Chiropractic adjustments, multisensory and sensorimotor integration in children with autism: A feasibility and pilot study.

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A thesis submitted to Auckland University of Technology in partial fulfilment of the requirements for the degree of Master of Health Science, non-endorsed (MHSc)

23 January 2019

Faculty of Health and Environmental Sciences

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Abstract

Background: Autism spectrum disorder (ASD) is a neurodevelopmental disorder that is estimated to affect one in 160 people worldwide and one in 100 New Zealanders. The diagnostic focus of ASD is on dysfunction in communication and social interaction, though evidence shows many children with ASD also have motor control and co-ordination issues. A growing body of evidence suggests these issues may be related to impaired sensorimotor integration (SMI) and multisensory integration (MSI). Chiropractic adjustments have been shown to have neuromodulatory effects on SMI and MSI in adult populations; however, this has yet to be explored in children with ASD.

Objectives: The primary aim was to assess the feasibility of all trial processes. Secondary aims were to assess the feasibility of using a chiropractic intervention in children with ASD and to gather pilot data on preliminary efficacy.

Methods: Eight children with ASD aged 7-15 years were recruited into a randomised controlled pilot study with a parallel group design. All study processes were assessed including recruitment, retention, completion rate and suitability of tasks. Data for preliminary efficacy was also collected. MSI was assessed using the sound-induced flash illusion. SMI was assessed using three subtests of the sensory integration and praxis tests, as well as a fine motor task. Children randomised into the intervention group received a single session of chiropractic adjustments. Those in the control group received a passive spinal range of motion intervention. Baseline and post-

intervention measures were assessed on the same day. All sessions were approximately two hours in duration.

Results: Feasibility aspects of this study highlighted challenges in recruitment, with eight children recruited over an eight and a half month period. Completion rates of the sound-induced flash illusion were low. Retention rate was 100%, as was compliance with the intervention and there were no adverse events reported. There were no between group differences on any of the outcome measures assessed.

Conclusion: The current study protocol is not feasible for recruitment of children with ASD into a full-scale trial assessing associations between a chiropractic intervention and SMI and MSI in children with ASD. Further piloting would be necessary to determine the most successful recruitment methods and outcome measures to use in such a study.

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Attestation of Authorship

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgements), nor material which to a substantial extent has been submitted for the award of any other degree or diploma of a university or other institution of higher learning.

Signed: Date: 23rd January 2019

Acknowledgements

First and foremost, I would like to acknowledge my amazing supervision team: Dr Kelly Jones, Dr Heidi Haavik and Dr Kelly Holt. Thank you all so much for all your time, effort, encouragement and knowledge. You have all been so supportive over this long journey and have taught me so very much, for that I am eternally grateful. I couldn't have done it without you.

In the words of a mother of a child diagnosed with autism, "I was grieving the loss of my son and looking at this new challenge. I was going to have to deal with this for the rest of my life, and I had no hope, and it is only with minor little accomplishments that my son with autism made that I was able to regain the hope bit by bit." (Woodgate, Ateah, & Secco, 2008, p. 7). Thank you to all the children and their families who participated, as well as all those who showed interest in this study. I appreciate the challenges involved for each child and family participating in this study and am so grateful for your time and effort. Also, to the good people at Autism New Zealand, Chiropractors in Auckland and Student Interns at the New Zealand College of Chiropractic. Thank you for promoting the study and assisting in recruitment. Research and the expansion of scientific knowledge cannot take place without people like you.

I would also like to acknowledge all of my colleagues at the Centre for Chiropractic Research, especially Rasmus, Melanie and Imran for all your work in running data

collection and generally helping me through the whole process. This study would not have run without you.

Finally, I would like to acknowledge all of my family and friends who helped push me through this journey. Especially my partner Troy, my mother Lyndy and brother Karl, thank you for believing in me and encouraging me, even when I had doubts. Lastly to my father Alan, I hope this makes you proud. This is for all of you.

Ethics Approval

This study was registered with the Australian New Zealand Clinical Trials Registry (reference number: ACTRN12616001720404p). Ethical approval was granted by the Northern A Health and Disability Ethics Committee (reference number: 17/NTA/58) and the Auckland University of Technology Ethics Committee (reference number: 17/266).

Chapter Overview

Chapter one sets the scene for this thesis, introducing autism spectrum disorder (ASD) and highlighting the impact for families affected by the disorder. Followed by a brief overview of all topics explored in this thesis.

Chapter two provides background information on ASD: the prevalence, societal impact, etiology and current treatment options. Motor control issues found in ASD are also explored and linked with sensory motor integration (SMI), multisensory integration (MSI) and neurophysiological findings. Finally, chiropractic adjusting will be introduced as a potential therapy for SMI and MSI dysfunctions found in ASD, based on current evidence that supports improved SMI and MSI with chiropractic adjusting in various adult populations.

Chapter three presents a review of the current literature surrounding the use of chiropractic adjusting for children with ASD. The aims of the current study will then be introduced.

Chapter four outlines the methods involved in all aspects of this pilot and feasibility study. Including recruitment, procedures for data collection and data analysis, as well as explanation of each outcome measure.

Chapter five presents the results of the current study reporting on all trial and intervention feasibility findings and the preliminary efficacy of chiropractic adjusting for children with ASD in relation to SMI and MSI performance.

Chapter six discusses the results, comparing and contrasting findings to the broader literature. Strengths and limitations are also discussed, followed by recommendations for future studies and finally conclusions of the current study.

Chapter 1: Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterised by dysfunction in communication and social interaction. As well as restrictive and repetitive behaviours such as repetitive movements, lining up of toys and fixation on certain objects (American Psychiatric Association & Task Force, 2013). As the name suggests, there are a wide range of presentations in ASD (Levy, Mandell, & Schultz, 2009) with classification according to severity of ASD traits (American Psychiatric Association & Task Force, 2013). Individuals with ASD range from high-functioning individuals who live independently in adulthood to low functioning, non-verbal individuals who require significant lifelong support (Howlin, Goode, Hutton, & Rutter, 2004). The Diagnostic and Statistics Manual (DSM) – V states that the diagnosis of ASD encompasses a range of conditions, including: autistic disorder, pervasive developmental disorder not otherwise specified and Asperger's disorder (also known as Asperger's syndrome). Previously these disorders were diagnosed separately (American Psychiatric Association & Task Force, 2013). Autistic disorder first described by Kanner (1943), was previously characterised as marked impairment across the three core clinical features: social interaction, communication and restriction in range of interests and activity, with onset prior to three years of age. (American Psychiatric Association, 2000). Preceding the implementation of the DSM – V there was controversy over whether high-functioning autism and Asperger's syndrome were actually distinct diagnoses (Barahona-Correa & Filipe, 2015). The defining feature of Asperger's syndrome was the lack of clinically significant delays in language and cognitive development (American Psychiatric Association, 2000),

indeed individuals with Asperger's syndrome are more likely to have a significantly higher intelligence quotient (IQ) when compared to those with high-functioning autism (Chiang, Tsai, Cheung, Brown, & Li, 2014).

Children with high-functioning autism and Asperger syndrome commonly describe a desire to be normal and fit in, as some struggle with repetitive verbal and physical bullying at school (Humphrey & Lewis, 2008). Among children with ASD it has been suggested that more than 50% do not have a single close friend (Dovgan & Mazurek, 2018). A recent investigation of school aged children with high-functioning ASD found that only half of the children reported being able to make friends with ease and being invited to social outings with friends, though fewer parents stated that this actually happens (Knott, Dunlop, & Mackay, 2006). There appears to be a correlation between IQ, number of friends and participation in extracurricular activities. Children with higher IQ tend to have significantly more friends and those with more friends usually show greater participation in activities (Dovgan & Mazurek, 2018). Furthermore, young children with ASD may exhibit anxiety related symptomatology (Hallett et al., 2013; Keen, Adams, Simpson, den Houting, & Roberts, 2017).

ASD not only affects the child diagnosed but also has life-long implications for their parents and families/whānau (Krauss, Seltzer, & Jacobson, 2004). Ongoing physical, financial and emotional demands of caring for a child with ASD can lead to parents feeling overwhelmed and chronically fatigued (Cashin, 2004), leading to increased risk for depression and anxiety (Piven et al., 1990). Some parents describe a feeling of being disconnected and isolated from the rest of the world and a loss of self, as their whole life is dictated by strict routines that revolve around their child with ASD

(Woodgate et al., 2008). While ASD has significant impacts on quality of life for children living with the disorder and their families, there are also significant implications for society.

Global estimates of ASD incidence are now one in 160 people (World Health Organisation, 2017), while in New Zealand (NZ), ASD is estimated to affect one in 100 people (Ministry of Health, 2017a). ASD is a lifelong disorder (Krauss et al., 2004), as there is currently no cure (Levy et al., 2009). Indeed, the exact cause of ASD is unknown (Newschaffer et al., 2007), the etiology appears to be multifactorial with a number of genetic (Rosenberg et al., 2009; Woodbury-Smith & Scherer, 2018) and environmental factors that are known to increase the risk of ASD (Grabrucker, 2012; Grafodatskaya, Chung, Szatmari, & Weksberg, 2010). Medications have been used to address co-morbidities, yet there are no medications that directly treat ASD (Myers & Johnson, 2007). Currently, there are a number of therapies directed at improving communication and social interaction and decreasing problem behaviours (*Autism Spectrum Disorder*, 2015). These include various forms of occupational therapy, speech therapy, and psychology (Seida et al., 2009). While all of these therapies are focused on the three core areas described in the diagnostic criteria, there are also other areas of dysfunction in ASD to be considered.

As well as dysfunction in communication and social interaction, children with ASD often have deficits in motor control such as poor balance, dyspraxia, poor handwriting skills, clumsiness or difficulty avoiding obstacles (Freitag, Kleser, Schneider, & von Gontard, 2007; Wing, 1981). Recent studies have shown quantitative differences between children with and without ASD in terms of their gait (Dufek, Eggleston,

Harry, & Hickman, 2017), dynamic balance (Minshew, Sung, Jones, & Furman, 2004) and motor co-ordination of both upper and lower limbs (Fournier, Hass, Naik, Lodha, & Cauraugh, 2010). Such impairments in motor control may be the result of disrupted sensorimotor integration (SMI) (Siaperas et al., 2012; Weimer, Schatz, Lincoln, Ballantyne, & Trauner, 2001). SMI refers to the communication that occurs between sensory and motor systems that enable us to effectively respond to and interact with our environment and others (Chen, Penhune, & Zatorre, 2009). Proprioception, or the awareness of oneself in space, is one such measure that has highlighted SMI impairments in children with ASD (Haswell, Izawa, Dowell, Mostofsky, & Shadmehr, 2009; Imperatore Blanche, Reinoso, Chang, & Bodison, 2012).

Along with poor SMI, children with ASD have also been shown to have poor multisensory integration (MSI) (Chan, Langer, & Kaiser, 2016; Paton, Hohwy, & Enticott, 2012; Russo et al., 2010). MSI the process by which the brain processes and integrates information from multiple senses to create one clear image of what is happening within the body and in the surrounding environment (Ohshiro, Angelaki, & DeAngelis, 2011; Stein, Stanford, & Rowland, 2014). Evidence of disrupted SMI and MSI in children with ASD suggests that they may be unable to effectively perceive their internal and external environment, or respond appropriately to any alterations or environmental cues. SMI and MSI affects the motor control systems (Nevalainen, Lauronen, & Pihko, 2014; Shadmehr, 2004), and may also impact higher order cognitive function, behaviour, and social interaction (Imamizu, 2010; Moreno-Lopez, Olivares-Moreno, Cordero-Erausquin, & Rojas-Piloni, 2016). Providing one possible explanation for positive correlations that have been found between degree of motor

impairment and severity of ASD traits (Freitag et al., 2007; Nebel, Eloyan, Barber, & Mostofsky, 2014). Despite these findings, there has been a limited amount of research investigating interventions to improve SMI and MSI in children with ASD.

One therapy that may have potential to improve SMI and MSI for children with ASD is chiropractic care. Chiropractic is a primary health care profession that utilises a form of manual therapy described as spinal adjustments, also known as spinal manipulation or spinal manipulative therapy. Chiropractic adjustments often involve a high-velocity, low-amplitude thrust, which may induce an audible release of the joint and aims to restore normal articular function (Bergmann, 2005). Recently, chiropractic adjustments have been shown to improve SMI and MSI in some adult populations (Daligadu, Haavik, Yielder, Baarbe, & Murphy, 2013; Haavik-Taylor & Murphy, 2010; Holt, Haavik, Lee, Murphy, & Elley, 2016; Lelic et al., 2016). However, there is limited evidence demonstrating effects on SMI and MSI in child populations, with only one pilot study in children with attention deficit hyperactivity disorder (ADHD) (Cade, 2017). There are a growing number of case studies reporting improvements in children with ASD following chiropractic care (e.g. improved score on the autism treatment evaluation checklist and parental report of decreased severity of ASD traits along with improved behaviour), though limited experimental or clinical trials (Kronau, Thiel, Jäkel, & Liem, 2016). Therefore, it is prudent to investigate if evidence of improved SMI and MSI with chiropractic adjustments in adults can be extrapolated to children with ASD. Though, feasibility of performing such a study must first be explored.

Chapter 2: Background Literature

Prevalence and burden

The World Health Organisation estimates that ASD affects 1 in every 160 people worldwide (World Health Organisation, 2017). However, it is difficult to calculate an accurate worldwide prevalence rate due to a lack of data from many developing countries, such as the sub-Saharan region (Onaolapo & Onaolapo, 2017). In the United States (US), the Autism and Developmental Disabilities Monitoring Network was established to monitor the prevalence of ASD in children aged eight years old, across multiple states. For the year of 2012 the overall ASD prevalence estimate across 11 states, was one in 68 children (Christensen et al., 2016). In 2014 this prevalence rate increased to one in 59 children, with higher rates among white non-Hispanic children and males were four times more likely to have ASD (Baio et al., 2018). ASD rates in NZ are also estimated to be greater than the worldwide prevalance rates though not as great as the US. Ministry of Health estimates suggest that one in every 100 New Zealanders are affected by ASD (Ministry of Health, 2017a), with a current median age of 12 years old and approximately 81% being male, for those accessing disability support servies (Ministry of Health, 2017b). While ASD was previously considered a relatively rare condition (May, Sciberras, Brignell, & Williams, 2017), there appears to be a global rise in prevalence according to studies conducted over the last 50 years (World Health Organisation, 2017). Some suggest that an apparent increase in prevalence is solely due to broadening diagnostic criteria, increased awareness of the disorder, improved identification and diagnosis occuring at a younger age (Matson & Kozlowski, 2011). While others maintain that these factors account for some of the rise, yet there may also be a true increase in

prevalence (Simonoff, 2012). Regardless of the cause of the rise, the rise in ASD globally places an increasing burden on society.

In addition to high prevalence, ASD is associated with significant economic and personal costs (Buescher, Cidav, Knapp, & Mandell, 2014; Lavelle et al., 2014). Estimated lifetime costs for a person with ASD without an intellectual disability range from £0.92 million in the United Kingdom (UK) to US$1.43 million in the US (Buescher et al., 2014). Further, Lavelle et al. (2014) estimate that it costs parents of children with ASD around US$17,000 per year to cover costs for health care, other therapy, education, other services and caregiver time. Based on these figures, the societal cost of providing care for children with ASD in the US would have been US$11.5 billion dollars in 2011, based on an estimated 673,000 children with ASD (Lavelle et al., 2014). In NZ, people with ASD were reported to be among the top three users of disability support services in 2016 (Ministry of Health, 2017b). Despite high prevalence and significant associated economic and personal costs for society and families, the exact cause of ASD remain unknown (World Health Organisation, 2017).

Etiology

The cause of ASD appears to be multifactorial, with a combination of genetic and environmental factors playing a role (Levy et al., 2009; Newschaffer et al., 2007). When considering genetic susceptibility and heritability of ASD family and twin studies have been used, comparing concordance rates of ASD among monozygotic twins to dizygotic twins (Bailey, Palferman, Heavey, & Le Couteur, 1998; Muhle, Trentacoste, & Rapin, 2004). Where concordance rate refers to the likelihood of both

twins being affected by ASD, as opposed to only one twin being affected. The largest and most recent study of 277 twins in the US found a concordance rate of 88.1% for monozygotic twins and 30.5% for dizygotic twins (Rosenberg et al., 2009). While previous smaller scale studies found concordance rates of ASD ranging from 91-94.7% for monozygotic twins and 0-30.8% for dizygotic twins (Steffenburg et al., 1989; Taniai, Nishiyama, Miyachi, Imaeda, & Sumi, 2008). Furthermore, families with one child with ASD have been found to have an ASD recurrence rate of 7.1%, which is greater than the prevalence rate for the general population (Chudley, Gutierrez, Jocelyn, & Chodirker, 1998). Broader ASD phenotypes have also been reported amongst family members of children with ASD. For example, parents and siblings not diagnosed with ASD have shown milder presentations of ASD traits, such as being untactful or aloof (Bailey, Palferman, et al., 1998; Piven, Palmer, Jacobi, Childress, & Arndt, 1997). While an increased rate of ASD among twins and siblings is higher than that of the general population, it is lower than concordance rates for single gene diseases (Muhle et al., 2004). This suggests that multiple genes contribute to the pathogenesis of ASD. This notion is supported by the lack of consistent findings in genome screens (Newschaffer et al., 2007), with numerous genes found to be involved with ASD (Woodbury-Smith & Scherer, 2018). While significant evidence suggests a genetic predisposition to ASD, it is also important to consider epigenetic and environmental factors.

Epigenetics explores how the expression of deoxyribonucleic acid (DNA) can change, without changing the actual genetic sequence encoded in DNA (Qiu, 2006). This may be due to a change in the histone proteins responsible for the shape of the packaging of DNA, or chemical alterations due to the process of methylation, both of which

control whether transcription is active or inactive (Grafodatskaya et al., 2010). These proteins and the process of methylation can be modified by interactions with the environment (Qiu, 2006). Recently there has been an increase in the number of studies investigating the role of epigenetics in the pathogenesis of ASD (Grafodatskaya et al., 2010). Duffney and colleagues found at least 42 potential genes that encode for proteins involved in epigenetic machinery to be implicated in ASD (Duffney et al., 2018). One such example is variations in the MTHFR gene, which increases the risk of ASD (Boris, Goldblatt, Galanko, & James, 2004). Other findings include specific genomic regions that are regulated epigenetically, such as duplication of the chromosome region 15q11-13 which occurs in 1-2% of ASD cases (Abrahams & Geschwind, 2008). As previously mentioned, environmental exposures can lead to changes in epigenetic markers such as methylation or changes to histone proteins. Prenatal exposure to the anti-epileptic medication Valproate is one such example, which has been shown to be associated with a greater risk of ASD, between 8.9-10.8% (Moore et al., 2000). Further investigation is required to fully understand the effect of epigenetic factors on the pathogenesis of ASD, as well as the role the environment has on this process.

A number of environmental factors may be involved in the pathogenesis of ASD (Grabrucker, 2012). There is significant evidence linking ASD with zinc deficiency, particularly during infancy and potentially prenatally (Yasuda, Yoshida, Yasuda, & Tsutsui, 2011). Zinc is involved in immune system regulation, thus poor zinc status may also be linked to increased prenatal infection (Grabrucker, 2012). Prenatal viral infection with influenza, rubella and cytomegalovirus has been associated with ASD (Pardo, Vargas, & Zimmerman, 2005), as well as any pathology of the placenta

(Anderson, Jacobs-Stannard, Chawarska, Volkmar, & Kliman, 2007). Correlations have also been found between ASD and increased prenatal maternal stress (either physical or psychological) where there is activation of the hypothalamic-pituitary-adrenal axis (Beversdorf et al., 2005). Moderate associations have also been found with prenatal or perinatal exposures to hazardous air pollutants, such as chlorinated solvents and diesel particulate (Windham, Zhang, Gunier, Croen, & Grether, 2006). There are also possible links with prenatal cocaine exposure (Davis et al., 1992) and alcoholism (Miles, Takahashi, Haber, & Hadden, 2003; Piven & Palmer, 1999). Pregnancy related factors, including: pre-term delivery, low birth weight, breech presentation, multiple birth and use of assisted reproductive techniques, have also been found to be associated with an increased risk of ASD, though most likely only account for approximately 1% of the increasing ASD prevalence (Schieve et al., 2011). Finally, both increasing maternal (Sandin et al., 2012) and paternal (van Balkom et al., 2012) age has been linked to an increased risk of ASD. From this summary it is clear that the pathogenesis of ASD is complex, involving both genetic and environmental factors. The sheer number of possible etiologies of ASD highlights the heterogeneity of the disorder, which lends to increased complexity when considering treatment and therapy options.

Current treatment approaches

Due to the heterogeneity of ASD, treatment approaches tend to be multidisciplinary, focusing mainly on aspects of symptomatology and comorbid factors (i.e. anxiety, ADHD and epilepsy) (Levy et al., 2009). The Centres for Disease Control and Prevention (CDC) has assigned categories for the different approaches to treatment and care, including: approaches for behaviour and communication; medication (to

treat comorbidities); dietary approaches; and complementary and alternative medicine therapies (*Autism Spectrum Disorder*, 2015). As there is currently no biological treatment to cure ASD, many treatment methods aim to improve an individual's abilities across the three core areas of deficit, being behaviour, communication and social interaction; or to treat comorbidities (Levy et al., 2009).

Oono, Honey, and McConachie (2013) conducted a systematic review and meta-analysis of 10 studies (2002-2012) examining parent-mediated interventions for children with ASD. The studies involved parents being trained by a professional to implement home-based interventions aimed at promoting social and communicative development, learning and/or behavioural control. Findings revealed significant improvements in the quality of parent-child interactions, subtle improvements in language comprehension, and a reduction in the severity of ASD traits (measured by tools such as the Childhood Autism Rating Scales and the Autism Diagnostic Observation Schedule). No significant improvements were found for children's expressive and receptive language, communication, or adaptive behaviour, nor were there any reports of decreased parental stress (Oono et al., 2013). Though this review was limited to parent-mediated therapy there is a greater pool of literature assessing other behavioural and communication based therapies.

Behavioural based and communication focused therapies are the most widely researched treatment methods for ASD (Brunner & Seung, 2009; Myers & Johnson, 2007). A recent meta-analysis of 29 studies that used an Applied Behaviour Analysis (ABA) intervention for children with ASD (n = 831, mean age: 41.89 months) found moderate effectiveness for improved adaptive behaviour and non-verbal IQ, as well as

moderate to high levels of effectiveness in expressive/receptive language, and verbal IQ (Makrygianni, Gena, Katoudi, & Galanis, 2018). No significant publication bias was found, however, of the 29 studies included in the analysis only two had a randomised, controlled experimental design. One such study by Eikeseth, Smith, Jahr, and Eldevik (2002) took place in a school setting and compared a Lovaas approach to ABA (n= 13, mean age: 66.31 months [SD: 11.31]) to an eclectic treatment, which reflected best practice at the time (n= 12, mean age: 65.00 months [SD: 10.95]). The eclectic treatment group received a range of therapies that were individually selected based on the specific needs of the child, such as sensory motor therapies and methods from Project TEACCH (Schopler, Lansing, & Waters, 1983). The ABA group had a 17.15-point increase in IQ ($p < 0.01$), a 27-point improvement in total language (expressive and comprehension combined) using the Reynell Developmental Language Scales ($p < 0.05$). As well as an improvement of 15.69 in communication ($p < 0.01$) and 11.23 in composite score ($p < 0.05$) on the Vineland Adaptive Behavioural Scales (Eikeseth et al., 2002). The remaining 27 studies of the Makrygianni et al. (2018) review were quasi-experimental designs, thus limiting the strength of these findings.

An umbrella review of 30 systematic reviews assessed five general types of psychosocial therapies: behavioural theory, parent-mediated, communication-focused, development of social skill and sensory motor interventions (Seida et al., 2009). Parent-mediated intervention studies found improved parent-child interaction, as well as possible improvements in communication behaviour (McConachie & Diggle, 2007). Communication and social skills focused reviews reported improvements in speech production (Millar, Light, & Schlosser, 2006) and social communication

(Bellini & Akullian, 2007) respectively. While a meta-analysis on music therapy found improvements in eye contact, gross motor tasks, verbal and comprehension skills (Whipple, 2004). Although the aforementioned reviews found various improvements for children with ASD across the five styles of intervention, relative effectiveness compared to other therapies was not assessed and most of the reviews had methodological weaknesses such as bias in selection of studies included in the reviews (Seida et al., 2009). Other therapy options for children with ASD include complementary and alternative medicine (CAM) therapies.

Whilst CAM therapies are often utilised by families of children with ASD, evidence to support the effectiveness and safety of such therapies are lacking (Levy et al., 2009). Höfer, Hoffmann, and Bachmann (2016) recent systematic review of 20 studies (n = 9540) found that CAM therapies were utilised by 28-95% (mean = 54%) of children and adolescents with ASD. With special diets and/or dietary supplements being the most commonly used CAM in 75% of studies included in the review (Höfer et al., 2016). When divided into three types of CAM therapy used with children with ASD, it is estimated 50% use biologically based therapies, 30% mind-body therapies and 25% use manipulation or body-based interventions (Hanson et al., 2007). Further, review of the literature highlights a dearth of clinical trials that utilise neurophysiological outcome measures to assess changes in motor control and neurological function associated with therapy for children with ASD.

Autism spectrum disorder and motor control

Historically, it was noted that clumsiness, or problems with motor co-ordination were a key clinical feature of Asperger's syndrome (Gillberg, 1998; Wing, 1981), with

Asperger (1944) describing motor clumsiness as a core feature of the syndrome in his original writings. From the DSM-III (American Psychiatric Association, 1980) to the DSM-V (American Psychiatric Association & Task Force, 2013) motor co-ordination or clumsiness has not been highlighted as a feature of autism or ASD. The diagnostic focus according to these iterations of the DSM is on dysfunctions in communication, social interaction, repetitive behaviours and limited interests (American Psychiatric Association & Task Force, 2013; American Psychiatric Association, 1980). Nevertheless, there is a growing body of evidence demonstrating links between ASD in children and dysfunctional motor learning and motor control. For example, children with ASD commonly present with balance difficulties, dyspraxia, poor handwriting skills, and clumsiness (Ghaziuddin & Butler, 1998; Ghaziuddin, Butler, Tsai, & Ghaziuddin, 1994; Gillberg, 1998; Holloway, Long, & Biasini, 2018; Siaperas et al., 2012; Wing, 1981). Children with ASD may also find it difficult to avoid obstacles, may frequently exhibit delays in reaching motor milestones (often by several months) and may experience difficulties with postural control (Freitag et al., 2007; Minshew, Sung, Jones, & Furman, 2004; Wing, 1981). Indeed, in a systematic review and meta-analysis Fournier et al. (2010) proposed that deficits in motor co-ordination should be considered a core feature of ASD.

A common theme that emerges when critiquing the evidence around motor control in children with ASD is that the strength of the evidence is often limited. This is commonly due to small sample sizes (typical n = 10 to 79), heterogeneity in the study sample, weaknesses in methodology (e.g. lack of a true control), and potential sources of bias (e.g. limited blinding). Furthermore, conflicting results across studies make it difficult to clearly elucidate the motor control issues within this group. Therefore,

Fournier et al. (2010) conducted a well-considered, good quality synthesis and meta-analysis to gain insights into the degree of motor impairments seen in ASD. Additionally, they aimed to determine if motor impairments distinguished the ASD group from typically developing controls. A total of 51 independent meta-analytic comparisons were made, from 41 studies that met criteria for inclusion. This was done as nine out of the 41 studies included had two or more subgroups of ASD diagnoses, with results reported separately (Fournier et al., 2010). No publication bias effect was found, though tests for heterogeneity confirmed there was a large degree of variability between the studies. With removal of the two largest outliers, a significantly large effect size (1.063) was found, revealing that those with autism, ASD and Asperger's syndrome all exhibited impairments in motor co-ordination in both upper and lower limbs ($p < 0.0001$) (Fournier et al., 2010). Due to the heterogeneity of the group, cases were further classified and examined in three ways: according to diagnosis (autism, ASD and Asperger's syndrome); comparing motor co-ordination of upper limb verses lower limb, and according to age of the participants. Large deficits in motor co-ordination were still apparent across all subcategories of diagnosis and age for both upper and lower limb assessments (Fournier et al., 2010). From this, Fournier et al. (2010) suggested that deficits in motor co-ordination should be considered a core feature of ASD, regardless of people's diagnosis or age.

Postural control is another area of motor control that has been suggested to be problematic in children with ASD (Wing, 1981). Minshew et al. (2004) aimed to determine if abnormalities in postural control were present in people with ASD and if these were age related. The study assessed postural control in 79 people diagnosed with autism (mean age: 17.0 years, SD: 10.4 [range: 5-52 years]) and 61 healthy

volunteers (mean age: 16.7 years, SD: 10.5 [range: 5-52 years]) using dynamic posturography. Conditions tested included a combination of either eyes open, eyes closed or sway-referenced vision with a stable platform or a sway-reference platform (Minshew et al., 2004). Individuals with autism were found to experience difficulties with postural control and this was statistically significant in conditions that involved a sway-referenced platform. This suggests that there may be impairments in multi-modal integration in individuals with autism (Minshew et al., 2004). Furthermore, postural control was found to improve in the control group from 5-15 years of age and then plateau. Children with autism however, did not show any improvement until 12 years of age and the adults in this group did not reach the adult levels of postural control seen in the control group (Minshew et al., 2004). This study demonstrates clear deficits in postural stability in ASD, though the study failed to mention its limitations and there was also no mention to blinding of outcomes assessors or data analysts. Furthermore, generalisability of the results may be limited as there was a large age range and no specification of the spread of participants according to age. Therefore, there is no way to determine how many participants were included in the analysis reporting that adults with autism never reached the same level of postural control as the adults in the control group. As such these results must be interpreted with caution, though it does appear that regardless of age, people with ASD may have an increased risk for difficulties with postural control.

In addition to poor postural stability, children with ASD may demonstrate differences in gait development. Dufek et al. (2017) conducted a comprehensive lower limb gait analysis, comparing 10 children with ASD (aged 5-12 years) to age and gender-matched controls free from ASD. To compensate for the relatively small sample size

the group assessed 20 trials per matched pair and used pairwise analysis. Results showed that children with ASD had greater variability throughout their gait cycle than control children. Therefore, the children with ASD had inconsistent movement patterns, which could affect their ability to quickly respond to environmental challenges and potentially increase the risk of falls (Dufek et al., 2017). Anterior to posterior as well as vertical ground reaction forces were also significantly different between groups. These findings suggest that children with ASD had less stability compared to controls and also did not demonstrate usual loading responses to effectively dampen impact forces during the gait cycle (Dufek et al., 2017). Furthermore, each child with ASD appeared to have their own unique motion and there were no specific patterns of gait apparent in the ASD group. These findings suggest that children with ASD have poorer proprioceptive awareness and decreased stability when compared to typically developing children (Dufek et al., 2017), which is consistent with findings from other studies (Minshew et al., 2004; Weimer et al., 2001). This study further highlights the degree of heterogeneity amongst children diagnosed with ASD. When taken with findings from other studies it would appear that a deficit in proprioception might in fact be an underlying challenge for those with ASD (Haswell et al., 2009; Imperatore Blanche et al., 2012; Weimer et al., 2001), though perhaps children develop their own unique coping strategy.

As clumsiness or poor co-ordination had been highlighted as a core feature of Asperger's syndrome but not given the same emphasis in autism, Ghaziuddin et al. (1994) compared motor control in 11 children with Asperger's syndrome (mean age 13.6 years, SD: 3.7) to 9 children diagnosed with high-functioning autism (mean age 12.9 years, SD: 3.8). Using the Bruininks-Oseretsky test to assess motor function

(Ghaziuddin et al., 1994), each group was compared to age matched normative data and with each other. No significant between-group differences were found with fine motor skills, gross motor skills, upper limb co-ordination and the battery composite scores, with both groups displaying co-ordination issues in all four areas (Ghaziuddin et al., 1994). To further this investigation, Ghaziuddin and Butler (1998) conducted a similar study examining three groups: autistic disorder (n = 12; mean age 10.3 years, SD: 2.9; mean Full scale IQ (FIQ): 78.4); Asperger's syndrome (n = 12; mean age 11.4 years, SD: 2.3, mean FIQ: 104.9) and pervasive developmental disorder – not otherwise specified (PDD-NOS) (n = 12; mean age 10.1 years, SD: 2.7; mean FIQ: 78.2). Results showed that each group displayed problems with motor co-ordination, the autistic group had the greatest level of impairment and Asperger's syndrome had the lowest level. However, once the results were adjusted for child IQ there was no statistical between-group differences (Ghaziuddin & Butler, 1998). These results suggest links between motor co-ordination and IQ scores, which could potentially be related to dysfunction in the prefrontal cortex (Funahashi & Andreau, 2013; Müller, Pierce, Ambrose, Allen, & Courchesne, 2001). While both studies demonstrate similar findings and used blinded outcome assessors, it is important to note that both studies had a relatively small sample size, thus limiting generalisability of findings to the broader population. The original study (Ghaziuddin et al., 1994) also did not give a full description of data analysis techniques. However, this was improved upon in the second study (Ghaziuddin & Butler, 1998), thus increasing the quality of the study.

Similarly, Freitag et al. (2007) quantitatively examined neuromotor function in 16 male adolescents (aged 14-22 years) diagnosed with high-functioning autism or Asperger's syndrome and 16 male typically developing adolescents (aged 14-22

years) using the Zurich Neuromotor Assessment. Adolescents with high-functioning autism or Asperger's syndrome demonstrated significant impairments in dynamic balance as well as diadochokinesis (the ability to quickly and repetitively move a limb from one position to an opposing position and back again), compared to typically developing adolescents (Freitag et al., 2007). These findings are consistent with those found in younger children (Ghaziuddin & Butler, 1998; Ghaziuddin et al., 1994).

Potential links between ASD motor control and social functioning

Freitag et al. (2007) went on to examine correlations between performance in the Zurich Neuromotor Assessment and parent ratings on the Child Behaviour Checklist, as well as algorithm scores from the Autism Diagnostic Interview – Revised. Correlations were found between motor performance in the Zurich Neuromotor Assessment and both the Child Behaviour Checklist and the Autism Diagnostic Interview – Revised. Specifically, lower scores on social interaction problems were associated with better performance in diadochokinesis (estimate -1.7, $p = .02$); trends were also found between better diadochokinesis and lower scores for communication (estimate -1.5, $p = .07$), as well as greater dynamic balance and decreased repetitive behaviour (estimate -.3, $p = .07$) (Freitag et al., 2007). On the basis of their findings, Freitag and colleagues suggested that there may be a link between level of social impairment in children with ASD and their degree of motor control difficulties. In general, those adolescents with the greatest degree of social impairment also performed more poorly in the assessments for motor control (Freitag et al., 2007). While the methodology of this study appears to be sound, some caution must be taken in interpretation and generalisation of the results due to the small sample size and the inclusion of males but not females. Nevertheless, this study provides preliminary

evidence that there may be a relationship between degree of motor control and level of social interaction in children with ASD, which warrants further investigation.

The relationship between motor performance and social interaction was further investigated by Holloway et al. (2018) who examined 21 boys (aged 48 – 68 months) diagnosed with ASD, using four outcome measures: the gross motor subscales of the Peabody Developmental Motor Scales Second Edition, the gross motor scale of the Miller Function and Participation Scales, the Social Skills Improvement System Rating Scales and the Childhood Autism Rating Scales Second Edition. Findings revealed moderately high correlations between social and gross motor skills. The authors also found that performance in balance and object manipulation skills could be used to predict or explain social skills. For example, boys with ASD who had decreased performance in balance and object manipulation also demonstrated poorer social skills according to the Social Skills Improvement System Rating Scales (Holloway et al., 2018). Further, compared to children rated mild to moderate, boys rated by a parent as severe on the Childhood Autism Rating Scale also had greater impairment in observed gross motor skills (Holloway et al., 2018). As with similar studies these findings should be interpreted with caution, as the sample was small (n = 21), limited to boys and it was a convenience sample. Taken together, the findings from Holloway et al. (2018) and Freitag et al. (2007) suggest a positive correlation between motor control abilities and aptitude for social interaction in children with ASD aged 4-6 years, and adolescents and young adults aged 14-22 years. These correlations between motor control and social interaction could be related to dysfunction in areas such as the cerebellum (Fatemi et al., 2012) and prefrontal cortex

(Müller et al., 2001; Takarae, Minshew, Luna, & Sweeney, 2007), which are also integral to SMI.

Autism spectrum disorder and sensorimotor integration (SMI)

Difficulties in motor control among children with ASD may be due to disruptions in SMI (Siaperas et al., 2012; Weimer et al., 2001). SMI is essential in learning and performing motor tasks, involving the feedback of somatosensory information from the periphery to the cortex, pertaining to the performance of a task (Bukowska, 2007; Imamizu, 2010). In its simplest form, SMI occurs in the spinal cord, such as with muscle spindle reflexes, where information from a stretch of the muscle spindle is sent to the spinal cord and a motor response is generated immediately at the spinal cord level before the afferent input reaches the cortex (Bukowska, 2007). However, most SMI is not this simple and requires processing and integration at higher levels.

Sensory information from the environment is relayed to numerous subcortical areas (including: the basal ganglia, brainstem, cerebellum, superior colliculus and vestibular nuclei) via the spinal cord or cranial nerves (Bukowska, 2007; Velasques, Cagy, Piedade, & Ribeiro, 2013). Through complex connections the afferent input is then conveyed to the cerebral cortex, involving areas such as but not limited to: the somatosensory cortex, primary motor cortex, posterior parietal cortex, premotor cortex, prefrontal cortex and supplementary motor area (Blumenfeld, 2002; Moreno-Lopez et al., 2016). Throughout this process the information is modulated, processed and integrated at multiple levels to plan a motor response to the stimuli, produce a motor command and ultimately execute a motor task (Velasques et al., 2013). It is important to note that the afferent input is processed along with an efference copy (i.e.

a copy of the original motor command from the primary motor cortex) to determine if the predicted motor outcome matches the actual motor outcome and thus allow for fine-tuning of the motor task (Imamizu, 2010). It is also suggested that when a motor task is repeated the brain recalls previous motor commands and past errors to improve performance (Herzfeld, Vaswani, Marko, & Shadmehr, 2014). The ability to perform motor tasks quickly and smoothly is suggested to be due to neural mechanisms that can predict outcomes of particular actions before they are executed, these mechanisms are known as internal models (Imamizu, 2010).

SMI can be assessed in a number of ways. Commonly measures of proprioception are used (Lackner & DiZio, 2005). Proprioception is the term used to describe one's awareness of their body in space (Blumenfeld, 2002), which can be assessed by measuring joint position sense (JPS). JPS is measured by an individual's ability to reproduce a particular angle, at a specified joint without using visual input (Smith, Crawford, Proske, Taylor, & Gandevia, 2009). Balance can also be used to assess SMI, as the ability to balance requires effective integration of proprioceptive, vestibular and visual input (Lackner & DiZio, 2005).

To investigate whether or not motor impairment or clumsiness in Asperger's syndrome was linked to proprioception, and thus SMI, Weimer et al. (2001) assessed 10 males (mean age 15.7 years, SD 3.6 [range 9.0-19.9 years]) diagnosed with Asperger's syndrome and 10 healthy male controls (mean age 15.9 years, SD 3.8 [range 8.3-20.9 years]). Language skills, intelligence, and motor performance were assessed. Measures used for motor assessment include: finger tapping, grooved pegboard, trail making and finger-thumb apposition, as well as assessments on

apraxia, ataxia and visuomotor integration. Results showed that children with Asperger's syndrome showed signs of apraxia rather than impairment in classic tests assessing motor function (Weimer et al., 2001). In particular, difficulty in one-leg balancing with eyes closed, suggesting that there may be issues with the vestibular system or proprioception. Considering children in the group were not showing any classical signs or symptoms of vestibular dysfunction, the authors suggested that the problem lies in the proprioceptive system (Weimer et al., 2001). Similar to other studies mentioned above, due to a small sample size that only assessed males with Asperger's syndrome, results must be interpreted with caution. Furthermore, the lack of information regarding blinding of outcomes assessors makes it difficult to truly assess for bias. These findings do however suggest that further research investigating SMI in children with ASD is warranted.

Further investigations into motor abilities, sensory integration and praxis in children with ASD and Asperger's syndrome were performed by Siaperas et al. (2012) and Smith Roley et al. (2015). Both studies utilised the Sensory Integration and Praxis Tests (SIPT) developed by Ayres (1989) in conjunction with the Movement Assessment Battery for Children – 2 and the Sensory Processing Measure. Smith Roley et al. (2015) conducted a retrospective study using clinical records from 89 children with ASD (aged 4-11 years old) comparing them to normative standardised scores for each measure. Using all 17 sub-tests of the SIPT, children with ASD performed poorly on tests of proprioceptive and vestibular function, but had relative strengths in subtests relying on the visual system (Smith Roley et al., 2015). Meanwhile, Siaperas et al. (2012) examined 50 boys with Asperger's syndrome (aged 7-14 years) and 50 age-matched, typically developing children. Using seven of the

SIPT subscales to assess proprioceptive and vestibular function, children with Asperger's syndrome had significantly lower scores across all tests compared to age-matched controls ($p < 0.001$) (Siaperas et al., 2012). A limitation to consider in both studies is that the SIPT is standardised for children aged between four to eight years old. Both studies included children above this age range. Therefore, it is possible that the degree of deficit found in the older children may be underestimated. It is also important to note that Siaperas et al. (2012) did not reveal if any blinding of outcomes assessors or data analysts took place. Thus, it is not possible to rule out bias during these processes. As Smith Roley et al. (2015) conducted a retrospective study, the weight of the evidence is less than that from Siaperas et al. (2012). However, when taken together, the findings of these studies further strengthen the argument that children with ASD have motor control issues that appear to be related to proprioception and vestibular function and thus SMI. With this high degree of dysfunction in these areas of motor control and SMI, it is important to investigate the structural and functional neurological differences that occur in ASD.

Neurological characteristics of autism spectrum disorder

Numerous studies have shown that there are both structural and functional differences that occur in the brains of children and adults with ASD (Allen & Courchesne, 2003; Anderson, Hooker, & Herbert, 2008; Belmonte et al., 2004; Herbert et al., 2004; Mostofsky, Burgess, & Gidley Larson, 2007). One of the most reproducible structural anomalies found is a decreased volume of the corpus callosum (Anderson et al., 2011; Just, Cherkassky, Keller, Kana, & Minshew, 2007; Schipul, Williams, Keller, Minshew, & Just, 2012). The corpus callosum mediates communication between left and right hemispheres of the cerebral cortex, responsible for motor control and higher

order cognitive function (Just et al., 2007). A decrease in size of the corpus callosum in ASD is suggestive of a decrease in interhemispheric communication (Anderson et al., 2011; Just et al., 2007; Schipul et al., 2012), which supports the theory of a decrease in long-range connectivity and an increase in local connections (Herbert et al., 2004). This is further supported by functional magnetic resonance imaging (fMRI) studies that have found a decrease in interhemispheric correlation (i.e. functional connectivity between hemispheres) at resting state (Anderson et al., 2011), during motor tasks (Mostofsky et al., 2009) and with executive function tasks (Just et al., 2007). At resting state the brain areas with the greatest decrease in functional connectivity were the frontal insula, which is involved with social processing (Anderson et al., 2011) and the superior temporal gyrus responsible for auditory processing and social intelligence (Baron-Cohen et al., 1999). The primary sensorimotor and lateral inferior premotor areas that control fine and gross motor skills (Mostofsky et al., 2007); and the fusiform gyrus, which is involved in social function and facial processing (Corbett et al., 2009) also showed a significant decrease in functional connectivity.

Other structural anomalies include: increased volume of cerebral white matter (Courchesne et al., 2001; Herbert et al., 2004; Mostofsky et al., 2007), an increased number of uncharacteristically narrow minicolumns in the frontal and temporal lobes of the cerebral cortex (Casanova, Buxhoeveden, Switala, & Roy, 2002), and cerebellar anatomical anomalies (Fatemi et al., 2012; Lee et al., 2002). Indeed previous studies examining the cerebella of those with ASD found 95% to have some kind of anatomical abnormality, most commonly a decreased number of purkinje cells (Bailey, Luthert, et al., 1998; Casanova, 2007; Herbert et al., 2004; Ritvo et al., 1986).

The cerebellum while having a significant role in motor control (Schweighofer, Lang, & Kawato, 2013; Thach, Goodkin, & Keating, 1992) has also been shown to be involved in non-motor attention tasks (Schmahmann, 2019). In a small-scale study, individuals with ASD (n = 8, aged 14-38 years) were compared to age and gender matched controls (n = 8, aged 13-39 years), for cerebellum activation when performing an attention task (Allen & Courchesne, 2003). After controlling for activation due to motor effects during the task, Allen and Courchesne (2003) found that those with ASD had significantly less activation during the attention task. Unexpectedly, those with ASD also had significantly greater activation of the cerebellum during a motor task (Allen & Courchesne, 2003). Conversely, Mostofsky et al. (2009) fMRI study demonstrated a decreased activation of ipsilateral anterior cerebellum, and a lack of activation of the contralateral cerebellum in children with ASD (n = 13, aged 8-12 years) compared to age and sex matched healthy controls (n = 13, aged 8-12 years) during a simple motor task. This coincided with a significantly greater activation of the supplementary motor area in the children with ASD. The lack of activation of the cerebellum may result in decreased filtering of somatosensory information causing an increase in activation of the cerebral cortex (Mostofsky et al., 2009).

This increase in activation of the cerebral cortex is congruent with the notion that individuals with ASD may have an imbalance in the excitation to inhibition ratio in the cerebral cortex (Rubenstein & Merzenich, 2003). Indeed, Hashemi, Ariza, Rogers, Noctor, and Martinez-Cerdeno (2017) demonstrated a decreased number of parvalbumin-expressing interneurons in three distinct areas of the prefrontal cortex involved in memory, auditory and verbal functions. This decrease could lead to a

decrease in inhibition of output from the pyramidal neurons in the prefrontal cortex and therefore disrupt the excitation/inhibition ratio (Hashemi et al., 2017). Conversely, at resting state there is evidence to suggest people with ASD have decreased activation of the 'Default Network' (DN), which represents a group of brain areas including the medial prefrontal cortex, posterior cingulate, inferior temporal lobe and the hippocampal formation (Plaza-Manzano et al., 2014). The activation of the DN at rest appears to be implicated with the production of spontaneous cognition and is also possibly involved in monitoring of the environment (Plaza-Manzano et al., 2014). Furthermore, it has been suggested that with an increase in social impairment there is a greater degree of under activity of the DN at rest, in people with ASD (Buckner, Andrews-Hanna, & Schacter, 2008).

Decreased activation of the ventromedial prefrontal cortex and right cerebellum has also been demonstrated with a measure of executive function known as temporal discounting (Murphy et al., 2017). Temporal discounting measures the ability to choose a greater delayed reward over an immediate smaller reward (Rubia, Halari, Christakou, & Taylor, 2009). Children with ASD appear to perform poorly in these tasks, which suggests an inability to effectively consider future outcomes of current decisions (Chantiluke et al., 2014). A recent fMRI study demonstrated that this preference of immediate reward was maintained in adults. This study also showed that with increasing age there was decreased activation of the ventromedial prefrontal cortex and right cerebellum with delayed choices in people with ASD when compared to healthy controls (Murphy et al., 2017). This suggests that individuals with ASD experience less functional maturation of executive functions with increasing age. These structural and functional anomalies in the corpus callosum, cerebellum,

prefrontal cortex and other areas provide part of the explanation for the neurophysiology underpinning disruptions in social interaction, communication, motor control, SMI, as well as MSI in children with ASD.

Autism spectrum disorder and multisensory integration (MSI)

There is evidence to suggest that children with ASD may also have abnormal MSI (Chan et al., 2016; Foss-Feig et al., 2010; Grossman, Schneps, & Tager-Flusberg, 2009; Kern et al., 2007; Morris et al., 2015; Paton et al., 2012; Russo et al., 2010; Stevenson et al., 2016; Stevenson et al., 2014). MSI refers to the way in which the brain receives, processes and integrates information from multiples senses (e.g. visual, auditory, somatosensory, vestibular) in order to create a clear perception of what is happening within the body and the environment and events happening within the environment (Ohshiro et al., 2011; Stein et al., 2014). When an event occurs each one of our senses conveys a report of that event; it is the combination and integration of these sensory reports that creates the individual's perception of that event. Thus giving greater capability for making behavioural decisions based on the synthesis of information (Stein et al., 2014). As we are constantly being bombarded by sensory information, MSI enables the brain to filter this input. There are two prominent features of MSI. First, is the principle of inverse effectiveness, whereby multisensory enhancement is greater with weaker multisensory stimuli than it is with stronger stimuli (Stein et al., 2014). Second, is the spatial/temporal principle, which states that there is greater multisensory enhancement with stimuli from the environment that originate from close spatial proximity within the same temporal window (Hillock, Powers, & Wallace, 2011; Ohshiro et al., 2011). The greater the space or time

between two stimuli the less likely they are to be integrated and perceived as the same event. Therefore, MSI combines stimuli from different senses that have a temporal and spatial relationship, removes redundant information and synthesizes a meaningful representation of the environment around us (Brandwein et al., 2011). A further benefit of MSI is that it allows for faster reaction time to an event than what occurs with uni-modal stimulation (Stein et al., 2014).

It is important to note that the ability to effectively integrate multisensory information is not present at birth (Stein et al., 2014). This ability develops overtime and is shaped by the environmental stimuli that the infant is exposed to, thus allowing that individual to develop a system of MSI that is optimal for their environment (Stein et al., 2014). There is evidence to suggest that infants as young as four months old show signs of integration of auditory and visual stimuli (Lewkowicz, 1992), yet the refinement of MSI continues throughout childhood and possibly into adolescence (Brandwein et al., 2011) and plasticity can remain in adulthood (Stein & Rowland, 2011). Nonetheless, the exact processes involved in the development of MSI in typically developing children is not yet fully understood, with much of the literature being based on animal models (Hillock et al., 2011; Stein et al., 2014). Indeed, the complex computations and neural circuitry involved in MSI in adults is still being investigated (Notter, Hanke, Murray, & Geiser, 2019; Shrem, Murray, & Deouell, 2017; Yu, Cuppini, Xu, Rowland, & Stein, 2018). Despite this incomplete understanding of all that is involved in MSI in healthy adult and child populations, MSI is being investigated in children with ASD.

MSI of audiovisual input in children with ASD has been assessed in a number of studies using a range of methodologies, with varying results (Brock, Brown, Boucher, & Rippon, 2002; Chan et al., 2016; Foss-Feig et al., 2010; Grossman et al., 2009; Paton et al., 2012; Russo et al., 2010; Stevenson et al., 2016; Stevenson et al., 2014). Two studies used the sound-induced flash illusion; Foss-Feig et al. (2010) to assess the temporal binding window of multisensory input, while Stevenson et al. (2014) examined whether multisensory binding mechanisms were intact in children with ASD. The sound-induced flash illusion can be described as a visual perceptual illusion. It occurs when a single flash of light is presented asynchronously with two or more beeps; however, the individual perceives two flashes occurring, instead of just the one that was presented. The illusion is believed to be a result of complex interactions between the visual and auditory cortices (Shams, Kamitani, & Shimojo, 2001). Interestingly, the results of these studies were conflicting; Foss-Feig et al. (2010) found that children with ASD (n = 29, age years: 12.60, SD: 2.6) had a wider temporal binding window and experienced the illusion more often than children with typical development (n = 17, age: 12.0 years, SD: 2.2). However, Stevenson et al. (2014) found that children with ASD (n = 31, mean age: 12 years) experienced the illusion less often than typically developing peers (n = 31, mean age: 12 years). Blinding was not reported in either study, and Foss-Feig and colleagues did not have an even number of participants in each group. The differences in the findings may be related to one of the above aspects or may be due to the methodological difference, as the time between auditory and visual stimuli was manipulated by Foss-Feig et al. (2010), yet kept constant by Stevenson et al. (2014). Despite the conflicts noted, both studies are suggestive of dysfunctional MSI. A broader temporal binding window suggests that audio and visual inputs that are separated by a greater amount of time

are being recognised as originating from the same event and thus integrated as one (Foss-Feig et al., 2010). Meanwhile, a decreased perception of the illusion insinuates that audio and visual stimuli are not being combined and recognised as the same event, therefore MSI is not occurring optimally (Stevenson et al., 2014).

Thus, this suggests children with ASD may struggle to predict and respond appropriately to internal and environmental cues. If a child were experiencing such challenges, it could be difficult for them to effectively communicate and interact with others and the environment around them. This then raises the question of whether disruptions in SMI and MSI in children with ASD could be related to, or underpinning the impairments seen in social domains. Considering this, it would then be prudent to investigate therapies that have the potential to improve SMI and MSI, for children with ASD.

Chiropractic, sensory motor integration and multi-sensory integration

Chiropractic is a therapy that may have the potential to improve SMI and MSI in children with ASD. There is literature to suggest that chiropractic adjustments help to improve SMI and MSI in adult subclinical pain patients, chronic pain patients, and geriatric populations (Daligadu et al., 2013; Haavik & Murphy, 2011, 2012; Haavik, Niazi, Holt, & Murphy, 2017; Haavik Taylor, Holt, & Murphy, 2010; Haavik-Taylor & Murphy, 2007, 2008, 2010; Holt et al., 2016; Lelic et al., 2016; Palmgren, Sandstrom, Lundqvist, & Heikkila, 2006). Haavik Taylor et al. (2010) and Haavik and Murphy (2012) summarised their groups research that was conducted over a 15 year period and presented a model for the neuromodulatory effects of chiropractic care on SMI. This model describes how dysfunctional or restricted skeletal joints may alter

sensory input, and thus somatosensory processing, which could then lead to abberant SMI (Haavik Taylor et al., 2010). Chiropractic adjustments aim to normalise joint function, restoring appropriate sensory input and therefore, improving somatosensory processing, which could then improve SMI (Haavik & Murphy, 2012). There is a collection of basic science studies that investigate some of the neurophysiological mechanisms behind chiropractic adjusting, some of those related to SMI and MSI are explored below. However, it should be noted that this literature presented below is based on adult popultions. Very few studies have been performed that assess the effect of chiropractic adjusting on SMI and MSI in children.

Haavik-Taylor and Murphy (2007) and Haavik-Taylor and Murphy (2010) investigated changes in SMI using somatosensory evoked potentials (SEPs). SEPs are an objective, sensitive and reliable measure (Nuwer, 1998) of neuronal responses to stimulation of the somatosensory system through movement or transcutaneous electrical stimulation (Macerollo, Brown, Kilner, & Chen, 2018). Through SEPs it is possible to measure different stages of somatosensory processing (Macerollo et al., 2018) to determine the integrity of primary somatosensory pathways and higher order cognitive function (Nuwer, 1998). The aforementioned studies were performed with adults who had subclinical neck pain (Haavik-Taylor & Murphy, 2007, 2010), that is adults who have a history of recurrent neck pain but were not experiencing any pain at the time of the experiements (Lee, Nicholson, Adams, & Bae, 2005). Also, both used passive cervical range of motion as a control and chiropractic adjustments as the intervention. Haavik-Taylor and Murphy (2007) found a significant decrease in the parietal N20 and frontal N30 SEPs peak amplitudes, that lasted 20 and 30 minutes respectively post chiropractic adjustment. These two SEPs peak complexes are known

to origniate at the cortical level, usually 20 and 30 milliseconds post median nerve transcutaneous electrical stimulation at the wrist (Macerollo et al., 2018; Valeriani, Le Pera, & Tonali, 2001). The N20 SEPs peak is known to reflect processing of the stimuli within the primary sensory coretx (Desmedt & Cheron, 1981). The N30 SEPs peak is on other hand a more complex peak reflecting processing within multiple brain regions including the primary motor cortex, premotor areas, prefrontal cortex, thalamus and basal ganglia (Kanovsky, Bares, & Rektor, 2003; Waberski et al., 1999) and is therefore considered to reflect early SMI (Kanovsky et al., 2003; Rossi et al., 2003). It has been suggested that this complex loop may be related to kinaesthesia and joint position sense (Passmore, Murphy, & Lee, 2014).

Haavik-Taylor and Murphy (2010) further explored these findings using a dual peripheral nerve stimulation SEPs ratio technique, stimulating both the median and ulnar nerves at the wrist. Consistent with previous findings, results showed a decrease in the frontal N30 peak, along with an decrease in the N30 MU/M+U ratio, which is believed to be indicative of an increased ability to inhibit or filter dual (median plus ulnar nerve) somatosensory input (Haavik-Taylor & Murphy, 2010). This dual peripheral nerve stimulation SEPs ratio technique was again used by Haavik et al. (2017) in a preliminary study of chronic pain patients (n = 6) to measure changes in cortical intrinsic inhibitory interaction over a period of time (control) and after a period of chiropractic care. No change was found over a two week baseline, though after 12 weeks of a chiropractic intervention there was a significant decrease seen again for the N30 SEPs peak ratio, which is suggestive of an increase in cortical intrinsic inhibitory interactions (Haavik et al., 2017). The decreased N30 SEPs peak ratio observed after chiropractic adjusting in both dual SEPs studies could reflect an

increase in somatosensory filtering, which has been suggested to be impaired in children with ASD (Mostofsky et al., 2009). While these studies have small sample sizes, which lends to limited generalisability of results, it is important to note that they are not designed as clinical trials. Rather, these studies were intended as basic science studies that investigate mechanisms rather than efficacy of treatments. At the very least, these studies suggest chiropracitc adjustments impact processing and integration of somatosensory (proprioceptive) information in adult subclinical and chronic pain populations.

The reproducibility of the same changes occuring at the N30 peak over the three studies gives weight to the evidence, that spinal adjustment appear to change proprioceptive processing within the neural generators of this particlular SEPs peak. The strength of this evidence would further be increased if a different research group were to reproduce the findings. In an effort to identify the specifc neural generators of the N30 SEPs peak that were changing with chiropractic adjusting Lelic and colleagues (2016) perfomed a brain source localisation study (with a cross-over design) of 19 volunteers with subclinical neck pain. This study further confirmed the finding of a decrease in N30 SEPs peak amplitude and identified the prefrontal cortex as the primary area involved in this change in SMI (Lelic et al., 2016). While the prefrontal cortex is involved in SMI, it is also responsible for performance of executive functions. That is, the integration and coordination of multiple neural systems for problem solving and achieving goals (Funahashi & Andreau, 2013). Therefore, the findings in the aforementioned studies suggest there are central changes to SMI following cervical spine adjustments in adults with subclinical neck pain. As previously mentioned, children with ASD experience difficulties in tasks

involving executive function, cognition and social processing. Which may be due to decreased functional connectivity related to the corpus callosum and prefontal cortex (Anderson et al., 2011; Hashemi et al., 2017; Just et al., 2007; Martinez-Sanchis, 2014; Murphy et al., 2017).

These changes in SEPs peak amplitudes and dual SEPs ratios are thought to reflect changes in proprioceptive processing. Subsequently, further investigations have shown changes in joint-position sense (JPS) following chiropractic adjustments (Haavik & Murphy, 2011; Holt et al., 2016; Palmgren et al., 2006). JPS is a measurement of proprioception - the brains awareness of where the body is in space, and thus a measure of SMI (Blumenfeld, 2002). Palmgren et al. (2006) conducted a prospective, randomised, controlled trial that assessed head repositioning accuracy – a measure of JPS for the cervical spine, as well as cervical range of motion and intensity of pain in 41 adults (intervention group n = 20, control group n = 21) with chronic cervical pain. Results showed a statistically significant improvement in all six aspects of head repositioning accuracy for the intervention group after five weeks of chiropractic adjusting plus exercise therapy, while the control group (exercise therapy and advice alone) demostrated improvements in only one aspect (Palmgren et al., 2006). While this study had strengths in its design the results must be interpreted with caution as there was a relatively small sample size.

Haavik and Murphy (2011), found that 25 subclinical neck pain patients (mean age: 25.7 years, SD: 4.3) had a significant improvement in elbow JPS following chiropractic adjusting of the cervical spine. Comparitively, 18 healthy control participants (mean age: 23.2 years, SD: 9.5) that did not receive chiropractic adjusting

demonstrated a decrease in JPS accuracy following a rest period. This suggests that adjusting dysfunctional cervical spine joints resulted in the participants being better able to perceive where their elbow was in space (Haavik & Murphy, 2011). Again, the interpretation and generalisability of these results is limited by the relatively small sample size. However, a randomised controlled trial by Holt et al. (2016), also demonstrated similar significant improvements in ankle JPS in 60 older adults (65+ years of age) over a 12 week period of chiropractic care. Combined, these studies provide some evidentiary weight to supporting the notion that chiropractic adjustments improve proprioception; specifically spinal, upper limb and lower limb JPS. As mentioned above, children with autism often present with clumsiness or have difficulty avoiding obstacles (Dziuk et al., 2007; Freitag et al., 2007), and have been shown to have difficulties surrounding proprioceptive awareness (Imperatore Blanche et al., 2012; Morris et al., 2015; Smith Roley et al., 2015; Weimer et al., 2001). Therefore, it would be useful to investigate if the improvements seen in JPS in adult populations with chiropractic adjusting, could also be found in children with ASD.

Changes in communication between the cerebellum and primary motor cortex have also been observed following chiropractic adjusting (Daligadu et al., 2013). Both the cerebellum and the primary motor cortex are known to be involved with SMI and motor control (Velasques et al., 2013), as well as cognition and emotional expression (Chafetz, Friedman, Kevorkian, & Levy, 1996). Daligadu et al. (2013), assessed 10 adults with subclinical neck pain and 10 healthy adult controls using transcranial magnetic stimulation to measure both cerebellar and cortical output. The subclinical neck pain group received a combined of chiropractic and a motor learning task, while the control group only performed the motor learning task. Both groups showed a

significant improvement in task performance, though a decrease in cerebellar inhibition was only seen in the subclinical neck pain group (Daligadu et al., 2013). Due to the small sample size and lack of a true control group further research in this area is required to confirm these findings. When taken in conjunction with other studies (Haavik et al., 2017; Haavik-Taylor & Murphy, 2010; Lelic et al., 2016; Niazi et al., 2015) these findings further emphasise that central neurological changes occur following chiropractic adjusting, which involve areas of the brain responsible for SMI, MSI, emotional regulation, executive functions, cognition and motor control.

As previously mentioned, there is a significant amount of evidence in the literature demonstrating multiple changes in brain regions of those with ASD that are vital for SMI, MSI, emotional regulation, executive functions, cognition and motor control, including the cerebellum, prefrontal cortex, corpus callosum and premotor areas (Allen & Courchesne, 2003; Courchesne, 2004; Courchesne et al., 2001; Herbert et al., 2004; Mostofsky et al., 2007), as well as impaired communication between various brain regions (Belmonte et al., 2004; Belmonte & Yurgelun-Todd, 2003; Mostofsky et al., 2009). As mentioned, children with ASD have trouble filtering somatosensory information causing an increase in activation of the cerebral cortex (Mostofsky et al., 2009). These kinds of brain changes have also been shown to be related to severity of ASD traits; e.g. the weaker the connectivity of certain brain areas the greater the severity of ASD traits as measured by total Social Responsiveness Scale scores (Nebel et al., 2014). Therefore, since chiropractic adjustments in adults with spinal dysfunction have been found to change communication between the cerebellum and primary motor cortex (Baarbé, Yielder, Haavik, Holmes, & Murphy, 2018; Daligadu et al., 2013), as well as change SMI in

the prefrontal cortex (Lelic et al., 2016), and increase filtering of somatosensory information at the cortical level (Haavik-Taylor & Murphy, 2010; Haavik et al., 2017), perhaps these changes may also occur in children with ASD.

Furthermore, Holt et al. (2016) showed improvements in MSI in older adults following 12 weeks of chiropractic care, using the sound-induced flash illusion to measure MSI of audio-visual input. At the conclusion of the trial the experimental group showed an improvement in the perception of the illusion toward that of healthy young adults (reflecting improved MSI), while the control group did not show the same changes (Holt et al., 2016). This is important as older adults who have been shown to experience the illusion more frequently have an increased risk of falls (Setti, Burke, Kenny, & Newell, 2011). As mentioned above, Foss-Feig et al. (2010) demonstrated that some children with ASD also had a greater susceptibility to experiencing the illusion compared to typically developing children. In this study the children with ASD had a temporal binding window, which was approximately double that of typically developing children (Foss-Feig et al.). Suggesting that these children may integrate temporally separate audio and visual stimuli into a single event.

There is a dearth of studies investigating changes in SMI and MSI in children with a chiropractic intervention. Recently a pilot study was conducted by Cade (2017), to investigate SMI using measures of oculomotor control in children with ADHD. Thirty children (aged 8-15 years) took part in this cross-over study, the chiropractic group displayed trends toward decreased target acquisition time, decreased number of distractor fixations, as well as a decrease in the number of forward and reverse saccades during a reading task. Most interestingly, the children showed a significant

decrease in reading time post chiropractic intervention, which is suggestive of an increase in oculomotor control and thus improvement in SMI (Cade, 2017). ADHD is a common comorbidity for children with ASD (Mattila et al., 2010), furthermore, children with ASD also demonstrate dysfunction in oculomotor control (Rosenhall, Johansson, & Gillberg, 2007; Takarae, Minshew, Luna, Krisky, & Sweeney, 2004). These visuo-motor deficits are believed to be associated with cerebellar dysfunction (Bakroon & Lakshminarayanan, 2016; Takarae et al., 2004). Structural and functional abnormalities of the cerebellum have been reported to be one of the most common findings in the brains of children with ASD (Fatemi et al., 2012). The cerebellum is known to play a pivitol roll in both voluntary and reflex movements, as well as motor learning, SMI, MSI and due to it's far reaching connections may also be involved with cognitive functions (Manzoni, 2007).

As highlighted above there is a growing body of research demonstrating chiropractic adjustments can improve SMI, MSI and proprioception in adult populations. There is also evidence that chiropractic adjustments can have a neural plastic effect on areas of the brain such as the cerebellum and prefrontal cortex that are known to be involved in SMI, MSI, executive functions, cognition and motor control (Baarbé, Yielder, Haavik, Holmes, & Murphy, 2018; Daligadu et al., 2013; Haavik et al., 2017; Haavik-Taylor & Murphy, 2010; Lelic et al., 2016; Niazi et al., 2015). This combined with the evidence presented regarding impaired SMI, MSI and proprioceptive awareness in children with ASD raises the hypothesis that chiropractic adjusting may have the potential to improve SMI and MSI in children with ASD. However, there is currently limited evidence to support this notion.

As there is a dearth of research investigating the effect of chiropractic adjustments on SMI and MSI in children with ASD, it is prudent to determine feasibility of conducting such a study. When assessing the feasibility of a study protocol it is important to assess all aspects of the study design including: study processes, resources, management and scientific reasoning (Van Teijlingen & Hundley, 2001). There are many factors to be considered, first and foremost the efficacy and efficiency of recruitment strategies must be assessed, which can be reflected by recruitment rates (Thabane et al., 2010). Followed by the retention rate and compliance of participants with the study processes, outcome measures and interventions used (Van Teijlingen, Rennie, Hundley, & Graham, 2001). Furthermore, the suitability of the outcome measures must be assessed (Van Teijlingen & Hundley, 2001), which may include the participant's ability to perform the tasks, whether participants are able to maintain focus throughout the entire duration assessment session as assessed by completion rates of tasks. Finally, data on preliminary efficacy of the intervention can also be assessed, in an effort to determine if further investigation for the proposed intervention is warranted. If sufficiently powered, the data could also be used for determining sample sizes for future full-scale studies (Thabane et al., 2010).

Chapter 3: Literature Review

Autism spectrum disorder and chiropractic

In the literature there is currently limited evidence for the use of chiropractic for children with ASD, as highlighted by two systematic reviews, the first by Alcantara and Alcantara (2011) and the second by Kronau et al. (2016). To determine if any new literature had been published regarding chiropractic and ASD since these systematic reviews, a review of the literature was performed. The following databases were searched: EBSCO Health Databases, MEDLINE (via Ovid), Scopus and Cochrane Library (via Wiley). Search terms used included: autism* AND chiropractic AND children, limited to full text in English, with the date range limited to 1998 – 2018. This date range was selected as the first known case study to report on chiropractic care for a child with ASD was published in 1998. Results from the search were manually filtered to remove any duplicates, ensure the articles included both children with autism spectrum disorder and chiropractic, as well as remove any studies involving animals or results that were not pertaining to efficacy of chiropractic or spinal manipulative therapy (e.g. periodicals, commentaries, etc.). The remaining articles were then cross-referenced to the studies reviewed by Kronau et al. (2016), all articles identified from the above search were included in the review, thus no additional studies were found. Lastly, a chiropractic database called Vertebral Subluxation Research was accessed. This database consists of three chiropractic journals that often contain case studies published by practicing chiropractors. A simple search using the term "autism" revealed five new case studies involving children with ASD since the review by Kronau and colleagues. Kronau et al. (2016)

reported on 13 articles to provide an update of the original review performed by Alcantara and Alcantara (2011). As it is the most recent publication and also of higher quality, due to its thorough and formal methodological quality assessment, this chapter will focus predominantly on the review by Kronau et al. (2016). This will be followed by a summary of the five new case studies published since the last systematic review.

Kronau et al. (2016) identified 13 articles relating to chiropractic care or spinal manipulative therapy for children with ASD. There was one randomised comparison trial, one case series and 11 case reports. All studies in the review reported favourable results, such as parent reported reductions in autistic symptoms, assessed with the Autism Treatment Evaluation Checklist (ATEC) (Autism Research A. R. Institute, 1999). However, the strength of this evidence is limited. Kronau et al. (2016) used a modified Downs and Black checklist (Downs & Black, 1998) to assess the quality of the randomised comparison trial by Khorshid, Sweat, Zemba, and Zemba (2006), which compared the use of two chiropractic techniques over a three month period for children with ASD. The two groups were full spine chiropractic adjusting (n = 7) and upper cervical care (n = 7), although children were randomised the method was not specified and demographic information was not provided (Khorshid et al., 2006). While improvement in ATEC scores was reported for both groups, there was a greater degree of improvement in the upper cervical care group, though no formal data analysis was performed (Khorshid et al., 2006). The methodological quality was considered poor, given its small sample size, insufficient reporting, and poor external and internal validity (Kronau et al., 2016). The case-series by Aguilar, Grostic, and

Pfleger (2000) was also rated as poor based on a reporting quality tool suggested by Carey and Boden (2003) due to the lack of a study question, poor description of the intervention and a lack of appropriate statistical analysis. Of the case reports, one was rated as poor quality, seven achieved a moderate score for reporting and three had good reporting (Kronau et al., 2016), based on assessment with the CARE checklist (Gagnier et al., 2014). Table 1 summarises all studies in the Kronau et al. (2016) review, including the outcome measures used and the quality rating of each study. It is interesting to note that apart from aspects of the ATEC and Childhood Autism Rating Scale (CARS) that allude to sensory processing, none of the studies investigating the use of chiropractic for children with ASD directly assessed SMI or MSI.

Since the review by Kronau et al. (2016), there have been five new case studies published (Boman & Wasem, 2017; Pappicco, 2018; Pellegrino, 2016; Russell, 2018; Scroggin, 2017), but no additional case-series or clinical trials were found. All five case studies were published in low ranking journals that are only listed on chiropractic research databases and cannot be found on other academic databases. To maintain consistency with assessment methods used in the review by Kronau et al. (2016) the quality of the five additional case studies was assessed by the thesis candidate (herein referred to as the primary researcher) using the CARE Checklist – 2016 (see https://www.care-statement.org). The updated CARE Checklist provides a score out of 29. A score less than 10 reflects poor reporting, a score from 10 to 20 is moderate and over 20 equates to good reporting.

All five studies were rated moderate in their reporting, with scores ranging from 10 to 14 (Table 1). Consistent with the 13 studies mentioned above, all studies reported on improvements in ASD symptomatology of the children following chiropractic care (e.g. improved communication, behaviour, sociability and sleep). However, this was mostly based on either the chiropractor's observations or parental report rather than using a standardised outcome measure, thus increasing the risk of bias. One case study reported improvements using the ATEC, however, both baseline and post intervention forms were completed at the end of the study. Specifically, at the end of the study participating parents were asked to recall what their child was like prior to commencing care to answer the baseline form (Pellegrino, 2016). Thus, findings were highly likely to have been impacted by recall bias. Similar to Kronau et al. (2016) review, the more recent studies did not assess SMI or MSI, with the exception of Scroggin (2017) who reported an improvement in tandem gait and thus balance, which can be considered a measure of SMI. While Pellegrino (2016) also alluded to improvements in SMI with chiropractic care, there were no direct measures stated in the article.

Table 1: Summary of chiropractic studies for children and young adults with ASD

Study	Study design	Study quality	Number of participants	Age (years)	Sex	Outcome measures
Khorshid, Swear, Zemba, and Zemba (2006)	Randomised clinical trial	Poor*	14	4-16	M: 13 F: 1	ATEC, X-ray, static palpation, motion palpation, leg length difference
Aguilar et al. (2000)	Case series	Poor*	26	3-13	M: 21 F: 5	X-ray, leg length difference, CARS, modified Autism Rating Scale
Amalu (1998)	Case study	Moderate*	1	5	F: 1	X-ray, thermal scan, motion palpation,
Warner and Warner (1999)	Case study	Moderate*	1	5	F: 1	Surface electromyography, thermal scan, motion palpation
Neally (2003)	Case study	Poor*	1	19	F: 1	Motion palpation
McCormick (2008)	Case study	Moderate*	1	4	M: 1	ATEC, surface electromyography, thermal scan, motion palpation
Hoffman and Russell (2008)	Case study	Moderate*	1	3.5	F: 1	Thermal scan, motion palpation
Marini and Marini (2010)	Case study	Good*	1	6	M: 1	ATEC, motion palpation
Cohn (2011)	Case study	Moderate*	1	3	M: 1	Surface electromyography, thermal scan, motion palpation

Study	Study design	Study quality	Number of participants	Age (years)	Sex	Outcome measures
Cleave, Alcantara, and Holt (2011)	Multiple Case study	Moderate*	2	17-20	M: 1 F: 1	Motion palpation
Scelfo and Chelenyak (2011)	Case study	Moderate*	1	9	M: 1	ATEC, X-ray, motion palpation,
Noriega, Chung, and Brown (2012)	Case study	Good*	1	6	M: 1	X-ray, thermal scan, static palpation, motion palpation, leg length difference, weight distribution, postural pelvic evaluation
Zielinski and Borkhuis (2013)	Case study	Good*	1	3	F: 1	Thermal scan, postural evaluation, motion palpation
Pellegrino (2016)	Case study	Moderate^	1	4	M	Gait analysis, leg length difference, static palpation, motion palpation, postural analysis, ATEC.
Boman and Wasem (2017)	Case study	Moderate^	1	6	M	Surface electromyography, thermal scan, range of motion, static palpation.
Scroggin (2017)	Case study	Moderate^	1	11	M	Thermography, postural analysis (using Spinal Analysis Machine), gait analysis, tandem gait, Romberg's test, leg length difference, X-rays, palpation.

Study	Study design	Study quality	Number of participants	Age (years)	Sex	Outcome measures
Pappicco (2018)	Case study	Moderate^	1	10	F	Postural analysis, thermal scan, palpation, neck quadruple visual analog scale, low back quadruple visual analog scale, short form survey (SF-36).
Russell (2018)	Case study	Moderate^	1	3	M	Thermography, postural analysis, spinal range of motion, vertebral subluxation exam.

Note. *Quality rating scores based on systematic review by Kronau et al. (2016), ^quality rating scores as assessed by primary researcher using the CARE Checklist. M = male, F = female.

The current clinical evidence suggests that there may be positive outcomes for children with ASD following chiropractic adjustments, such as improved score on the ATEC (Kronau et al., 2016; Pellegrino, 2016). However, the evidence comes mainly from case studies, with no high quality clinical research being performed to date. Therefore, further research is required to fully investigate the possible efficacy of chiropractic adjusting in children with ASD. As highlighted above there is evidence to suggest disrupted SMI and MSI in children with ASD, as well as evidence to support the use of chiropractic care to improve both SMI and MSI in some adult populations. Therefore, chiropractic care may be an appropriate intervention to consider for children with ASD due to the potential neuromodulatory effect of chiropractic adjusting. Despite the significant body of evidence supporting links between SMI, MSI and motor control in children with ASD, there appears to be a lack of research investigating interventions that may improve these areas of neurophysiology. Considering there is also evidence to support correlations between degree of motor impairment and severity of ASD symptomatology, investigation of interventions that may improve SMI and MSI associated with motor control is warranted.

Aims

To address gaps in the current literature, the overriding aim of the current study was to assess the feasibility of all study processes related to using a chiropractic intervention among children with ASD. Study processes included recruitment, efficiency of recruitment sources, conversion rates from enquiry to enrolment, reasons for non-participation, retention, randomisation, completion rate of outcome measures, suitability of outcome measures and any adverse events. Secondary aims were to assess the feasibility of a chiropractic intervention for children with ASD and to

collect preliminary data on the efficacy of a single session chiropractic intervention on SMI and MSI. This will be the first pilot trial of this nature, investigating the relationship between SMI and MSI in children with ASD and chiropractic adjusting.

Chapter 4: Methods

Design

This was a feasibility and randomised controlled trial (RCT) pilot study using a parallel design with two study groups (intervention and control). Feasibility and preliminary efficacy measures were assessed at baseline and/or immediately post-intervention. An RCT parallel design was chosen to minimise participant burden by only being required for one data collection session. As the duration of any effect from a single session of chiropractic adjusting is yet to be determined in children with ASD, assessments were administered immediately post-intervention. A parallel study design was also chosen to reduce possible confounding effects that could occur when using a crossover trial design.

Registration and approvals

This study was registered with the Australian New Zealand Clinical Trials Registry (reference number: ACTRN12616001720404p). Ethical approval was granted by the Northern A Health and Disability Ethics Committee (reference number: 17/NTA/58) and the Auckland University of Technology Ethics Committee (reference number: 17/266). See evidence of ethical approval in Appendix A.

Sample size

A proposed sample size of 30 participants was considered sufficient to enable the assessment of feasibility aspects of the study. Similar sample sizes have been used in other basic science studies examining the neuromodulatory effects of chiropractic

adjustments (Daligadu et al., 2013; Haavik & Murphy, 2011; Haavik-Taylor & Murphy, 2010; Lelic et al., 2016).

Participants

All participants were required to meet strict study criteria. Inclusion criteria were: aged 6-15 years at the time of assessment and parental report of a diagnosis of ASD or Asperger's syndrome. In order to fully participate in the trial, children also needed to be verbal and able to communicate and understand directions given to them by the research assistant. Exclusion criteria were: being non-verbal to exclude lower functioning children with ASD; hearing or vision impairments that may affect their ability to perform the outcome measures; diagnosed with a specific reading disorder (such as dyslexia) or genetic disorder (e.g. tuberous sclerosis, Fragile X syndrome, Down's syndrome) which may have a negative impact on MSI; and/or a history of seizures or traumatic brain injury to ensure that the flashing light used in the sound-induced flash illusion would not induce a seizure in any of the participants. To screen for impaired SMI and MSI parents were asked to answer the following question: "Does your child struggle to cope in environments where there is a lot going on? (E.g. environments that are loud/noisy, busy and/or bright)" A 'yes' to this question resulted in inclusion and a 'no' resulted in exclusion from the study. This was done in an effort to increase the likelihood of recruiting children with ASD who were experiencing difficulties with SMI and MSI, as loud/noisy, busy environments would have the potential to overload an individual with poor SMI and MSI.

Procedures

Recruitment and screening

Potential participants were identified via advertising and communication with Autism NZ support groups and chiropractors in Auckland, NZ. All groups and practitioners were contacted via e-mail, face-to-face and/or telephone and asked to display/distribute a copy of the study advertisement (See Appendix B). Given a poor initial recruitment rate over the first five months of the recruitment period, an amendment to ethics was made to allow use of the social media platform, "Facebook" to further support recruitment. The approved advertisement was shared by the Centre for Chiropractic Research, the primary researcher and the director of the CCR. Furthermore, the organisers of Facebook pages with a focus on autism in NZ were contacted to request advertising support. See Figure 1 for a flowchart of the recruitment process.

Any individuals or families interested in participating in the study were invited to contact the researchers directly by either telephone or e-mail (provided on the advertisement) to find out more about the study. Potential participants were then screened for all study inclusion and exclusion criteria. If eligible, interested families were emailed a parent and an age-appropriate child version of the study information sheet. Parents/caregivers (herein referred to as parents for ease of reading) and children were asked to carefully read over the information and encouraged to discuss the study with their family/friends, whānau and significant others. If children were unable to read the study information sheet, parents were asked to read and explain it to them. One week later, each family received a follow-up phone call or email to discuss the study further, discuss any questions, and to determine their interest in

participating in the study. In-person appointments were arranged, where appropriate.

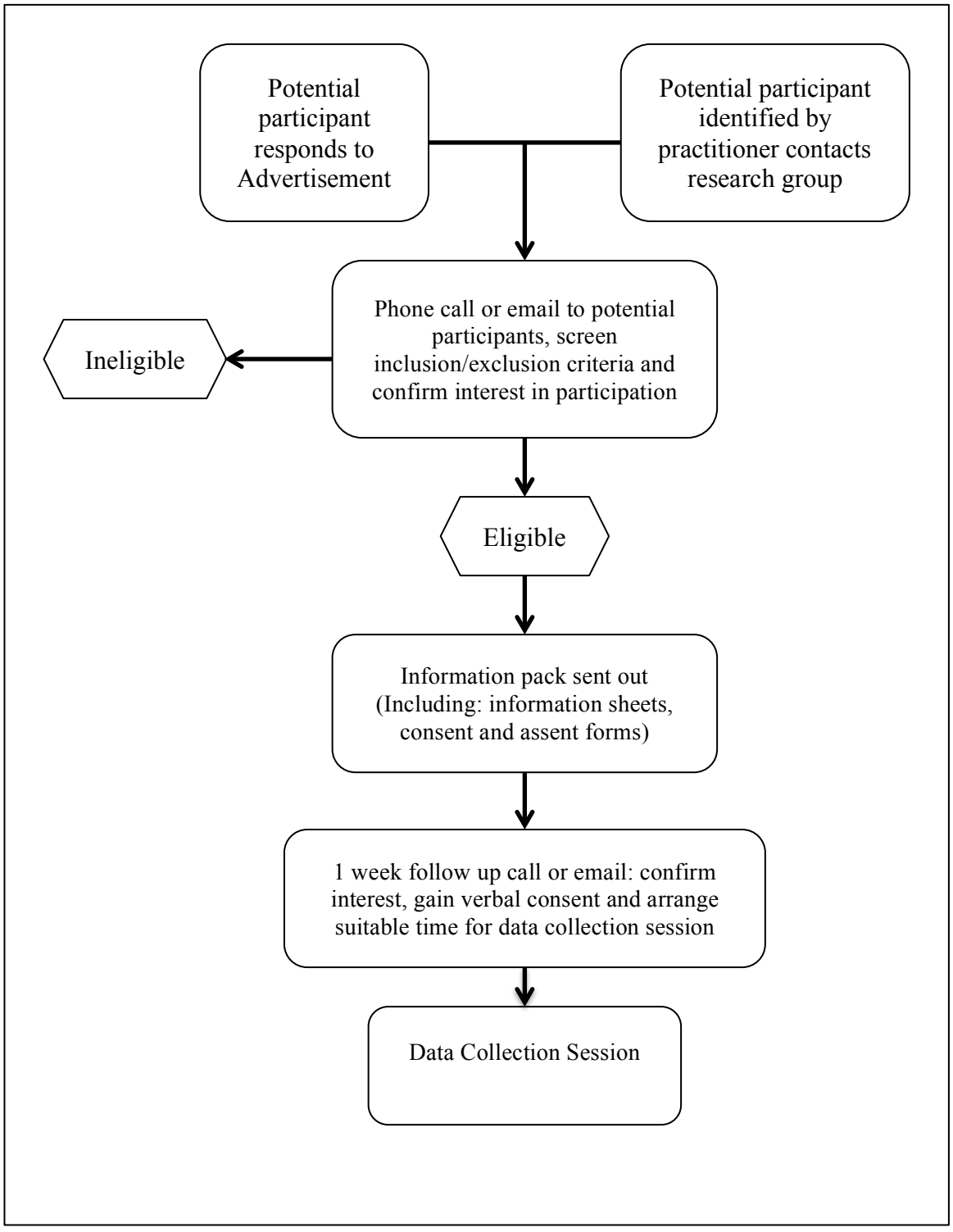

Figure 1. Recruitment and screening process

Assessments

Participants were invited to attend a single in-person assessment of approximately 2 hours duration. All assessments were held at the CCR at the NZ College of Chiropractic in Auckland. Following an opportunity to ask questions and prior to the collection of any study data, parents provided written informed consent. Children provided informed written consent or assent depending on their age and ability to understand the study process. This was determined by asking the child to repeat the study process back to the research assistant.

Following consent processes, each child completed a baseline assessment. A small quiet room was used for the data collection sessions, in an effort to decrease unwanted distractions. Research assistants, trained by the primary researcher, performed all data collection. First, children completed the sound-induced flash illusion, followed by the Sensory Integration and Praxis Tests (SIPT) and a fine motor task (fully described below in Outcome Measures – Preliminary Efficacy). This order was adhered to because the sound-induced flash illusion was the outcome measure of most interest. In other words, should children be unable to complete the entire baseline assessment, it was hoped that data could still be collected for the sound-induced flash illusion task. In an effort to maintain children's attention throughout the baseline assessment, each child was presented with a 'Study Certificate' at the beginning of their data collection session (see Appendix C) and given the option to add a sticker to their certificate at regular intervals. In addition, short breaks (approximately 2 minutes) were offered whenever children's attention seemed to be waning. Once baseline measures were completed the research assistant conducting the data collection left the room and a separate research assistant conducted randomisation. This was done to ensure the

outcomes assessor was blinded to group allocation.

Children randomised to the intervention group received chiropractic adjustment/s by a registered chiropractor. The chiropractic intervention was pragmatic in nature, where the practitioner used motion palpation, segmental joint play and tenderness to static palpation to identify dysfunctional motion segments of the spine; all common methods used by chiropractors (Triano et al., 2013). The purpose of the pragmatic nature of the intervention was to align with chiropractic clinical practice where only dysfunctional spinal joints receive adjustments when required. The chiropractic adjustments administered were high-velocity and low-amplitude in nature, where an audible release may be heard. This type of adjusting was chosen as it has previously been shown to affect the central nervous system in many ways (Daligadu et al., 2013; Haavik et al., 2017; Haavik-Taylor & Murphy, 2010; Holt et al., 2016; Lelic et al., 2016; Pagé, Nougarou, Dugas, & Descarreaux, 2014; Palmgren et al., 2006; Pickar, 2002). The adjustments were focused on the specific dysfunctional joints identified by the practitioner through the means described above. Each intervention session was approximately 10 minutes in duration.

Children allocated to the control group received a chiropractic assessment of the spine involving static and motion palpation, performed by a registered chiropractor. Followed by passive head and body movements through the normal spinal range of motion, in flexion, extension, lateral flexion and rotation, mimicking positioning of chiropractic adjustment set ups for each region of the spine. No chiropractic adjustments were performed. This control was not designed to be a placebo for chiropractic adjusting; it was to account for any changes in the outcome measures that

may be solely due to time, interaction with the chiropractor or other sensory input from palpation and passive movement of the spine that may occur during a chiropractic adjusting session. This type of control has been used successfully in a number of other studies (Cade, 2017; Haavik-Taylor & Murphy, 2007; Lelic et al., 2016; Niazi et al., 2015). Consistent with the intervention sessions, each control group session was approximately 10 minutes in duration.

After completion of control or intervention sessions the research assistant conducting data collection returned and the outcome measures were repeated. Throughout data collection parents could stay with their child, however, they were asked not to interact with or assist their child while performing the tasks. It was agreed up front that should any child show any signs of distress the session would be halted immediately. The child would be given a break and their parent/s would be consulted on the best way to manage such situations for their child. If the child were to settle and both child and parent/s were happy to continue then data collection could be commenced again. In the event of a child not settling or being unwilling to continue, the child and parent/s were to be given the option to reschedule data collection to another day or freely withdraw from the study. In the event of any adverse events (serious or minor) an, 'Internal Adverse Events Reporting Form' (see Appendix D) was to be completed with all details of the event: it's duration, the participant's interpretation and any action taken in relation to the event. However, no adverse events occurred throughout the duration of the study. See Figure 2 for a flowchart of the data collection session process.

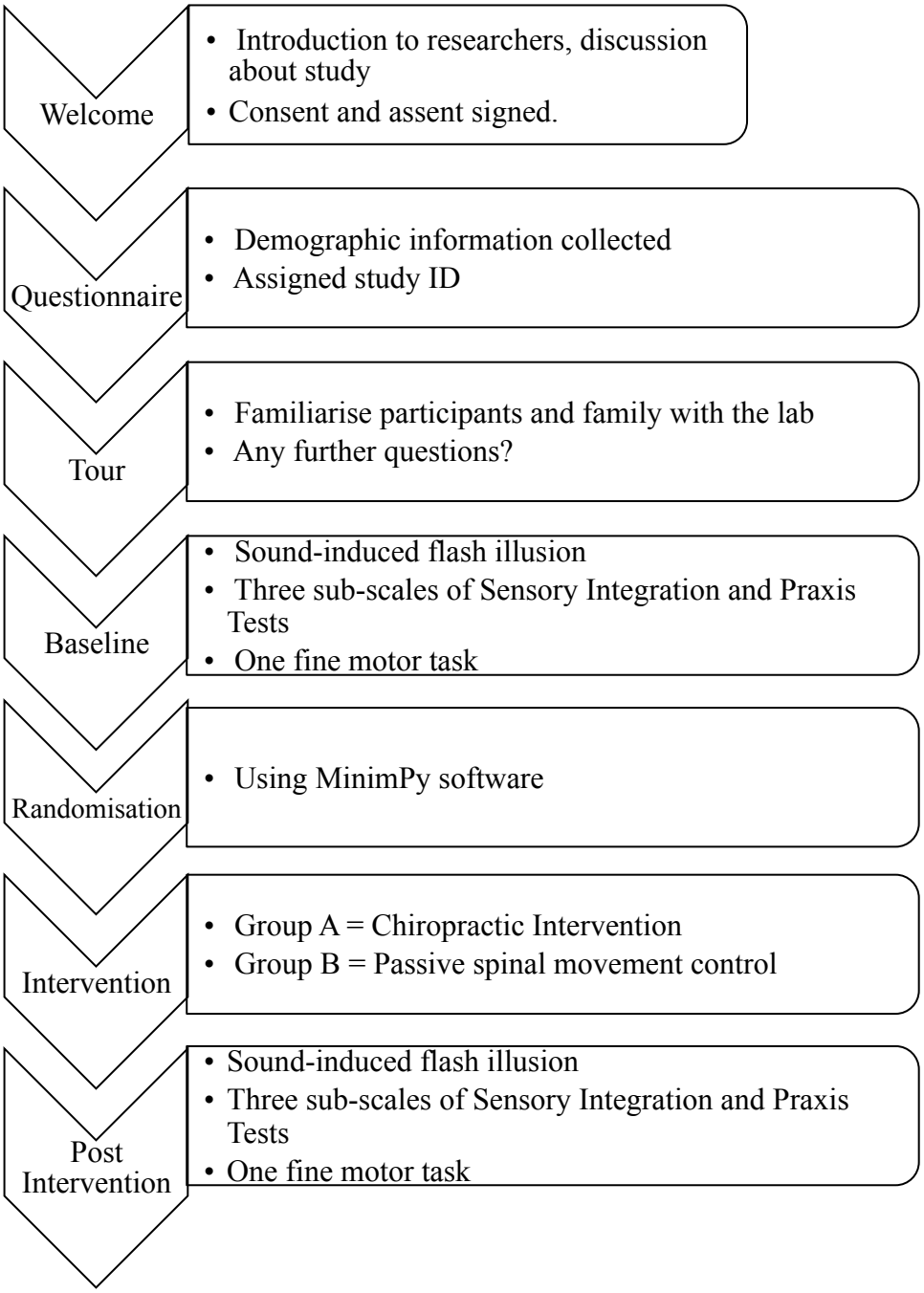

Figure 2: Flow diagram of data collection sessions

Trained study research assistants were blinded to group allocation, however, due to the physical nature of the intervention – chiropractic adjusting, it is not possible to blind participating children or practitioners providing the intervention. While participants were not directly told which group they were in, it may have been possible for them to guess. Parents were also asked not to discuss group allocation with their child until completion of post-intervention outcome measures.

Children were randomised into two groups using a free online randomisation program, MUI Online Minimisation or MinimPy (Saghaei & Saghaei, 2011 see: http://rct.mui.ac.ir/qminim/index.php). A research assistant that was not involved in data collection or data analysis conducted the randomisation. Each study group was balanced for child age (6-10 years old/11-15 years old), sex (boys/girls) and parent-reported autism diagnosis (ASD/Asperger's syndrome) to minimise differences across study groups due to these factors. Randomisation by autism diagnosis was done as it was recognised that some of the children may have been diagnosed prior to the implementation of the DSM-V, which combined the previously separate diagnoses of Asperger's syndrome and autism under the same umbrella term of ASD. Children with Asperger's syndrome have previously been identified as having higher IQ levels (Barahona-Correa & Filipe, 2015; Gillberg, 1998), which could potentially affect performance in the outcome measures.

Outcome measures

Trial feasibility (primary aim)

Trial feasibility was assessed by examining rates of recruitment (total number of

participants recruited / total duration of recruitment [months]), examining recruitment across referral sources of recruitment, conversion rates (from enquiry to enrolment [%]), assessing reasons for non-participation, participants accepting the results of randomisation (%), overall retention rate (%) and completion rates of pre and post-intervention outcome measures (%). Demographic data were collected using a study specific demographic information form (see Appendix E).

Any adverse events due to the outcome measures or chiropractic intervention used were to be tracked. A strict protocol was designed surrounding safety monitoring and adverse events, though, throughout the study there were no adverse events reported. In the occurrence of any adverse events (serious or minor) an 'Internal Adverse Events Reporting Form' was to be completed, the General Characteristics of the Common Terminology Criteria for Adverse Events grading (severity) scale (N. C. Institute, 2009) was to be used to determine if any adverse event was a severe adverse event. At least one of the three study supervisors was at the lab (or close by) to allow for immediate feedback if it were required. If any adverse event forms were completed they were to be immediately emailed to the supervision team to be reviewed and discussed at or prior to the next meeting.

Intervention feasibility (secondary aim)

Intervention feasibility was assessed by percentage rate of compliance with the chiropractic intervention.

Preliminary efficacy (secondary aim)

Preliminary efficacy of the chiropractic intervention was assessed using a MSI

measure, three SMI measures, and a fine motor skills task as described below. See Appendix F for the full study script.

Multisensory Integration – Using a protocol similar to that described in Setti et al. (2011), a custom built Sound-Induced Flash Illusion System assessed MSI. Each child sat on a chair at a desk approximately 60 centimetres (cm) away from the primary screen. The research assistant sat on the other side of the desk with a second screen facing away from the child. The research assistant manually initiated each trial and manually entered the participant's response to each trial. The screen used had a refresh rate of 60Hz to ensure the correct speed of the flash and decrease the likelihood of any faults or glitches occurring during the presentations. A white, disc shaped visual stimulus of 1inch in diameter, lasting 17 milliseconds (ms) was presented on a dark gray background, singularly or with a 190ms - 250ms stimulus onset asymmetry (SOA). This SOA was based on the findings of Foss-Feig et al. (2010), where children with ASD should experience the illusion 25-30% of the time. Between the presentation of each stimulus, a single cross hair was displayed at the center of the screen; this was used as a point for the child to focus on throughout the assessment period. An auditory stimulus of 10ms, 3500 hertz was presented simultaneously with the visual stimulus, using speakers. The auditory stimulus was either a single beep or two beeps. There were six experimental conditions used (as illustrated in Table 2): two beeps and one flash (illusion), one beep and one flash, two beeps and two flashes, one beep and two flashes, one flash and no beep, two flashes and no beep.

Table 2: Explanation of the six possible experimental conditions for the sound-induced flash illusion.

Experimental Condition	Explanation of Experimental Condition
1	2 beeps, 1 flash (the illusion)
2	1 beep, 1 flash
3	2 beeps, 2 flashes
4	1 beep, 2 flashes
5	0 beeps, 1 flash
6	0 beeps, 2 flashes

Prior to commencing this section of the experiment, participants were asked to ignore the beep noise and focus on the flash or flashes. A practice item was then presented; after the presentation the research assistant asked the child, "How many flashes did you see?" The research assistant then manually entered the child's verbal report of how many flashes they saw – one, two or none, directly into MATLAB (The MathWorks, Inc. See: https://mathworks.com). This same protocol was followed throughout. The research assistant manually initiated each presentation, ensuring the child's attention was on the task by asking, "Ready?" before each presentation. The research assistant then manually entered each verbal response from the child. Throughout the task the research assistant also gave positive reinforcement, using phrases like, "Great work", "Fantastic", "Keep going" and "Almost there".

The illusion was successful if the participant reported seeing two flashes when only a single flash was presented with two beeps. Susceptibility appears to be related to the ability of the individual to combine multisensory input (Shams et al., 2001). This trial consisted of 80 presentations in total per child, with 20 illusory presentations randomly interspersed amongst control trials. In order to maintain the attention and

focus of the child this outcome measure was presented in four blocks of 20 presentations. At the completion of the 20th presentation of each block, each participant was given the option to continue to the next block or have a short break of approximately 2 minutes. This was also an opportunity for the child to place a sticker on their study certificate if they desired.

Sensory Integration **–** Each child completed the following three subscales of the SIPT: Bilateral Motor Co-ordination, Kinaesthesia and Localisation of Tactile Stimuli. The SIPT is a standardised tool made up of a set of 17 tests that assess praxis and components of the visual, tactile, proprioceptive and vestibular systems of the body (Bodison & Mailloux, 2006). However, each test has been individually standardised, therefore all tests are suitable to be used in isolation. The three tests chosen for this study were selected as they were found to be those that children with ASD found difficult in a trial by Smith Roley et al. (2015). To make the tasks more appealing to the participants, each task was given a name to make it seem more like a game. The test-retest reliability and inter-rater reliability of SIPT were investigated by Ayres (1989). For the 17 subtests of the SIPT the test-retest reliability coefficients ranged from .48 to .93, with only five of the subtests having coefficients under .70. The inter-rater reliability was reported to range between .94 - .99, with assessors who had been trained in the administration of the SIPT (Ayres, 1989).

The Bilateral Motor Coordination subscale, to test the child's ability to coordinate movements of both upper limbs or lower limbs simultaneously. Renamed "Tapping Tunes" for this study. The participant sat facing toward the research assistant with bare feet flat on the ground on an A4 sized piece of paper. The research assistant

explained the task to the participant as described in the SIPT manual (Ayres, 1989). A trial was first performed to ensure the child understood the task, the research assistant first used their hands to tap a pattern and asked the child to copy the pattern tapped out, as if looking into a mirror. Once the child understood the process the task began, with 10 trials using hands and four trials with feet. Each trial was scored 0, 1 or 2; where 2 is an exact copy, 1 is approximately correct and 0 is unable to copy. At the completion of the task children were given a total score out of 28, which was used for data analysis. Therefore, the higher the score the better the child performed.

The Kinesthesia subscale tested each child's ability to reproduce positions of the hand and arm as positioned by the research assistant, while vision was occluded. Renamed "Going Visiting" for this study. The participant was first shown a 'practice run' on the back of the test sheet without their vision being occluded, to familiarise them with the task. A second 'practice run' was then performed with vision occluded. Once satisfied with their understanding the trial items were commenced, with occlusion of the participant's vision maintained throughout the whole session. The child's vision was occluded by placing a purpose built box over the test sheet and child's hands on the desk, shown in Figure 3. The task involved the research assistant moving the child's pointed finger to a designated position on the test sheet; they were told this first position was their 'home'. The research assistant then told the child they were going to take them visiting to a 'house' and to remember how to get there. The child's finger was then lifted up off the page and moved in a straight line to the designated spot on the test sheet for that trial. Their finger was left there for a couple of seconds then returned to their 'home' position. The research assistant then asked the child to return their finger to the 'house' they just visited and keep their finger on the spot. Margin of

error was then measured (cm, to two decimal places), from their fingertip to the specific point on the test sheet for that trial. This test had 10 trial items with the opportunity to repeat the two most erroneous responses. An average margin of error was then calculated for each child over the 10 trials and used for the data analysis.

The Localisation of Tactile Stimuli sub-scale tested the ability of children to identify the location of tactile stimuli (light touch administered by the assessor) on the hand and arm without using vision. This was renamed "Find the Spot" for this study. The research assistant explained the task according to the SIPT manual (Ayres, 1989). Occlusion of the child's vision was maintained throughout using the box shown in Figure 3. Using a face paint marker the assessor touched the child's hand or arm, the child was then asked to use a pointed finger to "find the spot". The child was asked to keep their finger in place until the assessor measured the margin of error (cm, to two decimal places), which was the distance between the tip of their finger and the centre of the dot left by the marker. This process was repeated for six locations on each arm, three on the anterior surface and three on the posterior surface, with the opportunity to repeat the two most erroneous responses – that is the two items with the greatest margin of error. The assessor manually wrote the distance on the score sheet after each item. At the conclusion of the trial the average margin of error was calculated for each child and this figure was used for data analysis.

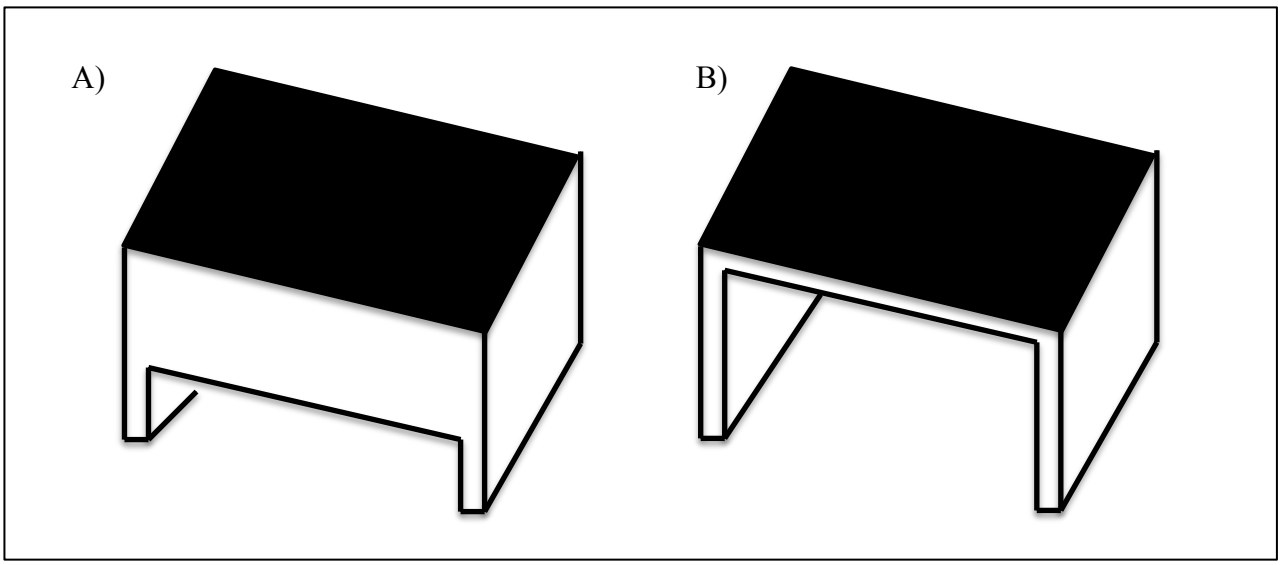

Figure 3: Illustration of purpose built box used for kinaesthesia and localisation of tactile stimuli tasks.

Note. Illustration of the box used to occlude vision during tasks, which was constructed out of cardboard. A) Represents the side facing the child, with a small gap for hands/forearms to fit into the box, while occluding vision. B) Represents the open side facing the research assistant, allowing for visualisation and manipulation of the child's hands/forearms during the kinaesthesia and localisation of tactile stimuli tasks.

Fine motor skills **-** A timed bead-threading task assessed each child's fine motor control. The successful completion of this type of activity requires intact SMI and MSI (Ohshiro et al., 2011; Seidler, Bo, & Anguera, 2012; Stein et al., 2014), thus this task was used to provide a proxy measure of SMI and MSI. Test batteries including similar bead threading tasks have previously been used in assessing fine motor skills in children with ASD (Freitag et al., 2007; Ghaziuddin & Butler, 1998; Provost, Heimerl, & Lopez, 2007). Large, coloured wooden beads and shoelaces were used for this assessment. The pack consisted of 30 beads, made up of five distinctively shaped beads in six different colours: red, yellow, green, blue, purple and orange (see Appendix G). Each child was given the opportunity to choose what colour beads they

wanted to work with. The child was shown a pattern card (see Appendix H) and asked to string the beads on in the same pattern as shown on the card, by the research assistant saying, "*Try to go as fast as you can but make sure you match the pattern on the card*". The card had three different bead patterns on it, however; only one pattern was shown to the child at a time, the other two were covered by a piece paper. The same three patterns were used for both pre and post measures. The research assistant used a stopwatch to time how long the participant took to complete the task. Once complete the research assistant noted if there were any mistakes and then the process was repeated for a total of three trials. The average time in seconds (s) over the three trials was calculated for each child and this was used for data analysis.

This task was chosen as it is simple enough to be used by clinicians in practice and because similar bead treading tasks appear in multiple test batteries assessing motor development, including: the Bayley Scale for Infant Development III (Bayley, 2005), Zurich Neuromotor Assessment (Largo, Fischer, & Caflisch, 2002), Bruininks-Oseretsky Test of Motor Proficiency (Bruininks, 1978) and the Peabody Developmental Motor Scales II (Folio & Fewell, 2000). Therefore, its use was exploratory in nature, to determine ease of use, suitability for assessing efficacy of an intervention and if there may be a learning effect.

Participant Safety

Study cessation protocol

The study was to be stopped if one of the following occurred: any severe adverse event where a child participant required hospitalisation or during the event of death of

a participant; or four participants experience mild to moderate adverse events (including ongoing soreness post chiropractic adjustment, psychological distress during data collection sessions or intervention, etc.). To allow for three chances to modify the data collection or intervention sessions before termination of the study.

Data management

During data collection sessions, raw data for the three SIPT were recorded manually on data collection forms purchased with the measure. Performance on the fine motor task was recorded using a study specific data collection form. After data collection was complete, all data were entered into a spreadsheet by the research assistant (see Appendix I). Data for the sound-induced flash illusion was recorded by the MATLAB program then copied into the spreadsheet by the research assistant. Hard copies of data were de-identified by using only the participant's study ID and date of birth; no other identifying information was on the forms. All data were stored in locked filing cabinets with access limited to the primary researcher, supervisors and research assistants involved in the study. All electronic data were stored on a password secured laptop, only accessible by the primary researcher, supervisors and research assistants involved in the study. The participant ID and date of birth were the only identifiers used in recording data and all forms containing any other identifying information (e.g. consent and assent forms) were kept locked in a separate filing cabinet in the research laboratory.

Statistical analysis

Trial feasibility (primary aim) was assessed using descriptive statistics (i.e. frequency

counts, percentage rates, proportions and measures of central tendency) based on recruitment rates, recruitment source, conversion rates (enquiry to enrolment), randomisation, and percentage rate of completion of tasks for baseline and post-intervention assessment measures. Intervention feasibility (secondary aim) was also assessed using descriptive statistics as described above based on rates of compliance within each study group. Compliance was defined as children co-operating with the chiropractor and completing the intervention sessions. Given the small sample size, the analysis of preliminary efficacy data (secondary aims) was also limited to using descriptive statistics. Raw data were used for the SIPT rather than using the computerised standard scores, as the aim was to assess any change in performance of the tasks rather than compare to standardised scores. Data checks performed included tests for normality, namely skewness and kurtosis values. Missing data were managed by pairwise exclusion of cases. Between group differences (post intervention – baseline) for each of the outcome measures were assessed by comparing mean values and standard deviations. While some data were presented in percentages, it is important to note that caution is required when interpreting percentages in sample sizes less than 100. Demographic data were also collected to assess possible confounding factors, this included gender, age, ethnicity, co-morbid diagnoses, medication, concurrent therapies and previous chiropractic care. The primary researcher conducted all data analysis using SPSS version 25.0 and was blinded to group allocation.

Chapter 5: Results

Trial feasibility (primary aim)

Recruitment

The overall recruitment rate was eight children over the eight and a half month recruitment period from 15th September 2017 to 31st May 2018. On average, this was the equivalent of one child per month (4.62 weeks). As the recruitment method changed throughout the study, it was deemed appropriate to analyse the recruitment rates for each method. For the first 27 weeks of recruitment there were a total of nine enquiries, which resulted in three children completing data collection, this corresponded to a recruitment rate of one child every nine weeks. After the amendment was approved on 21st March 2018 and the approved study advertisement was posted on Facebook, a further 17 enquiries were made over the remaining 10 weeks. From these enquiries five more children completed data collection sessions, which equated to a recruitment rate of one child every two weeks.

A total of eight children took part in the study and were randomised into two study groups. The intervention group consisted of three children diagnosed with ASD aged between 9-10 years (mean age = 9.67 years, standard deviation (SD) = 0.47). The control group consisted of five children diagnosed with ASD aged between 7-15 years of age (mean age = 10.4 years, SD = 2.87). Overall, six of the children were NZ European (75%); the remaining two were Samoan (25%). See Table 3 for full sample characteristics.

Table 3: Sample characteristics by group.

Characteristic	Intervention Group (n = 3)	Control Group (n = 5)
Sex (Male) n (%)	2 (66.67%)	2 (40.00%)
Mean age (years) (SD)	9.67 (0.47)	10.40 (2.87)
Age range (years)	9 – 10	7 – 15
Ethnicity, n (%)		
NZ European	1 (33.33)	5 (100.00)
Samoan	2 (66.67)	0 (0.00)
Co-morbid diagnoses, n (%)	1 (33.33)	2 (40.00)
Current medication use, n (%)	0 (0.00)	2 (40.00)
Currently receiving other Therapies, n (%)	2 (66.67)	2 (40.00)
Previously Adjusted (Yes), n (%)	0 (0.00)	4 (80.00)

Of the 26 potential leads, 18 (69.23%) did not participate in the study; of these, three (16.67%) were excluded for being outside the age range. Two (11.11%) were unable to find a suitable time for a data collection session, four (22.22%) were non-responders, and nine (50.00%) were non-consenting (see Table 4 for reasons for non-participation). The overall conversion rate from enquiry to enrolment was 30.77% (see Table 5 for conversion rates by referral source). The majority of children were recruited through chiropractors in Auckland (37.50%) as well as Facebook (37.50%); and the remainder through Autism NZ (12.50%) or had heard about the study from multiple sources – i.e. both Autism NZ and a chiropractor (12.50%).

Table 4: Reasons for non-participation.

Reason for Non-Participation	Number of Potential Participants
Not within specified age range	3
No longer interested	4
Concerned about child's ability to participate	2
Confirming diagnosis	1
Too far to travel	1
Child not interested	1
Non-responder	4
Unable to find time	2

Table 5: Source of recruitment, number of enquiries and enrollments with conversion rates

Source	Number of Enquiries	Number of Enrollments	Conversion rate (%)
Autism NZ	4	1	25.00
Chiropractor	4	3	75.00
Chiropractic Intern	2	0	0.00
Facebook	13	3	23.08
Multiple sources (Chiropractor AND Autism NZ)	1	1	100.00
Did not specify	2	0	0.00

Retention

The retention rate for the study was a 100%. There were no withdrawals from the study once participants consented and commenced data collection.

Acceptance of randomisation

All (n = 8, 100%) participants accepted the results of randomisation.

Task completion rate

Five of the eight children (62.50%) completed all of the baseline and post-intervention tasks. Five children (62.50%) completed the sound-induced flash illusion, seven children (87.50%) completed each of the SIPT measures and eight children (100%) completed the threading beads task at baseline and post-intervention. Individual completion rates of tasks (i.e. percentage of tasks completed per child) for baseline measures ranged from 50% - 100% (mean: 89.86%; SD: 17.60) across both study groups. Individual completion rates of tasks for post-intervention measures ranged from 20% - 100% (mean: 87.54%; SD: 25.52) across both study groups.

Adverse events

No adverse events were reported throughout the study.

Intervention feasibility (secondary aim)

Compliance with chiropractic intervention

There was 100% compliance with the chiropractic intervention.

Preliminary efficacy (secondary aim)

Table 6 reveals there were no between-group differences on the sound induced flash illusion task, nor on measures of bilateral motor co-ordination or localisation of tactile stimuli. There was a small reduction in margin of error on average kinesthesia scores for the intervention group (-0.36cm, SD: 1.16) and a small increase in margin of error for the control group (0.29cm, SD: 0.50). Less time was taken to complete the fine motor task in the control group (-4.26s, SD: 5.99) compared to the intervention group

(0.49s, SD: 4.25). However, small sample sizes precluded more testing, thus both of these between-group differences in outcomes could not be assessed for statistical significance.

Table 6: Between group comparison across five outcome measures assessing preliminary efficacy, using descriptive statistics.

Outcome measure	Intervention		Control	
	n	M (SD)	n	M (SD)
Sound-induced flash illusion (%)	2	0.00 (0.00)	3	5.00 (5.00)
Bilateral motor coordination (score)	3	0.00 (3.46)	4	0.50 (1.73)
Kinaesthesia (cm)	3	-0.36 (1.16)	4	0.29 (0.50)
Localisation of tactile stimuli (cm)	3	-0.04 (0.06)	4	-0.23 (0.70)
Threading beads (seconds)	3	0.49 (4.25)	5	-4.26 (5.99)

Note. n = number of participants included in the analysis, M = mean difference (post-intervention – baseline), SD = standard deviation.

Chapter 6: Discussion

This study aimed to assess the feasibility of undertaking a study to examine associations between a chiropractic intervention in children with ASD and their SMI and MSI. The primary aim was to assess the feasibility of all study processes. Secondary aims were to assess the feasibility of the chiropractic intervention and to assess the preliminary efficacy of the chiropractic intervention. Briefly, in regard to feasibility aspects, recruitment for this study was challenging with eight children recruited over 8.5 months. However, retention was 100%, with no withdrawals from the study and all participants accepted their group allocation. Overall, 62.50% of the children completed all of the tasks. The most challenging outcome measure for children was the sound-induced flash illusion, with only 62.50% of children completing the task. The stringing beads task appeared to be the easiest for all to perform, with a 100% completion rate. The chiropractic intervention and control session was well tolerated by all child participants. No adverse events were reported throughout the study and all children completed their treatment sessions. Preliminary efficacy of the chiropractic intervention could not be fully assessed due to the limited number of participants. Overall, the current study outcome measures and recruitment methods are not feasible for a full-scale, randomised clinical trial.

Trial feasibility

Despite efforts to recruit children through autism support networks, chiropractors and finally Facebook, participant recruitment was challenging. While interest in the study and recruitment rates did improve somewhat after introducing Facebook advertising,

recruitment was still ineffective. As only one randomised clinical trial investigating a chiropractic intervention for children with ASD has been conducted, which did not fully specify recruitment methods or rates (Khorshid et al., 2006), comparisons with findings of the current study must be drawn from a broader collection of studies. A pilot study by Aldred, Green, and Adams (2008) assessed the preliminary efficacy of a new social communication intervention for children with ASD. Twenty-eight children (aged two to five years) were recruited over 18 months. This corresponds to a recruitment rate of approximately one child every 2.75 weeks. Comparatively the overall recruitment rate of current study (one child per month) was less efficient and therefore, insufficient for a full-scale trial.

Paediatric pilot and feasibility studies involving a chiropractic intervention have shown varying efficiency in recruitment. Salmons (2018) feasibility study investigating the H-reflex and muscle strength in children with cerebral palsy achieved a recruitment rate of one participant every two weeks, which was deemed infeasible for a larger scale study. Cade (2017) demonstrated a recruitment rate of 2.73 participants per week, successfully recruiting 30 children with ADHD over a period of 11 weeks, for a trial assessing control of eye movement with a chiropractic intervention. Furthermore, the conversion rate of enquiries to enrolment (30.77%) was also low compared to other studies involving either a chiropractic intervention or children with ASD (Adams et al., 2012; Cade, 2017; Kasari et al., 2014; Kasari, Rotheram-Fuller, Locke, & Gulsrud, 2012; Salmons, 2018). This suggests that barriers to recruitment may not be solely due to the chiropractic nature of the intervention, though it may play a role. Other possible barriers to participation may be related to children's ASD diagnoses and the broader impact that can have on

families/whānau. It is recognised that parents of children with ASD are overburdened with the long term responsibilities associated with caring for a child with ASD, as it is a lifelong disorder (Krauss et al., 2004). The degree of psychological stress experienced by families of children with ASD has been found to be greater than that of typically developing children, with both parents and siblings more likely to experience depression (Piven et al., 1990). Furthermore, when comparing children with ASD to those with ADHD, Lee, Harrington, Louie, and Newschaffer (2008) found that there was a greater probability of parents of children with ASD experiencing depression. It is also well-established that disruptions to or irregularities in daily routines can further increase stress and anxiety for children with ASD and subsequently their families (Larson, 2006). Therefore, the commitment of participating in research could be considered an additional source of stress and anxiety for children and their families/whānau. Subsequently, parents of children with ASD may find it more difficult to have their child participate in research compared to parents of typically developing children or those with ADHD, for example. This may have been another driving force behind the difficulties in recruitment that were observed in the current study.

More broadly, recruitment of any children into RCTs is challenging for many reasons (Kaur, 2016). Children represent a vulnerable group, they may not fully grasp the study process and possible risks or benefits involved, and this uncertainty may create fear or anxiety for children (Punch, 2002). Furthermore, the child participant may not be able to provide their consent for participation; rather consent must be obtained from the parent along with assent from the child (Crane & Mroome, 2017; Edwards & McNamee, 2005; Peart & Holdaway, 2007; Punch, 2002). Each of these aspects

requires careful consideration when planning and conducting research involving children (Crane & Mroome, 2017). In the current study, parents were required to be present during all study assessments, requiring consideration not only of the child's schedule and ability to participate but also the parent's. Recruitment into small scale pilot studies is also known to be a challenging task, some attribute this to the limited funding available in such studies (Joseph, Keller, & Ainsworth, 2016). However, one might argue that the challenge may also be related to the fact that feasibility and pilot studies inherently lack the possible therapeutic benefits of larger scale clinical trials. The risk or burden of participating in a pilot study may therefore be viewed as greater than the perceived benefit for child participants and their parents.

Interestingly, the rate of participant recruitment was higher among families who were identified through chiropractors. Families who were advised of the study through a chiropractor were nearly three times more likely to take part in the study compared to families who were identified via other sources. This could be due to prior experience of chiropractic treatment and/or existing trust that has been developed as part of the patient – practitioner relationship (Chipidza, Wallwork, & Stern, 2015; Hall, Dugan, Zheng, & Mishra, 2001; Ridd, Shaw, Lewis, & Salisbury, 2009). Those who are already under chiropractic care may be more willing to follow a recommendation such as participating in a study. This is most likely the reason for a number of chiropractic studies utilising recruitment through chiropractors (Haas et al., 2004; Holt et al., 2016; Khorshid et al., 2006) or recruiting chiropractic students as participants (Goldenberg, Owens, & Pickar, 2007; Plaza-Manzano et al., 2014; Ward et al., 2014). Conversely, the broader public may be less aware of, have no experience

of, or do not fully understand chiropractic care, and therefore may perceive it as unsafe for children (Dunlop, 2018).

The current study had a 100% retention rate; participants were compliant with the study processes, despite being approximately two hours in duration. The retention rate of the current study was greater than that of the only clinical trial involving children with ASD and a chiropractic intervention, which had a retention rate of 93.3% (Khorshid et al., 2006). However, this clinical trial spanned a three-month period and therefore, required a greater time commitment than the current study. The aforementioned pilot studies by Cade (2017) and Aldred et al. (2008) also achieved retention rates of 100%. A broad range of retention rates have been reported in RCTs involving children with ASD and non-chiropractic interventions. Ranging from 64.6% - 100%, with the lowest retention rate occurring in a study where parents mediated the intervention (Adams et al., 2012; Bettison, 1996; Kasari et al., 2012; Wong, Kasari, Freeman, & Paparella, 2007). In the current study, it is likely that retention was successful as participants were only required for one data collection session. Thus, lowering the burden on child participants and their families is likely an important factor to consider when designing research aimed at families of children with ASD. A longer-term study requiring multiple interactions with the child participants may yield retention rates more similar to those in the RCTs mentioned above, though more research is required in this field.

Across both study groups, over half of all children completed all tasks in the baseline assessment. Interestingly, individual completion rates of tasks were somewhat lower in the post-intervention assessment. It may be that children became fatigued,

disinterested or over stimulated towards the end of the data collection session. As suggested by others, despite prior use in ASD populations standardised measures, such as the Sensory Integration and Praxis Tests used for this study may be challenging to administer in children with ASD due to issues of noncompliance and unresponsiveness (Case-Smith & Bryan, 1999). Furthermore, the heterogeneity amongst children with ASD may also hinder the administration of standardised tests. Children with ASD may also become fixated on certain tasks or activities that make it difficult to transition on to subsequent activities (Copeland, 2012; Gillberg, 1998; Happe & Frith, 2006). Indeed, restricted and repetitive behaviours are some of the core features of ASD (American Psychiatric Association & Task Force, 2013).

Findings also highlight several challenges associated with administering the sound-induced flash illusion task with children with ASD. At the commencement of data collection a stimulus onset asynchronicity (SOA) of 250ms was chosen. This selection was based on findings from the study by Foss-Feig et al. (2010), as this was described as the SOA at which children with ASD aged 8-17 years experienced the illusion approximately 25% of the time. After the third study participant, the SOA was changed to 190ms as only one of the three participants had experienced the illusion at all, and it was only 10% of the time in the post-intervention measures. Decreasing the SOA should increase the likelihood of participants experiencing the illusion (Foss-Feig et al., 2010; Shams et al., 2001). Due to the lower number of participants and the difficulty found in completing this task, only two more participants were able to complete the task, thus, no meaningful data were obtained. The low number of illusions experienced is consistent with Stevenson et al. (2014), who found that children with ASD were less susceptible to the illusion. However, in

considering the incomplete data of the remaining five participants, all but one participant did experience the illusion at least once. Therefore, the modified SOA (190ms) may be more appropriate to use in children with ASD aged between 7-15 years old, however this requires more investigation.

The sound-induced flash illusion has only been used twice before in studies involving children with ASD (Foss-Feig et al., 2010; Stevenson et al., 2014). The average age of the children in these studies was 12 years (Foss-Feig et al., 2010; Stevenson et al., 2014), being somewhat older than children in the current study. This task may be more suited to older children, with only one study using the sound-induced flash illusion in healthy children aged six to 12 years (Nava & Pavani, 2012). This study found a significant association between younger age and a greater number of errors when assessing ability to discriminate number of flashes presented either alone or with an auditory stimulus (Nava & Pavani, 2012). Together, these findings suggest that the younger children may not be as accurate when reporting the number of flashes presented, even in non-illusory conditions. These findings along with the findings of the current study suggest that the sound-induced flash illusion may not be suitable to use in children with ASD that are less than 10 years old.

An example of an outcome measure to assess MSI that may be more suitable for younger children with ASD, is the more passive measure used by Russo et al. (2010). This measure assessed auditory-somatosensory integration, rather than auditory-visual, allowing children to watch a silent movie during the task. Electroencephalography was used to measure uni-sensory conditions and MSI, of an auditory tone (similar to that used in the sound-induced flash illusion) and a vibro-

tactile stimulus either presented alone, simultaneously or together with a range of SOAs (Russo et al., 2010). Due to the use of electroencephalography this assessment does not rely on a conscious response from the children; therefore, it would decrease reporting bias and make it possible for younger or lower functioning children to participate. Furthermore, allowing children to watch a movie may help to increase their interest in the study and also increase their completion rate of tasks.

Intervention feasibility

All chiropractic and control sessions were well tolerated by children and parents, across both study groups. These findings are similar to the pilot study involving children with ADHD by Cade (2017) where participants completed a questionnaire relating to their experience and satisfaction with the study. In response to the chiropractic intervention, children and their parents gave anecdotal positive feedback; similarly the control session was well-tolerated and of the same style as the current study (Cade, 2017). High levels of parental satisfaction with paediatric chiropractic care were reported by Navrud, Miller, Eidsmo Bjørnli, Hjelle Feier, and Haugse (2014). Parents of 395 children (aged 0-36 months) completed a survey, 75.1% reported complete satisfaction with the care provided for their child (Navrud et al., 2014). It is possible that compliance in the current study may have also been related to parental satisfaction; however, this area requires further investigation in children with ASD. Future studies would benefit from collecting structured feedback from parents and children about their overall impressions of the intervention and their experience participating in the study.

Preliminary efficacy

In terms of potential efficacy of the chiropractic intervention, there were minimal between group differences across any of the outcome measures. Some improvements on the kinaesthesia task were evident in the intervention group from baseline and post-intervention testing, while the control group had a slight decline in performance. However, participant numbers were too small to be confident in this finding. Considering evidence from other studies, more simple perceptual tasks such as proprioception – like the kinaesthesia task used in the current study, appear to improve immediately following a single session of adjusting (Haavik & Murphy, 2011; Haavik-Taylor & Murphy, 2008; Holt et al., 2016; Niazi et al., 2015). While more complex neurological processes involving MSI, such as the sound-induced flash illusion and choice stepping reaction time, appear to require multiple sessions of chiropractic adjusting to show improvement (Holt et al., 2016). Indeed, Holt et al. (2016) found significant improvements in the sound-induced flash illusion over four and 12 weeks of chiropractic adjusting, while a choice stepping reaction time task only showed significant improvements after 12 weeks. Therefore, complex tasks involving recognition of a stimulus followed by initiation of a motor task (e.g. choice stepping reaction time and possibly the threading beads task in the current study) may require multiple sessions of chiropractic adjusting to show change. Further investigation with larger study samples and an extended period of chiropractic adjusting (e.g. over a 12 week trial) would be of interest to determine if children with ASD experience improvements in SMI and MSI, similar to those seen in adult studies with a chiropractic intervention (Daligadu et al., 2013; Haavik & Murphy, 2011; Holt et al., 2016; Lelic et al., 2016; Palmgren et al., 2006).

Strengths and limitations

Strengths of this study include its 100% retention rate and acceptance of the results of randomisation, as well as high levels of compliance with the study protocol across both groups. Limitations of this study include its small sample size, which not only impacted on data analysis for preliminary efficacy but also resulted in uneven distribution of participants across groups during the process of randomisation. Another limitation was the absence of structured child and parent-report feedback to determine in a more in-depth way the acceptability of study protocols. Furthermore, for those children who had previously been adjusted, the date of their last adjustment was not confirmed. Therefore, it was not possible to determine if previous adjustments may have confounded the results.

Future recommendations

Based on the findings of this study, future studies in this area should consider the use of social media platforms – such as Facebook, to improve the recruitment of children and families/whānau. Additional recruitment methods such as face-to-face presentations to autism support networks and perhaps advertising through schools may also promote recruitment. Presentations with question and answer sessions could help to overcome any potential barriers relating to a lack of knowledge among the general population regarding the safety of chiropractic adjusting. A future study could also consider advertising through additional healthcare practitioners who provide care for children with ASD, rather than chiropractors alone. Other suggestions include offering multiple assessment locations to reduce travel times for busy families, including weekend options. Reducing the number of outcome measures being assessed could further decrease participant burden. Further, any future study using

the sound-induced flash illusion to assess MSI in children with ASD, is recommended to focus on children aged 10 years and over or to consider the use of a more age-appropriate measure for younger children (i.e. a passive measure of MSI such as that used by Russo et al. (2010)). Passive outcome measures for younger children with ASD may increase compliance and thus increase completion rates of assessments (Kylliäinen, Jones, Gomot, Warreyn, & Falck-Ytter, 2014). Further studies investigating a dose-response relationship between chiropractic adjusting and neurophysiological changes would also be of interest. It is also recommended that future studies include a date of the last adjustment and perhaps include this as a factor for randomisation, to limit confounding variables. Structured child and parent-report feedback questionnaires are also recommended for future studies to determine the acceptability of study protocols and the chiropractic intervention, in a more in-depth way.

Conclusions

From the findings in this study, it is not feasible to perform a full-scale trial using the same protocol. This is largely related to recruitment difficulties. Further, the number and selection of outcome measures chosen for this study may not be suitable for a full-scale trial due to low rates of completion of some tasks. The chiropractic intervention was found to be acceptable in this small sample. Therefore, further pilot studies to test alternative methods of recruitment and suitability of outcome measures are required to advance knowledge of chiropractic as a potential means to improving SMI and MSI in children with ASD.

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Appendix A: Ethical approvals

Health and Disability Ethics Committees
Ministry of Health
133 Molesworth Street
PO Box 5013
Wellington
6011

0800 4 ETHICS
hdecs@moh.govt.nz

28 July 2017

Dr Kelly Jones
Faculty of Health and Environmental Sciences
National Institute for Stroke and Applied Neurosciences
AUT University
Auckland 1142

Dear Dr Jones

Re:	**Ethics ref:**	**17/NTA/58**
	Study title:	Can chiropractic adjustments change multi sensory integration and sensorimotor integration in children with autism? A pilot study.

I am pleased to advise that this application has been *approved* by the Northern A Health and Disability Ethics Committee. This decision was made through the HDEC-Full Review pathway.

Conditions of HDEC approval

HDEC approval for this study is subject to the following conditions being met prior to the commencement of the study in New Zealand. It is your responsibility, and that of the study's sponsor, to ensure that these conditions are met. No further review by the Northern A Health and Disability Ethics Committee is required.

Standard conditions:

1. Before the study commences at *any* locality in New Zealand, all relevant regulatory approvals must be obtained.

2. Before the study commences at *any* locality in New Zealand, it must be registered in a clinical trials registry. This should be a WHO-approved (such as the Australia New Zealand Clinical Trials Registry, www.anzctr.org.au). However https://clinicaltrials.gov/ is acceptable provided registration occurs prior to the study commencing at *any* locality in New Zealand.

3. Before the study commences at *a given* locality in New Zealand, it must be authorised by that locality in Online Forms. Locality authorisation confirms that the locality is suitable for the safe and effective conduct of the study, and that local research governance issues have been addressed.

After HDEC review

Please refer to the *Standard Operating Procedures for Health and Disability Ethics Committees* (available on www.ethics.health.govt.nz) for HDEC requirements relating to amendments and other post-approval processes.

Your **next progress report** is due by **27 July 2018.**

Participant access to ACC

The Northern A Health and Disability Ethics Committee is satisfied that your study is not a clinical trial that is to be conducted principally for the benefit of the manufacturer or distributor of the medicine or item being trialled. Participants injured as a result of treatment received as part of your study may therefore be eligible for publicly-funded compensation through the Accident Compensation Corporation (ACC).

Please don't hesitate to contact the HDEC secretariat for further information. We wish you all the best for your study.

Yours sincerely,

Dr Brian Fergus
Chairperson
Northern A Health and Disability Ethics Committee

Encl: appendix A: documents submitted
appendix B: statement of compliance and list of members

Appendix B: Study advertisement

AUT

Do you know any children with autism spectrum disorder?

We are looking for children with autism spectrum disorder, aged 6-15 years who would like to take part in a study.

We will be investigating if Chiropractic adjustments can change the way information is processed in the brain. In particular we will be focusing on how movement, touch, sound and sight are processed as well as fine motor skills.

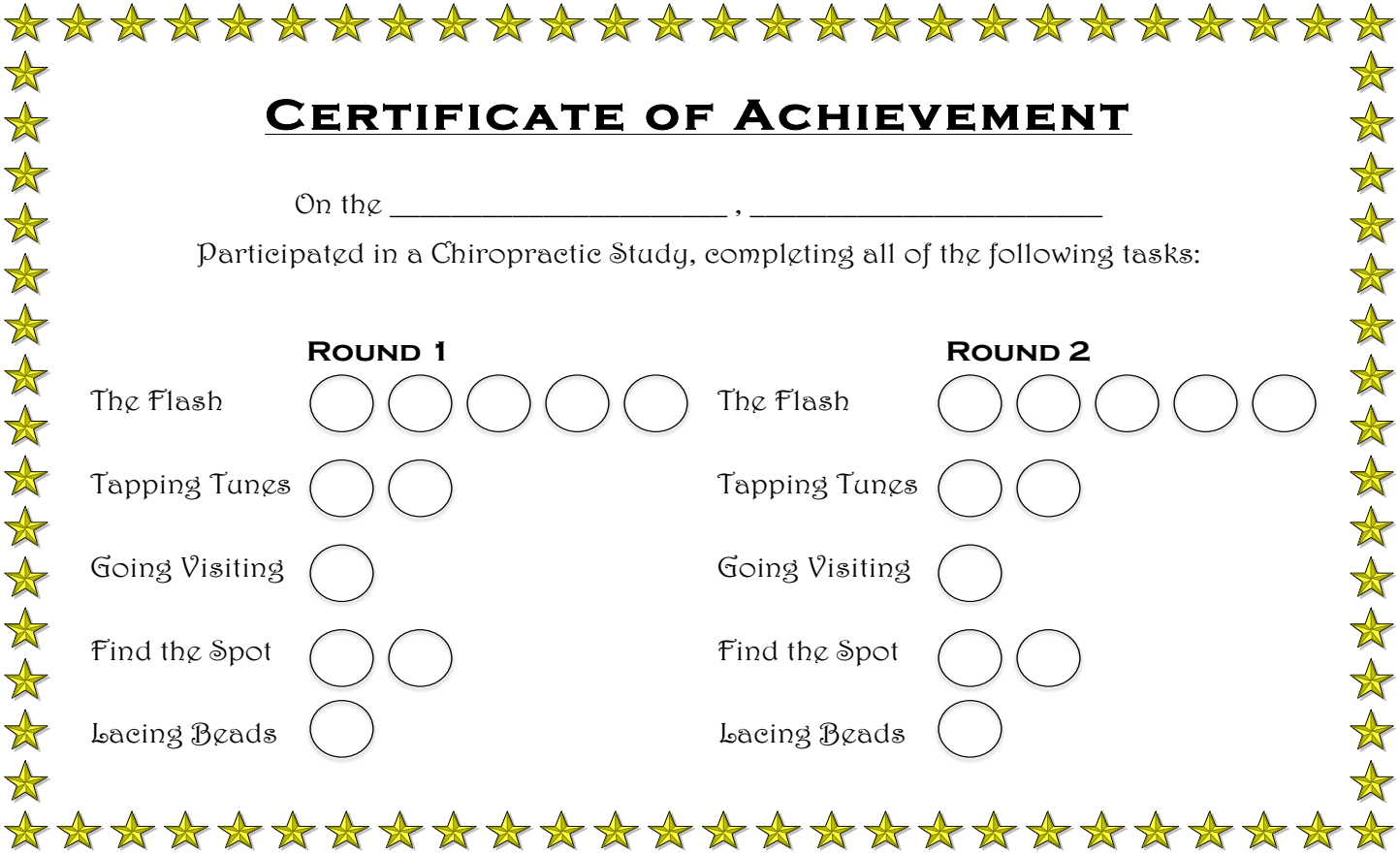
If you are interested in participating please email our primary researcher for more information:

Aisha Strand – aisha.strand.chiro@gmail.com

OR

Melanie Freiwald Ph: 0220972427

Appendix C: Study certificate



Appendix D: Internal adverse events reporting form

Internal Adverse Event Reporting Form

Can chiropractic adjustments change multi sensory integration and sensorimotor integration in children with autism? A pilot study.

Name of Trial Site: Centre for Chiropractic Research

Check the applicable boxes:	
1. ☐	The problem/adverse event is serious/life-threatening or involving risks to others;
2. ☐	The problem/adverse event was an unanticipated/anticipated (delete as appropriate)
3. ☐	The problem/adverse event is related to the study procedures.

ADMINISTRATIVE INFORMATION

Name of researcher informed of adverse event: _____

Date this report completed: / / _____

Type of report: ____ Initial ____ Follow-up

Research Participant's study identification number: _____

Date adverse event started / /

Internal Adverse Event Reporting Form

ADVERSE EVENT (AE) TYPE

____ Unanticipated ____ Anticipated

Seriousness of the Adverse Event (check all that apply):	____ Death ____ Life-threatening ____ Initial or prolonged hospitalization ____ Disability ____ Non-serious ____ Required intervention to prevent permanent impairment/damage ____ Emotional/Psychological Harm ____ Financial Harm ____ Other medically important condition ____ Other
Severity of the Adverse Event	____ Mild ____ Moderate ____ Severe ____ Life-Threatening ____ Fatal ____N/A

If death, date of death: / /

Adverse Event Attributed to:	____ Supplement ____ Underlying disease ____ Error/deviation in supplement administration, ____ Breach of Confidentiality (describe on separate sheet) ____ Information provided ____ Concomitant medication ____ Medical Intervention ____ Research Subject Complaint ____ Invasion of Privacy ____ Other suspected cause (describe on separate sheet) ____ Protocol violation
Has the same Adverse Event occurred previously in this study?	____ Yes ____ No If yes, how many times?:

SUBJECT DEMOGRAPHICS

Research Participant's gender: ____ M ____ F

Research Participant's Age in Years: _____

DETAILED UNANTICIPATED PROBLEM/ ADVERSE EVENT INFORMATION

Adverse Event Onset Date: / /

Adverse Event Termination Date: / / ____ N/A ____ Event Continuing
Description of Event **(include time relationship to investigational procedures):**
Action taken in response to Adverse Event:

If participant died, was an autopsy performed? ____ Yes ____ No ____ N/A

Date of autopsy: / / or ____ N/A

Internal Adverse Event Reporting Form

Relevant tests (e.g. x-rays) and results:	____ N/A
Describe treatment(s) of Adverse Event (Include medications used to treat this event.)	____ N/A
List name of Concomitant Medications (Do not include medications used to treat this event.)	____ N/A
Describe pre-existing conditions/relevant clinical history:	____ N/A

Date(s) of treatment(s) of the Adverse Event: / / or ____ N/A

Outcome of the Problem/AE:	____ Recovered/resolved ____ Recovering/resolving ____ Not recovered/not resolved ____ Recovered/resolved with sequelae ____ Fatal ____ Unknown ____ Other _____

Was the administration of the supplement stopped because of this Adverse Event? ____ Yes ____ No ____ N/A

Documentation accompanying the report (e.g., Progress Notes, Discharge Summary, Lab or Autopsy Reports, Other, etc.):	____ N/A
Description of any "other" documentation:	____ N/A

Internal Adverse Event Reporting Form

TYPE OF ADVERSE EVENT

Relationship of Event to study supplement ____ Unrelated ____ Unlikely ____ Possible ____ Probable ____ Definite

Does the participant need to be unblinded? ____ Yes ____ No

Report submitted to (check all that apply): ____ Sponsor (print or e-mail) ____ AUTEC ____ Northern X Regional Ethics Committee

IF UNBLINDING OF PARTICIPANT IS REQUIRED

What Treatment group was the subject assigned to? ____ Supplement _____ Placebo

PRODUCT AND DOSING INFORMATION

Did participant receive the dose specified in the protocol? ____ Yes ____ No

If not, what dose was given?

Date of first exposure to supplement? / /

Date of most recent exposure to supplement? / /

Total dose received prior to this event?

Total dose quantity administered to participant to date Date / / or ongoing _____

Was the administration of this product stopped because of this adverse event? ____ Yes ____ No

CONSENT/RISK/BENEFIT RATIO

Presently enrolled participants should be informed of Adverse Event: ____ Yes ____ No

Risk/Benefit Ratio has changed in light of Adverse Event: ____ Yes ____ No

Outcome

_____ Report Acknowledged/accepted without recommendation.
_____ Report Acknowledged/accepted pending receipt of additional information.
_____ Amendments required to study documents.

☐ **The Adverse event does not involve risk to subjects or others.**

Internal Adverse Event Reporting Form

Consent Form should be revised:	___ Yes ___ No	If yes, attach revised form with changes highlighted.

Participant Information Sheet should be revised:	___ Yes ___ No	If yes, attach revised form with changes highlighted.

Principal Investigator Signature: _____ Date _____

Date reviewed by Operations Group: ____ / ____ / _____

Appendix E: Demographic information form

STUDY ID: _____

DEMOGRAPHIC INFORMATION

1. Gender: _____
2. DOB: _____
3. Ethnicity: ☐ NZ European ☐ Māori ☐ Samoan

   ☐ Cook Islands Māori ☐ Togan ☐Niuean

   ☐ Chinese ☐ Indian ☐ Other _____
4. Living arrangement (alone or with others):

   _____
5. Year at school: _____
6. Any assistance at school:

   _____
7. Therapies used in management:

   _____

   _____

   _____
8. Medications and supplements:

   _____

   _____

   _____
9. ASD information:

   a) Date when diagnosed: _____

   b) Name of doctor who gave diagnosis: _____

   c) Type of ASD (if known): _____

   d) Any other comorbid diagnoses:

      _____

      _____

Appendix F: Study script

In the following script, scripting used for the three subsets of the SIPT was adapted from Ayres (1989).

"Hi [insert child's name here], *thank you for coming to play some games and help us today. We have five different games that we will be playing and we will play each one twice. To thank you for joining us we have a certificate for you to take home, and each time you complete a game you can put a sticker on your certificate* [show child the certificate and stickers – just the normal ones first, save the shiny ones for if they start to lose interest]. *If you want to have a break when we are playing the games, just let me know, we can stop whenever you want to. Are you ready to start the first game?"*

Sound-Induced Flash Illusion

"The first game we will play is called 'The Flash', we will be using computers to play this game. You will be sitting on this side and I will be sitting on that side. [Point out the chairs] *Come and have a seat."*

"In this game we need you to help us by letting us know when you see The Flash. You will be watching this white cross on the screen and a white circle will flash up on the screen just above it, we need you to tell us how many flashes you see. There will be either one, two, or sometimes there may not be a flash. You may also hear a beeping noise, but we just want you to tell us about the flashes. Do you understand? Can you explain that back to me?"

"This game is split into 5 rounds and you can put a sticker on your certificate and have a little break after each round. Does that sound ok? [Wait for response] *Cool, lets get started."*

"Watching the screen… Are you ready?" [As soon as the child says 'Yes' press the button – keep watching them throughout to make sure they are watching the screen before pressing the button]

"How many flashes did you see? [Wait for response, enter into computer] *Great, ready for the next one?"*

Continue like this through out the round of 20 presentations, using words like *"Great", "Good job", "Well done", "Awesome work",* etc. to encourage them to keep going. Let them know when, *"there's only 5 left of this round"* and "*last one".* At the end of each round offer, "*Would you like to put a sticker on your certificate?"*

Repeat process for 5 rounds. "*Now we are ready for the second game, this one is called 'Tapping Tunes'"*

Bilateral Manual Co-ordination

"For this game you will sit in this chair and I'll sit across from you in this one, with our feet flat on these white sheets of paper. We need to have our shoes off for this one, [take shoes off]. *First we will start with our hands, we will do a practice one first."*

"Watch my hands move. When they are through moving, you do the same thing." [Demonstrate Trial 1] *"That's correct."* – if performed well, otherwise. – "*Be sure to move smoothly like this".* [Move the child's hands smoothly through the pattern, if needed.] *When I begin with this hand* [Hold up your left hand], *You begin with this hand* [Touch the child's right hand]. "*When I begin with this hand"* [Hold up your right hand], *"You begin with this hand"* [Touch the child's left hand].

If the child performs the trial incorrectly, demonstrate the trial item again and if they do an insufficient number of movements, say: "*Do it as many times as I did it"* and then continue on to the test items by saying: *"Watch me do another one"*.

Demonstrate Item 1 and if necessary say: "*Now you do it"*. [NB: If the child starts with the wrong hand remind them to start with the mirror-image hand, only remind them of this once and if they continue to start with the wrong hand they aren't penalized for this.] Continue to demonstrate the rest of the hand test items, saying: *"Now you do it."* If necessary. [NB: If they do four consecutive items incorrect – discontinue the arm items and go onto the feet.]

OFFER [especially if they're losing interest]: "*Well done, would you like to put a sticker on your certificate now?"*

"Now we'll do the same thing with our feet. Watch me. [Perform Trial item] *Now you do it."* If the child has trouble executing the movements, move the child's feet through the motions – make sure the action is reciprocal. Then demonstrate the trial item one more time*, "Watch me do another one".* Then start test item 11 – 14, saying, *"Now you do it"* if necessary [NB: Discontinue the feet items if the child does 2 consecutive items incorrectly]

"Nice work; lets put another sticker on your certificate!" Place sticker on certificate. "*You're doing really great, are you ready to start the third game?"*

Kinesthesia

Have the desk set up with the trial side of the paper facing up (loosely taped to the desk). "*We are going to play a game called 'Going Visiting.' I will take your finger to different 'pretend' houses. Point your finger like this."* Demonstrate by holding up

your hand pointing your index finger, if the child's left hand is on the table, place it in their lap saying: "*We'll put this hand down here so we won't run into it.*"

Hold the child's right index finger on the lateral edges of the distal interphalangeal (DIP) joint and place the child's finger tip at the beginning of the line for Trial A, then say: "*This is where you live. I'm going to take you to House A. Think how it feels to go there so you can come back to House A by yourself."* Holding their index finger by the DIP joint, lift the hand and place it so their fingertip is at the arrow end of Trial A. [NB: Only talk to the child while their finger is still NOT while moving]

"*This is where House A is. Remember where House A is so you can come back to it. Leave your finger here awhile."* Release their finger and allow 3 seconds of silence for child to concentrate. "*I'll take you home"* Grasp their finger again, lift their hand and go back to the beginning of Trial A. "*This is where you live. Now put your finger on House A."* [NB: If the child is off target, help them to get more exact placing, saying: *Place the tip of your finger exactly on the arrow.*]

"*Now let's see if your other hand can play the game without your eyes helping it. To do that, I will use this shield.* [Position shield.] *It will be easier for you to feel where your finger is if you close your eyes."* Grasp the child's left index finger – remind them to point it if necessary, then place their finger on the start of Trial B.

"*This is where you live. I'm going to take you to House B. Think how it feels to go there so you can come back to House B by yourself."* Holding their index finger by the DIP joint, lift the hand and place it so their fingertip is at the arrow end of Trial B.

"*This is where House B is. Remember where House B is so you can come back to it. Leave your finger here awhile."* Release their finger and allow 3 seconds of silence for child to concentrate. "*I'll take you home"* Grasp their finger again lift their

hand and go back to the beginning of Trial B. "*This is where you live. Now put your finger on House B. Now leave your finger on the spot until I finish measuring."* Use a red pen to record the response by putting an inverted "V" with the point at the exact middle of the child's index fingernail and write the Trial number inside and quickly draw a line connecting the arrowhead to the inverted V. Remove the shield. "*On this one we can look to see how close you came to the house."* Help them examine their finger placement relative to the end of Trial B, if the understand, continue to the test items. Untape the test sheet and flip over and tape it into position, keep using the shield so the child doesn't see the test items before starting.

"*That part of the game was practice for you to learn how. Now, for the rest of the game, your hands will play without your eyes helping them. We will go to different houses. Can I please have your right finger pointed again?"* Grasp their finger in the same way as before and place it at the start of Item 1.

"This is where you live. I'm going to take you to the first house. Think how it feels to go there so you can come back to the first house by yourself." Holding their index finger by the DIP joint, lift the hand and place it so their fingertip is at the arrow end of Item 1. "*This is where the first house is. Remember where the first house is so you can come back to it. Leave your finger here awhile."* Release their finger and allow 3 seconds of silence for child to concentrate. "*I'll take you home"* Grasp their finger again lift their hand and go back to the beginning of Item 1. "*This is where you live. Now put your finger on the first house. Leave your finger on the spot until I finish measuring how close you are."* Use a red pen to record the response by putting an inverted "V" with the point at the exact middle of the child's index fingernail and write the Item number inside and quickly draw a line connecting the arrowhead to the inverted V. Repeat this process for each Item, alternating hands. [NB: If it is easier for

the child's understanding the houses can be referred to as House 1, House 2, etc. Instead of first house, second house, etc. If the child insists on seeing how well they went, say: "*You may look at all your answers at the end of the game when we are finished".*]

For more sophisticated and co-operative children, you may only need basic cues, e.g.: "*This is your house. This is the second (third, etc.) house. This is your house. Now go back to the second (third, etc.) house."*

Re-administer the two items that the child performed most poorly (by quickly measuring the items that appear to be the furthest away from their target) and refer to them as "House 11" and "House 12" but record them as the actual trial number but place a small 2 outside of the inverted V.

"*You're doing such a great job; lets put another sticker on your certificate, only two more games to play for the first round."*

Localisation of Tactile Stimuli:

"*This game we call 'Find the Spot', first we will do a practice one where you can use your eyes. Place your arms on the desk like this* [place arms on desk palms down] *I am going to touch you lightly with this pen. Put your finger where I touch you. Put your finger here.* Touch the back of the child's left hand with the tip of the pen, if necessary say: "*Put your finger exactly on the spot I touched."* If the child does not put their finger on the spot, show them how to do it – using a pointed index finger

"*Now let's see how close you can put your finger when you can't see where I touch you.* [Place the shield over the child's arms] *Put your finger here."* Immediately after the word 'here' touch the point identified as Item 1 with the pen. "*If your finger doesn't land on the right spot, move it until it is on the right spot."* Wait for them to

stop moving. *I'm going to measure you with this ruler. Leave your finger there until I finish.*

Use this same procedure for the remaining items, ensuring you have their attention before the stimulus by saying, "*Put your finger here"* or "*Here's another."*

Half way through ask the child to turn their hand over e.g. *"Now let's try the other side, turn your hands over"* Re-administer the two items with the largest distance and score in the second spaces on the protocol sheet.

"*Fantastic! Let's put some stickers on your certificate, only one more game left."* (NB: If they start to loose attention half way through – before they supinate their arms offer the first sticker reward)

Fine motor (bead threading) task:

"*This is the final game for the round/day; we call this one 'Lacing Beads', what colour would you like to play with?* Show them the box of beads and once they pick a colour, take all of the beads of that colour out and place them on the desk.

"*There are three patterns that we would like you to make by stringing these beads onto the shoe lace, like this* [demonstrate with one bead], *I'm going to time you while you make the patterns. Try to go as fast as you can but make sure you match the pattern on the card, okay?"*

"Here is the first pattern [place the first pattern card on the desk – facing the child], *ready? Set? Go!"* Start the stopwatch when you say go and stop as soon as the child is finished.

"Excellent, now lets take the beads back off, here is the second pattern [place the second pattern card on the desk – facing the child], *ready? Set? Go!"* Start the stopwatch when you say go and stop as soon as the child is finished.

"Well done! Let's take those bead back off again, and this is the last pattern [place the third pattern card on the desk – facing the child], *ready? Set? Go!"* Start the stopwatch when you say go and stop as soon as the child is finished. [NB: Be sure to mark down which beads were in the correct order on the scoring sheet, as well as the time taken]

"*Awesome work, you finished all of the games for the round/day, let's put the last sticker on your certificate."*

If that was their baseline, then say: "*And now you're going to be checked by the chiropractor, come this way"* Take them to where they do their intervention/control session

If that was their post intervention test, then say: "*Thank you so much for coming down to play these games with us today. It was really nice to meet you. You did such an amazing job!"*

Appendix G: Beads used for the threading beads task

Appendix H: Shape-based patterns used for the threading beads task

Pattern 1:

Pattern 2:

Pattern 3:

Appendix I: Data collection spreadsheet

Number of illusions:	X	Motor coordination:		Kinaesthesia:		Tactile stimulation:		Patterns:	
Notes		Trial	Score	Trial	cm	Trial	cm	Trial	Sec
		1		1		1		1	
		2		2		2		2	
		3		3		3		3	
		4		4		4			
		5		5		5		Notes	
		6		6		6			
		7		7		7			
		8		8		8			
		9		9		9			
		10		10		10			
		11				11			
		12		Notes		12			
		13							
		14				Notes			
		Notes							