The Impact of Early Comprehensive Intervention on the Mirror Neuron System in Autism Spectrum Disorders

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Abstract

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The mirror neuron system (MNS) has attracted significant interest within the scientific and lay communities. The study of mirror neurons has a relatively short but rich history. The MNS has been implicated in a series of cognitive functions including action recognition, imitation, empathy, and language. The broken mirrors hypothesis was asserted in the context of a series of attempts to propose a singular theoretical cause for the ostensibly unrelated and distinct symptoms of ASD. The aim of this study was to examine neural functioning in light of early comprehensive intervention, using an established paradigm assessing EEG mu attenuation. Using a randomized design, children were assigned to either receive comprehensive intervention following the Early Start Denver Model (ESDM), or were encouraged to pursue resources in the community (COM) while receiving standardized assessment and monitoring. Two years after completing the intervention, EEG was collected during the execution and observation of simple grasping actions performed by familiar and unfamiliar agents. Spectral power in the mu range, a putative index of MNS functioning, was calculated. Mu attenuation during the observation of grasping actions did not differ between the ESDM and COM groups, as both groups displayed attenuation to the

observation of motor actions. However, there was a significant interaction in how the two groups viewed familiar and unfamiliar individuals executing identical actions. While the COM group showed no significant difference between viewing familiar and unfamiliar individuals, the ESDM group showed significantly greater attenuation when viewing a parent or caregiver executing a grasping action, compared with the observation of an unfamiliar individual executing the same action. Our findings suggest that the ESDM may have a unique impact on the mirror neuron system in ASD.

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Acknowledgments

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Dedication

This project is dedicated in memory of my grandfather, Victor Marshall, M.D. (1914 - 2016). He possessed an insatiable curiosity, and always wished to know more about science, medicine, psychology, and beyond. During his professional life, he volunteered a remarkable 50% of his week providing services to underserved populations far before it was fashionable. He continued learning and teaching his entire life, retiring as professor emeritus in the USC School of Medicine in 2007 at the age of 92, before moving to Seattle. I discussed this project with him many times, and he would have enjoyed seeing its completion.

Introduction

Autism Spectrum Disorders: Definition, Prevalence, Etiology, and Diagnosis

Autism spectrum disorders (ASD) are characterized by deficits in social and communicative functioning, as well as repetitive behaviors and circumscribed interests (International Classification of Diseases-10th Revision, ICD-10, World Health Organization, WHO, 1992). This categorization previously included autistic disorder, Asperger's disorder, childhood disintegrative disorder, and pervasive developmental delay not otherwise specified (PDD-NOS), collectively organized under the heading of Pervasive Developmental Disorders (PDD) in the Diagnostic and Statistical Manual – 4th Edition (DSM-IV TR; American Psychiatric Association, 2000). Currently, these diagnoses have been subsumed under the general category of autism spectrum disorders in the DSM-V (American Psychiatric Association, 2013).

Definition. The definition of autism has evolved extensively over the past few decades. While Kanner proposed one early description in 1943, his definition was far more limited than modern-day definitions. Autism was later incorporated into professional diagnostic manuals such as the International Classification of Diseases (ICD-9) in 1977 (World Health Organization) and the *Diagnostic and Statistical Manual of Mental Disorders, third edition* in 1980 (DSM-III; APA). The DSM-III definition included impairment in social responsiveness, communicative ability, and abnormal responses to environmental stimuli. It also included the requirement of onset of symptoms within the first 30 months of life (APA, 1980). Pervasive Developmental Delay – Not Otherwise Specified (PDD-NOS) was added in a 1987 revision to include children meeting only part of the diagnostic criteria. Difficulties with the environment were redefined as restricted interests and the requirement of early onset was also removed (APA, 1987). Asperger's disorder and Rett's syndrome were added to the list of Pervasive Developmental Disorders in the DSM-IV (APA, 1994) and DSM-IV-TR (APA, 2000).

Finally, in the DSM-V the separate social impairments and communication impairments were combined into a single category, and the abnormal responses and restricted interested were categorized as repetitive or restricted "patterns of behavior" which includes sensory challenges with the environment (APA, 2013). These are the current two categories of impairment required for a diagnosis of autism spectrum disorder. Intellectual disability, a long-standing but complex comorbidity with ASD, is now assessed separately, and a diagnosis of ASD can be given with or without cognitive impairment.

Prevalence. The changes in diagnostic criteria over time have complicated the study of historical prevalence of ASD. Recent prevalence estimates have been increasing at an alarming rate. A prevalence estimate of 1 in 150 was released by the Center for Disease Control and Prevention (CDC) in 2007. The CDC's estimate increased to 1 in 110 in 2009, 1 in 88 in 2012, and finally 1 in 68 in a 2014 report (CDC, 2014). The factors contributing to these increases have been hotly debated. Some have questioned these recent increases, especially considering subtle but potentially significant changes in case ascertainment (Mandell & Lecavalier, 2014; Zablotsky, Black, Maenner, Schieve, & Blumberg, 2015).

Previous best estimates of autistic disorder placed in incidence at 22/10,000 or 1 in 455, whereas for all forms of ASD the incidence rises to 70/10,000 or 1 in 143 (Saracino, Noseworthy, Steiman, Reisinger, & Fombonne, 2010). Prevalence rates of autism and PDD have increased over time, as studies have found a positive correlation between year of publication and reported prevalence (Fombonne 2005, 2009a). Various reasons have been suggested for the observed increase, and while a true underlying increase in incidence cannot be ruled out, 5 auxiliary factors have been identified that potentially contribute for the reported growth including: broadening of the case definition, diagnostic substitution, changes in case identification procedures, changes in policies and awareness, and improved detection (Saracino et al., 2010).

Chakrabarti and Fombonne (2005) argue that a broadening conceptualization of autism, reflected in a broadening of the diagnostic criteria, have contributed to increased prevalence rates. This notion is corroborated by a study conducted by Kielinen, Linna, and Moilanen (2000) in Finland, which assessed a single sample of subjects according to differing historical definitions of ASD. Different prevalence rates were reported depending upon which definitions were used (Kanner's original definition versus the use of the ICD-10 and DSM-IV) lending credence to the evolution and broadening of autism as factors influencing epidemiological estimates.

Diagnostic substitution or diagnostic shifting, the refinement and relabeling of mental disorders according to categorical trends, has been suggested based on a corresponding decrease in the reporting of Mental Retardation (MR) as the incidence of ASD has risen (Bishop, Whitehouse, Watt, & Line, 2008; King & Brearman, 2009; Shattuck, 2006). There are noted limitations to this theory (Fombonne, 2009b)

and some studies have failed to observe a corresponding decrease in MR diagnosis (Newschaffer, Falb, & Gurney, 2005).

Methods of case identification also impact epidemiological studies (Fombonne, 2003, 2005). Studies may choose to examine education databases (Newschaffer et al., 2005), convenience samples (Williams, Atkins, & Soles, 2009), or engage in other methods of recruitment and assessment. These differences in screening and technical diagnostic procedures can also influence estimates.

Changes in public awareness and policies related to availability of services may also affect the diagnosis of ASD (Saracino et al., 2010). Parents may actively seek out an ASD diagnosis if it gives their child better access to services. Campaigns about early risk markers and the benefits of early intervention may provide greater encouragement than in previous years (for example see Learn the Signs. Act Early, Center for Disease Control and Prevent, CDC, 2010).

Finally, methods of detection have improved and developmental research has contributed to earlier diagnosis of ASD. Even if the underlying prevalence was stable, such innovations increase prevalence (Hertz-Picciotto & Delwiche, 2009). Prevalence rates will continue to rise as diagnostic instruments increase in sensitivity, extending diagnoses to previously unexamined populations.

In a recent population level study in Sweden of 19,993 twins over a 10-year period, the prevalence of specific symptoms of the autism phenotype were assessed by telephone interview. These were compared to the incidence of a registered diagnosis of ASD over the same 10-year period. Results showed that while the registered incidence of ASD significantly increased between 1993 and 2002, the incidence of underlying symptoms was constant (Lundstrom, Reichenberg, Anckarsater, Lichtenstein, & Gillberg, 2015). These findings highlight symptoms of ASD and the external and societal factors that impact the likelihood of receiving a formal diagnosis.

Etiology. There is strong evidence that genetic factors contribute to autism spectrum disorders. In a study by Folstein and Rutter of 21 pairs of twins, both members of 4 of 11 pairs of monozygotic twins met criteria for autism, in contrast to 0 of 10 pairs of dizygotic twins. Five additional monozygotic twin pairs showed a cognitive abnormality, in contrast to 1 pair of dizygotic twins. In summary, 36% of the monozygotic pairs both met criteria for autism, and 82% displayed a shared cognitive abnormality, in contrast to none of the dizygotic pairs both meeting criteria for autism, and only 10% sharing a cognitive

abnormality (Folstein & Rutter, 1977). The authors conclude “concordance rates in conjunction with the very low prevalence of autism in the general population point to a strong genetic determination” (p.728). While this early study did not provide a comprehensive model or explanation of genetic inheritance of autism, it provided early evidence for a genetic contribution to ASD.

A follow up study confirmed these findings and extended them to include broader autism traits. In a study of 44 sets of twins (and triplets), including Folstein and Rutter’s (1977) original pairs of twins, Bailey and colleagues found a 60% concordance rate for autism among monozygotic twins, and a 0% concordance rate among dizygotic twins. Interestingly, when examining the presence of broader autism traits, a 92% concordance rate emerged for monozygotic twins and 10% rate for dizygotic twins (Bailey et al., 1995). While Folstein & Rutter’s original study used a very limited definition of autism, the follow-up study by Bailey (1995) examining broader traits provided a better understanding of the potential genetic contribution to autism spectrum disorders. Using liability threshold modeling, a broad heritability estimate was calculated to be between 91 and 93 percent (Bailey et al., 1995).

Additional research examining the rate of recurrence in siblings points to a genetic liability for ASD. Ozonoff and colleagues, as part of a Baby Siblings Research Consortium funded by the National Institute of Health, followed 664 infants with an older sibling diagnosed with ASD. Enrolled by 18 months and assessed for ASD at 36 months using the ADOS and Mullen Scales of Early Learning, 132 participants met criteria for ASD at 36 months, including 29 female participants. This yielded a recurrence rate of 18.7 percent, indicating a significant risk-increase compared with the general population (Ozonoff et al., 2011). This provided further evidence for genetic factors contributing to the incidence of ASD.

A large-scale genetics study of ASD was undertaken as part of the Simons Foundation Autism Research Initiative. It included over 2000 families which met the gold-standard diagnostic criteria for ASD (Filipek et al., 1999) from across the country, diagnosed and recruited at some of the nations leading universities with established autism clinics. For each child with ASD, a comprehensive evaluation was completed including measures of ASD, cognitive functioning, language, adaptive functioning, emotional and behavioral symptoms, and motor skills. Additional measures were completed for family members. A blood sample was taken from each family member and stored in a common repository (Fischbach & Lord,

2010). This study represented a major step forward in identifying ASD, assessing the largest sample to date with a precise, comprehensive, and consistent methodology across cases.

A number of findings emerged from this landmark study, some of which were unexpected. While the phenotypic presentation of ASD across the 12 university-based sites was consistent, the clinical diagnoses based on the DSM-IV-TR were not uniform. These “best-estimate” clinical diagnoses, using the same standardized measures and rigorously controlled protocols across sites did not yield matching results (Lord et al., 2012). This finding influenced the committee charged with updating the definition of autism in the DSM-V to retire the diagnoses of Asperger’s disorder and Pervasive Developmental Delay – Not Otherwise Specified, and subsequently use the umbrella classification of autism spectrum disorders (Hazen, McDougle, & Volkmar, 2013).

The most common genetic variant that emerged from the Simons Simplex Collection (SSC) was a deletion or duplication at the 16p11.2 locus. However, this particular event accounted for less that 1 percent of the ASD sample in the SSC. This finding spawned a follow up project termed the Simons Variation in Individuals Project, which changed the methodology for pursuing the genetics of autism. Instead of gathering a carefully clinically-defined sample based on rigorous diagnostic criteria, a sample was ascertained driven by a specific genetic event, namely a deletion or duplication at 16p11.2 (The Simons VIP Consortium, 2012).

In an unexpected scientific turn of events, the follow-up study examining 85 participants with 16p11.2 deletion resulted in an autism hit rate of only 21-24 percent (Hanson et al., 2015). The deletion at 16p11.2 more commonly resulted in a diagnosis of Developmental Coordinator Disorder (58%), Phonological Processing Disorder (56%), and Mixed Expressive/Receptive Language Disorder (46%). This complicated an already complex picture of autism genetics given that the most commonly identified single genetic contributor to ASD did not cleanly lead to an ASD phenotype.

A further analysis of the SSC sample using constrained autism sub-phenotypes did not result in greater homogeneity of genotypes (Chaste et al., 2015). In other words, identifying subtypes of ASD based on diagnosis, cognitive scores, or symptom profiles did not substantially correlate with particular genotypes. The process of exploring the genetics of ASD over the past decade clearly evidences the

advantages of using biologically defined psychiatric disorders over clinically defined constructs (Duyzend & Eichler, 2015).

***Specific Genetic Contributions*.** The large dataset from the Simons Simplex Collection (SSC; Fischbach & Lord, 2010) which includes comprehensive genotype and phenotype information, has provided a fertile ground for further research. The evolution of methodologies for efficiently scanning the human genome for genetic events related to development, such as exome sequencing (O'Roak et al., 2011) and molecular inversion probe (MIP) sequencing (Hiatt, Pritchard, Salipante, O'Roak, & Shendure, 2013; O'Roak, Vives, Fu, et al., 2012) have exponentially added to the utility of this extant dataset and revolutionized research capabilities. This has uncovered the contributions of gene-disrupting mutations (O'Roak, Vives, Fu, et al., 2012) including copy number variations (CNV ;Fernandez et al., 2010; Freitag, Staal, Klauck, Duketis, & Waltes, 2010; Girirajan et al., 2013) and single nucleotide variations (SNV; Jacquemont et al., 2014; Turner et al., 2015).

In a study of 209 individuals with ASD, exome sequencing identified gene-disrupting mutations in 25% of cases (O'Roak, Vives, Girirajan, et al., 2012). In another study of 44 genes across 2,446 individual with ASD, 6 specific gene-disrupting mutations were identified, estimated to account for 1% of sporadic cases of ASD (O'Roak, Vives, Fu, et al., 2012). Additional analysis of the SSC sample confirmed 6 large CNV loci, as well as 71 risk loci when smaller deletions were included (Sanders et al., 2015). In a further study using whole-genome sequencing to analyze 208 genomes from 53 families with one child with ASD, multiple smaller previously sub-threshold CNVs were implicated in some cases of simplex ASD (Turner et al., 2016). Published estimates suggest that identified genetic contributors may account for as much as 30% of simplex cases and 45% of female cases of ASD (Iossifov et al., 2014). A comprehensive calculation based on a review of current literature may yield an even higher estimated percentage of ASD cases with an identified genetic contributor.

Environmental Factors. There has been extensive discussion about the impact of environmental factors on the incidence of autism spectrum disorders. Most studies pointing to environmental factors show that within a population exposed to a certain factor, the rate of autism is higher than in the general population. For example, in a sample of 100 cases of thalidomide exposure during embryonic development, 4 went on to meet criteria for ASD (Strömland, Nordin, Miller, Akerström, & Gillberg, 1994).

In another study of 57 children with prenatal exposure to valproic acid, an anticonvulsant, 6 children went on to meet criteria for ASD (Moore et al., 2000). Another study of the neurological disorder Möbius syndrome included 5 children who met criteria for ASD, 3 of which had prenatal exposure to misoprostol, an abortifacient. The authors report that 60% of the ASD cases had a history of misoprostol exposure (Bandim, Ventura, Miller, Almeida, & Costa, 2003).

There are a few flaws with this methodology. As the reported incidence of ASD in the general population has increased, the argument that the incidence rate in these particular exposure samples is higher than expected may no longer hold true. Furthermore, it is erroneous to draw conclusions about ASD in general from a set of 4, 5, or 6 cases which met criteria for ASD within a specific sample. While there are individuals with Down syndrome who have been diagnosed with ASD, it seems flawed to propose trisomy 21 as a cause for autism. Finally, an increased risk for autism falls short of representing a fundamental cause for ASD. While research into the relationship between neurotoxic exposure and ASD may be of interest, headings such as “Direct evidence for environmental causation of autism” (Landrigan, 2010) seem unwarranted.

It is clear that neurotoxins can play a role in disrupting embryonic development with significant neurological consequences. Indeed, environmental factors may play a role in parsing small percentages of the sample of children diagnosed with ASD. However, the current research stands at showing that in a given sample of individuals affected by neurotoxicity there are cases of ASD, and among cases of ASD there are instances of neurotoxicity. This emphasizes the heterogeneity of ASD diagnosis and its encompassing of multiple and distinct etiologies.

In summation, autism spectrum disorders describe a series of different etiologies that contribute to social impairment. Current research has documented that genetic contributors are a significant factor in developing these impairments or “types” of autism. However, the current clinical diagnostic systems fall short of being able smoothly classify these phenotypes. As the science of tools of genetics evolve, our understanding of psychiatric disorders will continue to advance.

Role of the School Psychologist. The school psychologist can play a prominent role in providing services to families affected by autism spectrum disorders. While positions and responsibilities may vary across districts and schools, the school psychologist has the potential to have significant impact

on a child's access to and quality of services. This could include screening and diagnosis, case management, and intervention.

Screening. Screening is an important component of the diagnostic process. It serves to identify children at risk for social problems and helps focus clinical resources. Professionals who have familiarity with autism symptomology should conduct regular developmental screening utilizing standardized instruments (Filipek et al., 1999). A formal diagnostic evaluation can be quite resource intensive, and thus an accurate screening process is integral to ensure resources are being deployed effectively.A number of screening procedures have been shown to be effective in assessing risk for autism spectrum disorders. These include standardized screening instruments (for review, see Wilkinson, 2009), teacher nomination (Hepburn et al., 2008), and the establishment of an autism screening team (Noland & Gabriels, 2004). Multiple strategies could be effectively integrated into a school or district-wide screening procedure.

The school psychologist is often an integral piece of the building-level referral process. Designing an effective referral procedure that employs evidence-based strategies for developmental screening will best serve children and families, and maximize efficiency for district and school resource allocation. But effective screening is not sufficient; a plan must be in place to move from screening to diagnosis.

Diagnosis. It is recommended that the diagnosis of autism be conducted by a specialist who possesses expertise in ASD. It should include a direct and formalized observation of the child, in conjunction with a parent interview. The evaluation should also include the assessment or symptoms not directly related to ASD such as hyperactivity, anxiety, depression, intellectual ability, and language. These areas are necessary to determine if further specialized evaluation is needed and for treatment planning (Filipek et al., 1999).

With specialized training, a school psychologist is capable of completing every part of the diagnostic process of ASD. This includes using gold-standard diagnostic instruments such as the autism diagnostic observation scale (ADOS; Lord et al., 2000), autism diagnostic interview – revised (ADI-R; Lord, Rutter, & Le Couteur, 1994). Trainings in these instruments are available from a number of autism centers and individual instructors.

Autism has been a reportable special education category since 1992 with the passing of the individuals with disabilities act (IDEA). The federal regulations do not stipulate that the diagnostic criteria

of the *Diagnostic and Statistical Manual* (American Psychiatric Association, 2013) or the *International Classification of Diseases* published (World Health Organization, 2010) must be followed. Autism thus remains an independent educational category. As states are required to interpret and implement IDEA, the definition of ASD is subject to interpretation by states (Noland & Gabriels, 2004). IDEA (1999) defines autism as follows:

> Autism means a developmental disability significantly affecting verbal and nonverbal communication and social interaction, generally evident before age three, that adversely affects a child's education performance. Other characteristics often associated with autism are engagement in repetitive activities and stereotypical movements, resistance to environmental change or change in daily routines, and unusual responses to sensory experiences. (34 C.F.R. § 300.7)

Here autism is defined broadly such that a diagnosis based on the DSM-IV, DSM-V, or ICD-10 would smoothly meet criteria. Washington State for example uses the same language as the federal guidelines (WAC 392-172A-01035). No autism-specific procedure is outlined by IDEA or state rules, thus utilizing the gold-standard and evidence-based diagnostic tools such as those recommended by Filipek and colleagues (1999) should be undeniably adequate.

If a school psychologist has completed training to utilize autism-specific diagnostic instruments such as the ADOS and ADI-R, an evaluation of ASD can proceed like other evaluations. Appropriate screening measures are utilized, testing sessions are scheduled, and measures and reports are completed. If a school psychologist has not completed specific training in the evaluation of ASD, a referral procedure should be in place. This would ideally include a district-based autism screening team or a licensed psychologist on a retainer with the district (Noland & Gabriels, 2004). If these resources are not in place, a list of autism centers or practitioners with the requisite expertise in ASD should be made available to the family to pursue a complete diagnostic evaluation.

Case Management. The educational needs of a child with ASD are varied and complex. One unique challenge is that ASD deficits are not always readily apparent. This is compounded as children with ASD often display discrepancies in traditional cognitive profiles (Joseph, Tager-Flusberg, & Lord, 2002). A child might score within the normal range on IQ tests, and even on standardized assessments of

social functioning such as the Vineland Adaptive Behavior Scales (Sparrow & Cicchetti, 1985) and still manifest significant impairment in executive, emotional, and social functioning (Mundy, 1993).

The National Research Council (NRC) convened a committee of leading experts to make educational recommendations for children ASD. The committee recommended that children with ASD be assessed across multiple domains and contexts, including developmental evaluations, examination of variability in skill sets, translation to real life problems, social functioning, and behavioral functioning (2001). This is undoubtedly a demanding endeavor, but is requisite for the accurate assessment of a complex disorder such as ASD.

Furthermore, they note that since autism includes impairments across a variety of domains, evaluations might require professionals from multiple disciplines, including psychology, speech and language pathology, neurology, pediatrics, psychiatry, audiology, as well as physical and occupational therapy. In some situations, the involvement of professionals not typically available in school settings might be warranted (National Research Council, 2001).

Intervention. It is recommended that goals for children with ASD "affect a child's participation in education, the community, and family life" (National Research Council, 2001). More specifically, these goals should include social skills, language development, (including expressive verbal language, receptive language, nonverbal communications skills, and a functional symbolic communication system), engagement and flexibility in developmentally appropriate tasks, play, fine and gross motor skills, cognitive skills (symbolic play and academic skills), conventional/appropriate behaviors, and independent organizational skills and skills for success in a regular classroom (National Research Council, 2001).

A number of interventions are considered evidence-based practices for ASD. While not all may be available in a school setting, it would be appropriate for a school psychologist to make comprehensive recommendations, especially given the varying levels of awareness regarding available interventions and best practices (Dillenburger, Jordan, Mckerr, Devine, & Keenan, 2013). Particularly, a series of evidence-based intervention systems have emerged with some common core features.

Naturalistic Developmental Behavioral Interventions (NDBI) represent intervention programs that are based in well-researched developmental and behavioral principles. Common features of NBDIs include a focus on the antecedents of behavior, behavioral responses, and feedback in the environment.

Most have a manualized system which includes monitoring the fidelity of implementation. Individualized goals are developed and progress is carefully monitored, often based on clearly defined criteria of objectively observable behavior. When possible, the programs follow the child's lead, as this most commonly leads to intrinsic reinforcement and generalization. The teaching environment is often designed specifically to maximize rewards for adaptive behaviors and behavioral learning. Prompts and modeling are used to provide learning opportunities, but supports are faded to promote independence (Schreibman et al., 2015).

A few NDBIs which have been studied recently include the Early Start Denver Model (Geraldine. Dawson et al., 2010; Geraldine Dawson et al., 2012), pivotal response training (Koegel & Koegel, 2006; K Pierce & Schreibman, 1997; Schreibman & Koegel, 1996), reciprocal imitation training (Ingersoll & Dvortcsak, 2006; Ingersoll, 2010, 2012), and a program focusing on joint attention, symbolic play, engagement, and regulation (Connie Kasari, Freeman, & Paparella, 2006; Connie Kasari, Gulsrud, Freeman, Paparella, & Hellemann, 2012).

Parent education is an ideal component of any intervention program. Parent involvement improves outcomes (Ingersoll & Dvortcsak, 2006; C. Kasari et al., 2014; Connie Kasari, Gulsrud, Paparella, Hellemann, & Berry, 2015; Schreibman & Koegel, 1996; Wetherby et al., 2014) and in some instances even mediates outcomes (Green et al., 2010). Recent research has also indicated that while parent education is effective, direct parent training, including practicing intervention techniques with both the parent and child present, surpasses parent education in its effectiveness (Bearss et al., 2015).

Barriers. There are unfortunately many barriers to the school psychologist doing more for children with ASD. The role of a school psychologist is often complex, impacted by how it is situated within schools and districts. Limited training opportunities, conflicting responsibilities, and limitations on district resources can potentially interfere with a school psychologist's ability to implement best practices for a child with ASD.

The instruments used in the diagnosis of autism, including the autism diagnostic observation scale (Lord et al., 2000) and the autism diagnostic interview (Lord et al., 1994), are not part of the standard cognitive and academic instruments that make up most practicum curricula at school psychology programs. School psychologists would need to independently pursue training opportunities

after graduation or request district support for professional development. Qualified training opportunities may not be available in every local setting.

In the Seattle area some encouraging developments have occurred. The school psychology program at the University of Washington currently offers a practicum experience specifically related to the diagnosis of ASD. This will ensure participating students are well equipped to be involved in the diagnosis of ASD and the accurate interpretation of diagnostic evaluations conducted in other community settings. Further, the Seattle Public Schools has sent a team of school psychologists to complete ADOS training at the University of Washington Autism Center. These developments may indeed change the landscape regarding the involvement of school psychologists in ASD evaluations.

The role of school psychologist varies immensely across districts and even schools. Some roles include intervention services such as counseling and social skills groups, while others are limited to testing and writing reports. Effective case management and progress monitoring are essential but time-intensive. Conflicting responsibilities may hinder the school psychologist from effectively engaging the various roles required to effectively serve children with ASD.

As noted above, the National Research Council concluded that it might be necessary to engage professionals not typically found in school settings in order to adequately serve children with ASD (2001). For behavioral issues, a board-certified behavior analyst would be a likely choice for a consultant. Even though speech language pathologists and occupational therapists are part of the standard school personnel, their actual availability for intervention and progress monitoring may be limited. Thus garnering the necessary resources to cater to the diverse needs of a child with ASD may remain a challenge. While a school psychologist may make recommendations for utilizing personnel not readily available within the school district, this practice is not always encouraged, as this may put financial pressure on the school or district.

Summary of Autism Spectrum Disorders. Autism spectrum disorders are complex, and their specific definition has evolved extensively over time. Many of the current prevalence estimates are flawed, but it is clear that a significant portion of children face developmental challenges and social impairment. The etiology of these social challenges is quite varied. Recent research has identified genetic contributors to ASD, but the classical clinical classification systems do not smoothly correlate with the

underlying genotypes or phenotypic expression. As basic science and genetics progresses, it will likely continue to revolutionize our understanding of psychiatric disorders.

In the meantime, autism spectrum disorders remain a clinically meaningful construct. It assists in the identification of social impairments and aids in treatment planning. Professionals can design and implement intervention programs based on their effectiveness with this specific population. The school psychologist has a prominent role to play in screening, diagnosis, case management and intervention. Despite system-wide barriers, the school psychologist has the potential to make a significant impact on the children and families he or she serves. Specific education, training, and experience with ASD and related disorders will maximize this potential.

Neural Theories of Autism Spectrum Disorders

It has been long established that autism is a biological disorder. The manifest social deficits in autism spectrum disorders have led to multiple theories of etiology. One prominent theory asserts that differences in connectivity between brain regions leads to impairment in functioning. Given that social interactions are arguably one of the most complex human activities, involving the simultaneous integration of multiple brain systems from visual and perceptual to emotional and cognitive areas, impairments in brain connectivity would likely manifest in social functioning. Another prominent theory asserts that dysfunction in specific areas related to social functioning lead to impairments in social perception and social interaction.

These theoretical models were proposed during a time where a singular model of autism remained a reasonable scientific ambition. Varied explanations were proposed, including cascading consequences of early developmental deficits (Rogers & Pennington, 1991), a host of dysfunctional neural regions and systems, and individual differences in abstract psychological constructs. While research into the genetics of ASD have implicated multiple and distinct etiologies, attempts to offer a singular characterization of ASD continue (Van de Cruys et al., 2014). Popularity and interest in these singular theories has fluctuated dramatically over the past two decades.

Interconnectivity Hypothesis. Just and colleagues (2004) argued that underconnectivity across brain regions may play a fundamental role in the etiology of ASD. In a study of 17 “high-functioning autistic participants” (p. 1813) and 17 controls matched on IQ and age, they used fMRI during sentence

comprehension to examine activation in Wernicke's area and Broca's area. The ASD group showed greater activation in Wernicke's area and reduced activation in Broca's area compared with controls. Further, a measure of synchronous activation across brain regions, termed functional connectivity, was reduced in the ASD group compared with controls (Just, Cherkassky, Keller, & Minshew, 2004). The authors propose that underconnectivity across brain regions, resulting in integration deficits, may be a viable theory to explain the neurobiology of ASD.

A follow-up study was conducted using fMRI to examine activation during an executive functioning task. Specifically, the Tower of London task was utilized, in which participants are required to plan multiple steps ahead in order to match an ordered pattern. In a sample of 18 individuals with ASD and 18 control subjects matched on age, gender, and IQ, the groups did not differ on behavioral results. The areas of activation in the brain were also similar across groups, and the authors make a point to minimize any differences in spatial activation. However, there were observed differences in "functional connectivities" (p.955) in the ASD group between frontal and parietal areas (Just, Cherkassky, Keller, Kana, & Minshew, 2007). The authors also note differences in the size of the corpus callosum (Just et al., 2007).

Just and colleagues (2007) place the underconnectivity theory in the context of previous whole-brain processing theories. These include the complex information processing theory, which asserts that basic processing mechanisms remain intact, while later more complex brain processes are disrupted across multiple functional domains (Minshew, Goldstein, & Siegel, 1997), and the weak central coherence theory, which similarly highlights that localized information processing remains intact while the integration of information is disrupted (Hill & Frith, 2003).

An EEG study by Murias, Webb, Greenson, and Dawson (2007) examined EEG coherence during rest as a measure of functional connectivity in a sample of 18 adults with ASD and 18 controls. They found locally elevated connectivity in frontal and temporal areas, along with reduced global connectivity between frontal and other areas of the brain. They conclude that the ASD profile includes both patterns of overconnectivity and underconnectivity across different brain regions (Murias, Webb, Greenson, & Dawson, 2007).

Kana, Libero, and Moore (2011) build off the theory proposed by Just and colleagues (Just et al., 2007, 2004), but incorporate other connectivity disruptions, including underconnectivity and overconnectivity. They highlight deficits in theory of mind, cognitive flexibility, and communication ability, as being potentially explained by this disrupted connectivity. Noting the general complexity of social interactions, they discuss how information processing speed and difficulty with inhibition can lead to the misinterpretation of information, including social cues. The authors conclude with a proposal that disrupted cortical connectivity emerges as a powerful theory with explanatory potential at "behavioral, cognitive, and neural levels" (p.427; Kana, Libero, & Moore, 2011).

Prat and Stocco (2011) offer an extension of this theory to include disrupted functioning in the basal ganglia. They argue that disruption in the basal ganglia provides a needed connection between the cognitive characteristics of ASD and commonly observed differences in motor development, including repetitive motor behaviors and fine and gross motor deficits. Theoretical models place the basal ganglia at the center of routing information to and from the frontal lobes. The basal ganglia have also been implicated in basic cognitive functions such as language and set-shifting, along with motor movements. Dysfunction in the basal ganglia could lead to abnormal synchronization and deficits in advanced cognitive processes. They suggest that insofar as the basal ganglia is involved in routing multiple types of information, it may be a prominent neural component of the disrupted connectivity theory (Prat & Stocco, 2012).

Williams (2011) makes an important comment on Kana and colleagues (2011) theory. She first notes that the proposed theory does not clarify the causal relationship between brain and behavior. It fails to explain whether, for example, joint attention deficits are a result of abnormal neural connectivity or result in abnormal neural functioning. Furthermore, differences in brain connectivity have been reported in other disorders such as dyslexia (Gabrieli, 2009) and schizophrenia (Karlsgodt et al., 2008). It is therefore difficult to conclude that neural connectivity is a unique explanation of the neural basis of ASD (D. L. Williams, 2011).

Vissers and colleagues (2012) provide a comprehensive review of the literature regarding disrupted connectivity in ASD. They conclude that there is a notable degree of evidence from fMRI studies for reduced connectivity between frontal and parietal regions during the performance of

cognitively loaded tasks. Resting state MRI studies also corroborate this finding. Some DTI studies report results consistent with the under-connectivity reported in fMRI and MRI studies. However, the EEG and MEG research remains inconsistent (Vissers, Cohen, & Geurts, 2012).

Vissers and colleagues (2012) boldly note that the connectivity hypothesis as it currently stands is lacking. Most of the empirical support for the hypothesis comes for post-hoc correlations. They rightly suggest that research that outlines specific questions and hypotheses in advance to test via precisely designed experiments will help further our understanding of the relationship between brain connectivity and ASD symptomology.

Understanding the specific etiology behind neural deficits is key to furthering our understanding of ASD. While post-hoc correlational differences are interesting, they fall short in providing a comprehensive and testable theory of autism spectrum disorders.

A potential strength of the interconnectivity theory is that it has been purported to provide a comprehensive explanation of both social deficits and repetitive or stereotyped behaviors. While correlations have been observed between repetitive behaviors and functional connectivity in the posterior cingulate cortex and parahippocampal gyrus, it is unclear whether this is a cause or consequence of repetitive behaviors (Monk, Peltier, Wiggins, & Weng, 2009).

Social Information Processing Hypothesis. Brothers (1990) suggested specific regions of the brain primarily associated with social functioning such as the amygdala and orbitofrontal cortex (Brothers, 1990). She highlights research conducted with macaque monkeys (Brothers, Ring, & Kling, 1990) demonstrating selective response to social stimuli in neurons in the amygdala and nearby regions. She further explores the unique neural system for social cognition in hominids in an evolutionary framework (Brothers, 1990).

Many brain areas have been implicated in social processing deficits in ASD. In a study examining performance on a series of neuropsychological tasks, Dawson and colleagues (1998) compared responses across groups of children with autism, Down syndrome, and typical development. The group of children with autism took significantly longer to reach criterion on a rule-learning task (Delayed Non-Matching to Sample), and committed more errors in the process of meeting criterion. Similarly, they also achieved fewer correct searches on reversal trials in a delayed response task. Based on previous

research into these tasks, the authors suggested deficits in ASD in the medial temporal lobe and the dorsolateral prefrontal cortex (G Dawson, Meltzoff, Osterling, & Rinaldi, 1998).

The anterior cingulate system has also been hypothesized to play a significant role in social processing. Though lacking any direct evidence, Mundy (2003) reviewed studies examining the dorsal medial-frontal cortex and the interior cingulate system, and their relationship to theory of mind and joint attention respectively. These systems were suggested as a "neural substrate for socio-cognitive deficits in autism" (p. 793, Mundy, 2003). The anterior cingulate system has also been implicated in repetitive behavior (Thakkar et al., 2008) and response inhibition (Agam, Joseph, Barton, & Manoach, 2011).

The orbito-frontal cortex is involved in social reward and reinforcement (Rolls, 2000). Baron-Cohen and colleagues (1999) evaluated the ability to identify mental state terms in a group of children with ASD and typical development. They hypothesized that this ability is related to theory of mind. In a related task, they assessed blood flow via single photon emission computerized tomography (SPECT) to identify which brain regions were involved with this task in the health brain. Individuals with ASD performed significantly worse on the mental state terms task. Results in the second task indicated increased activation in the orbito-frontal cortex. According to the authors, this implicated the orbito-frontal cortex as a region of neural dysfunction in ASD (Baron-Cohen et al., 1999).

Baron-Cohen and colleagues (2000) also proposed an amygdala theory of autism based on post-mortem evidence of increased cell density (Rapin & Katzman, 1998), an animal model of Kluver-Bucy syndrome, and structural and functional neuroimaging (Baron-Cohen et al., 1999, 2000). Baron-Cohen also put forth a theory of dysfunction related to the superior temporal sulcus (Baron-Cohen & Ring, 1994).

A number of studies have implicated the superior temporal sulcus (STS) in processing social information. The STS is involved in the interpretation of goal-directed actions (Pelphrey, Morris, & McCarthy, 2004), with specific sensitivity to tracking biological motion and attributing intentions (Pelphrey & Carter, 2008b), including congruency between action and perceived intention (Wyk, Hudac, Carter, Sobel, & Pelphrey, 2009). It is suggested that dysfunction in the STS may underlie neural mechanisms of social deficits in ASD (Pelphrey & Carter, 2008a).

The fusiform gyrus plays a prominent role in the processing of human faces (Mccarthy, Puce, Gore, & Truett, 1997). A study by Schultz and colleagues examined face processing and object

processing in the fusiform gyrus (FG) and the inferior temporal gyri in groups with ASD and typical development. While both groups demonstrated greater activation in the inferior temporal gyri when viewing objects, when viewing faces, the groups differed significantly. The typical group showed greater activation in the fusiform gyrus when viewing faces, while the ASD group showed greater activation in the inferior temporal gyri (Schultz et al., 2000). Additional research showing FG abnormality found reduced neuronal size and population in in 7 post-mortem ASD cases (Van Kooten et al., 2008).

Activity in the inferior frontal gyrus and pars opercularis has been a focus of significant research over the past decade. Considered to be related to the mirror neuron system, fMRI research has examined activity in this area in response to the observation and imitation of motor actions. A notable study by Dapretto and colleagues (2006) showed reduced activation among individuals with ASD in the inferior frontal gyrus in response to the observation of emotional facial expressions (Dapretto et al., 2006). It was suggested that dysfunction in the mirror neuron system may “underlie the social deficits” (p.28; Dapretto et al., 2006) in ASD. This hypothesis and subsequent research will be treated at length in a later section of this paper.

A number of other brain regions have also been enmeshed in the discussion of the neural basis of ASD (for a review, see Brambilla et al., 2003), including the hippocampus (Aylward et al., 1999; Rojas et al., 2004) and cerebellum (Fatemi et al., 2012; Rapin & Katzman, 1998). As the study of social neuroscience expands, it will provide new avenues for studying the social brain and its dysfunction.

In summary, the social information processing hypothesis implicates a series of specific brain regions related to social functioning that may be impaired in ASD. While identifying group differences in neural functioning has advanced our theoretical models of ASD, and provided insight into potential biological aspects of social functioning, the theory does not represent a singular parsimonious explanation of ASD.

One major limitation is the failure to account for repetitive and stereotyped behaviors. These behaviors are traditionally part of the core symptomology of ASD (Kanner, 1943). However, the emphasis on particular aspects of autism symptomology have varied over time (Volkmar & McPartland, 2014). If autism spectrum disorders are redefined to focus exclusively on social deficits, the models of specific

neural deficits appear more compelling. Without this redefinition, the social information processing hypothesis remains lacking.

Neural Theories in a Developmental Framework. The social motivation hypothesis might be considered related to the social information processing hypothesis. However, it avoids some of the limitations of some the generic versions of the social information processing hypothesis and interconnectivity hypothesis by making a definitive statement about the casual relationship between brain and behavior and delineating a specific brain network impacted in ASD.

Chevallier, Kohls, Troiani, Brodkin, and Schultz (2012) make a compelling argument for what they term the "social motivation theory of autism". According to this theory, social motivation has "downstream effects on the development of social cognition" (p.231, Chevallier, Kohls, Troiani, Brodkin, & Schultz, 2012). Restated, "deficits in social cognition are therefore construed as a consequence, rather than a cause, of disrupted social interest (p.231-232, Chevallier et al., 2012). In other words, social motivation is a preeminent cause of abnormal development in social brain circuitry. While this might remain a matter of debate, Chevallier and colleagues at least make a clear statement on their position, avoiding objections raised regarding the casual ambiguity of some neural hypotheses of ASD (D. L. Williams, 2011).

Chevallier and colleagues note the importance of social orienting, social reward, and sustained social attention both behaviorally and evolutionarily. They also highlight a neural network related to the social motivation construct based in the amygdala, ventral striatum, and orbitofrontal cortex.

Most refreshingly, Chevallier and colleagues clearly outline the limitations of the social motivation hypothesis. They note its limitations in explaining repetitive behaviors and circumscribed interests, and they question whether a single explanation can account for the diverse symptomology of ASD. While they limit the scope of their hypothesis, they cogently demonstrate the "explanatory power" (p.237) of the social motivation hypothesis compared with other theories in terms of its ability to comprehensively account for the social deficits of ASD (Chevallier et al., 2012).

Attentional factors. Attentional factors may play a role in observed differences in brain activation patterns. A 2005 paper by Dalton and colleagues, using simultaneous eye-tracking and fMRI, showed that both FG and amygdala activation were positively correlated with time of gaze at eyes. This highlights

the necessity of including perceptual and attentional factors in the pursuit of identifying the neural basis of ASD. It also muddles the casual relationship between brain and behavior in proposed neural theories.

In a landmark study by Jones and Klin (2013), they prospectively examined a sample of siblings at-risk for developing ASD and a group of typical controls from birth. They found that infants that went on to develop ASD showed typical gaze patterns during the first two months of life. This was followed by a steep decline in gaze fixation to eyes between 2 and 6 months, in stark contrast to the typically developing controls (Jones & Klin, 2013). This finding challenged many classical congenital theories of autism and prompted new thinking about the developmental nature of ASD.

Yoon and Vouloumanos (2014) review Jones and Klin's (2013) "surprising data" (p.273) and note two potential explanations of the developmental trajectory of autism in early life. One theory is that gaze behavior is indeed typical during the first months of life, but a steep decline subsequently occurs. Within this model, the possibility of keeping a child on a typical developmental trajectory remains intact. An alternative theory is that there are in fact extant congenital differences in gaze behavior, but these are inconsistent with the predicted deficit model. According to this theory, children who go on to develop ASD may have higher levels of gaze behaviors which are subsequently biologically corrected, resulting in the observed decline between 2 and 6 months of age (Yoon & Vouloumanos, 2014).

Another logical permutation should be noted. It is quite possible that congenital differences exist which are not reflected in gaze behavior during the first 2 months of life. While there are no observed differences during this period, more advanced developmental and social systems are not yet apparent either. Social orienting and smiling behavior comes online during a shift from 8-12 weeks (Wörmann, Holodynski, Kärtner, & Keller, 2014). Thus gaze behavior should not be overgeneralized to be commensurate with comprehensive neural development.

Kennedy and Adolphs (2012) proffer a "network view" of social cognitive processes in contrast to a view of "isolated neural structures" (p.559). This allows for the inclusion of essential neural concepts such as compensation. "No social process can be attributed to a single structure alone; instead a network view of brain function is required" (p.560).

They further highlight some key points regarding the examination of social functioning. Since social cognition relies on a number of different neural substrates, damage to one area can result in a

network-wide disturbance. While this distribution across different areas creates a vulnerability to disruption, it also opens the possibility of compensation. As the complexities of the social world increase with age, adequate social functioning requires adaptation and "tuning" across multiple stages of development. It is suggested that this lies at the heart of why so many developmental disorders result in disruptions in social functioning (Kennedy & Adolphs, 2012). While distinguishing definitively between the "social" and "non-social brain" may not be completely possible or useful (Adolphs, 2003, 2010) , it remains incomprehensible why social functioning might be disrupted while other cognitive processes remain intact (Kennedy & Adolphs, 2012).

Kennedy and Adolphs (2012) stress the importance of considering developmental interactions across the brain when examining neural development. Just as the individual's environment plays a substantial role in the brain's development, no brain region develops in isolation. Rather a series of networks mature to work in concert. The brain's early plasticity and potential for compensation plays a primary role in altering the development of specific regions and network connectivity.

Summary of Neural Theories of ASD. Autism spectrum disorders are biological disorders. There is substantial evidence that individuals with ASD manifest differences in neural activity compared to typical samples. These differences have been observed with regard to activity in specific brain regions and connectivity across brain networks. Two prominent hypotheses about the neural basis of ASD focus on each of these features respectively.

The interconnectivity hypothesis emphasizes differences in functional connectivity across the brain, often focusing on increased local connectivity and decreased global connectivity. The strength of this theory lies in its explanatory power of intact perceptual and cognitive systems often observed in ASD. The limitations of this theory lie in its generality. It explains social deficits only insofar as they are particularly complex and integrated activities. The theory is also limited in its ability to differentiate ASD from other pervasive developmental disorders.

The social information processing hypothesis generally focuses on differences in activity in specific brain regions associated with particular cognitive functions. It naturally focuses on those cognitive abilities that have an impact on social functioning. The strength of this theory lies in its explanatory power of the social deficits prominently featured in ASD. One limitation is that it implicates a series of disparate

areas in the brain while often omitting a unifying principle. Because social functioning is complex, many particular systems are vulnerable to disrupting social processing.

The brain does not develop in isolation. It is influenced by social, perceptual, and attentional factors. The social motivation hypothesis posits an independent construct that has “downstream” effects on brain development. Activity in the brain depends on what is being paid attention to, and this in turn affects the developing brain. Neural networks provide primary interactions between brain regions. These systems have the potential to provide avenues for compensation and pathways to functional deterioration.

Autism spectrum disorders are heterogeneous. There is likely no single neural pathway that explains the entirety of autism. But understanding specific neural features of psychopathology can inform our understanding of brain development. As we understand the unique features of both typical and atypical neural development, we open possibilities of targeted interventions that can alter the course of development towards adaptation, functionality, and fulfillment.

The Mirror Neuron System in Autism Spectrum Disorders

The mirror neuron system (MNS) has attracted significant interest within the scientific and lay communities during the past two decades. It represents an exciting concept about the human brain’s ability to simulate, interpret, and interact with the world around it. To understand this system accurately, it is necessary to examine its humble scientific beginnings and to assess the relationship between the neurological facts and the theories that have garnered so much attention.

The relatively recent discovery of mirror neurons traces back to a series of experiments conducted by Giacomo Rizzolatti and colleagues at the University of Parma, Italy. Rizzolatti was studying motor activity in macaque monkeys using single neuron recording. His team “incidentally” discovered that a particular group of neurons in the F5 area fired in response to the observation of the experimenter performing specific actions such as picking up a piece of food (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992). Further in-depth study demonstrated that indeed a particular group of neurons in the F5 area fired both when the monkey executed and observed actions such as grasping and placing. It was proposed that these “mirror neurons” represented an execution and observation matching system, and that a similar system existed in humans (Gallese, Fadiga, Fogassi, & Rizzolatti, 1996).

Exploring Mirror Neurons. Further evidence indicated that mirror neurons corresponded not to the visual presentation of an action, but rather to the triggering of a mental representation. In an incisive experiment, Umilta and colleagues displayed identical stimuli of a hand reaching (for an object), but the actual grasping of the object was hidden from view. This was either preceded by a display of trial of identical grasping with the object in full view, or the grasping motion with no object. In other words, if the monkey were primed with a visual representation of the action in advance, would it create a visual representation based on the observation of a truncated version of the action? Indeed, a subset of F5 neurons fired only in the condition where the object grasping was presented in advance, demonstrating that these neurons create a mental representation of the action which can be cued, even in the absence of the complete action (Umiltà et al., 2001). This showed a subset of neurons in the F5 area are not merely responding to the visual presentation, but are involved in the mental representation of an action. In the literature, this is commonly referred to as partially occluded paradigm.

Solidifying the role of the MNS in mental representation rather than visual response, neurons in the F5 area also respond to auditory stimuli, even in the absence of visual stimuli. Kohler and colleagues demonstrated that certain F5 neurons fire in response to a sound associated with a particular action, such as paper ripping or dropping a stick, while responding similarly to corresponding visual stimuli. This provided additional evidence that mirror neurons correspond to the neural representation of actions (Kohler et al., 2002).

Evidence also emerged showing that the mirror property extends beyond hand actions, but also includes mouth actions. In a study by Ferrari and colleagues, experimenters executed specific gestures in front of the monkey, including grasping a piece of food, sucking juice from a syringe, smacking or protruding lips, and tongue protrusion. Based on these experiments, the authors highlight that ingestive mouth neurons have very similar mirror properties to hand neurons. Both are triggered in response to object directed actions only, whereas a mere presentation of the object or the observation of a similar but not goal-directed action will not trigger the neurons (Ferrari, Gallese, Rizzolatti, & Fogassi, 2003).

Ferrari and colleagues also reported a new class of neurons which they named “communicative mouth mirror neurons” (Ferrari et al., 2003). The authors argue that these unique neurons fire in response to non-object-directed actions, including lip-smacking and tongue protrusion. They go on to discuss why

the brain systems for ingestion and communication would be related, asserting that “communicative gestures (e.g. lip-smacking, lips protruded face) are ritualizations of ingestive actions that are used for affiliative purposes” (Ferrari et al., 2003, p.1713). In other words, actions related to food can be communicative in function, and play a role in the development of social relationships. This is consistent with previous suggestions that the MNS may play a role in the development of language (Rizzolatti, Fadiga, Gallese, & Fogassi, 1996).

One flaw in this conclusion, which Ferrari and colleagues note, is that previous research by Umiltà and colleagues (2001) demonstrates that mirror neurons can fire in response to partially occluded gestures, meaning the observer’s mirror neuron system can make inferences about the direction of partially observed actions. Thus lip-smacking or tongue portrusion may, neurologically speaking, be interpreted as goal-directed actions. However, the idea of mirror neurons as the biological basis of language was too exciting to ignore, and would continue to be a focus of mirror neuron theory.

Another class of neurons activate in response to the observation of an object which could be grasped, as opposed to the observation of a grasping action. These neurons were termed “canonical neurons” as opposed to mirror neurons (Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Rizzolatti & Arbib, 1998). This term has decreased in use over the past decade, likely due to further advances in the understanding of how the brain responds to different classes of objects and concepts (Connor, 2005; R. Q. Quiroga, 2012; R. Quiroga, Reddy, Kreiman, Koch, & Fried, 2005).

Caggiano and colleagues executed a series of experiments demonstrating that mirror neurons differentially encode proximity (Caggiano, Fogassi, Rizzolatti, Thier, & Casile, 2009), alternative viewing perspectives (Caggiano et al., 2011), and the subjective value of the viewed action (Caggiano et al., 2012). They argue that mirror neurons therefore encode not just the observation of an action, but also higher-level processing including the organization of behavioral responses. This approach furnishes added complexity to the proposed functioning of the mirror neuron system.

Measuring Mirror Neurons in Humans. Much of the research on motor neurons is conducted using monkeys because of the unique opportunity to directly record brain activity by placing electrodes in the brain. Ethical considerations prevent this methodology from being employed in human research, except in specific circumstances. Thus, in order to pursue the natural question of whether a mirror neuron

system exists in humans, a series of indirect methods for measuring human brain activity have been utilized.

Preliminary evidence of a mirror neuron system in humans emerged from multiple experiments shortly after the publication of the first papers identifying the MNS in monkeys. A study using transcranial magnetic stimulation (TMS) in a sample of 12 typical subjects found that motor evoked potentials from hand muscles increased during the observation of motor actions including the grasping of a series of commonly used objects such as spheres and boxes (Fadiga, Fogassi, Pavesi, & Rizzolatti, 1995). Another study using positron emission tomography (PET) in a sample of 7 adults demonstrated that the observation of object being grasped by an examiner activated brain areas with motor properties including the inferior frontal gyrus (Grafton, Arbib, Fadiga, & Rizzolatti, 1996).

A 1954 study using electroencephalography (EEG) originally documented changes in alpha in response to the observation of movement displayed in movies (Gastaut & Bert, 1954). It was noted to be recorded best from central electrodes and this "mu activity was attenuated by voluntary movement and somatosensory stimulation but was minimally affected by visual stimulation" (Kuhlman, 1978, p.92). The desynchronization of alpha in response to biological motion has subsequently been documented in congruence with hand and foot movements (Pfurtscheller, Neuper, Andrew, & Edlinger, 1997), and in both adults (Cochin, Barthelemy, Lejeune, Roux, & Martineau, 1998) and children (Cochin, Barthelemy, Roux, & Martineau, 2001).

Further EEG research demonstrated that the mu rhythm attenuated not only in response to the execution of actions, but also to the observation of motor actions (Muthukumaraswamy & Johnson, 2004). Similar to the research on the monkey MNS (Gallese et al., 1996), a study of 12 typical adults compared activation during the observation of a flat hand, a precision grip of a block of wood, and a the formation of an identical grip in the absence of any target object. Results indicated that the mu rhythm appeared to be more sensitive to goal-directed actions rather than empty motor gestures (Muthukumaraswamy, Johnson, & McNair, 2004). One apparent difference however is that the human MNS does in fact react to non-object-directed actions, albeit to a lesser extent. This highlights a noteworthy difference between the primate and human MNS, namely that the primate MNS seems limited to object or goal-directed actions, whereas the human system is also sensitive to non-object-directed actions. This may be due to the fact

that in the human system, gestures may have meaning in and of themselves, and the MNS involvement in the interpretation of non-object-directed gestures might relate to the evolution of language (Rizzolatti & Arbib, 1998; for review, see Pineda, 2005).

While electroencephalography provides excellent temporal resolution of brain activity, it lacks in spatial resolution as it is generally limited to recording electrical brain activity that can be read on the scalp. Though post hoc methods have been developed for identifying the source of EEG activity, other modalities can directly assess the location of brain activity. One such modality is functional magnetic resonance imaging (fMRI), which tracks hemodynamic changes in the brain and images the blood-oxygen-level-dependent (BOLD) contrast signal to identify brain activity. As such, fMRI has excellent spatial resolution precisely identifying where activity occurs in the brain. However, neurons fire and communicate much quicker than blood moves within the brain, thus fMRI lacks significantly in temporal resolution. Nonetheless, it remains a valuable tool for pinpointing brain activity.

Iacoboni and colleagues (1999) used fMRI BOLD signals to assess brain activity during the imitation and observation of finger movements. Two areas were identified with mirror properties, Brodmann's area 44 (BA44) or the pars opercularis, and the right anterior parietal cortex. These areas are respectively analogous to the areas identified in the original mirror neuron research in monkeys (di Pellegrino et al., 1992; Gallese et al., 1996; Rizzolatti et al., 1996). Further research indicated that the MNS is sensitive not to only to actions, but that MNS activity is modulated by contextual cues. In a study of 23 typical adults, participants observed the grasping of a coffee mug in two conditions, one in the context of a breakfast scene implying an intention of a specific goal such as drinking or cleaning, and another condition of identical grasping motions against a blank background. Results indicated greater activation to the grasping motions in context, evidencing the role of the human MNS in interpreting the intentions of actions (Marco Iacoboni, Molnar-Szakacs, Gallese, Buccino, & Mazziotta, 2005).

Carr and colleagues (2003) showed that the observation of emotional facial expressions resulted in activation across a broad network within the brain, including the superior temporal cortex, insula, and amygdala. They also replicated activation in the pars opercularis (BA44). The authors argued that connections between the action representation systems and the limbic system provide the neural mechanism for empathy (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003).

A series of theoretical papers emerged subsequently linking mirror neurons with empathy. Gallese proposed the “shared manifold hypothesis” suggesting that the reflexive activation of the MNS leads to the experience of sensations and emotions observed in others, resulting in a shared “intersubjectivity” (Gallese, 2001, 2003). This included extensions of this automatic and “embodied simulation” to a series of psychodynamic constructs such as unconscious communication, projection, empathy, and transference (Gallese, Eagle, & Migone, 2007). Iacoboni further argued that greater imitation abilities would lead to better emotion recognition in others which in turn would lead to greater empathy (Marco Iacoboni, 2009). While these papers represented interesting expansions of the human MNS, the theory outpaced experimental data to support these constructs.

In addition to observing BOLD activation, other methods using fMRI have been employed to assess MNS activity in humans. In fMRI adaptation paradigms, suppression of activity over time is assessed to indicate overlapping cortical responses. This is based on single neuron recordings in monkeys where particular neurons reduce their firing rate when repeatedly presented with a specific stimulus or class of stimuli. Dinstein and colleagues used this method to investigate MNS activity in humans (2007), demonstrating mirror properties in a "small number of cortical areas" (p.1424). Kilner and colleagues used this same method to demonstrate mirror properties in the inferior frontal gyrus (IFG), considered a homologue of area F5 in the monkey (Kilner, Neal, Weiskopf, Friston, & Frith, 2009).

Magnetoencephalography (MEG) is yet another modality for evaluating brain activity. What sets MEG apart is that it provides both excellent temporal resolution and spatial resolution. MEG mu rhythms have been previously observed in adults during rest (Salmelin & Hari, 1994). Nishitani and Hari (2000) utilized this method to examine brain activity during the execution, imitation, and observation of hand actions. Their results demonstrated activation in BA44 across all 3 conditions, leading them to suggest that the pars opercularis (BA44) is the "orchestrator" of the MNS. Given the high temporal and spatial resolution, they were able to detect different patterns of activation across conditions. In the imitation and observation conditions, the activity began in the left occipital area (BA19) and then continued to BA44, and finally to the right BA4. In the execution condition, the activity began in BA44 and then continued to BA4. Stronger activation, remarkably double in amplitude, was observed in the imitation condition as compared with the observation and execution conditions. One theory proposed is that imitation includes

activation of neural processes related to both execution and observation. Another proposed theory is that imitation results in a more primary activation of the MNS (Nishitani & Hari, 2000).

While these various modalities rarely crossover directly, Arnstein and colleagues (2011) conducted a keenly designed study recording fMRI and EEG simultaneously. The study was designed to address the "flourishing but often separate literatures on the MNS using fMRI and EEG" (p.14243). Their findings indicated that observation and execution triggered mu attenuation and correlated with BOLD activity in key MNS areas, including the inferior parietal lobe (IPL), dorsal premotor cortex (dPM), and primary somatosensory cortex (BA2). Interestingly, separate voxels in BA44 were correlated with execution and observation respectively, in contrast to the same voxels correlating with execution and observation in other areas (Arnstein, Cui, Keysers, Maurits, & Gazzola, 2011). The authors suggest that BA44 may not be the primary source of mu suppression, despite what had previously been suggested in the MNS literature. They also suggest that there may be multiple components of the MNS circuitry, while a smaller subset or specific brain region may be ultimately responsible for mu suppression. These ambiguities highlight the challenges of even the best indirect recording methodologies.

The first direct evidence of human neurons with mirror properties came fairly late in the evolution of mirror neuron research. But in 2010, Mukamel and colleagues published findings from single neuron recording in humans. Utilizing a population of 21 patients with pharmacologically intractable epilepsy, electrodes were implanted directly in the brain for the purpose of identifying areas for potential surgical intervention. With informed consent, the experimenters completed a series of execution and observation experiments while the electrodes were in place for clinical purposes (Mukamel, Ekstrom, Kaplan, Iacoboni, & Fried, 2010).

One limitation of this procedure is that the placement of electrodes is chosen exclusively for the purpose of identifying seizure activity. Thus the researchers could not specify areas of interest. Nonetheless, a number of interesting findings emerged from this research. Notably, there are indeed neurons in the human brain that fire both in response to the execution and observation of motor actions, including hand grasps and facial expressions. Substantial numbers of these cells were identified in the medial frontal lobe and the medial temporal lobe (Mukamel et al., 2010). While these areas are not exactly analogous to the areas along the lateral wall of primate brain focused upon in the original single

neuron recordings in monkeys, they do demonstrate definitive mirror properties of neurons in the human brain. Further, they identify neurons with mirror properties in the supplementary motor area (SMA), an area identified as having mirror properties in an early PET study (Grafton et al., 1996) and early studies of the mu rhythm (Babiloni et al., 1999), prior to the popularity of the term mirror neurons. The authors argue that mirror neurons may have varying functions across different areas of the brain.

Another interesting finding that emerged from this research is that a particular subset of neurons displayed differential responses to execution and observation. These neurons exhibited an excitation response during execution and an inhibition response during observation. This subset may provide a control system for differentiating self and other as well as limiting unwanted reflexive imitation (Mukamel et al., 2010; see Ferrari, Bonini, & Fogassi, 2009; Kraskov, Dancause, Quallo, Shepherd, & Lemon, 2009).

In summation, the study of mirror neurons has a relatively short but rich history. The original research in monkeys demonstrated an execution/observation matching system sensitive to object-directed actions. It likely involves the triggering of a mental representation of an observed action.

Research quickly emerged evidencing a corresponding execution/observation matching system in the human brain. This system has generally been measured indirectly through different modalities and methodologies, though direct single neuron recording has demonstrated neurons with mirror properties in the human brain. The human MNS not only codes object and goal-directed actions, but demonstrates sensitivity to intention and context (Marco Iacoboni, 2005), non-object directed gestures (Rizzolatti & Arbib, 1998), and other forms of biological motion (Pineda, 2005). This elaborate human neural system has been implicated in a series of cognitive functions including action recognition, imitation, empathy, and language.

The Broken Mirrors Hypothesis. Williams and colleagues suggested the first coherent argument for mirror neuron dysfunction in autism. They argued that the MNS represented a good candidate for a “prime mover” which resulted in a cascade of developmental impairments in ASD (Williams, Whiten, Suddendorf, & Perrett, 2001). This was not the first attempt to offer a unified theory of ASD. Rather, the broken mirrors hypothesis was asserted in the context of a series of attempts to propose a singular theoretical cause for the ostensibly unrelated and distinct symptoms of ASD. While it

was noted that the heterogeneity of ASD might dissuade the theorist from positing a singular cause, they argue that the commonalities among the core symptoms permit such consideration of a “core dysfunctional mechanism” (p.293).

The idea that a singular cause might account for the seemingly disparate symptoms of ASD was a popular one. Jaak Panksepp (1979) noted the lack of agreement regarding primary and secondary symptoms of autism, and suggested that the opiate system underlies the series of deficits related to autism (Panksepp, 1979). Hobson (1988) proposed the Affective Theory of autism, arguing that autism is “irreducibly” a disorder of “affective and social relations” (p.253). This affective deficit leads to an inability to recognize emotional states, pragmatic deficits, and deficits in symbolic abilities and pretend play.

Baron-Cohen and colleagues (1985; 1988) proposed a Cognitive Theory of autism, arguing that an impaired meta-representational deficit leads to impairment in theory of mind and impairment in symbolic abilities. These in turn lead to specific social deficits and pragmatic deficits, and deficits in pretend play respectively. Leekam and Perner (1991) later questioned whether a meta-representational was indeed consistent with the presentation of autism.

Rogers and Pennington (1991) proposed that the primary deficit in ASD is an impaired differentiation between self and other. This leads to deficits in imitation, emotion sharing, and theory of mind. These in turn lead to deficits in pretend play, pragmatics, and join attention. Again, they propose a single construct, which results in a “cascade” of other impairments.

All the aforementioned theories each propose a specific construct, which when deficient, cascades into the series of specific deficits observed in autism. This trend continued as new concepts in neuroscience emerged. Baron-Cohen and colleagues (2000) proposed “The amygdala theory of autism”, highlighting how amygdala dysfunction might lead to social deficits in ASD. Thus the 2001 paper from Williams and colleagues was consistent with the research environment at the time in proposing a singular autism hypothesis, and should be viewed in that context.

The mirror neuron researchers did not shy away from asserting that MNS dysfunction might be the fundamental deficit in ASD. Echoing previous theoretical papers (Rizzolatti & Craighero, 2004), Oberman and Ramachandran (2007) argued that the MNS as a system of internal simulation provided the

underpinnings for imitation, theory of mind, empathy, and language. They definitively suggested that dysfunction in this system played a central role in the symptoms of ASD.

Empirical Evidence. Avikainen, Kulomäki, and Hari (1999) documented the first investigation of mirror neuron dysfunction in ASD. In a sample of 5 individuals with ASD and 8 control subjects, brain activity was recorded using magnetoencephalography (MEG) during a motor execution task and a separate observation of another person executing the same task. A verbal theory of mind task was also administered.

While the two groups differed on the theory of mind task, there was no significant difference in activation of the primary motor cortex during the observation task. Though the attenuation (implying activation) in both groups was more pronounced during the execution of the task, there was significant attenuation for both groups during the observation task. This led the authors to conclude that mirror neuron dysfunction did not account for observed deficits in “mindreading and imitation”. It is unclear how the authors draw any conclusions related to imitation given that imitation was not assessed. Limitations of this study include the minuscule sample size of 5 individuals with ASD, potentially contributing to a type II error (Williams et al., 2001). Additionally, the sample characterization was merely based on ICD-10 criteria as interpreted by a neurologist or psychiatrist. Of the five subjects in the ASD group, four had a diagnosis of Asperger’s syndrome and one had a diagnosis of autism, a broad inclusion criteria by research standards.

Oberman and colleagues (2005) offered the first empirical evidence of mirror neuron dysfunction in autism spectrum disorders. Electroencephalography was utilized to assess attenuation of the mu rhythm, which previous studies indicated served as a marker of mirror neuron activation (Muthukumaraswamy & Johnson, 2004). In a sample of 10 individuals with ASD and 10 controls matched for age and gender, they observed attenuation of the EEG mu rhythm in response to the subject opening and closing his or her own hand, indicating activation of the mirror neuron system. However, during the watching of a video of someone else executing an identical hand movement, the control group exhibited mu attenuation indicating activation of the mirror neuron system, while the ASD group failed to show attenuation. Results were reported from EEG recorded from the scalp over the sensory motor cortex at C3, Cz, and C4.

It is important to note sample characteristics as the literature is reviewed, and specifically how precisely each study defined its sample of autism spectrum disorder and typical development. All subjects in this study were male, with an IQ above 80. Subjects ranged in age from 6 to 47 years, with a mean age of 16.5 across groups. In this study, the ASD group was defined as "diagnosed with either autism or Asperger's syndrome by a clinical psychologist." Subjects met DSM-IV criteria for a diagnosis of Autistic disorder or Asperger's disorder" (p.192). All subjects were termed "high functioning" and possessed verbal comprehension abilities consistent with age expectations.

Dapretto and colleagues (2006) followed with additional evidence from a paradigm using functional magnetic resonance imaging (fMRI). Using a sample of 10 individuals with ASD and 10 age, gender, and IQ-matched controls, the paradigm involved the imitation and observation of static facial expressions. Findings indicated that the two groups differed in the brain regions utilized during the imitation task.

During the imitation task, the typical group showed activation in Brodmann's area 44, also known as the pars opercularis in the inferior frontal gyrus, which previous research identified as an area with mirroring properties (Geyer, Matelli, Luppino, & Zilles, 2000; Rizzolatti & Arbib, 1998). This area is considered to be a homologue of the F5 area in the macaque monkey, the original area noted by di Pellegrino and colleagues (1992) and Gallese and colleagues (1996) in their identification of the execution and observation matching system. In contrast, the ASD group did not show activation in this area. Furthermore, during the observation task, the typical group showed significantly greater activation in the Brodmann's area 44 as compared with the ASD group. Both groups showed activation in visual and motor areas, including the fusiform gyrus, and the motor-related areas of the amygdala. Dapretto and colleagues theorized that while the typical group utilized areas of the brain associated with mirroring functions in order to imitate the observed facial expressions, the ASD group relied on more basic motor and visual areas.

To note, the accuracy of the imitation of the facial expressions was not assessed. However, the sample of participants was carefully characterized, with all ASD participants meeting criteria on the Autism Diagnostic Observation Scale (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R). Scores on the social subscales of the ADI-R and the ADOS were negatively correlated with activation in

the pars opercularis, implying a relationship between social impairment and suppressed activation of this identified mirror area.

Williams and colleagues, some of whom had been involved in documenting imitation deficits in autism (Williams, Whiten, & Singh, 2004) and crystalizing the hypothesis of mirror neuron dysfunction in ASD (Williams et al., 2001), followed with another fMRI study in 2006. A sample of 16 individuals with ASD and 15 age and gender-matched controls were recruited for participation. They selected the execution and observation paradigm developed Iacoboni and colleagues' (1999) which documented the mirror neuron system's involvement in imitation.

Results indicated different patterns of activation in the right temporal-parietal junction in the ASD group as compared with controls, implying an alternative network of brain regions involved in imitation in individuals with ASD. Strengths of the study included a well-characterized ASD sample, with subjects meeting criteria on both the ADOS and ADI, and the use of an established fMRI paradigm, even utilizing identical stimuli to Iacoboni and colleagues original MNS study (1999). The noteworthy limitation of this study is that it failed to replicate the fundamental activation in the Brodmann's area 44 specified in the original Iacoboni paper (1999) in either ASD or control subjects. It did however imply disparate neural networks involved in imitation for individuals with ASD (J. H. G. Williams et al., 2006).

Evidence for structural differences in MNS areas was provided by Hadjikami and colleagues (2006). Using structural MRI in a sample of 14 individuals with ASD and 14 controls matched for age, IQ, and handedness, findings revealed cortical thinning in key areas previously implicated in mirror neuron functioning, including the pars opercularis in the inferior frontal gyrus (IFG), the interior parietal lobule (IPL), and the superior temporal sulcus (STS). Further, thinning is these areas was correlated with social and communication symptoms as assessed by the ADI-R. Notably, the ASD group met criteria based on the ADI-R, ADOS, and the diagnosis of an experience clinician.

Bernier and colleagues (2007) contributed another well-designed study of the MNS in ASD. They used EEG to examine mu wave attenuation in a sample of 14 adults with high-functioning ASD and 15 controls matched on IQ and age. In addition, they assessed imitation ability using an elaborate behavioral imitation paradigm (Mature Imitation Task; Rogers, Cook, and Gneiss-Hess, 2005).

An execution and observation procedure was used involving the precision grip of a wooden block (Muthukumaraswamy & Johnson, 2004), and the observation of a video of another person executing the same action. Replicating the finding of Oberman and colleagues (2005), both groups showed mu wave attenuation indicating the activation of the MNS system during the execution condition, but while the typical group demonstrated attenuation during the observation condition, the ASD group failed to show attenuation during observation. Importantly, imitation ability assessed in a distinct behavioral paradigm was positively correlated with mu attenuation, implying a link between the mirror neuron system and imitation abilities.

Another study followed examining the impact of familiarity on MNS activation (Oberman, Ramachandran, & Pineda, 2008). Findings indicated that individuals with ASD failed to show MNS activation when viewing actions performed by a stranger, but showed MNS activation to the observation of an action executed by a familiar individual. Control subjects showed MNS activation to actions performed by a stranger or familiar individual. The authors theorized that the previously observed dysfunction in the MNS in ASD was due to the actors being unfamiliar. They further theorized that for individuals with ASD, identification is a key factor in the activation of the MNS. For typical individuals, this basic execution-observation matching system is not as sensitive, and activates regardless of familiarity. To note, the ASD group showed impairment in imitation ability compared with controls, but no significant correlation was observed between imitation and EEG.

Another study EEG investigated MNS activation in children with ASD. In a sample of 14 children ages 5 to 7 with ASD and 14 age and gender-matched controls, activation of the MNS was observed in response to biological movement for the control group but not for the ASD group. Atypical hemispheric activation was also observed in the ASD group (Martineau, Cochin, Magne, & Barthelemy, 2008). MNS activation was defined as desynchronization in the theta band. While theta is different than the traditional 8-13 Hz mu band, there is evidence that mu may change over time (Chiang, Rennie, Robinson, van Albada, & Kerr, 2011). The atypical hemispheric activation is not particularly compelling, given that “typical” activation was defined based on the current control sample and not based on previous research.

Using MEG, Honaga and colleagues examined the post-movement beta rebound (PMBR), essentially a documented increase in beta frequency power following the execution, imagination, and

observation of movement. The ASD group consisted of 6 individuals with a mean age of 26.4 years meeting DSM-IV criteria based on the diagnosis of “experienced psychiatrists”, and 10 “normal subjects” (p.142). All participants demonstrated an IQ of 70 or above on the Wechsler Adult Intelligence Scale-Revised (WAIS-R), though comparisons between groups were not reported. During the observation condition, the ASD group showed significantly reduced PMBR as compared with controls in MNS regions, notably the sensorimotor area, premotor cortex, and superior temporal gyrus. The authors concluded that this provides evidence for MNS impairment in ASD (Honaga et al., 2010).

Schulte-Rüther and colleagues (2011) designed an fMRI study involving the judgment of observed emotional expressions (other-task), the identification of personal emotions elicited by the observation of expressions (self-task), and the observation of neutral expressions to establish a baseline (control-task). The sample consisted of 18 adults with ASD and 18 gender, age, and IQ-matched controls. Participants with ASD met ICD-10 and DSM-IV criteria based on a semi-structured diagnostic interview, and met criteria on the ADOS. The ASD group failed to show activation in the right IFC (BA44/45) during the other-task, similar to the observation task in previous MNS studies, whereas signficant activity was observed in the control group. Importantly, this study also utilized concomitant eye-tracking to monitor visual scanning patterns. No differences in fixation on the face, eye, or mouth regions were observed between groups across all conditions (Schulte-Rüther et al., 2011), eliminating attention and gaze patterns as counfounding factors.

Intact Mirrors. In 2009, a study emerged challenging the broken mirrors hypothesis. In a sample of 20 children with “high functioning autism” (HFA) and 19 control subjects, no group differences were observed in mu suppression. This was taken to evidence intact functioning of the MNS in ASD (Raymaekers, Wiersema, & Roeyers, 2009), challenging the prevailing theory.

Diagnoses of ASD in this sample were confirmed using the ADI-R. While the authors correctly note that the ADI-R is the “gold standard” interview related to ASD, invoking Filipek and colleagues (1999), they fail to note that to meet the “gold standard”, the ADI-R is to be used in conjunction with the ADOS and expert clinical judgment (Filipek et al., 1999). Further, the authors report scores on the Social Responsiveness Scale (SRS), Social Communication Questionnaire (SCQ), Child Behavior Checklist (CBCL), and Disruptive Behavior Disorder Rating Scale (DBD). While it is to be expected that the ASD

and control group would differ on scores related to social and communication functioning such as those included in the SRS and SCQ, the groups manifested significantly different scores on internalizing and externalizing behavior on the CBCL, and different scores related to attention, hyperactivity, oppositional defiant behavior, and conduct disorder on the DBD. This set of observed differences on the DBD is particularly concerning. It implies that the sample of individuals with HFA had a series of comorbid issues related to other disorders, not generally consistent with an ASD profile.

Further research using fMRI indicated intact action perception in ASD. In a study of 12 adults and 12 controls, both the ASD group and control group showed common activation patterns in response to dynamic and static stimuli (Grèzes, Wicker, Berthoz, & de Gelder, 2009). These activation patterns included networks previously implicated in action perception including the superior temporal sulcus (STS), intraparietal sulcus (IPS), the precentral gyrus, and the inferior frontal gyrus (IFG) –the aforementioned Brodmann's area 44 or pars opercularis. This finding is in stark contrast to previous research failing to show activation in the pars opercularis in ASD (Dapretto et al., 2006).

There were differences between groups observed in the activation of the amygdala, Brodmann's area 45 –the inferior frontal gyrus, and the dorsal premotor cortex. Taken together, the authors argue that individuals with ASD share more in common than previously thought in terms of basic action perception, including gestures with emotional content, but differ in terms of the activation of emotion processing regions of the brain (Grèzes et al., 2009).

Another fMRI study followed, examining movement selectivity in a sample of 13 adults with high functioning autism and 10 controls. Both groups showed intact movement selectivity responses in the anterior intraparietal sulcus (aIPS) and ventral premotor cortex (vPM; Dinstein et al., 2010). This study was particularly persuasive because both groups followed a previously documented pattern of activation (Dinstein, Hasson, Rubin, & Heeger, 2007), as opposed to simply finding no group differences. There was larger within-subject variation observed in the ASD group, though not statistically significant across groups.

Another well-designed study utilized EEG to assess mu attenuation, while simultaneously using eye-tracking technology to ensure attention. This effectively limits the possibility that differences in MNS activation are due to differences in attending to the stimuli. In a sample of 20 males ages 11 to 26 and 20

age, gender, and IQ-matched controls, no significant differences were observed across groups in visual attention, and all groups demonstrated mu suppression to the observation of hand movements. The ASD group was defined using DSM-IV criteria and an “in-house” translation of the ADI-R. Notably, scores on the ADI-R communication subscale were positively correlated with mu power, such that those with greater communication impairment showed more limited activation of the MNS (Fan, Decety, Yang, Liu, & Cheng, 2010). The combination of EEG and eye-tracking makes this study particularly compelling, proactively accounting for any potential differences in attention, and providing a plausible explanation for previously documented differences.

The relationship between the EEG mu rhythm and imitation was also reportedly examined, failing to demonstrate statistical significance (Fan et al., 2010). However, imitation ability was defined as the number of incorrect movements during an execution task, and not based on a formalized evaluation of the accuracy of imitation of face or hand gestures. Specifically, participants were asked “to manipulate the chessman in same manner as shown.” Graduate students then coded the number “errors, i.e. additional or incorrect movements” (p.983). Oddly, the paper cites “Bernier et al., 2007” in its description of the imitation task. In point of fact, the paradigm employed by Bernier and colleagues is quite elaborate, and evaluates the imitation of a series of distinct single and dual hand gestures and facial expressions. Coders specifically evaluate finger placement, orientation, and errors such as overshooting or additional or incorrect movements. Perhaps by quoting “Bernier et al., 2007” the authors were referring to the aspect of the paradigm in which they employed “trained graduate students who were blind to the diagnostic status of the participants” (p.983).

An aberrant finding emerged in a 2010 fMRI study of 7 individuals with ASD and 8 controls. Martineau and colleagues found increased activation in the pars opercularis (Brodmann’s Area 44) in the inferior frontal gyrus, indicating enhanced activation of the MNS in individuals with ASD. This is in direct contrast with previous studies demonstrating limited activation in this area (Dapretto et al., 2006; J. H. G. Williams et al., 2006). The authors argued that this provided further evidence for “atypical activation” of the MNS in ASD. No information was given regarding how the 7 individuals with ASD were diagnosed or what inclusion criteria were employed (Martineau, Andersson, Barthélémy, Cottier, & Destrieux, 2010).

***Parsing Divergent Findings*.** Some notable attempts were made to parse these divergent findings regarding the MNS in ASD. In an fMRI study of 21 adult males ages 18-54 and 21 control subjects matched on age and IQ, Bastiaansen and colleagues (2011) failed to show any group differences in the activation of Brodmann's area 44. However, when they divided the groups by age, an interesting finding emerged. When limiting the sample to the eight youngest subjects in each group, activation in Brodmann's area 44 was significantly less in the ASD group compared with the control group. When limiting the sample to the oldest subjects, no significant differences in activation across groups were observed. Further analysis demonstrated that activation in Brodmann's area 44 increased in the ASD group across age during emotion perception. There were no differences in activation across age in the typical group.

The authors suggest that the MNS may have a different pattern of development in ASD. They report correlations between age and scores on the Social Functioning Scale (SFS; 1990), indicating an improvement in social skills over time. They further suggest that targeted interventions may speed up social skills development in ASD (Bastiaansen et al., 2011), asseting that age may be a key factor in parsing the contradictory of findings relating to MNS functioning in ASD.

Another significant attempt to understand the divergent MNS findings replicated a classic paradigm (Muthukumaraswamy & Johnson, 2004) to assess MNS activation in humans. In a carefully characterized sample of 19 children with ASD and 19 age-matched controls, Bernier and colleagues found no significant differences between groups in mu attenuation were observed (Bernier, Aaronson, & McPartland, 2013). This was particularly noteworthy because Bernier and colleagues had published one of the original papers identifying mirror neuron dysfunction in a sample of adults with ASD (Bernier, Dawson, Webb, & Murias, 2007). While group differences were not observed, there were individuals in both the ASD group and control group who failed to demonstrate mu attenuation. Further, a significant correlation across groups was observed between mu attenuation and imitation ability. This was consistent with previous research documenting a relationship between imitation ability and mu attenuation (Bernier et al., 2007).

The authors argued that imitation ability could be the key factor in understanding the divergent findings related to MNS functioning in ASD. While imitation deficits are commonly associated with ASD

(for review, see Williams et al., 2004), they are not part of the diagnostic criteria. Thus even rigorously characterized samples of individuals with ASD could vary drastically in imitation ability. Given the perpetually small sample sizes in much of the MNS research in ASD, variation in imitation ability could conceivably contribute to the observed variability in MNS functioning across studies.

A further attempt to understand divergent MNS findings examined sub-bands within mu. While mu is classically defined as activity in the 8-13 Hz range, Dumas and colleagues divided the spectrum into 2 distinct bandwidths, 8-10 Hz and 10-13 Hz based on a series of explorations into the EEG alpha rhythm (for review, see Bazanova and Vernon, 2013). In a study of 10 adults with ASD and 30 typical controls, mu suppression was observed across groups when all electrodes were included. There were no differences in the observation or execution conditions within these parameters When analysis was limited to the central electrodes, the ASD group failed to show attenuation to hand gestures in the combined 8-13 Hz range. However, upon further analysis, the observed difference between groups at the central electrodes was primarily driven by activity in the 10-13 Hz range, while activity in the 8-10 Hz range was not statistically different across groups (Dumas, Soussignan, Hugueville, Martinerie, & Nadel, 2014).

A further topographic analysis revealed that control participants exhibited significant attenuation in the 8-13 Hz range across the entire scalp, and most intensely over the occipito-parietal region during observation. When the 8-10 Hz band was isolated, the ASD group exhibited attenuation over the occipito-parietal region while the control group exhibited attenuation over the entire scalp. When the 11-13 Hz band was isolated, no attenuation was exhibited during the observation condition in ASD group, while significant attenuation was exhibited in the control group across the entire scalp. Finally, an increase in alpha activity was observed in the frontal region in the ASD group, while attenuation was observed in the occipito-parietal region in the control group (Dumas et al., 2014).

While this study does not harmonize the entire history of divergent findings regarding the MNS in ASD, it does evidence that the ASD brain is interpreting actions through different processes than the neurotypical brain. It also specifically suggests that finer-grained analysis, including source-localization and the subdivision of the power spectra historically associated with mu, will assist in understanding differences in the processing of biological motion in ASD.

Status of the Broken Mirrors Hypothesis. Of the 21 studies reviewed above, 12 indicated a dysfunction of the MNS in ASD (Bastiaansen et al., 2011; Bernier et al., 2007; Dapretto et al., 2006; Dumas et al., 2014; Hadjikhani, Joseph, Snyder, & Tager-Flusberg, 2006; Honaga et a., 2010; Martineau, Cochin, Magne, & Barthelemy, 2008; Nishitani, Avikainen, & Hari, 2004; Oberman et al., 2005, 2008; Schulte-Rüther et al., 2011; Yamasaki et al., 2010). Six studies showed completely intact MNS function (Avikainen, Kulomäki, & Hari, 1999; Dinstein et al., 2010; Fan et al., 2010; Grèzes et al., 2009; Marsh & Hamilton, 2011; Raymaekers et al., 2009), while 2 failed to replicate the basic paradigm (Williams et al., 2006) or had anomalous findings (Martineau et al., 2010). One study neither confirmed or rejected the broken mirrors hypothesis, but suggested imitation deficits, often but not always present in ASD, represent the primary behavioral correlate of MNS dysfunction (Bernier et al., 2013).

By modality, 8 out of 21 studies used EEG (Bernier et al., 2007; Bernier et al., 2013; Dumas et al., 2014; Fan et al., 2010; Martineau et al., 2008; Oberman et al., 2005, 2008; Raymaekers et al., 2009), one of which used simultaneous eye-tracking (Fan et al., 2010), 8 used fMRI (Bastiaansen et al., 2011; Dapretto et al., 2006; Dinstein et al., 2010; Grèzes et al., 2009; Marsh & Hamilton, 2011; Martineau et al., 2010; Schulte-Rüther et al., 2011; Williams et al., 2006), one of which also used simultaneous eye-tracking (Schulte-Rüther et al., 2011), 2 used structural MRI (Hadjikhani et al., 2006; Yamasaki et al., 2010), and 3 used MEG (Avikainen et al., 1999; Honaga et al., 2010; Nishitani et al., 2004).

***Limitations*.** A number of limitations plague the mirror neuron literature in ASD. Diagnosis of ASD is a complex process, and the gold-standard of diagnosis is quite time-consuming and involves a standardized observation of the child, parent interview, and expert clinical judgment (Filipek et al., 1999). In research settings, this commonly involves the administration of the ADOS, ADI-R, and diagnosis by an experienced clinician. Over half of the reviewed studies fail to meet this standard (Avikainen et al., 1999; Bastiaansen et al., 2011; Fan et al., 2010; Grèzes et al., 2009; Marsh & Hamilton, 2011; Martineau et al., 2010, 2008; Oberman et al., 2005, 2008; Raymaekers et al., 2009; Schulte-Rüther et al., 2011; Yamasaki et al., 2010). Failing to use the most precise instruments undoubtedly leads to greater heterogeneity in such a broad-spectrum disorder, likely making the ASD group less constricted and more typical. Notably, only one of the studies showing completely intact MNS functioning across groups used the gold-standard

diagnostic criteria for ASD (Dinstein et al., 2010). This study was also unique in how it chose to assess MNS functioning, as discussed below.

Another constant limitation in the MNS literature in ASD is sample size. The first study showing intact MNS functioning had only 5 participants in the ASD group (Avikainen et al., 1999). The first two studies to demonstrate MNS dysfunction had only 10 participants in each group (Dapretto et al., 2006; Oberman et al., 2005). A large effect size (J. Cohen, 1988) would be required in order to have sufficient power to detect group differences. Given the recent research on the multiple genetic etiologies associated with ASD (Gerdts & Bernier, 2011; Girirajan et al., 2013; O'Roak, Vives, Fu, et al., 2012; Pinto et al., 2014), it is likely that the individuals comprising the ASD groups across many of the studies had distinct etiologies.

Another challenge in examining the literature is the multiple modalities and paradigms used to investigate MNS activity in humans. Even within the same modality, different paradigms examining different brain areas are used to assess MNS activity. For example, when Dinstein and colleagues reported intact mirrors in individuals with ASD (Dinstein et al., 2010), they utilized an fMRI paradigm where MNS activity was defined as differential suppression over time in the anterior intraparietal sulcus (aIPS) and ventral premotor cortex (vPM). This is drastically different from paradigms the original fMRI paradigms examining MNS activity based on BOLD activation levels in the pars opercularis in the inferior frontal gyrus (BA44; Dapretto et al., 2006; Schulte-Rüther et al., 2011). Both may be valuable paradigms in cognitive neuroscience, but each involves different brain systems and processes, and carries with it a corresponding set of potential pathways to disruption or intact functioning.

Parsing. Some important attempts were made to parse the inconsistent research on the MNS in ASD. Bastiaansen and colleagues suggested that age is the essential factor. Younger subjects with ASD showed differential activity compared with controls, while older subjects showed similar activity to controls (Bastiaansen et al., 2011).

This theory however does not sufficiently account for the current discrepancies in the literature. It was further challenged in a study reexamining extant datasets, including some mentioned above (Oberman et al., 2005, 2008; Pineda et al., 2008; Raymaekers et al., 2009). The follow up analysis indicated that mu suppression in response to observation of movement decreases over time in both

typical and ASD samples, while differential patterns are observed during execution. Thus, further research into the developmental changes in mu over time may be needed to understand how this hypothesis might fit into the existing literature (Oberman et al., 2013).

Bernier and colleagues provided evidence that mu attenuation is primarily associated with imitation ability and not diagnosis. Imitation deficits are common in ASD (Williams et al., 2004), but they are not part of the diagnostic criteria. Thus ASD research samples would likely have varying imitation skills and would therefore have varying MNS results (Bernier et al., 2013). The heterogeneity of ASD research samples, especially given the different standards used for inclusion across studies, remains a plausible explanation of the current literature.

Dumas and colleagues identified differences in sub-bands within the 8-13 Hz spectrum defined as the mu rhythm. Differences in ASD were driven by activity in the 10-13 Hz range, while activity in the 8-10 Hz range was similar across groups. Further analysis showed differences in topographic distribution of activity. While not providing a complete explanation of the current literature, the findings suggested future directions including the use of finer grained methods of analysis.

Summary of the MNS in ASD. The broken mirrors hypothesis emerged during a period where the scientific community still considered autism a construct with a potentially singular etiology. It was an outgrowth of a series of attempts to provide a unified theory of autism. Just like the theory of mirror neurons outpaced empirical science, and was oversimplified in the scientific and lay communities, the broken mirrors hypothesis was often interpreted beyond the empirical evidence and was oversimplified to researchers and the public. As Vittorio Gallese, one of the authors of the original MNS study, states unequivocally, “I do not subscribe (and never did) to the thesis that autism equals broken mirrors. To the best of my knowledge, we do not have any reliable, single physiopathological hypothesis able to coherently explain the multifarious clinical aspects of ASD” (Gallese, Gernsbacher, Heyes, Hickok, & Iacoboni, 2011a).

While the MNS may or may not live up to being the “most hyped concept in neuroscience” (Jarrett, 2012), or revolutionize psychology the way DNA revolutionized biology (Ramachandran, 2000), it will nonetheless likely remain an important construct in cognitive and social neuroscience. The application of this construct to clinical psychology and psychiatry, and specifically to autism spectrum disorders, will

likely evolve as these fields evolve in their own right. Genetics continues to shift our understanding of psychiatric disorders, and as precisely defined biological subtypes emerge, cognitive and social neuroscience will likely play a key role in identifying the neural mechanisms of psychopathology.

Comprehensive Intervention for Autism Spectrum Disorders

Without a clear understanding of the causes of autism, there have historically been many different approaches to treatment. Early theories of autism were proffered in the context of a prevailing psychodynamic and psychoanalytic conception of psychiatric disorders. However, traditional psychodynamic therapies proved ineffective (Kanner & Eisenberg, 1955, as quoted in Lovaas, Koegel, Simmons, & Long, 1973). Alternative interventions were sought. With inconsistent results from pharmacological interventions, behavior modification began to garner momentum.

What follows is not an exhaustive review of the literature related to autism intervention. Such a treatment is beyond the scope of this project. Rather, below is a brief history of a few seminal case studies, which set the stage for rigorous randomized-control trials, and established behavior modification as a core methodology for teaching functional skills to individuals with autism. It is designed to provide some background and context for the current examination of the impact of a comprehensive intervention program on neural functioning.

Early Behavioral Intervention. The use of behavioral principles to shape functional behavior has a long and checkered history. Researchers at the University of Washington report on using operant conditioning to help a young child diagnosed with autism. The child, Dicky, was diagnosed with childhood schizophrenia at age 3 and admitted to Western State Hospital. He failed to display social or verbal skills and struggled with nutrition. He also regularly displayed self-injurious behavior and refused to sleep at night. Due to cataracts and subsequent surgeries, he needed to wear glasses to see but refused. Dicky was approaching a critical period in the development of his vision; if he continued to refuse wearing glasses, he might permanently lose his vision. This led to the invitation for Montrose Wolf and Todd Risley, both behavioral researchers at the University of Washington, to consult on training Dicky to wear glasses (Wolf, Risley, & Mees, 1964).

Wolf and Risley manipulated the consequences of Dicky's behavior to address his behavioral challenges. A time-out and isolation procedure was implemented in which Dicky was placed in a room with a closed door when he exhibited tantrum behavior. The tantrum behavior decreased and was nearly absent after two and half months (Wolf et al., 1964).

During this period, Dicky began receiving more frequent visits from his parents and spending time at home. A bedtime routine was implemented which concluded with Dicky in bed with the door open. If Dicky left his bed, he was instructed to return to his bed or the door would be closed. If he refused to comply the door was closed. If he stayed in his bed, the door would remain open. While a series of intense tantrums ensued during the first five nights, by the sixth night Dicky remained in bed and went to sleep. Subsequently there were very few problems with bedtime (Wolf et al., 1964).

Getting Dicky to wear glasses proved more difficult. After 5 weeks of using minor reinforcers, Wolf and Risley abandoned the role of consultant and began to implement the behavior therapy directly. After withholding breakfast and lunch with limited progress, a very hungry Dicky began responding by mid-afternoon to ice-cream. Other reinforcement such as going for a walk or ride in the car, having a snack, or outdoor play was made contingent on wearing glasses. Verbal cues were paired and eventually Dicky would put on his glasses with only a verbal cue. When Dicky was released from the hospital, he was wearing his glasses for around 12 hours per day (Wolf et al., 1964).

Other reinforcers increased Dicky's verbal behavior. Beginning with using food as reinforcement, Dicky went from labeling pictures with a prompt to labeling pictures and objects spontaneously, and even responding consistently to common social questions. The authors express a foundational principle, that "the more powerful food reinforcers were evidently necessary for initial strengthening, but weaker conditioned reinforcers, such as adult attention and approval, were effective for maintaining and expanding the original repertoire (p.311, Wolf et al., 1964). Dicky's parents were then able to use more naturalistic reinforcement to increase his language and communication capabilities.

A later study followed Dicky's progress as he enrolled into a Preschool Laboratory at the University of Washington. At first, Dicky refused to participate in academic activities and initiated a minor version of his previous tantrum behavior whenever any demands were directed towards him. This included minor self-injurious behavior which disrupted the learning environment. A room was then

arranged similar to the isolation room used previously. The time-out and isolation procedure was implemented and resulted in a 30-minute time-out in response to a behavioral tantrum. A 12-minute time-out was implemented 6 classes later, and a 9-minute time-out 14 classes later. No other self-injurious behaviors were exhibited and no time-outs were needed for the subsequent 63 class days. Building off the previously extensive use of time-out and isolation, only 3 uses of the time-out room were necessary to extinguish the self-injurious behavior in the new setting (Wolf, Risley, Johnston, Harris, & Allen, 1967).

Once the self-injurious behavior was essentially extinguished, focus turned to a pinching behavior which was being exhibited multiple times per day. In response to pinching, Dicky was sent to his time-out room. The behavior immediately diminished and was exhibited only four times in the subsequent 74 classes, also followed by a time-out. Toilet training was also completed at school using M&Ms and ice cream as reinforcers. (Wolf et al., 1967). These positive outcomes were achieved using a combination of reinforcers (ice cream and candy) and reinforcement withdrawal (isolation).

Ivar Lovaas, who completed his graduate work at the University of Washington, published a series of papers highlighting the role of operant conditioning in shaping behavior. His methods and conclusions remain an ongoing source of controversy and discussion. His early research reported on the effectiveness of using electric shock to promote social behavior (Lovaas, 1965), the impact of LSD on autism symptoms (Simmons, Leiken, Lovaas, Schaeffer, & Perloff, 1966), and the use of other aversive techniques in reducing self-injurious behavior (Lovaas & Simmons, 1969).

Lovaas and colleagues (1973) published a foundational and elaborate description of 20 children treated with behavior therapy. The 20 children had an independent diagnosis of autistic disorder, and displayed severe symptoms including sensory deficits, limited social affect, self-stimulatory and self-injurious behavior, echolalia and the absence of language. Using contingent reinforcement, ignoring, aversive techniques such as electric shock, and reinforcement of incompatible behavior, substantial gains were demonstrated in cognitive abilities, adaptive behavior, and language, and a reduction in maladaptive behaviors (Lovaas et al., 1973).

It is interesting that Lovaas points out the variability of individuals and heterogeneity of symptoms that fall under the label of autism. “The delineation of ‘autism’ is one area that will demand considerably more work. It has not been a particularly useful diagnosis. Few people agree on when to apply it. It is not

a functional term in the sense that it is neither related to a particular etiology nor to a particular treatment outcome (p.156, Lovaas et al., 1973).

Comprehensive Randomized-Control Trials. Lovaas executed the first randomized-control trial of intervention for individuals with autism. Capitalizing on previous research in applied behavior analysis, Lovaas designed a rigorous trial to examine the impact of comprehensive early intervention. His study would represent a turning point in the expectations and possibilities of autism intervention.

Lovaas was deliberate and explicit in his design, to create "a special, intense, and comprehensive learning environment for very young autistic children" (p.4, Lovaas, 1987). He was also explicit about his goal, namely that this environment would allow some children with autism "to catch up with their normal peers by first grade" (p.4, Lovaas, 1987). Both his methods and goals were revolutionary, and the concept of "normalizing" children remains controversial to this day (Helt et al., 2008; Mundy, 1993).

The sample included 61 children with an "independent" diagnosis of autism. The process included structured interviews, child observation, and formal psychological testing, loosely corresponding to the current gold-standard (Filipek et al., 1999), though tied to the DSM-II and DSM-III. When the trial began, the children were under 40 months of age or 46 months with echolalia, and were required to have had a mental age of 11 months by the time they were 30 months of age (Lovaas, 1987).

Of the 61 subjects, 40 were assigned to one of two groups, either an experimental group or a control group. The experimental group received 40 hours or more of 1 on 1 behavioral treatment each week. The control group receive 10 hours or less of 1 on 1 treatment each week. The experimental group received treatment for 2 or more years. Two families withdrew during the first 6 months, while all other families continued with the program until its conclusion, leaving a final sample of 38 children.

Of these 38 children, 19 were assigned to the experimental group, while 19 were assigned to the control group. While this study is often credited as the first randomized-control trial of comprehensive behavioral intervention, the assignment of subjects to groups was not strictly random. Lovaas notes this limitation, but asserts that assigning subjects based on staff availability, independent of subject characteristics, assured "unbiased groups" (p.4, Lovaas, 1987). An additional 21 subjects were recruited from another study to serve as a comparison to the first control group to evaluate any potential selection bias.

In the experimental group, a team of student therapists implemented the intervention program across settings, including home, school, and community. Parents received training as well. The first year of treatment focused on compliance, imitation, toy play, and generalization. Aggressive and self-stimulatory behaviors were the primary targets for extinction during the first year. During the second year, treatment goals expanded to include expressive language, peer play, and generalization to community settings. Strategies included ignoring, time-out, and shaping behaviors. Aversive strategies were used as a last resort, including a loud “no” or slap on the leg (Lovaas, 1987).

The control group received similar 1 on 1 treatment but reduced in quantity to 10 hours or less per week. Aversive strategies were not utilized in this group, due to the limited availability to teach alternate replacement behaviors. Some subjects received additional treatment from community-based programs (Lovaas, 1987).

Lovaas found significant differences between groups at post-treatment. The experimental group scored 30 IQ points higher than the control group. Within the experimental group, Lovaas describes 9 of the 19 participants as “recovered”, while 8 continued to be in supported classrooms for language, and 2 remained in classrooms designed for those with intellectual disabilities (Lovaas, 1987). The paper primarily focuses on these two outcome measures.

Lovaas’ findings were indeed revolutionary. He highlights that the prevailing expectations held out little hope for substantial developmental gains for children with autism. He shattered this notion by showing that evidence-based teaching methods employed with great quality and quantity can lead to meaningful and remarkable gains.

Lovaas notes that not all children made equal gains with this high quality and quantity of intervention. Eight children in the experimental group made more moderate gains compared to the “recovered” cases, and 2 children made more minimal gains, as evidenced by their educational placement. Lovaas suggests the possibility of distinct etiologies within ASD, a finding generally accepted currently.

Lovaas’ discussion of the gains within the “recovered” group may be overstated based on our current understanding of ASD. He writes, “on the basis of testing to date, the recovered children show no permanent intellectual or behavioral deficits and their language appears normal” (p.8, Lovaas, 1987).

While this may be true based on the standardized measures used, it does not address recovery from the social deficits associated with ASD. Other broad statements such as “during treatment they showed a broad improvement across all observed behavior” (p.8, Lovaas, 1987) may be overstated as well.

While the gains in IQ scores remain outstanding and impressive, the additional measures of classroom placement, while informative, do not provide an explicit cognitive profile or specific comparative gains in contradistinction to the control group. It is unclear what precise factors contribute to educational placements in the Los Angeles area, and what advocacy by the families or support staff was employed to procure those placements. This also limits the ability to replicate one of the paper’s primary findings.

Despite these limitations, providing intervention for 19 individuals who met criteria for autism according to the DSM-II and DSM-III, improving their IQ scores, and procuring general educational placements for nearly half the group remains a significant achievement, independent of a precise randomized-control comparison. The study remains a cornerstone in the development of comprehensive intervention programs from children with ASD. Lovaas demonstrated definitively that a carefully designed environment using evidence-based teaching practices in high quality and quantity can provide the opportunity for substantial cognitive and functional gains.

Follow-up. A follow-up study was conducted to examine whether the remarkable gains reported in the aforementioned study were sustained over time. McEachin and colleagues (1993) assessed the same 19 children in Lovaas’ experimental intervention group, and compared them with the original 19 children in the control group, along with another age-matched control group. This was essential given previous research findings which indicated that children with autism may regress in skills once treatment had concluded (Lovaas et al., 1973). The findings of the follow-up study supported the notion that those with the best outcomes in the experimental group retained their gains approximately six years later (McEachin, Smith, & Lovaas, 1993).

The assessment included a standardized measure of intelligence (Wechsler Intelligence Scale for Children-Revised, Wechsler, 1974) and two parent report measures, one assessing adaptive behavior (Vineland Adaptive Behavior Scales, Sparrow, Balla, & Cicchetti, 1984) and another designed to assess psychiatric symptoms (Personality Inventory for Children, Wirt, Lachar, Klinedinst, & Seat, 1977). The

authors argue that taken together, these three measures provide “a comprehensive evaluation of intellectual, social, and emotional functioning” (p.363, McEachin et al., 1993).

McEachin and colleagues report that the experimental group maintained gains in intellectual functioning and displayed significantly higher adaptive skills than the control group from the original 1987 study. The results from the parent report measure of psychiatric symptoms were unclear and not convincingly interpreted. The measure is no longer used so it is difficult to interpret the results clearly. One subject (J.L.) had scores that appear to be divergent from the rest of the group, which the authors argue skewed the data for the experimental group. They also report that this child was moved from a general education setting and placed in a classroom with support for language delays. The reported percentage of children from the experimental group in general education remained the same, due to the fact that another child was moved from a supported classroom to general education (McEachin et al., 1993).

As with the original 1987 Lovaas paper, some findings may be overstated. The authors outline the objective of the current study as determining to what extent children were “free of autistic symptomatology” (p.360, McEachin, 1993). They further argue that the intelligence test and two parent report measures comprehensively assess intellectual, social, and emotional functioning” (p.363, McEachin et al., 1993). Though the authors specifically tout “avoiding overreliance on intelligence tests” (p.369, McEachin et al., 1993), direct observation of the child is limited to a single data point within an intelligence test. The rest of the social and emotional measures are based on parent report, which may be influenced by parental bias. With the subsequent development of direct observation measures of autism symptomology, it is difficult to find conclusive support within this study that even the “best outcome” cases were free from any social deficits associated with ASD.

Another salient finding is a stated conclusion regarding treatment intensity. Highlighting the fact that the experimental group received 40 hours per week of 1 on 1 intervention, in comparison to the “up to 10 hours a week” for the control group, they state that “this result confirms that our subjects had problems that responded only to intensive treatment” (p.369, McEachin et al., 1993). No data was provided about intervention services received across groups between 1987 and 1993.

The authors rightly note that minimal explanation is provided regarding the children in the experimental group who did not “recover”. Both the 1987 and 1993 reports seem to gloss over the fact that this indeed represents the majority of the group. While this remains a fair criticism, it must be considered in the context that minimal evidence existed for any effective intervention program. Similar to methods still used within social psychology (Ross & Nisbett, 1991), the object was not to demonstrate that the comprehensive intervention program leads to recovery in every case, but that comprehensive intervention can lead to recovery. Translated into more conservative modern terminology, the goal of the study was to establish that comprehensive early intervention could substantially improve long-term outcomes for children with ASD.

McEachin and colleagues aptly assert that further research is needed to examine how intervention impacts neurological structures. It would be a number of years before a rigorous investigation of comprehensive early intervention on neurological functioning was executed.

Replication. A further study attempted to replicate Lovaas’ findings, and address some of the methodological flaws in the original study. Smith and colleagues executed a study with true random assignment, employing the Lovaas intervention methodology (Smith, Groen, & Wynn, 2000). The findings added to the literature regarding the effectiveness of intervention but continued to raise questions about efficacy and treatment response.

The study took place at UCLA under Lovaas’ Young Autism Project. The investigators however maintain that one of the strengths of the current study was that the personnel “met the qualifications specified” but were “independent of Lovaas” (p.271, Smith et al., 2000). The only contact was “quarterly, one-hour consultations pertaining to…administrative issues” (p.273, Smith et al., 2000). The investigators had conducted treatment under the supervision of Lovaas for a decade combined (Smith et al., 2000). Taken together, the study can be considered an implementation inline with the Lovaas methodology but without his direct involvement in day-to-day clinical supervision.

Twenty-eight children were recruited to participate in the study, with a chronological age between 18 and 42 months. Of these children, 14 were diagnosed with autism and 14 were diagnosed with pervasive developmental delay not otherwise specified (PDD-NOS). Each child received an independent diagnosis from a licensed psychologist at a California State Regional Center. Notably, the IQ range was

broader than the original Lovaas study, as participants had an IQ between 35 and 75 at time of entry into the study.

The children were randomly assigned into *intensive treatment* or *parent training* using a matched-pair, random assignment procedure. Once 4-8 children had been recruited, groups were divided based on a diagnosis of autism versus PDD-NOS, and then matched into pairs based on IQ. One member of each pair was assigned to intensive treatment, while the other was assigned to parent training (Smith et al., 2000). This addressed one of the methodological flaws in the original Lovaas study (1987) where children were assigned to treatment based on staffing availability.

It was originally intended for the intensive treatment group to receive 30 hours of treatment per week, 10 hours less than the original Lovaas study. However, due to practical impediments including cancelations (commonly due to scheduling and child illness), the intensive treatment group received 24.52 hours per week. Further, once children acquired basic skills such as short phrase speech, compliance to verbal requests, appropriate toy play, and could complete adaptive self-care tasks, treatment shifted from 1 on 1 to naturalistic support in a group environment. The authors report this occurred approximately one year after treatment began, with “large variation across children” (p.273, Smith et al., 2000). This is in stark contrast to the primarily 1 on 1 treatment provided in the original study (Lovaas, 1987). Also, if the children did not achieve mastery of the skills mentioned above within 18 months, they were enrolled in special education classes and the treatment was phased out. Another difference included limiting requirements on parents, whereas in the original study at least one parent was required to take a leave of absence from his or her employment in order to support the intervention (Lovaas, 1987; Smith et al., 2000).

The parent training group received in-home training for 5 hours per week across 2 sessions. This training continued for “3 to 9 months” (p.274, Smith et al., 2000). Parents were expected to provide 5 additional hours of intervention each week based on the principles taught during the training sessions. These sessions included instruction in discrimination learning, discrete trial training, and functional analysis of behavior, all based on the Lovaas manual (Lovaas, 1981). The parent trainer worked directly with the child for a 2 to 3 minute interval, then asked the parent to repeat the task with the child, and then

provided feedback to the parent. Children also participated in public school-based special education classes for 10-15 hours per week, with no involvement from the research team.

Fidelity procedures were similar to Lovaas' 1987 study. Student interventionists needed to pass a knowledge-based test on the Lovaas treatment method, an observation-based test of competence in discrete-trial teaching, and favorable supervisor ratings. Supervisors completed a minimum of 1500 hours of 1 on 1 treatment as part of the UCLA Young Autism Project, demonstrated "mastery of research pertaining to applied behavior analytic treatment for children with pervasive developmental disorder", displayed proficiency at "designing and implementing treatment plans", and favorable supervisor and parent ratings (Smith et al., 2000). No measures of ongoing fidelity were indicated, other than favorable supervisor ratings, for which no interval of assessment was provided.

Children in the intensive intervention group did make significant gains compared with the parent training group. However, the gains were more modest than those reported previously (Lovaas, 1987; McEachin et al., 1993). On average, children in the intensive intervention group scored 16 points higher on IQ measures compared with the parent training group. This is in contrast to a 31-point difference reported previously (Lovaas, 1987). Similarly, 27% of children in the intensive intervention group achieved placement in regular education classes, in contrast to 47% reported by Lovaas (1987). While differences in behavior problems and adaptive behavior were reported previously (McEachin et al., 1993), no significant between-group differences were observed on measures of behavior problems or adaptive behavior (Smith et al., 2000).

In summary, the study by Smith and colleagues is significant in terms of its rigorously randomized design and technical independence from Lovaas' direct clinical supervision. They confirmed previous findings of positive outcomes regarding IQ and educational placement. However, these gains were more modest than previously reported. The reported differences may be due to multiple factors. The treatment hours were significantly less (24.52) than the original study (>40), indicating quantitative levels of intensity may be an important factor in outcomes. While Smith and colleagues (2000) did not find that IQ predicted outcomes, the average IQ at intake in the intensive intervention group was 50 compared with an average score of 63 in Lovaas' (1987) intervention group.

Expansion. A team at the University of Washington executed a study of comprehensive early intervention for toddlers. Using a rigorous randomized design, 48 children between 18 and 30 months with a diagnosis of an autism spectrum disorder were randomized into an intervention group or assessment and monitoring group. The intervention program incorporated a series of evidence-based practices using established principles of applied behavior analysis along with relationship-based intervention (Geraldine Dawson et al., 2010).

All participants scored at 35 or above as measured by the Mullen Scales of Early Learning (Mullen, 1995). Preexisting neurological conditions such as fragile X syndrome, significant motor impairment, major physical or chronic conditions, or drug exposure were excluded (Geraldine Dawson et al., 2010). Participants met criteria for ASD based on the gold-standard assessment recommendations (Filipek et al., 1999). To date, this is the only randomized trial that utilized the gold-standard diagnostic criteria including standardized parent interview, standardized observation of the child, and DSM-IV diagnosis from an expert clinician.

The intervention group was expected to receive 20 hours of treatment per week from University of Washington clinicians based on the Early Start Denver Model (ESDM). Parents were expected to deliver an additional 5 hours per week of intervention based on parent training. At the conclusion of 2 years, the intervention group received 15.2 hours per week of ESDM intervention. The authors highlight logistical challenges such as vacations and illness as common impediments to treatment hours. Parents in the ESDM group reported implementing ESDM strategies for an additional 16.3 hours per week, with another 5.2 hours per week in other therapies such as speech services, occupational therapy, or developmental preschool. In total, the ESDM group averaged around 36 hours per week of intervention, though only 15.2 hours per week were direct 1 on 1 ESDM intervention (Geraldine Dawson et al., 2010).

The assessment and monitoring group received an average on 9.1 hours of individual therapy per week, provided by community practitioners. An additional 9.3 hours were reported for participation in group interventions such as developmental preschool. Thus, the assessment and monitoring group received an average of around 18 hours per week in intervention. Both groups received annual comprehensive assessments of IQ, adaptive behavior, language development, and autism

symptomology, from clinicians at the University of Washington who were blind to participant status (Geraldine Dawson et al., 2010).

Out of the original sample of 48 children, 1 child withdrew from the assessment and monitoring group after 1 year, and 2 children withdrew from assessment and monitoring by the 2-year time point. There was 100% retention in the ESDM intervention group at the 2-year time point. At intake, the groups showed no significant differences in age, IQ, gender, adaptive behavior, or autism symptomology (Geraldine Dawson et al., 2010).

***Results*.** At the first year time point, some significant differences were observed across groups. The ESDM group increased 15.4 IQ points on average, compared with 4.4 IQ points in the assessment and monitoring group. No significant differences were observed in autism symptomology, as assessed by the ADOS and repetitive behavior scale (RBS: Lam & Aman, 2007). Consistent with previous reports (Smith et al., 2000), the intervention and control groups did not differ on adaptive behavior (Geraldine Dawson et al., 2010).

At the two-year time point, additional significant differences were observed. IQ scores in the ESDM group increased 17.6 points on average, compared with 7.0 points in the monitoring group. Differences in receptive and expressive language were also significant, with the ESDM group gaining 18.9 points compared with 10.2 points in expressive language, and 12.1 points compared with 4.0 points in expressive language. Groups also differed on adaptive skills, with the ESDM group maintaining standard scores on the Vineland Adaptive Behavior Scales, compared with an 11.2-point decline in the assessment and monitoring group. As standard scores are adjusted for developmental expectations, the authors argue the observed differences represent steady progress in the ESDM group, with relative stagnation or decline in the monitoring group. No observed differences were significant regarding autism severity, as assessed by the ADOS and RBS (Geraldine Dawson et al., 2010).

Significant changes in diagnostic status were also reported across groups. While 7 children in the ESDM group went from a diagnosis of autistic disorder to PDD-NOS, only 1 child in the monitoring group improved in diagnostic status. Nonetheless, these changes in diagnostic status were not reflected in the coded ADOS severity scores based on standardized observation (Geraldine Dawson et al., 2010). While

educational placement was a key outcome in previous comprehensive intervention studies, this variable was not yet available as an outcome for toddler intervention.

A follow-up study conducted two years after post-treatment showed additional significant differences between the ESDM intervention and assessment and monitoring group. Firstly, gains apparent at exit from treatment in the ESDM group were generally maintained at follow-up. These included gains in IQ and adaptive behavior. While scores of autism symptomology were not significantly different upon exit from intervention at age 4, the ESDM group displayed significantly fewer ASD symptoms at age 6 as assessed by direct observation during the ADOS. Differences were also significant in adaptive behavior. Interestingly, IQ differences were no longer significant between groups at age 6 (Estes et al., 2015).

Evidence of Outcomes Across Domains. Reichow and colleagues (2014) undertook a meta-analysis to examine the impact of early intensive behavioral intervention on functional outcomes. A review of available literature resulted in five studies which utilized 20-40 hours of applied behavior analysis per week (H. Cohen & Smith, 2006; Howard, Sparkman, Cohen, Green, & Stanislaw, 2005; Magiati, Charman, & Howlin, 2007; Remington et al., 2007; Smith et al., 2000). These studies were carefully reviewed and overall effect sizes were calculated for outcomes across domains (Reichow, Barton, Boyd, & Hume, 2014).

Across the five studies, 203 participants were included in the analysis. Each study also included a "treatment-as-usual" control group. Positive effects were found for IQ (g = 0.76; 95% CI 0.40 to 1.11; p < 0.0001), adaptive behavior (g = 0.69; 95% CI 0.38 to 1.01; p < 0.0001), expressive (g = 0.50; 95% CI 0.05 to 0.95; p = 0.03) and receptive language (g = 0.57; 95% CI 0.20 to 0.94; p = .03), daily communication skills (g = 0.74; 95% CI 0.30 to 1.18; p < 0.001), socialization (g = 0.42; 95% CI 0.11 to 0.73; p < 0.001, and daily living skills (g = 0.55; 95% CI 0.24 to 0.87; p < 0.001: Reichow et al., 2014).

Reichow and colleagues highlight a considerable risk for bias within these datasets, due to the fact that four of the five studies did not use a randomized design. Other than the study by Smith and colleagues (2000) reviewed above, the group assignment in the remaining four studies was based on parent preferences. Thus while quantitative evidence supports the effectiveness of early intensive

behavioral intervention, there are significant methodological limitations to the current datasets which limit definitive conclusions (Reichow et al., 2014).

The review by Reichow and colleagues (2014) excluded the Lovaas (1987) study and subsequent follow-up (McEachin et al., 1993) due to the fact that the comparison group was not "treatment-as-usual" (TAU) but a lower intensity behavioral intervention (Reichow et al., 2014). This is moderately compelling, though TAU is not truly uniform across participants. It is unclear why Reichow and colleagues did not include the Dawson and colleagues randomized-control trial of ESDM (Geraldine Dawson et al., 2010), as it is not mentioned or referenced in the review, despite the search of literature reportedly executed in 2011 (Reichow et al., 2014).

Factors Predicting Better Outcomes. Beginning with the original Lovaas (1987) intervention study, it was clear that certain participants had superior outcomes to their peers. However, determining which children would eventually have the best outcomes remained elusive. Some subsequent studies have examined particular factors that lead to best outcomes with moderate success.

In a sample of 21 children ages 2 to 5 who received ESDM intervention in a group setting, Vivanti and colleagues (2013) report that functional use of objects, goal-understanding, and imitation abilities were correlated with the best outcomes after 1 year of intervention. There was also a negative correlation observed between autism symptom severity and gains in expressive language. Interestingly, overall cognitive abilities, social attention, chronological age, or developmental age at intake were not correlated with outcomes (Vivanti, Dissanayake, Zierhut, & Rogers, 2013). A similar study of 49 preschool children who received ESDM intervention in a group setting supported the notion that symptom severity was negatively correlated with outcomes. However, age at intake was in fact correlated with better outcomes, evidencing the importance of early intervention (Eapen & Crncec, 2016).

Impact of Comprehensive Behavioral Intervention of Neural Functioning. A high profile study by Dawson and colleagues (2012) described evidence for changes in brain activity which was attributed to early comprehensive behavioral intervention. Following up on the randomized-control trial of the ESDM (Geraldine Dawson et al., 2010), EEG activity was recorded at time of exit from intervention. This included electrophysiological evaluation of the ESDM intervention group, the assessment and

monitoring group (treatment-as-usual), and a group of age-matched typical controls (Geraldine Dawson et al., 2012).

Results indicated that the ESDM group displayed decreased alpha power and increased theta power when viewing faces. The assessment and monitoring group displayed an opposite pattern, with increased alpha and decreased theta power when viewing faces compared with objects. The typical control group displayed patterns similar to the ESDM intervention group. The ESDM and typical groups also displayed a faster negative deflection (Nc) to faces compared with objects, while the assessment and monitoring group displayed faster Nc to objects compared with faces (Geraldine Dawson et al., 2012).

Strengths of the study include its rigorously randomized design and typical control group. Limitations discussed by the authors include 40% attrition in the ASD group, no consistent pre and post EEG measurements, and overall sample size (Geraldine Dawson et al., 2012). Also, no differences were observed in N170 processing or other EEG or ERP paradigms with previously consistent ASD findings.

Two additional studies are worthy of note. Voos and colleagues conducted an elegantly designed case study of the impact of Pivotal Response Treatment (PRT), an evidence-based parent training methodology, upon neural functioning in 2 children with ASD. Using a pre and post fMRI paradigm, greater activation was observed after 4 months of treatment in key brain areas related to biological motion (right posterior superior temporal sulcus, fusiform gyrus, dorsolateral and ventrolateral prefrontal cortex (Voos et al., 2013). Though the brain areas affected were not entirely uniform across the two cases, the investigation nonetheless demonstrated that intervention can impact neural functioning.

Ventola and colleagues (2015) also used fMRI to examine a group of 10 children before and after 4 months of PRT. Baseline assessment revealed two distinct groups, one with hyperactivation and one with hypoactivation in the right posterior superior temporal sulcus, compared with a typical sample of 5 children. The hyperactivation group demonstrated reduced activation in thalamus, amygdala, and hippocampus post treatment, while the hypoactivation group demonstrated increased activation in the ventral striatum and putamen (Ventola et al., 2015). Again, while the results were not uniform across groups or brain regions, they do indicate a relationship between intervention and neural functioning.

Summary of Comprehensive Intervention. Though no cure for autism has been established, strong evidence has emerged from case studies to rigorously designed randomized-control trials demonstrating the effectiveness of behavioral techniques for teaching functional skills to children with autism spectrum disorders. Early intervention leads to the best outcomes, supporting gains in cognitive abilities, adaptive skills, and language. There is further evidence that comprehensive early intervention can reduce autism symptoms and alter or "normalize" neurological functioning. Additional research examining long-term outcomes, using both clinical and neurophysiological assessment and precise experimental paradigms, will further our understanding of the impact of comprehensive early intervention.

Purpose and Hypotheses

This study aims to examine neural functioning in light of comprehensive early intervention. One of the foundational randomized intervention studies in autism spectrum disorders noted the promise of examining "the extent to which early intervention alters neurological structures" (p.371, McEachin, Smith, & Lovaas, 1993). The current study capitalizes on the rigorous randomized design of the Early Start Denver Model (ESDM) comprehensive early intervention program study (Dawson et al, 2010), and applies a carefully defined and established social neuroscience paradigm indexing mirror neuron system (MNS) functioning. This approach enables us to compare neural functioning in young children with autism spectrum disorders who have received comprehensive early intervention. The primary aim of the proposed study is to investigate the impact of the Early Start Denver Model invention program on MNS functioning, as assessed by EEG mu attenuation. Given evidence that ESDM impacts neural functioning (Webb et al, 2012), ESDM targets social cognitive behaviors such as imitation (Dawson et al., 2010; Rogers, Dawson, & Vismara, 2012) and that MNS functioning is linked to imitation ability (Bernier et al, 2007; 2013), I hypothesize that more normalized MNS functioning, as demonstrated by mu attenuation in response to the observation of motor actions, will be reflected in the intervention group as compared with the control group. A secondary aim of the proposed study is to examine the relationship between neural functioning and social behavior, proposed to be impacted by the intervention program (e.g., imitation

ability). Given previous findings (Bernier et al, 2007; 2013, Dapretto et. al, 2006; Iacoboni & Dapretto, 2006) my hypothesis is that social behavior, reflected in imitation ability scores and socialization scores on observation and parent report measures, will correlate with neural functioning of the mirror neuron system. It is further hypothesized that while mu attenuation will correlate with social behavior, it will not correlate with general autism symptomology.

Methods

Participants

Forty-eight children were recruited to participate in a trial of comprehensive early behavioral intervention study at the University of Washington. Inclusion criteria included chronological age between 18 and 30 months and a documented diagnosis of an autism spectrum disorder, including autistic disorder and pervasive developmental delay not otherwise specified (PDD-NOS). Diagnoses were independently verified according to rigorous research criteria, including structured observation of the child using the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000), standardized parent interview using the Autism Diagnostic Interview – Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994), and clinical judgment by a clinician with expertise in autism spectrum disorders, following gold-standard diagnostic procedures (Filipek et al., 1999).

Children were randomized into two groups using a stratified randomization procedure based on gender and IQ, as assessed by the Mullen Scales of Early Learning (MSEL; Mullen, 1995) at time of entry. The intervention group received two years of comprehensive early intervention based on the Early Start Denver Model for 15.2 hours per week (ESDM group). The control group (COM group) received regular assessment and monitoring and was encouraged to pursue services available in the community. Measures of IQ, autism symptoms, adaptive behavior, and repetitive behavior were collected by clinicians who were blind to subject status at one-year post-entry and two years post-entry into the study. These findings have been previously reported (Geraldine Dawson et al., 2010).

The original 48 participants in this randomized controlled trial were recruited to participate in a follow-up study when the children were 6 years of age, approximately 4 years post-entry. Of the original

sample, 39 children participated in the follow-up study. Clinicians who were blind to subject status collected measures of IQ, autism symptoms, adaptive behavior, and repetitive behavior. Results from these measures were recently reported (Estes et al., 2015).

Of the 39 children that participated at the 6-year old time point, 27 participants agreed to participate in the EEG assessment. This involved recording videos of a primary parent or guardian performing standardized motor actions. These videos were used during the EEG assessment to examine potential differential brain responses to the observation of actions performed by familiar versus unfamiliar people. Of the 27 EEG participants, 20 completed the EEG assessment successfully and produced usable EEG data. Of the 7 participants who agreed to complete the EEG but did not produce usable data, 4 were in the ESDM group and 3 were in the COM group. Of the 4 participants in the ESDM group, 3 completed the session but failed to produce rest data free from movement artifacts, while 1 subject only completed part of the paradigm. Of the 3 participants in the COM group, 1 failed to produce rest data free from movement artifacts, and 2 refused to complete the session by pulling off the EEG cap.

The 20 participants that completed the EEG assessment contained 10 participants from the ESDM and 10 from the COM group. The subgroup of 10 children that received ESDM and participated in the EEG did not significantly differ from the overall ESDM group in terms of IQ, adaptive behavior, or autism symptoms. Results of these comparisons are listed in Table 1. The subgroup of 10 children in the COM group did not significantly differ in terms of adaptive behavior or autism symptoms, but they did significantly differ on IQ, as the subgroup that completed the EEG had significantly higher IQ than the general COM group. Results of these comparisons are listed in Table 2.

The ESDM and COM groups that participated in the EEG did not differ significantly in age, gender, verbal IQ, nonverbal IQ, adaptive behavior, or ADOS scores. Results of these comparisons are listed in Table 3. Thus the EEG assessment was conducted on well-matched groups.

EEG Assessment

Brain activity was recorded at rest and during the observation and execution of motor actions using a 128-electrode EEG system (Electrical Geodesics, Eugene OR). The electrical brain activity was

analog filtered (01. Hz high-pass, 100 Hz elliptical low-pass), amplified, and digitized at 500 samples per second. Impedances were below 50 kΩ with signals referenced to the vertex at acquisition. EEG and video were recorded simultaneously using NetStation 4.3. This allows for subsequent video inspection of the session to ensure the participant was attending to the presented stimuli, and assists with identifying eye blink and other movement artifacts.

EEG Paradigm. The paradigm included three conditions adapted from an established procedure designed to assess mu attenuation via EEG as an index of mirror neuron activation (Muthukumaraswamy & Johnson, 2004). The paradigm included an observe condition, an execute condition, and a rest condition to evaluate baseline activity. In the observe condition, participants watched a 6-second clip on a video monitor displaying a hand grasping a block of wood. A photocell installed on the video monitor allowed the EEG recording to be time-locked to the display of the grasping motion. In the execute condition, participants grasped a block of wood identical to the one displayed in the video clip. A sensor on the block of wood allowed the EEG recording to be time-locked to the participant's grasping motion. In the rest condition, participants sat with eyes opened and watched a plus sign on the monitor.

Within the observe condition, participants observed videos of their parent or guardian conducting a grasping motion, as well as an unfamiliar person executing the same grasping motion. The blocks proceeded as follows: Unfamiliar Observe (10 trials), Familiar Observe (10 trials), Execute (10 trials), Rest (30 seconds), Unfamiliar Observe (10 trials), Familiar Observe (10 trials), Execute (10 trials), Rest (30 seconds).

EEG Analysis. While signals are referenced to the vertex at acquisition, signals were re-referenced to an average reference offline. Artifact detection was conducted using video inspection, an automated algorithm in NetStation 4.3, and manual visual inspection using NetStation 4.3 and Matlab to identify movement artifacts. The rejection rate did not differ across groups, with an average rejection rate of 53.38% (ESDM 52.50%, COM 54.25%).

Following procedures outlined by Muthukumaraswamy and colleagues (2004), the conditions were divided into 2-second epochs, and a fast Fourier transform (FFT) was performed to normalize the data. Similar to previously described methods (Babiloni et al., 1999; Muthukumaraswamy et al., 2004;

Muthukumaraswamy & Johnson, 2004; Pfurtscheller et al., 1997), a specific Hz range was selected for each subject. Individual spectral plots were generated, and the Hz band yielding the maximum difference in power between the execute condition and rest condition was selected. Power was averaged across trials within conditions and across blocks, and these values were then exported to Matlab in order to provide a single numerical value representing the average power for a given condition.

This paradigm yields a score representing a scale dependent variable of mu attenuation. This is calculated by computing the log of the ratio between the observe and rest condition. The dependent variables of interest are the log of the ratio of the observe-familiar over the rest condition, and the log of the ratio of the observe-unfamiliar over the rest condition. This yields a single numerical value representing mu attenuation for a given subject in a given condition, which can be compared across conditions and across subjects.

Imitation Ability

Imitation skills were evaluated using a procedure utilized in two previous mirror neuron studies (Bernier et al., 2013, 2007). The procedure (Mature Imitation Task; Rogers, Cook, & Greiss-Hess, 2005) comprehensively assesses the imitation of single-hand movements, complex two-hand movements, and face gestures. The gestures were displayed in a series of 6-second video clips, including 8 face gestures, 8 single-hand movements, and 6 complex hand movements. The final gesture was displayed for at least 3 seconds and remained until the imitation attempt was completed. Coders who were blind to subject status used video recordings to evaluate imitation accuracy, including accuracy of position, orientation, or expression, and track errors or artifact movements, including repetition, overshooting, and approximations, yielding scores for face imitation, hand imitation, and complex-hand imitation, including errors in each category. Coders maintained an interrater reliability greater than .90.

Results

Mu Attenuation

An examination of studentized residuals revealed no outliers (> ±3). Shapiro-Wilk's test ($p > .05$) and visual inspection of Q-Q Plot indicated the data was normally distributed. Levene's test showed homogeneity of variance ($p > .05$) and Box's test of equality of covariance matrices showed homogeneity of covariances ($p = .750$). *t*-Tests revealed no significant differences in overall power between groups during the observe familiar $t(18) = .38$, $p > .05$, observe unfamiliar $t(18) =$., 96, $p > .05$, and rest $t(18) = 1.42$, $p > .05$ conditions, indicating consistent recording and analysis across groups.

A two-way repeated measures ANOVA was computed to examine main effects of group and familiarity on mu attenuation, as well as the interaction between the two. As shown in Figure 1, results indicated no main effect for group ($F(1,19) = 49.68$, $p > .05$, partial $\eta^2 = .000$) and no significant difference between mu attenuation to familiar and unfamiliar actions within subjects, $F(1,18) = 2.35$, $p > .05$, partial $\eta^2 = .115$. However, there was a significant familiarity by group interaction, $F(1,18) = 6.405$, $p < .05$, partial $\eta^2 = .262$, with the ESDM group showing significantly greater attenuation during familiar observation (see Figure 1).

Correlational Analyses

Correlational analyses of mu attenuation with a series of measures collected at the time of the EEG were evaluated. These include global conceptual ability as assessed by the Differential Abilities Scale II (DAS-II; Elliot, 2006), hand and face imitation as assessed by the Mature Imitation Task (Rogers, Cook, & Greiss-Hess, 2005), and autism symptoms based on the ADOS (Lord et al., 2000) calibrated severity score. A correlation between mu attenuation during observation across conditions and face errors (see Figure 2) approached significance ($p = .044$), but did not reach significance when accounting for multiple comparisons (significance with Bonferonni correction requires $p < 0.006$). Results are displayed in Table 4.

Discussion

The primary aim of this study was to examine neural functioning in light of early comprehensive intervention. Using a randomized design, children were assigned to either receive comprehensive intervention following ESDM, or were encouraged to pursue resources in the community. Two years after completing the intervention, EEG was collected during the execution and observation of simple grasping actions performed by familiar and unfamiliar agents. Spectral power in the mu range, a putative index of MNS functioning, was calculated.

Mu attenuation during the observation of grasping actions did not differ between the ESDM and COM groups, as both groups displayed attenuation to the observation of motor actions. Further, the degree of familiarity with the agent performing the action did not differ across all participants. However, there was a significant interaction in how the two groups viewed familiar and unfamiliar individuals executing identical actions. While the COM group showed no significant difference between viewing familiar and unfamiliar individuals, the ESDM group showed significantly greater attenuation when viewing a parent or caregiver executing a grasping action, compared with the observation of an unfamiliar individual executing the same action. In other words, neural activity in the MNS in the ESDM group differed when viewing familiar and unfamiliar individuals executing similar actions.

Both groups displayed mu attenuation during the observation of motor actions. This is consistent with a series of studies indicating intact MNS functioning in ASD (Avikainen et al., 1999; Dinstein et al., 2010; Fan et al., 2010; Grèzes et al., 2009; Marsh & Hamilton, 2011; Raymaekers et al., 2009). The finding stands in contrast to a greater number of studies evidencing a disruption in MNS functioning in ASD (Bastiaansen et al., 2011; Bernier et al., 2007; Dapretto et al., 2006; Dumas et al., 2014; Hadjikhani et al., 2006; Honaga et al., 2010; Martineau et al., 2008; Nishitani et al., 2004; Oberman et al., 2005; Schulte-Rüther et al., 2011; Yamasaki et al., 2010). While the preponderance of studies found atypical MNS activity in ASD, no study to date has examined whether intervention can influence MNS functioning in ASD. Our finding of intact functioning may be influenced by high volume of intervention both groups received (Estes et al., 2015).

MNS functioning likely develops as a result of the observation of motor actions, the execution of motor actions, and the corresponding sensorimotor experience (Cook, Bird, Catmur, Press, & Heyes, 2014; Gallese, Gernsbacher, Heyes, Hickok, & Iacoboni, 2011b). Given that infants with ASD may naturally spend less time looking at people and shifting gaze from objects to people (observing object-directed actions) than typical infants (Swettenham et al., 1998), this may result in observational and experiential deficits for children with ASD. Indeed reduced exposure may impact the development of imitation skills, which may have a multifarious effect upon other developmental systems, as research has demonstrated an association between the imitation of body movements with language development, and the imitation of object-directed actions with play skills (Stone, Ousley, & Littleford, 1997).

Given the high volume of intervention hours across both the ESDM and COM groups, the children with ASD in our study likely received substantial exposure to people and object-directed actions, likely paired with specific training and rewards related to play and imitation. This may have had have the effect of normalizing MNS activity in our ASD sample.

Our results further suggest that unique features of the Early Start Denver Model intervention program may influence the development of neural circuitry. The ESDM includes a strong focus on promoting social relationships, including joint attention and shared engagement, positive social affect, adult responsiveness, and verbal and non-verbal communication. Parents are taught specific strategies and asked to implement these strategies across activities (Dawson et al., 2010). These factors may alter the relationship that children with ASD have with parents and caregivers. This may in turn modulate attention and motivation, and early training and experience may alter the child's neural responsiveness to familiar individuals.

Previous research indicates across both typical and ASD populations show differential responses to familiarity. Face-processing studies indicate that the brain differentially responds to familiar faces, including differential responses to parents (Taylor et al., 2009). Webb and colleagues demonstrated that the P2 and N250 ERP components were sensitive to personal familiarity across both typical adults and adults with ASD (Webb et al., 2010). Key and Stone (2012) also demonstrated a familiarity effect in infants viewing pictures of their mother compared with a stranger. Both typical and infant-siblings of a

child with ASD showed differential amplitude responses to familiar and stranger differences in N290 and P400. Typical infants also showed a latency differentiation in P400 which was not present in the infant-sibling group. It is noteworthy that concomitant eye-tracking showed no differences in fixation patterns across groups (Key & Stone, 2012).

While simultaneous eye-tracking was not recorded in this study, previous research suggests that differential responses to familiarity in ASD are due to differences in neural activation and not attention or gaze patterns (Sterling et al., 2008). This includes evidence that individuals with ASD do not exhibit different gaze patterns to familiar and unfamiliar faces (Sterling et al., 2008), and that gaze patterns to faces do not differ between individuals with ASD and those with typical development (Gillespie-Smith, Doherty-Sneddon, Hancock, & Riby, 2014).

Pierce and colleagues (2004) showed increased activation in the posterior cingulate, amygdala, and medial frontal lobes in response to familiar faces in typical adults (Karen Pierce, Haist, Sedaghat, & Courchesne, 2004). Other studies have also demonstrated increased activation to familiar faces in the posterior cingulate cortex (Shah et al., 2001). Similarly, the observation of actions executed by same-race individuals compared with different-race individuals results in greater activation in the inferior parietal lobule (IPL; Liew, Han, & Aziz-Zadeh, 2011). Pierce and colleagues (2008) later showed that individuals with ASD demonstrated normal face processing to their mother or other children, but abnormal responses to unfamiliar adults (Karen Pierce & Redcay, 2008).

Using a paradigm similar to the current study, Oberman and colleagues (2008) used EEG to examine mu attenuation to familiar and unfamiliar motor actions. In a sample of 13 individuals with ASD and 13 IQ-matched controls, the ASD group failed to show mu attenuation to strangers, but demonstrated mu attenuation to familiar individuals executing a motor action. In contrast, the typical group showed mu attenuation to the observation of both strangers and familiar individuals (Oberman et al., 2008).

In our study, both groups with ASD showed mu attenuation to strangers and to familiar individuals. While this may be due to both groups receiving a high volume of intervention as noted above, the finding may also be influenced by the use of a full video of the unfamiliar individual executing the motor action. In the Oberman (2008) paradigm, the unfamiliar condition contained only a video of a hand

without a person visible in the screen, whereas the familiar condition contained both the familiar individual and hand. This requires an inference as to the presence of an unfamiliar person. Given documented deficits in holistic processing in ASD (Behrmann, Thomas, & Humphreys, 2006; Geraldine Dawson, Webb, & Mcpartland, 2005; Nakahachi et al., 2008), this may have influenced the lack of attenuation to the unfamiliar condition in the ASD group (Oberman et al., 2008).

Overall, the presence of a familiarity effect is consistent with existing literature. Our finding may be interpreted as MNS specific, indicating unique responsiveness within the MNS to familiarity. Previous research has demonstrated MNS sensitivity to context (Iacoboni, 1999), intention (Iacoboni, Molnar-Szakacs, Gallese, Buccino, & Mazziotta, 2005), and even experience with the action being performed (Calvo-Merino, Grèzes, Glaser, Passingham, & Haggard, 2006).

But the observed difference may also be the result of modulation from other brain regions sensitive to familiarity (Perkins, Stokes, McGillivray, & Bittar, 2010). With connections to the limbic system (Carr et al., 2003), empathy and emotional valence may influence neural activation, as well as attentional, perceptual, and motivational factors. For example, the anterior cingulate cortex has been implicated in both personal familiarity (Donix et al., 2010; Shah et al., 2001) and vicarious responses to pain (Morrison, Lloyd, di Pellegrino, & Roberts, 2004), supporting the notion of multiple systems involved in human action perception (Filimon, Nelson, Hagler, & Sereno, 2007). Regardless of the particular mechanisms involved, our findings suggest a unique impact of ESDM on neural development in a carefully designed paradigm. Consistent with previous research indicating differences in neural functioning between the ESDM and COM group (Geraldine Dawson et al., 2012), our study provides further evidence for this differentiation.

Although not evaluated in the current design, our findings provide further complementary evidence that disruption of the MNS is not specific to the diagnosis of ASD. There was no correlation between MNS activity and autism symptomology. Nonetheless, our findings do not necessarily indicate intact MNS functioning in ASD. Similar to the findings of Oberman and colleagues (2008), it is apparent that individuals with ASD can demonstrate intact MNS functioning, which has indeed been well documented in recent literature (for review, see Dumas, 2014).

Limitations

There are some noteworthy limitations to this study. One major limitation is sample size. With ten subjects in each group, it boasts a similar sample size to other clinical EEG studies and MNS studies. However, the sample size restricts power to detect correlations. Thus the lack of correlations between the MNS and behavioral presentation should be interpreted cautiously. Larger studies should provide a more complete analysis of potential factors related to the MNS.

Another limitation to the study is due to the nature of the control group. In many intervention studies, the control group receives no intervention or delayed intervention Due to high quality intervention resources available in Seattle and near the University of Washington, the COM group likely received high quality intervention. It is indeed remarkable that the COM group received a similar number of intervention hours to the ESDM group. Without details of the individual interventions received, it is difficult to precisely characterize the COM group. However, the observed interaction appears to be a feature of the unique aspects of the ESDM methodology.

One additional limitation is a lack of baseline MNS functioning prior to the intervention. Ideally, MNS functioning would have been assessed at two different time points pre and post intervention. In this instance, we were forced to rely on data from a single time point and draw conclusions retrospectively about the impact of intervention. Nonetheless, the finding that the groups were similar across measures of IQ, adaptive behavior, and autism symptoms make the comparison compelling.

Conclusion

While there has been much discussion about the role of mirror neurons in autism, EEG mu attenuation remains an established methodology for examining the neural correlates of action observation. This study utilized a well-designed randomized controlled trial to examine the impact of the Early Start Denver Model on this neural system. Our findings suggest that the ESDM has a unique impact on the mirror neuron system in ASD.

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Table 1.

Comparison of Full ESDM Sample and Sub-sample that Completed the EEG

Measures	Full Sample ESDM *n* = 21		EEG ESDM *n* = 10			
	M	*(SD)*	*M*	*(SD)*	*t*	*p*
IQ						
Verbal IQ	90.33	(26.38)	103.80	(10.36)	2.51	.021
Non-verbal IQ	91.29	(22.52)	98.80	(11.67)	1.50	.149
GCA	90.52	(26.36)	101.80	(11.48)	2.01	.059
Vineland						
ABC	81.41	(17.27)	86.25	(10.91)	1.10	.290
Socialization	79.24	(16.03)	84.88	(13.29)	1.41	.179
Autism Symptoms						
ADOS Rest/Rep	2.48	(1.97)	1.70	(0.95)	-1.82	.084
ADOS Soc/Affect	8.76	(5.47)	7.20	(3.85)	-1.27	.220
ADOS Total	11.24	(6.87)	8.90	(4.20)	-1.54	.141

Note. GCA = General Conceptual Ability; ABC = Adaptive Behavior Composite

* $p < .05$ when adjusted for multiple comparisons using Bonferroni (controlling familywise by construct). Observed unadjusted *p*-values also given.

Table 2.

Comparison of Full COM Sample and Sub-sample that Completed the EEG

Measures	Full Sample COM *n* = 18		EEG COM *n* = 10				
	M	*(SD)*	*M*	*(SD)*	*t*	*p*	
IQ							
Verbal IQ	78.72	(27.56)	97.00	(17.11)	4.72	<.001	*
Non-verbal IQ	86.44	(17.73)	96.70	(9.63)	3.57	.003	*
GCA	80.06	(23.24)	94.30	(15.17)	3.98	.001	*
Vineland							
ABC	72.06	(13.86)	79.00	(12.01)	2.71	.017	
Socialization	69.44	(13.81)	76.78	(10.85)	2.98	.010	
Autism Symptoms							
ADOS Rest/Rep	4.17	(2.46)	3.20	(2.89)	-2.03	.059	
ADOS Soc/Affect	11.83	(4.85)	10.60	(5.46)	-1.22	.239	
ADOS Total	16.00	(6.57)	13.80	(7.50)	-1.67	.114	

Note. GCA = General Conceptual Ability; ABC = Adaptive Behavior Composite

* $p < .05$ when adjusted for multiple comparisons using Bonferroni (controlling familywise by construct). Observed unadjusted *p*-values also given.

Table 3.

Comparison of Measures Collected at Age 6:

ESDM and COM Subsamples that Completed the EEG

Measures	ESDM *n = 10*		COM *n = 10*			
	M	*(SD)*	*M*	*(SD)*	*t*(77)	*p*
IQ						
Verbal IQ	103.80	(10.36)	97.00	(17.11)	1.08	.297
Non-verbal IQ	98.80	(11.67)	96.70	(9.63)	0.44	.666
GCA	101.80	(11.48)	94.30	(15.17)	1.24	.232
Vineland						
ABC	86.25	(10.91)	79.00	(12.01)	1.30	.214
Socialization	84.88	(13.29)	76.78	(10.85)	1.38	.187
Autism Symptoms						
ADOS Rest/Rep	1.70	(0.95)	3.20	(2.89)	-1.56	.137
ADOS Soc/Affect	7.20	(3.85)	10.60	(5.46)	-1.61	.125
ADOS Total	8.90	(4.20)	13.80	(7.50)	-1.80	.088

Note. GCA = General Conceptual Ability; ABC = Adaptive Behavior Composite

* $p < .05$ when adjusted for multiple comparisons using Bonferroni (controlling familywise by construct). Observed unadjusted *p*-values also given.

Table 4.

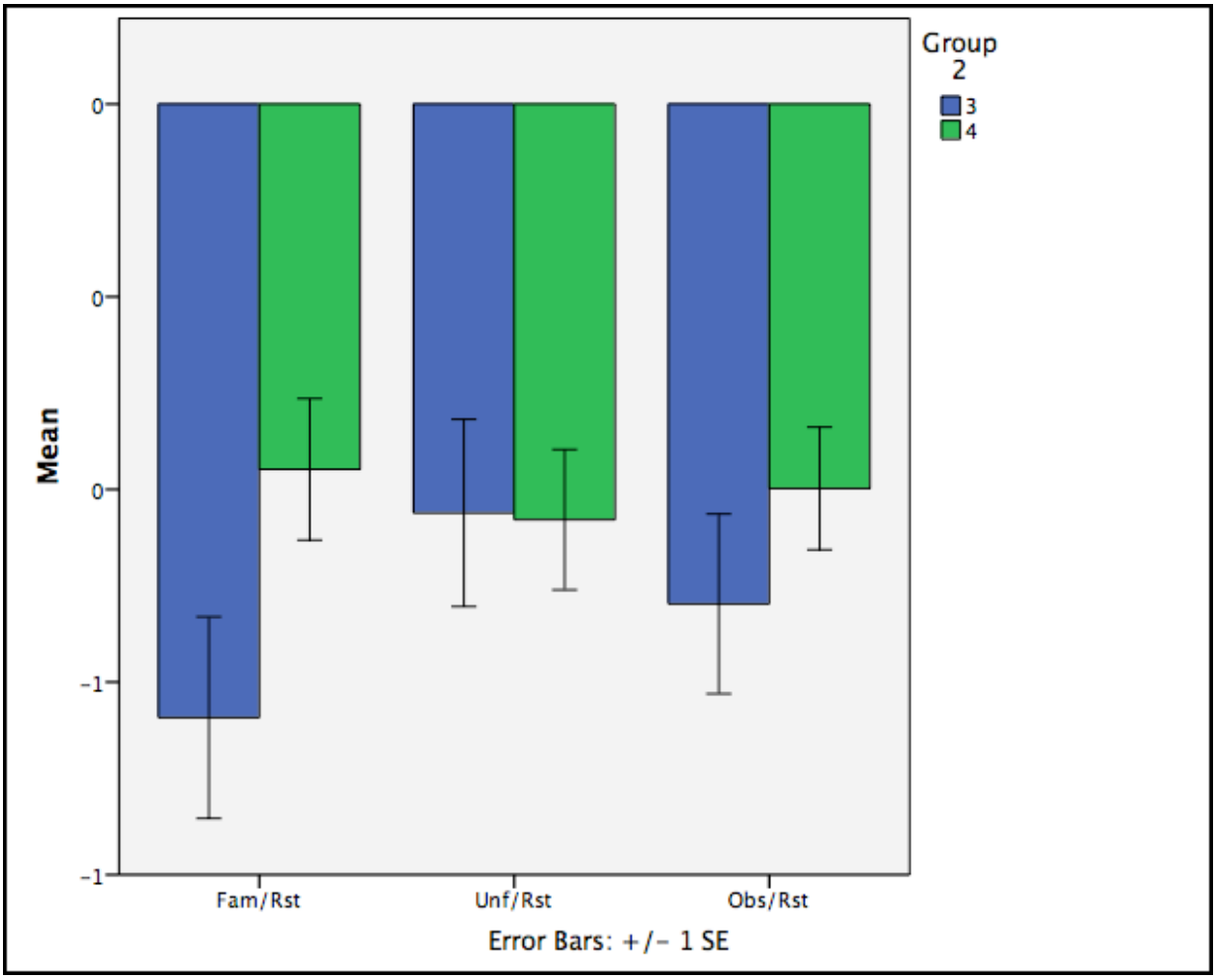
Correlations between Obs/Rst and Measures of IQ, Imitation, and ASD Symptom Severity

Obs/Rst	Pearson Correlation Sig. (2-tailed)	Obs/Rst							
GCA	Pearson Correlation Sig. (2-tailed)	-0.334 0.149	GCA						
Single Face Total	Pearson Correlation Sig. (2-tailed)	0.021 0.931	0.019 0.938	Face Imitation					
Single Face Total Errors	Pearson Correlation Sig. (2-tailed)	.455* 0.044	-0.033 0.891	0.206 0.383	Face Errors				
Single Hand Total	Pearson Correlation Sig. (2-tailed)	-0.251 0.286	0.151 0.525	.614** 0.004	0.101 0.673	Hand Imitation			
Single Hand Total Errors	Pearson Correlation Sig. (2-tailed)	0.206 0.385	-0.071 0.768	0.42 0.065	.721** <.0001	.505* 0.023	Hand Errors		
Complex Hand Total	Pearson Correlation Sig. (2-tailed)	-0.115 0.629	0.128 0.59	.600** 0.005	0.012 0.961	.767** <.0001	0.382 0.096	Complex Hand	
Complex Hand Total Errors	Pearson Correlation Sig. (2-tailed)	-0.209 0.377	-0.07 0.768	0.402 0.079	0.161 0.498	.594** 0.006	.573** 0.008	.492* 0.028	Complex Hand Errors
ADOS Calibrated Severity Score	Pearson Correlation Sig. (2-tailed)	-0.193 0.416	0.092 0.701	-0.215 0.363	-0.174 0.464	0.008 0.973	-0.057 0.813	0.003 0.989	-0.169 0.476

*. Correlation is significant at the 0.05 level (2-tailed).

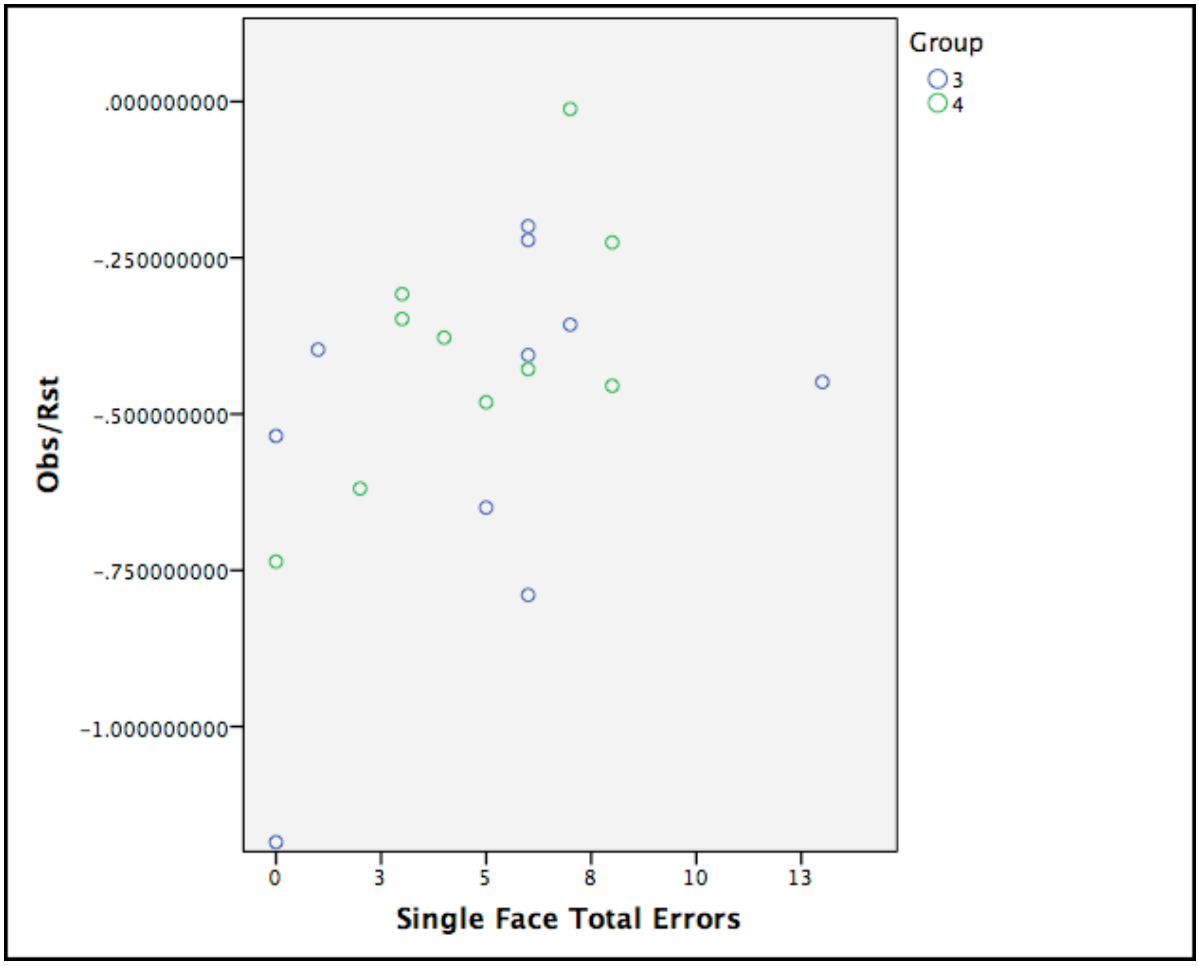
**. Correlation is significant at the 0.01 level (2-tailed).

Figure 1.



Attenuation of mu rhythm in response to familiar (Fam) and unfamiliar (Unf) actors, and both (Obs) executing a motor action

Figure 2.



Correlational analysis of Observe/Rest with Single Face Errors. A trend emerges with greater mu attenuation correlating with fewer face errors.