb across the right Inferior Parietal and Supramarginal Gyrus. There are a number of implications for this pattern of findings. Firstly, these findings may indicate that a child's social and communication abilities determine the level of haemodynamic activity in these areas. Secondly, that social and communication abilities might play a role in the dysregulation of neuroanatomic structures within the social brain network (Kita et al., 2011). In other words, a child's social and communication abilities may impact the haemodynamic response shown in specific parts of the cortex. Lastly, this relationship between expressive language and areas of the social brain network could indicate ASD subgroups. If this is the case, subgroups based on neuroanatomical and clinical characteristics could lead to more targeted interventions for children with ASD that is unique to their subgroup needs.

Clinical Implications

Collectively, the factors examined throughout the Chapters in this thesis contribute to our understanding and conceptualisation of how young children with ASD

respond to intervention. As a result, consideration of these factors could improve the design, implementation, and evaluation of the interventions that children receive. Consequently, this could reduce and eliminate disparities in outcomes and allow for more children with ASD to receive greater benefits from intervention. In particular, Chapters Two and Three provide further evidence that could potentially inform policies around the optimal age when children should be enrolled for intervention and the amount of time that children should receive intervention.

Further, the research outlined in Chapter Four suggests that children's initial verbal abilities may have a significant role in determining the outcomes, particularly in receptive language. The finding that children receiving the ESDM intervention may have disparate outcomes based on their initial verbal skills has implications for clinical practice, as an understanding of a child's initial verbal abilities at enrolment could be considered when designing and implementing intervention plans. In this way, children with ASD can be appropriately matched to receive intervention that is specific to their needs and starting at a level that is suitable to their initial abilities.

There are two possible ways in which services could be tailored to initial abilities. The first possibility is that some children with ASD with lower language abilities receive intensive speech therapy prior the ESDM. Initially, assessments would be administered prior to intervention to capture baseline language skills of each child. This would assist with identifying which children with ASD may require language assistance prior to intervention. These identified children would receive a tailored language intervention before commencing the ESDM therapy. If improvements are found in language skills at the end of the intervention, they could commence ESDM therapy. Given that this approach would control for differences in language abilities,

future research would be able to examine the efficacy of the intervention and the subsequent outcomes.

The second approach is related to the modification of the ESDM therapy and tailoring the delivery to the child's abilities. If a child had received language intervention and minimal progress had occurred, a modified version of the ESDM could be administered to accelerate the acquisition of communication and social skills. A combination of both naturalistic and behavioural interactions could be used to promote social attention and social reward. (Hayward, Gale, & Eikeseth, 2009; Koegel, Koegel, Harrower, & Carter, 1999). For children with language difficulties, the same principals could be utilised, however, these learning opportunities could be specific to language related tasks. Future research would benefit from examining outcomes from a more tailored ESDM approach for children who experience language difficulties. Chapters Five and six provide evidence of the versatility of fNIRS, and its capacity to identify differential haemodynamic responses between children with ASD and typically developing children. In Chapter Six, the examination of the haemodynamic response was completed using a portable fNIRS device in an environment that was familiar to the children. Parents also had the option to have their child sit on their lap during the fNIRS session. The results of Chapter Six also indicate that children on the spectrum may be underutilising areas of the brain that are known to process social stimuli. Further to this, the findings demonstrate that social and communication abilities may differentially impact haemodynamic outcomes between children with ASD and typically developing children. Taken together, these findings suggest that fNIRS can successfully examine the haemodynamic response between different clinical groups in an ecologically valid environment that may be otherwise difficult to obtain with other neuroimaging techniques.

Limitations

There were a number of limitations within the datasets used within this thesis. Firstly, there was missing data in relation to the scales and assessments utilised in Chapters Three and Four. Furthermore, some scales such as parent completed VABS were excluded from analysis due to very low numbers. However, this is a reflection of the reality of data collection within clinical populations. While a number of scales and assessments were still available for the analysis, future research with a more complete data set would be ideal. This would assist in gaining a better understanding of the factors that influence intervention outcomes and associations between brain connectivity and subsequent clinical presentations.

It is to be noted that research detailed in Chapters Three and Four did not include a control group, and hence it is not possible to definitively attribute the changes made over time to the intervention rather than maturation over time. The inclusion of a control group within these studies would have provided a more robust study design through which to assess the relationships of interest. Moreover, the addition of a comparison group (children with ASD who received a different therapy) would also help to evaluate whether these outcomes are unique to children receiving the ESDM or apply to other EIBI models.

Furthermore, the accuracy of the results in Chapters Three and Four could have been improved if less third-party rating scales were utilised and blinding to the research question occurred. Although two assessments were administered by a trained researcher with the child, a number of assessments were completed by a parent. Further to this, all assessments were administered by researchers who were aware of the general research

question. Collectively, direct assessments and blinding would have improved the accuracy of the data collected (overestimation) and reduced the risk of bias.

The fNIRS study was limited by the small number of children in the ASD group. Although initially a substantial number of children had signed up for the study, many of the children were unable to tolerate wearing the fNIRS cap. This was mainly due to the children's sensory issues. Although attempts were made at a subsequent time point to re-test these children, they were still unable to tolerate the fNIRS cap. Given that most children with sensory sensitivities were unable to participate in the study, it is possible that further associations between brain activity and clinical presentations may have been missed. For instance, in Chapter Six, expressive language was found to be related to haemodynamic activity. However, further conclusions regarding potential subgroups based on expressive language outcomes could not be made due to the low number of participants in the ASD group. With the inclusion of more children in the ASD group, the study might have been able to more definitively examine associations between haemodynamic activity and differences in social measures.

Conclusions

This thesis utilised clinical measures to examine factors that impacted intervention outcomes. It also utilised fNIRS to investigate differences in haemodynamic activity between children with ASD and typically developing children during social conditions. The thesis also explored the relationship between haemodynamic activity and social and communication abilities. The results obtained provide support for better outcomes in social and communication skills for children receiving the ESDM intervention. In particular better outcomes are found with increased duration, younger age at enrolment and greater initial verbal abilities. This thesis also

demonstrated that children with ASD showed atypical functioning in parts of the social brain network compared to typically developing children. It also provided evidence that social and communication abilities impact specific haemodynamic activity differentially between children with ASD and typically developing children. Taken together, this demonstrates that children with ASD may have impairments in social and communication abilities which impacts brain connectivity. Ultimately, this may have implications for treatment outcomes; however, specific factors appear to play a critical role in determining outcomes. This has significant implications for clinical facilities where these factors could be considered at diagnosis and prior to the commencement of therapy.

Furthermore, the finding that children with ASD have an atypical haemodynamic response to social stimuli that is moderated by social and communication abilities also has significant implications. These results imply that social and communication performance impacts the haemodynamic response differentially. In turn, these results suggest that there might be underlying subgroups based on preference to social and non-social stimuli and associated social and communication abilities. With these findings in mind, future research should examine brain activity as well as social and communication abilities over time. This will assist in establishing where baseline brain activity is occurring and how this might change for children who receive a specialised intervention. Furthermore, a longitudinal design will help to further investigate how differential social and communication skills impacts brain activity overtime. Overall, this thesis provides important implications for future clinical practice and research by expanding our understanding of the factors that impact intervention outcomes and how children with ASD might be processing social information.

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Appendix A

fNIRS ASD Study Protocol

List of equipment

Surface Pro

Surface Pro charger

Presentation laptop

Presentation laptop charger

Presentation USB Licence key

Laptop parallel port adaptor

Display monitor

Monitor, VGA and power cables

NIRSPORT device

Trigger cable

fNIRS cap/s with grommets

fNIRS cap of shower cap

Optode sets

fNIRS USB cable

Trigger Cable Measuring tape

NIRSport baseplate

Back pack

Procedure

Participant recruitment & preliminary head measurement

- Inform parents of the study (distribute information sheets/ attend information events)
- Ask parents/participant if they have any questions
- Ask them to read and sign consent forms if they decide to participate
- If feasible, measure the child's head circumference and record it

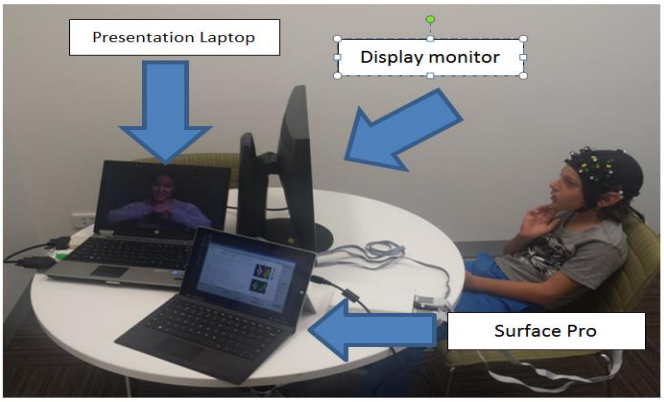
Session 1 - Screening & practice session

- Set up room as a testing environment (see below)
- Introduce the people in the room who will be helping with testing
- Explain the study and procedure to parents and child
- Give protocol booklet to parents to read with child being tested
- Let child familiarise themselves with the dummy cap (old EEG caps)
- Measure child's head circumference for correct fNIRS cap size selection
- Place fNIRS cap on child's head and perform a mock set up:
    - Fit the appropriate cap over child's head
    - Play movie on laptop while they wear the cap
    - Monitor child as they wear cap for ten minutes while watching a movie - If child is able to sit and tolerate cap while watching a movie then book a test session for child.
- Ask parents if there are any individualised approaches that may help during testing
- Follow this up through:
    - Phone call with parents
    - Questions
    - Ask during preparation session what the best approach with their child is
    - Ask if there are any possible treats or reinforcements that could be used

Room and equipment setup <u>before</u> session 2 begins

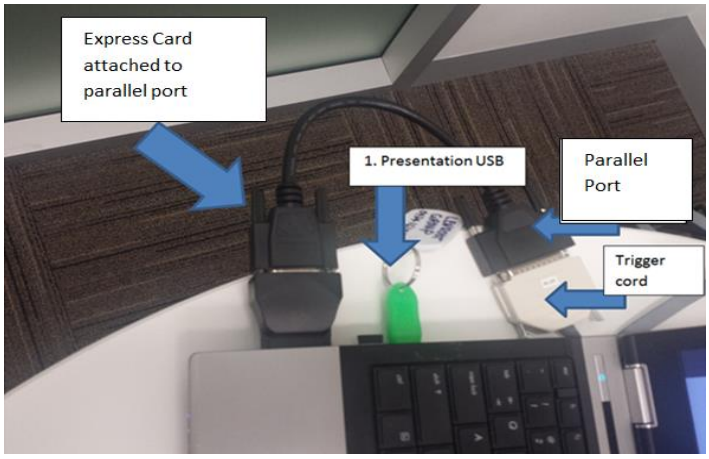
- **Room Setup**
    - Place desk and a suitable number of chairs in the testing room
    - Arrange the table so that it is located near wall power outlets, and away from windows
    - Arrange chairs so that the experimenter is opposite the participant/parent
    - Remove any potential distractions from the room
    - Close blinds and dim or turn off lights to reduce the risk of ambient light contamination

- **Equipment setup - Surface Pro, Presentation Laptop and Monitor**
    - Position the Surface Pro and Presentation laptop at one end of the table facing the experimenter's chair (See picture below)

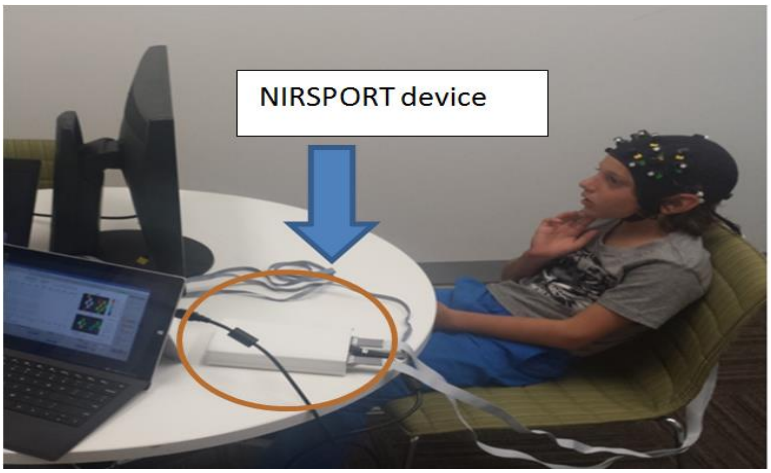


    - Connect the respective chargers to the Surface Pro and the Presentation laptop and plug their power cables into the power board or wall outlets
    - Position the monitor at the opposite end of the table facing the participant's chair
    - Connect the monitor power cable to the back of the monitor and insert the other end into the wall outlet
    - Ensure one end of the VGA cable (blue tip cord) is plugged into the display screen and the other end is plugged into the presentation laptop (see pictures below)

    - Insert the parallel port adaptor into the ExpressCard slot on the left side of the Presentation laptop (it will lock into place with a "click")Insert the Presentation USB license key into a USB port of the side of the Presentation laptop (see picture below)

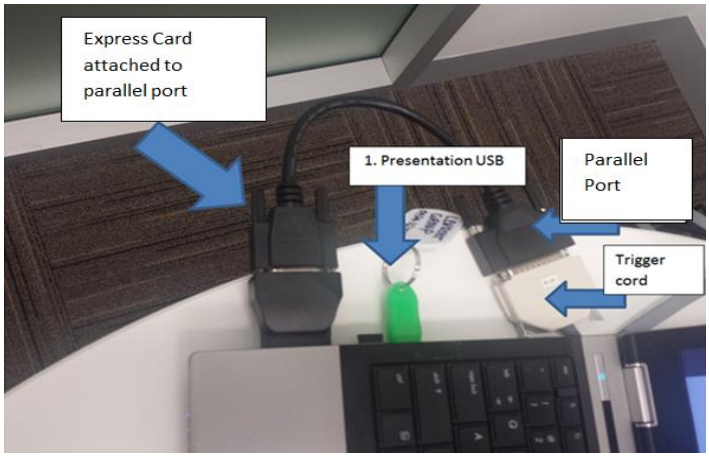


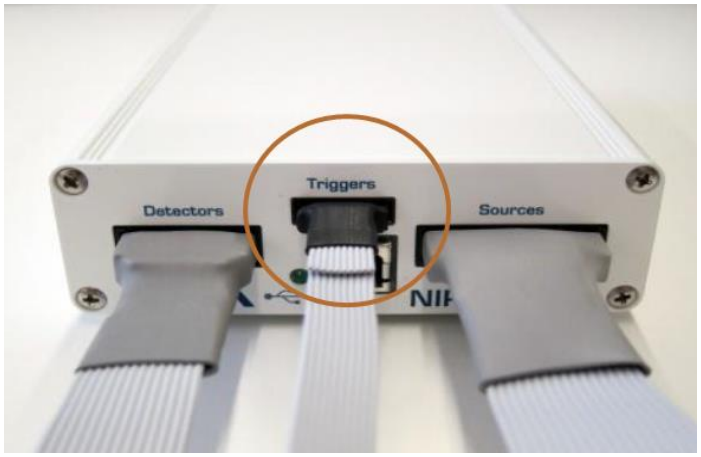
- **Equipment setup – NIRSPort device**
    - Position the NIRSport device near the monitor on the desk in front of participant's chair (See picture below)



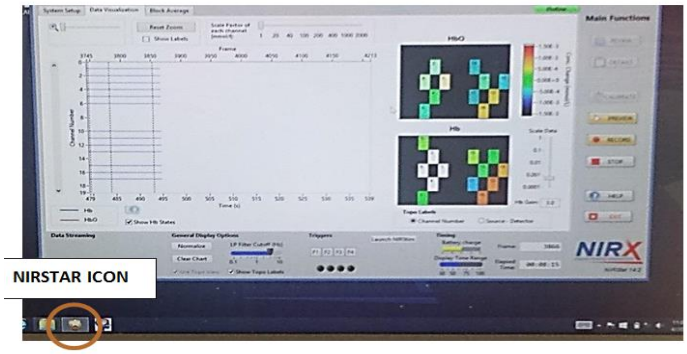
    - Connect the NIRSPort charger cable to back of the NIRSPort device and insert the other end into the power board or wall outlets
    - Insert the square end of the USB cable into the port on the front of the NIRSPort device and insert the flat end of the cable into the USB port on the Surface Pro (see picture below)

- Once connected the system goes through a start-up sequence during which the green status indicator lights up and then starts to blink. At this point, the data link to the host PC is established.
- A green blinking LED in the front panel signifies proper USB connection and readiness for operation. The green LED will keep blinking all through system operation until the USB connection is terminated.
- A dark or continuously lit green LED signifies connection problems
- Connect the larger end of the trigger cable to the parallel port on the Presentation laptop and insert the smaller end into the “Triggers” port on the front of the NIRSPort device (see picture below)

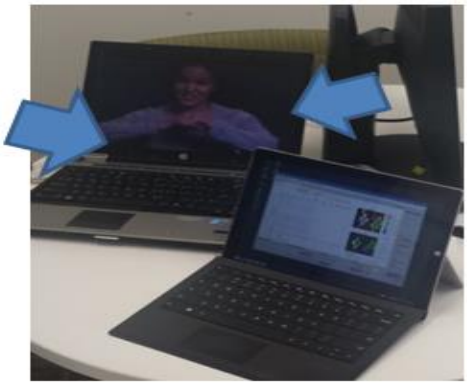


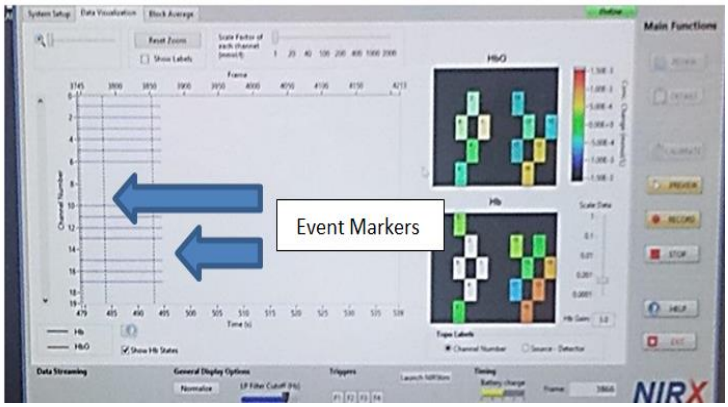


- **Equipment start-up**
  - Turn on power at wall outlets/powerboard for Surface Pro, Presentation laptop and NIRSPort device
  - Turn on Surface Pro and enter password “NIRSPort”
  - Turn on Presentation Laptop, no password required
  - Open NIRStar software on the Surface Pro (pictured below)

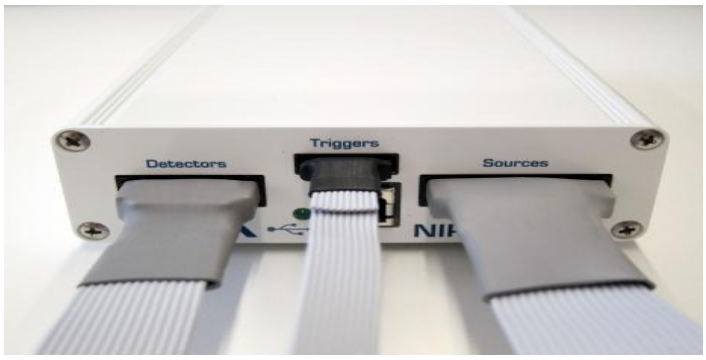


  - Open Presentation software on Presentation laptop
- **Equipment check**
  - Confirm that sound is enabled on the Presentation laptop
  - Confirm that the screen of the Presentation laptop is mirrored on the external monitor
  - Confirm that NIRSPort is functional by starting a “Preview” recording session in NIRStar
  - Confirm that Presentation is functional by selecting and running the “Social.exp” file in the “soc_toy” folder on the desktop of the Presentation laptop – video stimuli should be visible on the external monitor (with sound) (see picture below) and event markers should be visible as vertical lines in NIRStar recording preview (see picture below). If markers not visible check that the trigger cable and express card is connected correctly at both ends.



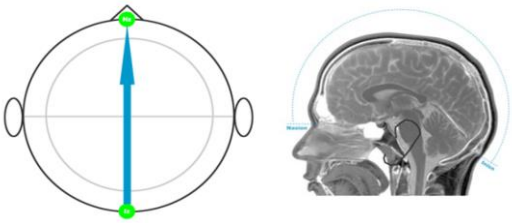


- **Connect NIRS cap**
    - Plug detectors and sources cords that are attached to the cap into NIRSport device (Pictured below)
    - If you are using the backpack, have it ready to store Surface Pro and NIRSport device into baseplate

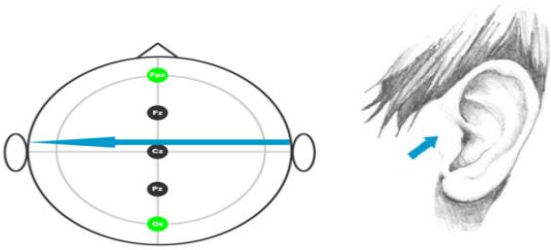


Session 2 -Testing

- Greet child and caregiver
- If child's parent/caregiver/teacher is attending the testing session, ask caregiver if the child would like to sit on their lap throughout the experiment. If not, guide child to seat.
- Place the correct size fNIRS cap on the child's head based on previous head measurements in session 1
- Measure the midpoint of the brain using measuring tape to measure:
- From the nasian (the bridge of the nose) to inian (Bump located at the back of the skull) over the head- mark mid-point on cap (see picture below)

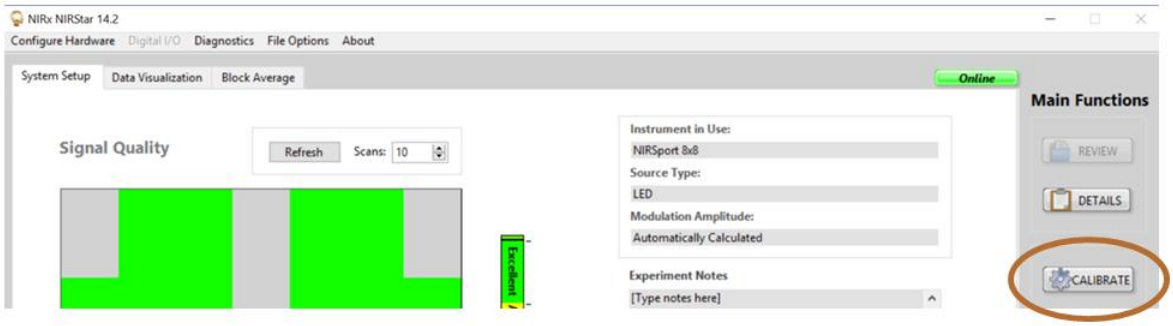


- From the left and right peraicular joints (where the jaw connects with the skull)- mark on cap

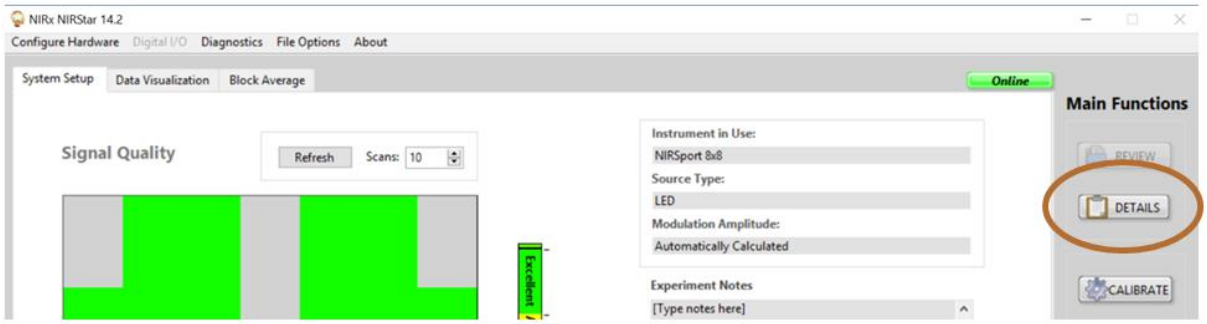


- Determine CZ by the intersection of these two midlines- mark on cap

- Adjust the fNIRS cap until the CZ spot is aligned
- Ensure room is dim so that the light does not interfere with participants probes
- **NOTE: BEFORE TESTING, REMOVE ALL CHARGERS FROM DEVICES USED IN THIS EXPERIMENT!**
- Return to "NIRSTAR software" on the Surface Pro:
- Press calibrate on front screen

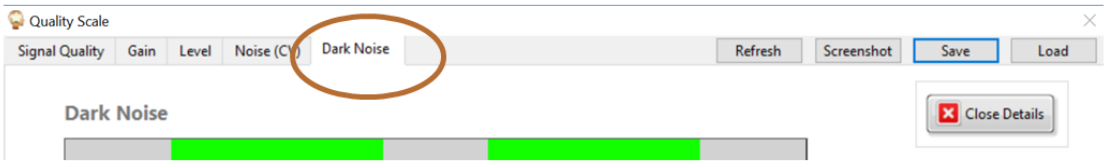


- Once calibration is complete, click on details from the right hand menu on the front screen (see picture below)



- Check Signal Quality, Gain, Level and Noise (Pictured Below)

- Check dark noise (see picture below)



- If any signals are displaying **red or white within the squares**, adjust the following items
    - lighting, turn lights off in the room
    - ensure all chargers are removed from devices
    - Adjust sources and detectors on the head
    - Fit the participant with an overcap/ dark shower cap
    - Press the calibrate button again(ask participant to remain still)
    - Check quality of signals again and adjust accordingly
- Once signal quality is mostly green with no red or white squares showing, close the details window and start recording.
- Press Record on the NIRSTAR program (remember to add participants details when asked)
- Go to presentation laptop
- Start the experiment in "Presentation"
- Remember to add participants name into presentation when asked (this happens just before the experiment runs)
- **NOTE: before leaving the room, ensure markers are being shown on display screen in NIRSTAR when stimuli starts!**
- Run time of the experiment is around 15 minutes
- Stop recording when all stimuli (video/auditory) has ended
- Check files are placed correctly into the data folder on the Surface Pro

What will happen after testing?

- Slowly remove the cap
- Tell parent and child that this part of the experiment is now complete
- Remind parent/s to complete parent questionnaires and to drop completed questionnaires to the preschool reception or post the questionnaires back to the person collecting them.
- If the participant came with preschool worker- return participant to their classroom

Appendix B

Preschool	Included/ excluded	Initials Identifier	Date of Testing	Head size	Assessment complete	ADOS complete	MSEL complete	Days	Comments
Children with ASD									
Liverpool KU Autism	Included	JP 2016-12-21_001	21st Dec 2016	51	Yes	Yes	Yes	Mon/Thu	Completed
	Excluded	SM	21st April 2017	52	Yes	Yes	Yes	Thu/ Fri	Was able to wear cap for small amounts of time while being distracted with lollies. Only sat through 5 minutes of video before becoming upset and restless.
	Excluded	JK	22nd April 2017	53	Yes	Yes	Yes	Mon/ Tue	Mock scan unable to complete, would not sit in chair, or stay in room. Became very upset and unable to settle. Refused cap after several attempts
	Excluded	DC	April 18th 2017	53	Yes	Yes	Yes	Mon/Tue/wed	Re-book at later date Became very unhappy during assessment, unable to keep cap on head for longer than a minute. Mock scan- unable to complete- walked around room, wouldn't sit in chair, asked if he wanted to put on cap, he replied "NO" several times. Spoke with Loan who said he no longer wore hats
	Excluded	DS	21st April 2017	51	Yes	Yes	Yes	Wed/Thu/Fri	Did not want to keep cap on head. Wore cap for 1 minute then attempted to remove cap during assessment. Was able to communicate well with his mother. Became aggressive and upset
	Included	VT 2017-05-01_001	1st May 2017	50	Yes	Yes	Yes	Mon/Tue	Assessment 100% complete
	Excluded	DP		53	Yes	Yes	Yes	Wed/thu/fri	Dylan's mum said he would not sit through the session and pulled out of study
	Excluded	WW		52	Yes	Yes	Yes	Wed/thu/fri	Mother states Wally doesn't like hats and people touching his head
	Excluded	MS		53	Yes	Yes	Yes	Mon/Tue	Mock scan incomplete. Maddison sat in chair, watched some of the show presented but yelled "no" several times when asked if the cap could be placed on her head. She then became restless and ran around the room.
	Excluded	JF	-		Yes	Yes	Yes	All week	Excluded based on behaviours during the ADOS/MULLENS

KU Briar Autism	Included	GF 2017-12-07_002	7th dec 2017 9.30am	50	Yes	Yes	Yes	THUR/FRI & every second WED	Assessments complete
	Excluded	CC	7th Dec 9am	51	No	Yes	Yes	THUR/FRI & every second WED	Unable to sit through testing session longer than 5 minutes. CC wore cap for 5 minutes then it had to be removed
	Included	CD 2017-12-07_003	7th DEC 10:00am	50	Yes	Yes	Yes	THUR/FRI & every second WED	Assessments completed
	Included	PE 2017-11-21_002	21st Nov 2017 10am	50	Yes	Yes	Yes	THUR/FRI & every second WED	Assessments completed
	Included	Christopher McLeod 2017-11-21_001	Tuesday 9.30am 21st Nov		Yes	Yes	Yes	MON/TUE and alternate WED	Assessments Completed
	Included	JB 2017-12-07_004	THUR 7th Dec 10:30AM		Yes	Yes	Yes	Mon and Tues one week and Mon/Tue/Wed following week	Assessments Completed
Typically Developing Children									
KU Liverpool TD	Included	JA 2017-08-29_001	29th August 9.30am	52	No	N/A	Yes	Mon/Tue	Assessments Completed
	Included	IK 2017-08-29_002	31st July 10:30	51	No	N/A	Yes	Mon/Tue	Assessments Completed
	Included	AS 2017-08-29_003	1.45pm 29th August		No	N/A	Yes	Tue/Wed	Assessments Completed
		Tuesday							
UNSW TD	Included	FV 2017-11-07_002	Tue 7th Nov 10:19am		Yes	N/A	Yes	DOB 8/11/2012	Assessments Completed
	Included	EM 2017-11-07_003	Tue 7th Nov 1pm		Yes	N/A	Yes	DOB 21/11/2012	Assessments Completed

	Included	SB 2017-11-07_004	Tue 7th Nov 3.30pm		Yes	N/A	Yes	DOB 11/11/12	Assessments Completed
		Wednesday							
	Included	RL 2017-11-08_001	Wed 8th Nov 8.30am		Yes	N/A	Yes	DOB 14/11/2013	Assessments Completed
	Included	NR 2017-11-08_002	Wed 8th 3.30		Yes	N/A	Yes	DOB 17/2/2011	Assessments Completed
		Thursday							
	Included	AB 2017-11-09_001	Thurs 9th Nov 8:15am		Yes	N/A	Yes	DOB 23/05/2013	Assessments Completed
	Included	ME 2017-11-09_002	Thurs 9th Nov 9.30am		Yes	N/A	Yes	DOB 13/11/2013	Assessments Completed
		Tuesday							
	Included	AP 2017-11-09_003 And NIRS-2017-11-13_002	Thurs 9th AND Monday 13th Nov 9am		Yes	N/A	Yes	DOB 15/04/2013	Assessments Completed (Second assessment completed as recording stopped during first session)
	Included	JR NIRS-2017-11-13_003	Monday 13th Nov 10am		Yes	N/A	Yes	DOB 25/3/2014	Assessments Completed

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Conflicts of interest

None