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A Disembodied Mind: The Role of Dysfunctional Simulation Systems
in the Social and Cognitive Deficits of Autism Spectrum Disorders

A Dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy

in

Psychology

by

Lindsay Meredith Oberman

Committee in charge:

Professor Vilayanur Ramachandran, Chair
Professor Leslie Carver
Professor Ralph-Axel Müller
Professor Jaime Pineda
Professor Piotr Winkielman

2007

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University of California, San Diego

2007

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PUBLICATIONS

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Oberman, L.M., McCleery, J.P., Ramachandran, V.S., Pineda, J.A. (in press). EEG evidence for mirror neuron activity during the observation of human and robot actions: Toward an analysis of the human qualities of interactive robots. *Neurocomputing*

Oberman, L.M. Pineda, J.A. & Ramachandran, V.S. (2007) The Human Mirror Neuron System: A Link Between Action Observation and Social Skills. *Social Cognitive and Affective Neuroscience*, 2, 62-66.

Oberman, L.M. & Ramachandran, V.S. (2007) The simulating social mind: The role of simulation in the social and communicative deficits of autism spectrum disorders. *Psychological Bulletin*, 133, 310-327.

Ramachandran, V.S. & Oberman, L.M. (May 13, 2006) Autism: The search for Steven, *New Scientist* 48-50.

Ramachandran, V.S. & Oberman, L.M. (November, 2006) Broken Mirrors: A Theory of Autism, *Scientific American* 62-69.

Pineda, J.A & Oberman, L.M. (2006) What Goads Nicotine Addicts to Smoke? *Brain Research*, 1121, 128-135.

Oberman, L.M., Hubbard, E.M., McCleery, J.P., Ramachandran, V.S., Pineda, J.A. (2005). EEG evidence for mirror neuron dysfunction in autism. *Cognitive Brain Research*, 24, 190-198.

FIELDS OF STUDY

Major Field: Experimental Psychology (focus in Cognitive Neuroscience)

Studies in typical and clinical aspects of the mirror neuron system through

Electroencephalography

Professors V.S. Ramachandran and Jaime A. Pineda

Studies in Electromyography of embodied cognition

Professors V.S. Ramachandran and Piotr Winkielman

ABSTRACT OF THE DISSERTATION

A Disembodied Mind: The Role of Dysfunctional Simulation Systems
in the Social and Cognitive Deficits of Autism Spectrum Disorders

by

Lindsay Meredith Oberman

Doctor of Philosophy in Psychology

University of California, San Diego, 2007

Professor Vilayanur Ramachandran, Chair

Disorders on the autism spectrum are characterized by deficits in social and communicative skills, such as imitation, pragmatic language, theory of mind, and empathy as well as the presence of restricted, repetitive, and stereotyped patterns of behaviors, interests and activities. Elucidating the underlying neural bases of these deficits has been a challenge because the behavioral manifestations of this disorder vary both in severity (low and high-functioning) as well as in expression (autistic disorder, Asperger's disorder, pervasive developmental disorder—not otherwise specified). The recent discovery of mirror neurons in macaque monkeys by Rizzolatti and colleagues, however, may provide a basis for explaining some of the behavioral deficits seen in individuals with autism spectrum disorders (ASD). Mirror neurons are primarily thought to be involved in perception and

comprehension of motor actions, but they may also play a critical role in higher order cognitive processes such as imitation, empathy, and language. Studies across several labs, including our own, using different techniques have suggested that the MNS is dysfunctional in individuals with ASD. The following dissertation includes our original discovery of this dysfunction as well as follow-up studies aimed at further characterizing the extent of the dysfunction in this population and factors that may modulate it.

Study 1 was conducted to investigate the response of the MNS to observed human and inanimate actions as well as performed actions in individuals with ASD. Results suggest a dysfunction in this system in ASD as evidenced by a lack of mu suppression (an EEG index of MNS functioning) in response to the observation of human actions. Study 2 followed up on this finding exploring the extent of this dysfunction and if it could be ameliorated by the presentation of socially relevant stimuli. Results of this study replicated the original finding in a different sample, finding no significant mu suppression to the observation of an unfamiliar person in the ASD group. However, if the person in the video was either a member of the participant's family or the participant himself performing the action, the ASD group showed a "normal" degree of suppression. Thus, the dysfunction disappeared when the stimulus was familiar to the participant. Study 3 investigated the role of a mirror-like system in another domain, facial mimicry. Results suggest a delay in the appropriate spontaneous mimicry response to observed facial expressions in the ASD group. Despite showing a "normal" amplitude of response and overall activity level, the latency of a response was

approximately 150 milliseconds delayed as compared to the control group.

Together, these results provide a candidate functional mechanism underlying some of the enigmatic behavioral deficits that characterize disorders on the autism spectrum as well as provide hope for the development of therapeutic interventions aimed at improving the functioning of the MNS and similar simulation systems throughout the brain.

Chapter 1

Abstract

Autism Spectrum Disorders (ASD), a subgroup of pervasive developmental disorders, affects an estimated one in every 150 births (Rice et al., 2007) and is largely characterized by deficits in social and communicative skills as well as the presence of restricted, repetitive, and stereotyped patterns of behaviors, interests and activities. Since ASD's original description in 1943 (Kanner, 1943), multiple theories have been developed attempting to explain the etiology of this enigmatic disorder. To elucidate the underlying pathology in autism, researchers must look for candidate neural structures whose specific functions precisely match the particular symptoms unique to autism. Along these lines, the mirror neuron system (MNS) has recently been implicated as a candidate mechanism whose impairment may account for the social and cognitive deficits that are core symptoms of ASD.

1.1 Social and Cognitive Deficits in Autism Spectrum Disorders (ASD)

Disorders on the autism spectrum are characterized by qualitative impairments in skills such as imitation, theory of mind (TOM), empathy and pragmatic language skills (DSM-IV-TR, 2000). Recent reports suggesting an increased prevalence of these disorders have hastened the search for a parsimonious mechanism mediating the wide variety of symptoms present in this population. Those searching for this elusive mechanism hope that, when found, this discovery will lead to more effective treatments based on the underlying neural basis of the disorder, rather than the resulting behavioral symptoms.

One of the first theories developed to explain the symptoms of ASD, (Baron-Cohen, 1988), stressed the primacy of a “metarepresentation” or a TOM impairment, from which other social and communicative deficits stemmed. TOM, as used by Baron-Cohen (1988) was defined as the ability to form a mental representation of another individual’s thoughts or beliefs. Empirical studies such as the ones conducted by Baron-Cohen and colleagues (1985, 1986) provide evidence for impairments in this type of social cognition in children with ASD.

Baron-Cohen and colleagues (1985, 1986) designed a task, called the “Sally-Anne” test aimed at assessing a child’s TOM abilities. In this task, the child is given a cartoon and told a version of the following story, “Sally puts a ball in the basket then goes away. While Sally is away, Ann moves the ball to the box.” The child is then asked, “Where will Sally look for the ball?” The vast majority of both four-year-old typically-developing children and mental age-matched children with Down’s Syndrome passed this test, answering that Sally would look for the ball in the basket (where Sally

thinks it is). Whereas, the majority of children, adolescents and adults with autism failed this test, answering that Sally would look for the ball in the box (where the child thinks it is). This study also included a control task that asked participants to order a picture sequence based on physical causality. In this task, individuals with autism performed at a normal level, indicating that their impairment in understanding beliefs as psychological causes of behavior was not a result of a general inability to understand causality (Baron-Cohen et al., 1985, 1986).

A similar finding was also reported in another study (Perner et al., 1989) in which participants were shown a Smarties © tube and asked to guess what was inside. When participants were shown that in fact pencils (rather than the expected candy) were inside, they were then asked to predict what the next child who comes in would guess was in the box. Typically-developing children answered “Smarties”, their original false belief. In answering this way, it is inferred that typically-developing individuals are able to represent the counterfactual knowledge that the next child would have, that they themselves know is wrong. The majority of children with autism, however, answered “pencils,” reflecting an inability to inhibit their own current beliefs and infer false beliefs in others. These findings have been interpreted as support for a selective deficit in understanding the psychological mechanisms that underlie human behavior based on internal beliefs.

The main argument against TOM as the primary deficit in ASD concerns the timing of typical development of these types of metarepresentational abilities. If TOM was the primary deficit, it would have to present prior to other impairments; however, metarepresentational abilities of the type described above are not reliably present until

between the third and fourth birthdays in typically developing children, while behavioral deficits are apparent in children with autism well before their third birthdays. This suggests that the TOM deficit may be a consequence of an earlier, more fundamental impairment, rather than a primary deficit. The metarepresentational hypothesis, though imperfect, set the stage for other theories implicating underlying impairments in self-other representational processes (e.g. Hobson, 1989; Rogers and Pennington, 1991).

Hobson (1989) proposed that the variety of social and cognitive deficits seen in individuals with ASD is a result of an underlying impairment in affective processing. He claimed, based on mother-infant interaction studies (including Murray and Trevarthen, 1985) that typically developing infants are innately sensitive to other's emotions. Furthermore, individuals with autism are born with a dysfunction in this innate ability, which then leads to impairments not only in empathy, but also TOM, formation of abstract representations, pretend play, emotion recognition and pragmatic language.

From the very first description, an affective impairment has been suggested to be a core-deficit. Kanner in his 1943 paper, "Autistic Disturbances of Affective Contact" (Kanner, 1943), concluded that these children "have come into the world with an innate inability to form the usual, biologically-provided affective contact with people" (p. 250). Since then, multiple experimental studies have confirmed that individuals with autism generally fail to display appropriate behavioral empathetic responses to the distress of another person (Bacon et al., 1998; Corona et al., 1998; Sigman et al., 1992).

While implicating a similar underlying mechanism, Rogers and Pennington (1991) suggested that imitation, rather than TOM or empathy, may be the core deficit. Specifically, they proposed that the imitative impairments seen in children with ASD result from an underlying biological impairment which limits their abilities to “form and coordinate social representations of self and other at increasingly complex levels via amodal or cross-modal representational processes” (p. 151). As imitation is thought to develop prior to the other diagnostically impaired social skills (Rogers and Pennington, 1991), the underlying dysfunction in self-other representation abilities might first manifest itself as a behavioral imitation impairment. Additionally, it was proposed by Rogers and Pennington (1991) that imitation skills are critical building blocks for early affective, social and communicative development. Thus, an impairment in this domain could have deleterious consequences to a developing child.

A multitude of studies performed over the past several decades (reviewed by Williams et al., 2004) suggest that imitation deficits are pervasive in ASD. The first suggestion of an imitation deficit in ASD was made in 1953 (Ritvo & Provence, 1953) with an anecdotal report of a mother describing the inability of her 21-month old to play pat-a-cake simply from watching her. The only way the child could learn the game was to have the mother hold his hands and put them through the appropriate movements.

Since this original report, dozens of empirical studies have been published detailing the specific characteristics of the imitation deficits seen in ASD. The first review of this literature, conducted by Rogers and Pennington (1991), found strong evidence for the existence of an imitation deficit affecting simple body movements and actions with symbolic meaning. What became apparent as more studies were conducted

was that the imitation deficits in ASD varied based on the specific task the child was asked to perform and the child's age. For example, it has been suggested that the development of language might be necessary to derive benefit from the symbolic meaning of a gesture in an imitation task which includes meaningful gestures (Williams et al., 2004). Thus, older children and those with stronger language skills will perform better on imitation of symbolic gestures as compared to younger children or those with weaker language skills (Rogers et al., 1996; Green et al., 2002). A common characteristic of the imitation deficit in individuals with ASD are reversal errors – that is, producing the movement with a 180 degree transformation. Reversal errors are also commonly seen in typically-developing pre-schoolers (Ohta et al., 1987) thereby suggesting that the imitative deficit in ASD may be characterized as a delay of normal development rather than an absolute deficit (Whiten & Brown, 1999).

Though these theories differ on what behavior is considered the primary core deficit, they all stress the importance of the capacity to form representations of other individuals' states, whether these are mental states in order to have TOM, emotional states for empathy and emotion recognition, or physical states needed for imitation. Also embedded in each of these theories is the suggestion that impairment of one ability can lead to deficits in other domains of social processing. Finally, Baron-Cohen(1988), Hobson (1989), and Rogers and Pennington (1991) all suggest that this deficit in self-other mapping is a result of an underlying neurological dysfunction.

A recent review of the literature pertaining to the social and communicative deficits in ASD by Oberman and Ramachandran (2007) proposed a mechanism linking these theories under one comprehensive mechanism, namely simulation. This theory

suggests that ASD is a result of a developmental impairment of functional “simulators.” In this review we propose that the ability to imitate, mentalize (have TOM), empathize and use social communication all depends on a primary ability to simulate. This simulation account proposes that when typically developing individuals perceive another person in a certain situation, they will automatically and unconsciously project that perception back onto their own motor, cognitive and emotional representations in order to run an internal simulation (Gallese, 2003). This simulation, in turn, allows the observer to create an embodied understanding of the observed person’s behaviors, thoughts and feelings, leading to the exact skills that are deficient in individuals with ASD. Thus, this theory does not suggest a primacy of any one behavior, but rather a single impairment in a functional mechanism (similar to the one proposed in previous theories) that leads to the diagnostic behavioral impairments. See Figure 1 for a comparison between the four theories proposed in this section.

1.2 Brain Regions Implicated in Autism Spectrum Disorders

Though still classified as a “mental” disorder, research over the past couple decades has uncovered multiple neural abnormalities associated with the behavioral symptoms which characterize ASD. One of the first brain regions implicated in autism was the amygdala (Baron-Cohen et al., 2000). This theory was based on several lines of evidence. First, primate lesion studies found that lesions of the amygdala resulted in monkeys who failed to initiate social interactions and failed to respond appropriately to social gestures (Kling & Brothers, 1992). Other evidence comes from post-mortem studies finding increased cell density in the amygdala of individuals with autism

(Bauman & Kemper, 1994). Functional imaging also shows significant reductions in activity of the amygdala during a mentalizing task (Baron-Cohen et al., 1999).

Additionally, there is physiological evidence supporting a dysfunction in limbic connections resulting in an abnormal pattern of skin conductance response to visual stimuli in individuals with ASD (Hirstein et al., 2001). Though Baron-Cohen and his colleagues stress the role of the amygdala in autism, they are quick to highlight that other neural regions also show abnormalities.

Another brain region thought to play a role in the social deficits of ASD is the medial prefrontal cortex (paracingulate cortex). This region is activated during TOM tasks in typically-developing individuals when participants are asked to reflect on both their own and another individual's mental state (Fletcher et al., 1995; Gallagher et al., 2000; Vogeley et al., 2001; Brunet et al., 2000; Castelli et al., 2000). The same region also has reduced activity during similar tasks in individuals with ASD (Happé et al., 1996; Baron-Cohen et al., 1999; Castelli et al., 2002).

The third region which has been implicated in the social deficits in ASD is the superior temporal sulcus (STS). Non-human primate single unit studies (Oram and Perrett, 1994) as well as human neuroimaging studies (Bonda et al., 1996; Grossman et al., 2000) show activity in this region in response to biological actions (see Allison et al., 2000 for a review). Additionally, detection of eye-gaze in monkeys (Perrett et al., 1985) and humans (Hoffman & Haxby, 2000; Puce et al., 1998) and inferred intentional action of inanimate shapes based on movement patterns in humans (Castelli et al., 2000) also activate the STS. This brain region also shows abnormal activity patterns in individuals with ASD during facial recognition (Chritchley et al., 2000; Schultz et al.,

2000), mentalizing (Castelli et al., 2002) and eye gaze processing (Pelphrey et al., 2005) tasks. Studies also find reduced grey matter volume in anatomical MRI scans in this population (McAlonan et al., 2004).

The fourth brain region heavily studied in autism is the fusiform gyrus. The fusiform gyrus is thought to be critically involved in face processing in neurotypical individuals (see Cabeza and Nyberg, 2000; Clark et al., 1996; Haxby et al., 1994; Kanwisher, 1999; and Puce et al., 1995). Recent studies suggest that individuals with ASD also have reduced activation of this area during a face processing task (Hubl et al., 2003, Pierce et al., 2001, and Schultz et al., 2000).

A fifth brain region found to be impaired in individuals with ASD is the cerebellum. The cerebellum is thought to contain neurons termed “emulator neurons” (Grush, 2004; Ito, 1984; Wolpert, Zoubin, & Flanagan, 2001; see Decety, 1996, for a review). Grush (2004) proposes that these neurons aid in perception through an emulatory loop that receives input and mimics both the input from the senses and feedback from the observer’s own outputs, thus creating a mechanism that unites perception of the outside world and knowledge of the internal state of the observer. Additionally, Ivry and colleagues (see Ivry et al., 2002 for a review) suggest that the cerebellum is critical in tasks which require efficient temporal processing. Damage to the cerebellum in individuals with autism has been shown through post-mortem studies indicating reduced Purkinje cells and MRI studies indicating reduced volume (see Courchesne, 1997 for a review). Thus, abnormal development of the cerebellum may contribute to the deficits in social interaction in ASD either through dysfunctional

“emulator neurons” or dysfunctional temporal processing, discussed later in this dissertation.

The five regions, listed above are certainly not an exhaustive list of the neural abnormalities in ASD. However, a more exhaustive discussion of brain regions implicated in ASD would be outside the scope of this dissertation. If one simply considers the five regions discussed above, the complexity of the story begins to emerge. These regions span the entire brain from anterior to posterior, cortical to subcortical, and motor to perceptual to cognitive systems, making a unifying link difficult to conceive. Recently, however, Oberman and Ramachandran (2007) proposed a new hypothesis that unified both the behavioral and neurological findings. This hypothesis claimed that the core deficit in ASD is a dysfunction in neural systems responsible for simulation. Consistent with the behavioral theories proposed in the previous section, Oberman and Ramachandran (2007) suggest that a dysfunction in representing others’ states within one’s own system may underlie many of the social and communicative deficits seen in ASD. They suggest that the superior temporal sulcus and the cerebellum may be involved in simulations of body states while the amygdala and medial prefrontal cortex may be involved in simulations of thoughts, beliefs and emotions. They also suggest that these brain regions can be considered part of the extended mirror neuron system, discussed below.

1.3 The Mirror Neuron System, a Candidate Mechanism

In addition to the several individual brain regions discussed in the previous section, a recently discovered system of neurons, namely the Mirror Neuron System,

has also been suggested to underlie the behavioral deficits in ASD. This system was originally described by Rizzolatti and colleagues based on studies of the macaque premotor cortex. Using single-unit electrophysiology, Rizzolatti and colleagues discovered that a portion of neurons in area F5 of the macaque premotor cortex responded not only when the monkey performed an action, but also when the monkey watched the researcher perform a similar action (Di Pellegrino et al., 1992). The team named this system of neurons the “Mirror Neuron System”, because it appeared that the observed action was “mirrored” or simulated within the monkey’s own motor system. In addition to the original mirror neurons found in the macaque’s premotor cortex, neurons in the inferior parietal lobule (PF) have also been found to have “mirror” properties (Fogassi et al., 1998; Gallese et al., 2002).

In the first attempt to localize the human MNS, Fadiga and colleagues (1995) used transcranial magnetic stimulation (TMS) to investigate whether the premotor cortex in humans responded when the participants watched others’ actions. Based on anatomical cytoarchitecture, they identified the homologous region to the macaque F5 as human Brodmann’s area 44/45 (“Broca’s area”). Fadiga and colleagues found that TMS applied over Broca’s area resulted in greater motor evoked potentials (MEPs) when the participant observed another person moving as compared to a baseline rest condition. Furthermore, the pattern of muscle activation evoked by TMS during action observation was very similar to the pattern of muscle contractions present during the execution of the same action.

Subsequent to this neuromagnetic study, positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies (Decety et al., 1997;

Iacoboni et al., 1999) showed selective activity in the frontal operculum (Brodmann's area 44/45) and the anterior parietal cortex when participants watched human actions.

Two additional regions of the human cortex that appear to have "mirror" properties have recently been discovered. The first, the superior temporal sulcus, was originally identified for its selective response to the observation of biological motion in monkeys (Oram & Perrett, 1994; Perrett et al., 1990) and in humans (Bonda et al., 1996; Puce et al., 1998). In addition to its visual properties, human superior temporal sulcus (STS) also responds to the imitation of an action (Iacoboni et al., 2001). This activation is greater during imitation than during control motor tasks and continues to respond even when the participant's view of his/her hand is obscured.

The second region is the so-called extrastriate body area (EBA). The EBA was first classified by Downing and colleagues (2001) based on its response to the visual perception of human bodies and body parts. A recent study conducted by Astafiev and colleagues (2004) report fMRI activation in this region in response to the participant moving his/her own arm or leg toward a target in the absence of visual feedback. This activation was also present after controlling for attention and sensory properties of the target. Thus, it appears that multiple regions of the human brain may be capable of motor simulation (inferior frontal gyrus, inferior parietal lobule, superior temporal sulcus, extrastriate body area and the cerebellum).

The aforementioned findings provide strong evidence that an action observation/execution matching system, similar to that found in the macaque premotor and parietal cortices, exists in the human brain. Since the original studies, specific properties of the human MNS have been investigated. Studies report that unlike the

macaque system, human mirror neurons respond to goal-directed, non-goal-directed and pantomimed actions (Buccino et al., 2001; Grezes et al., 2003), whereas the monkey system only responds to goal-directed actions (Gallese et al., 1996). Additionally, human mirror neurons are selective to actions within the observer's motor repertoire. In other words, if the observer is unable to match the observed action to a motor representation within his own system, the mirror neurons may not respond (Buccino et al., 2004; Stevens et al., 2000). The individual need not be familiar or skilled at the action, but only physically capable of performing it. For example, actions such as grasping and biting which humans share with other primates will activate the human MNS whether the observed action is performed by a human or a macaque. However, observing a dog barking, which is not part of the human motor repertoire, does not activate this system, but rather is processed in lower level perceptual systems (Buccino et al., 2004). Furthermore, actions that are part of the human motor repertoire, but are not familiar to the observer will not activate the MNS as strongly as familiar actions. This property was demonstrated in a study conducted by Calvo-Merino and colleagues who recorded fMRI data from expert dancers and found increased activity to the observation of others performing familiar styles of dance movements, as compared to unfamiliar styles matched for low-level visuo-motor properties (Calvo-Merino et al., 2005).

Though there is ample evidence for the existence of the MNS, its function has yet to be clearly delineated. In their original paper, Di Pellegrino and colleagues (1992) proposed that the MNS may help an observer understand the actions of others by mapping it onto his own motor representations. Additionally, when human participants

are instructed to observe actions with the intent to imitate (as opposed to remember) the MNS is selectively involved in the imitation condition (Decety et al., 1997). This finding has led researchers to propose a critical role of the MNS in human imitation skills.

The location and properties of the MNS lend it well to functions such as motor imitation and motor processing; however, preliminary data suggests that mirror neurons in the premotor cortex may also be sensitive to the goals and intentions of actions (Gallese et al., 1996; Iacoboni et al., 2005). Additionally, fMRI studies identify overlapping regions that respond to both the experience and perception of thoughts and emotions (Mitchell et al., 2005, 2006; Morrison et al., 2004; Singer et al., 2004; Wicker et al., 2003) in medial prefrontal cortex and areas of the limbic system. Finally, fMRI and lesion studies indicate that regions of primary and secondary sensory cortices are not only involved, but also necessary for normal performance on TOM and empathy tasks (Avenanti et al., 2005; Adolphs et al., 2000). The involvement of mirror-like systems in the comprehension of internal states such as thoughts and emotions is reviewed below.

Single-unit studies with macaques suggest that a proportion of mirror neurons are “broadly congruent,” (Gallese et al., 1996) meaning they respond to the performance of an action and the observation of an action with a similar goal even if the exact physical properties of the action differs. Similarly, a recent fMRI study supports the claim that the human premotor MNS is sensitive to the intentions and goals of observed actions. In a recently-published study, Iacoboni and colleagues (2005) showed participants videos of four different types of actions. The first video showed a

person grasping objects in the absence of any context. The second video depicted scenes containing objects in a context with no actions. The third video showed someone grasping a cup with the intention to drink, while the fourth video showed the same action, but in a different context that implied the intention to clean. The posterior part of the inferior frontal gyrus and the adjacent portion of the ventral premotor “hand area” (both within regions thought to be part of the human premotor MNS) were more active in the two intention conditions as compared to the other two non-intention videos. Additionally, the drinking intention condition resulted in significantly more activation than the cleaning intention videos. These findings suggest that, like that of the monkey, the human premotor MNS is sensitive to the underlying intention that motivates perceived actions.

Mirror-like systems in the medial prefrontal cortex, Brodmann’s Area 9, may also be involved in our ability to infer internal mental states of others. Though not traditionally thought of as part of the MNS, this area responds both when participants are asked to make judgments regarding their own abilities, personality traits and attitudes (Johnson et al., 2002; Kelley et al., 2002) and when asked to attribute intentions to characters in a comic strip (Brunet et al., 2000) or infer another person’s knowledge about a familiar or unfamiliar object (Goel, 1995). A recent study that asked participants to evaluate their own emotional responses to a picture and to infer the mental state of the individual in the picture (Ochsner et al., 2004) found that the medial prefrontal cortex responded during both conditions. Thus, it seems conceivable that the same region of the brain that is involved in representing our own mental states is also involved in inferring mental states of others. Similar to the shared representation for the

perception and performance of actions mediated by premotor mirror neurons, a system of neurons in the medial prefrontal cortex may serve to create a mirror-like shared representation for the experience and perception of mental states.

In three fMRI studies (Wicker et al., 2003; Singer et al., 2004; Morrison et al., 2004), empathy for specific emotions activated similar networks of cerebral cortex as the actual experience of that emotion. Both the experience of disgust (while inhaling foul smelling odorants) and the observation of others performing facial expressions of disgust activates the same regions of the insula and the anterior cingulate cortex (Wicker et al., 2003). Additionally, both the experience of a physically painful stimulus and the knowledge that a loved one is experiencing the same painful stimulus activates the anterior insula and rostral anterior cingulate cortex bilaterally (Singer et al., 2004). These areas were also correlated with individual empathy scores, indicating that the more activity produced in these regions, the better the individual's ability to empathize with others. Similarly, another study (Morrison et al., 2004) found that receiving a painful pin-prick and watching a stranger receive the same pin-prick activated dorsal anterior cingulate cortex.

In addition to these fMRI findings, lesion studies have identified paired deficits in the production and recognition of specific emotions. These findings speak to the necessity of these regions for typical processing of emotions. Damage in the amygdala, for example, appears to impair both the expression and recognition of fear (Adolphs et al., 1994; 1999; Sprengelmeyer et al., 1999). Similarly, damage in the insula and basal ganglia results in a paired impairment in the experience and recognition of disgust (Calder et al., 2000). Lastly, both the experience and recognition of anger appears to

depend on the dopamine system with a dopamine antagonist impairing both processes (Lawrence et al., 2002).

1.4 Evidence for Mirror Neuron Impairments in Individuals with ASD

If many of the behavioral deficits seen in individuals with ASD are a result of underlying impairments in neural systems involved in self-other representation abilities, and the MNS is thought to mediate this ability, then one should expect to find impairments in the MNS in individuals with ASD.

Five independent research groups have reported findings supporting this proposal. The first study to find evidence for MNS impairments in ASD was conducted in our laboratory by Altschuler and colleagues (Altschuler et al., 2000) who recorded mu wave suppression, an index of the integrity of the MNS, in one child with autism. Preliminary results showed a lack of suppression to the observation of actions in others, suggesting a possible impairment in the MNS. In a follow-up study, (Oberman et al., 2005) we corroborated this finding by demonstrating an absence of mu wave suppression in a sample of 10 individuals with ASD while they watched videos of another person's actions. While typically-developing individuals showed significant mu wave suppression during the observation of action, indicating normal MNS functioning, participants with ASD showed no significant change in mu power from a baseline condition. A detailed description of this study can be found in chapter 2 of this dissertation.

Nishitani and colleagues (Nishitani et al., 2004) found evidence of an impaired MNS in individuals with ASD using magnetoencephalography (MEG). Participants

were presented with still pictures of a woman performing orofacial gestures and were instructed to imitate these gestures. Cortical activations were recorded over occipital cortex, superior temporal sulcus, inferior parietal lobe, inferior frontal lobe and primary motor cortex. Though the activations in individuals with Aspergers Syndrome (AS) were similar to the neurotypical individuals for occipital cortex, superior temporal sulcus and inferior parietal lobe, activations in inferior frontal lobe and primary motor cortex were weaker and had a greater latency in the AS group as compared to the control group. Similarly, Villalobos, Mizuno, Dahl, Kemmotsu, and Müller (2005) found that area 44, the prefrontal mirror neuron area, had reduced functional connectivity with primary visual cortex in individuals with autism, as compared with matched controls. Taken together, these findings suggest that the deficit is not in low-level visual processing, but rather in higher-order cognitive processes in the prefrontal regions or connectivity between early visual processing areas and prefrontal cortex.

Another group (Theoret et al., 2005) recorded TMS-induced MEPs while participants watched videos of finger movements that were directed either toward or away from the observer. In the control group, both types of actions resulted in increased MEPs recorded from the observer's index and thumb muscles. The clinical group, consisting of individuals diagnosed with ASD, only showed increased MEPs to actions directed toward the observer (self-directed or allocentric), and no significant change from baseline in the away (other-directed or egocentric) movement condition. The researchers explain this result in terms of a mirror neuron deficit leading to impairment in simulating egocentric actions and a general self-other representation deficit.

Most recently, Dapretto and colleagues (2005) published a study in which they investigated activity in the MNS in individuals with ASD using fMRI. Participants were asked to both imitate and observe emotional facial expressions while experimenters measured the blood oxygen level dependent (BOLD) signal in regions thought to be part of the MNS. While typically-developing individuals showed activation in visual cortices, primary motor, premotor (including the inferior frontal gyrus, MNS region), limbic and cerebellar regions, individuals with ASD did not show this pattern, and specifically showed no significant activation of the inferior frontal gyrus. Additionally, the activity that was observed in the MNS regions in individuals with ASD was correlated with symptom severity, as indexed by the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview (ADI).

In conclusion, converging evidence suggests that a mirror-like simulation system may account for many of the social and cognitive deficits seen in ASD. The studies reviewed in the following chapters aim to further characterize this deficit. Chapter two details an EEG study conducted to examine the response of the MNS to observed actions in individuals with ASD (Oberman et al., 2005). The study discussed in chapter three follows up on this finding by expanding the stimuli to include both social and nonsocial stimuli as well as familiar and unfamiliar actors. Chapter four uses EMG to examine spontaneous mimicry responses to observed facial expressions. The results of the three studies discussed in the following chapters both support and extend the simulation theory described above as well as provide potential targets for new therapeutic interventions.

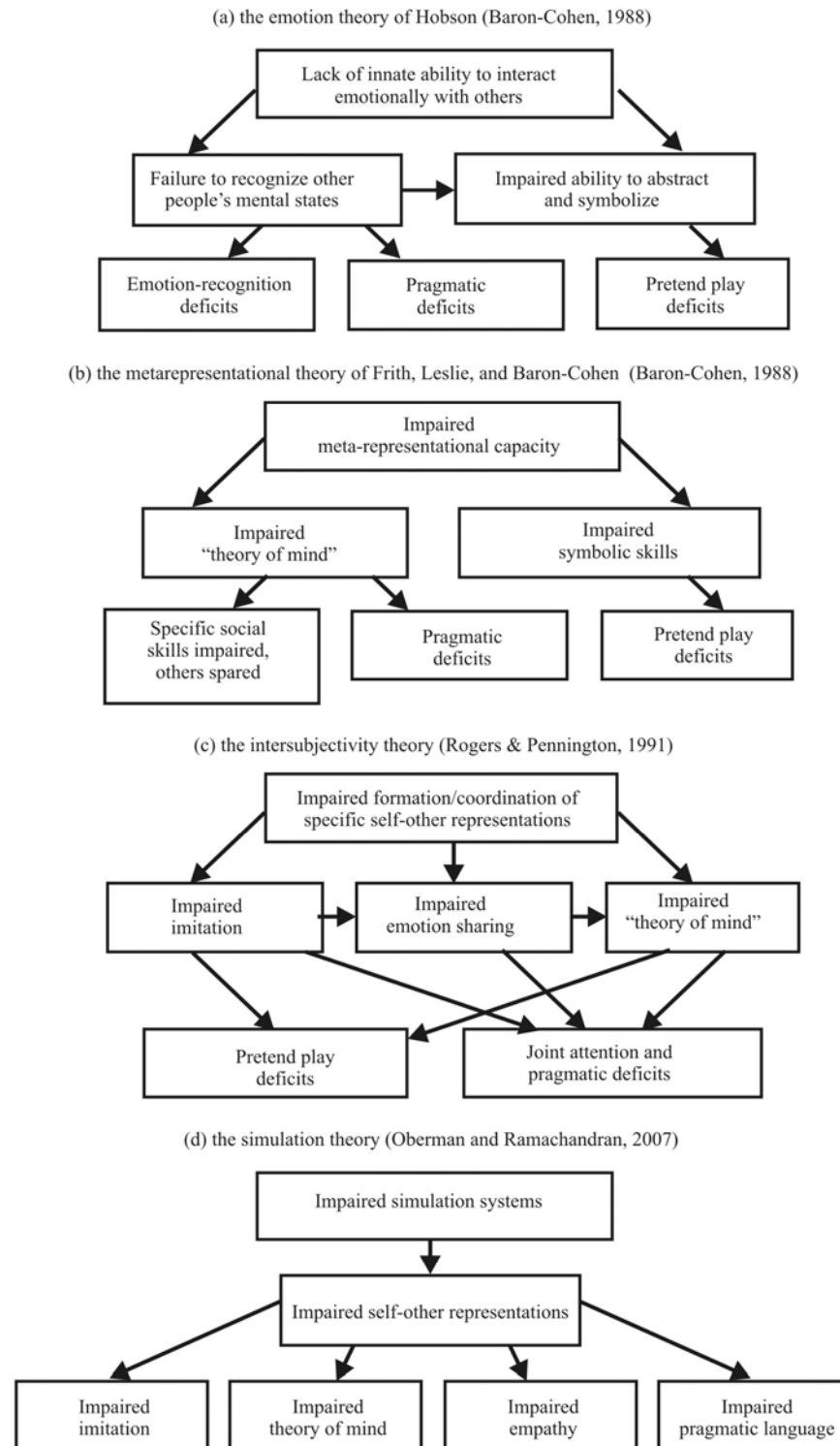


Figure 1.1 Comparison of Autism Theories Top flow chart represents Hobson (1989), Second represents Baron-Cohen et al., (1985), Third represents Rogers and Pennington (1991), and Fourth represents Oberman and Ramachandran (2007).

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Chapter 2

Abstract

The EEG Mu rhythm, 8-13 Hz oscillations recorded over sensorimotor cortex, is blocked by movement, observed movement, and imagined movement. Its similarity in functional properties to the Mirror Neuron System (MNS) has led researchers to use the mu wave as an index of MNS functioning. Previous research has suggested that a dysfunctional MNS may explain the pathology observed in Autism Spectrum Disorders (ASD). Because EEG oscillations in the mu frequency are thought to reflect mirror neuron activity, one method for testing the integrity of the system is to measure mu responsiveness to executed and observed movement. The current study investigated whether individuals with ASD show a dysfunction in this system, given their behavioral impairments in understanding and responding appropriately to others' behaviors. Mu wave suppression was measured in ten high-functioning individuals with ASD and ten age- and gender-matched control participants while watching videos of 1) a moving hand, 2) a bouncing ball, and 3) visual noise, and 4) moving their own hand. Control participants showed significant mu suppression to both performed and observed hand movement. The ASD group showed significant mu suppression to performed hand movements but not to observed hand movements. These results support the hypothesis of a dysfunctional MNS in high-functioning individuals with ASD.

2.1 The EEG Mu Rhythm, an Index of Mirror Neuron Activity

As evidenced by the studies described in the previous chapter, several different methodologies have been utilized to characterize the human MNS in both neurotypical and clinical populations. One such methodology, the electroencephalogram (EEG) mu rhythm provides an inexpensive, noninvasive option that is well suited for use with clinical populations. As with most measures used in human neuroscience, EEG does not directly measure the activity of individual neurons. Thus it is impossible to say with complete certainty that EEG mu suppression is equivalent to measuring the mirror properties of a single neuron, but its use as an indirect index is justified based on both functional and anatomical correlations between the two.

At rest, sensorimotor neurons spontaneously fire in synchrony leading to large amplitude EEG oscillations in the 8–13 Hz (mu) frequency band (Gastaut, 1952). When participants perform an action, these neurons fire asynchronously, decreasing the power of the mu-band oscillations (Pfurtscheller et al., 1997; Samelin & Hari, 1994). Additionally, studies dating back to 1954 find that, similar to mirror neurons, mu oscillations respond specifically to self-performed, observed and imagined actions (Gastaut and Bert, 1954; Cochin et al., 1998; Babiloni et al., 2002; Pineda et al., 2000). Additionally, both mirror neurons (Rizzolatti and Fadiga, 1998) and mu oscillations only respond to animate stimuli (Altschuler et al., 1997; Oberman et al., 2005), and respond more to target-directed actions as compared to non-goal-directed actions (Muthukumaraswamy et al., 2004). Finally, both mirror neurons (Buccino et al., 2001) and mu oscillations seem to respond in a somatotopic manner (Pfurtscheller et al., 1997).

The use of mu suppression as an index of mirror neuron activity is also validated by anatomical and physiological evidence of strong cortico–cortico connections between human and non-human primate ventral premotor cortex (including the region thought to contain mirror neurons) and primary sensorimotor cortex where the mu rhythm is generated and recorded (Muakkassa and Strick, 1979; Godschalk et al., 1984; Matelli et al., 1986; Ghosh et al., 1987; Nishitani and Hari, 2000; Tokuno and Nambu, 2000; Dum and Strick, 2002; Shimazu et al., 2004). Additionally, preliminary evidence suggests that inhibiting inferior frontal gyrus through TMS leads to a blocking of the mu rhythm (Pineda, personal communication). Thus, the response of the mu rhythm to observed actions is thought to be the downstream effect of mirror neuron activity in the premotor cortex.

2.2 EEG Evidence for Mirror Neuron Dysfunction in Autism Spectrum Disorders

Mirror neurons are primarily thought to be involved in perception and comprehension of motor actions (Rizzolatti et al., 2001), but they may also play a critical role in higher order cognitive processes such as imitation (Iacoboni et al., 1999; Rizzolatti et al., 2001), theory of mind (Gallese and Goldman, 1998), language (Rizzolatti and Arbib, 1998), and empathy (Carr et al., 2003), all of which are known to be impaired in individuals with autism spectrum disorders (Bacon et al., 1998; Baron-Cohen, 2001; Frith, 1989; Kjelgaard and Tager-Flusberg, 2001, Rogers et al., 2003).

Because of the correspondence between the behavioral deficits seen in ASD and the theorized functions of the MNS, many have suggested that individuals with ASD may have MNS impairments (Altschuler et al., 2000; Dapretto et al., 2005; Gallese,

2003; Nishitani et al., 2004; Oberman et al., 2005; Oberman and Ramachandran, 2007; Theoret et al., 2005; Villalobos et al., 2005; Williams et al., 2001). Williams and colleagues (2001) were the first to propose a detailed model outlining this relationship. They suggested that dysfunctional development of the MNS, possibly as a result of a combination of genetic and environmental factors, could lead to impaired self-other representations and imitation. This, in turn, could lead to impaired social and communication abilities such as theory of mind, joint attention, empathy, and language, which are the defining features of autism.

The goal of the current study was to test whether individuals with ASD would show dysfunctional mirror neuron activity as reflected by mu suppression. Mu suppression was measured in a sample of high-functioning individuals with ASD and age- and gender-matched typically developing controls. Participants performed four tasks: 1) watching a video of a moving hand, 2) watching a video of two bouncing balls (non-biological motion), 3) watching visual white noise (baseline) and 4) moving their own hand. We hypothesized that control participants would show mu suppression in the observed hand movement condition, whereas the ASD participants would show a lack of suppression during this condition, indicating an impairment in mirror neuron functioning. However, as there is no reason to believe that other motor systems in the area of sensorimotor cortex are impaired in ASD, oscillations in the mu frequency band should be suppressed in both typically developing and ASD participants in the self-movement condition. Furthermore, because mirror neuron activity seems to be selective to biological motion (Rizzolatti and Fadiga, 1998), we predicted no mu suppression in either group to watching bouncing balls.

2.3 Methods

2.3.1 Participants

Our original sample consisted of 11 individuals with ASD and 13 age and gender-matched control participants. All participants in the study were male. The ASD group was composed of ten individuals diagnosed with autism and one individual diagnosed with Asperger's Syndrome. One participant with autism and two control participants were excluded prior to analysis due to excessive movement artifacts that resulted in an inability to obtain sufficient EEG data. One additional control participant was excluded prior to analysis due to a technical malfunction in the EEG system. Therefore, our final sample consisted of ten individuals with ASD and ten age- and gender-matched controls. Participants ranged in age from 6-47 years (ASD: $M = 16.6$, $SD = 13.0$; Control: $M = 16.5$, $SD = 13.6$; $t(18) = 0.017$, $p > 0.98$). One individual was left handed in the ASD group, whereas in the control group 3 individuals were left-handed.

ASD participants were recruited through the Cure Autism Now Foundation, the San Diego Regional Center for the Developmentally Disabled, and the Autism Research Institute. Control participants were recruited through the UCSD Center for Human Development subject pool, and the local community. Individuals were included in the ASD group if they were diagnosed with either autism or Asperger's syndrome by a clinical psychologist. Participants met DSM-IV-TR (2000) criteria for a diagnosis of Autistic Disorder or Asperger's Disorder. In addition, participants in the ASD group exhibited the following diagnostic behaviors at the time of testing, including, but not limited to: awkward use of pragmatics, intonation, and pitch in communication; lack of

initiation of social interactions; and obsessive preoccupation with the order and specific details of the study. All participants were considered high-functioning, defined as having age appropriate verbal comprehension and production abilities and an IQ greater than 80 as assessed by either school assessments or psychometric evaluations from a clinician. Participants without age appropriate verbal comprehension and production abilities were excluded from the study. Participants were given age-appropriate consent/assents (for participants under the age of 18). In addition, in order to ensure that participants understood the procedure and the tasks involved, a picture board was created and the study was fully explained, in age-appropriate language, prior to their participation. This project was reviewed and approved by the UCSD Human Research Protections Program.

2.3.2 Procedure

EEG data were collected during four conditions: 1) *watching a video of a moving hand*: Participants viewed a black and white video of an experimenter opening and closing the right hand with the fingers and thumb held straight, opening and closing from the palm of the hand at a rate of approximately 1 Hz. The hand subtended 5° of visual angle when open and 2° when closed and was medium gray (8.6 cd/m^2) on a black background (3.5 cd/m^2). 2) *watching a video of two bouncing balls*: two light gray balls (32.9 cd/m^2) on a black background (1.0 cd/m^2) moved vertically towards each other touching in the middle of the screen and then moving apart to their initial starting position. This motion was visually equivalent to the trajectory taken by the tips

of the fingers and thumb in the hand video. The ball stimulus subtended 2° of visual angle when touching in the middle of the screen and 5° at its maximal point of separation. 3) *watching visual white noise*: full-screen television static (mean luminance 3.7 cd/m^2) was presented as a baseline condition. All videos were presented at a viewing distance of 96 cm. During the final condition, *moving own hand*, participants opened and closed their right hand in the same manner as they observed in the video. Participants watched their hand at a comfortable viewing distance, the hand held at eye level. All trials were 80 seconds in length and were presented twice in order to obtain enough clean EEG data for analyses. The order of the conditions was counterbalanced across participants, with the constraint that the *moving own hand* condition always followed the *watching a video of a moving hand* condition so that the participants had a model on which to base their movement.

Data were collected in an electromagnetically and acoustically shielded chamber, with the child sitting in a comfortable chair. Brief breaks were taken between videos. To ensure that participants attended to the video stimuli during the watching hand movement and bouncing balls conditions, they were asked to engage in a continuous performance task. Between four and six times during the 80-second video, the stimuli stopped moving for one cycle (a period of one second). Participants were asked to count the number of times stimuli stopped moving and report the number of stops to the experimenter at the end of the block.

2.3.3 EEG Data Acquisition and Analysis

Disk electrodes were applied to the face above and below the eye, and behind each ear (mastoids). The linked mastoids were used as reference electrodes. Data were collected from 13 electrodes embedded in a cap, at the following scalp positions: F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, T5, T6, O1, and O2, using the international 10-20 method of electrode placement. Following placement of the cap, electrolytic gel was applied at each electrode site and the skin surface was lightly abraded to reduce the impedance of the electrode-skin contact. The impedances on all electrodes were measured and confirmed to be less than 10 Kohms both before and after testing. EEG was recorded and analyzed using a Neuroscan Synamps system (bandpass 0.1-30 Hz). Data were collected for approximately 160 seconds per condition at a sampling rate of 500 Hz.

EEG oscillations in the 8-13Hz frequency recorded over occipital cortex are influenced by states of expectancy and awareness (Klimesch, 1998). Since the mu frequency band overlaps with the posterior alpha band and the generator for posterior alpha is stronger than that for mu, it is possible that recordings from C3, Cz, and C4 might be affected by this posterior activity. Therefore, the first and last ten seconds of each block of data were removed from all participants to eliminate the possibility of attentional transients due to initiation and termination of the stimulus. A one-minute segment of data following the initial 10 seconds was obtained and combined with the other trial of the same condition, resulting in one two-minute segment of data per condition.

Eye blink and eye and head movements were manually identified in the EOG recording and EEG artifacts during these intervals were removed prior to analysis according to standard criteria (Goldensohn et al., 1999). Data were coded in such a way that the analysis was blind to the participants' diagnosis. Data were only analyzed if there was sufficient "clean" data with no movement or eye blink artifacts. Each cleaned segment data was further segmented into epochs of 2 seconds beginning at the start of the segment. The integrated power in the 8-13 Hz range was then computed using a Fast Fourier Transform on the epoched data (1024 points). A cosine window was used to control for artifacts resulting from data splicing.

Two measures of mu suppression were calculated. First, we calculated the ratio of the power during the observed hand movement and self hand movement conditions relative to the power during the baseline condition. Second, we calculated the ratio of the power during the observed and self hand movement conditions relative to the power in the ball condition. A ratio was used to control for variability in absolute mu power as a result of individual differences such as scalp thickness and electrode impedance, as opposed to differences in mirror neuron activity. The ratio to the ball condition was computed in order to control for the attention to counting or any effects due to stimulus stopping during the continuous performance task and processing of directional motion. Since ratio data are inherently non-normal as a result of lower bounding, a log transform was used for analysis. A log ratio of less than zero indicates suppression whereas a value of zero indicates no suppression and values greater than zero indicate enhancement. Suppression is then analyzed using t-tests to compare the log suppression values of each condition to zero.

2.4 Results

2.4.1 Behavioral Performance

To ensure that the participants were attending to the stimuli, during the hand and ball conditions, they were asked to count the number of times the stimuli stopped moving. Since all participants performed with 100 percent accuracy on this continuous performance task, we infer that any differences found in mu suppression are not due to differences in attending to the stimuli.

2.4.2 Mu Suppression

Power in the mu frequency at scalp locations corresponding to sensorimotor cortex (C3, Cz, and C4) during the self-initiated action and watching action conditions was compared to power during the baseline (visual white noise) condition by forming the log ratio of the power in these conditions for both groups (Figure 2 A,B). Although data were obtained from electrodes across the scalp, mu rhythm is defined as oscillations measured over sensorimotor cortex, thus only data from C3, Cz, and C4 are presented.

The control group (Figure 2A) showed significant suppression from baseline in mu oscillations at each electrode during both the self-initiated hand movement condition (C3 $t(9) = -3.97$, $p < 0.002$; Cz $t(9) = -2.85$, $p < 0.01$; C4 $t(9) = -4.00$, $p < 0.002$), and observed hand movement condition (C3 $t(9) = -3.99$, $p < 0.002$; Cz $t(9) = -3.21$, $p < 0.005$; C4 $t(9) = -2.78$, $p < 0.01$). The ASD group (Figure 2B) also showed significant mu suppression during the self-initiated hand movement condition (C3 $t(9) =$

-2.27, $p < 0.03$; Cz $t(9) = -1.91$, $p < 0.05$; C4 $t(9) = -2.50$, $p < 0.02$). Unlike controls, the ASD group did not show significant suppression during the observed hand movement condition (C3 $t(9) = -0.64$, $p > 0.25$; Cz $t(9) = -0.98$, $p > 0.15$; C4 $t(9) = -0.74$, $p > 0.20$). The failure to find suppression in the ASD group was not due to differences in baseline μ power (C3 $t(9) = -0.99$, $p > 0.30$; Cz $t(9) = -0.69$, $p > 0.50$; C4 $t(9) = -0.47$, $p > 0.50$). Lastly, neither group showed significant suppression from baseline during the non-biological motion (bouncing balls) condition (ASD: C3 $t(9) = -0.73$, $p > 0.20$; Cz $t(9) = 0.49$, $p > 0.65$; C4 $t(9) = -0.25$, $p > 0.40$; Control: C3 $t(9) = -1.45$, $p > 0.08$; Cz $t(9) = -0.54$, $p > 0.30$; C4 $t(9) = 0.00$, $p > 0.50$).

Additional ratios were calculated comparing the power during the observed hand movement and self hand movement conditions to that of the ball condition for both groups. Results were consistent with the baseline ratios. The control group still showed significant suppression in the self hand movement condition (C3 $t(9) = -2.84$, $p < 0.01$; Cz $t(9) = -2.14$, $p < 0.03$; C4 $t(9) = -2.93$, $p < 0.009$), and observed hand movement condition (C3 $t(9) = -1.80$, $p < 0.05$; Cz $t(9) = -2.05$, $p < 0.04$; C4 $t(9) = -2.67$, $p < 0.02$). The ASD group again showed suppression in the self hand movement condition (C3 $t(9) = -3.97$, $p < 0.002$; Cz $t(9) = -2.85$, $p < 0.01$; C4 $t(9) = -4.00$, $p < 0.002$) but not in the observed hand movement condition (C3 $t(9) = 0.40$, $p > 0.65$; Cz $t(9) = -1.38$, $p > 0.1$; C4 $t(9) = -0.44$, $p > 0.3$).

Since the μ frequency band overlaps with the posterior alpha frequency band (recorded from O1 and O2) and the generator for posterior alpha is stronger than that for μ , it is possible that recordings from C3, Cz, and C4 might be affected by this posterior activity. As all conditions involved visual stimuli and the eyes were open

throughout the study, we would not expect a systematic difference between conditions in posterior alpha activity. Additionally, by eliminating the first and last ten seconds of each block, we reduced the possibility of alpha modulations due to attention affecting our mu power results. Consistent with this, other than C3, Cz, and C4, no electrodes showed a consistent pattern of suppression in the frequency band of interest. These results indicate that the modulations of mu activity we observed in C3, Cz, and C4 were not mediated by posterior alpha activity.

In order to rule out the possibility that our results were influenced by the large age range, a Pearson r correlation coefficient was calculated for each log ratio at each electrode site. Neither group showed a significant correlation between mu suppression and age in any condition or electrode site. The average of the 9 Pearson r coefficients for each group were -0.08 (range -.56 to .39) for the control group and -0.05 (range -.55 to .28) for the ASD group with non-significant p values which were all greater than 0.10.

2.5 Discussion

The lack of suppression in the ASD group during the observed hand movement condition suggests a dysfunction in the MNS. The additional lack of any significant correlation between age and mu wave suppression in the ASD group also suggests that this dysfunction is not something that improves over the lifespan. Furthermore, the lack of suppression during the observation conditions in the ASD group is contrasted with significant suppression to their own movement, which is indicative of normal functioning of other sensorimotor systems involved in self-performed actions. The

results of the current study provide evidence that a dysfunctional MNS may contribute to many of the behavioral deficits observed in individuals with ASD. However, since the sample in this study was solely composed of high-functioning males, the generalizability of the findings to females or lower-functioning individuals is unclear and requires further investigation.

The low spatial resolution of EEG does not allow for differentiation between activity selective to the MNS and activity in other regions that are part of a larger action observation/execution network. It is possible that mu wave suppression is reflecting both activity in the premotor MNS and that activity in areas such as STS (Carey et al., 1997; Perrett et al., 1990) and inferior parietal cortex (Buccino et al., 2001; Parsons et al., 1995), which are involved in action recognition and may modulate the activity in the premotor MNS (Muthukumaraswamy and Johnson, 2004; Muthukumaraswamy et al., 2004). Further investigations with higher spatial resolution techniques, such as fMRI and high resolution EEG may be able to dissociate between these two sources of activation.

Williams et al. (2001) suggest that early developmental failures of the MNS may result in a cascade of developmental impairments characterized by ASD. Our results are consistent with the proposed role of the MNS in ASD, but cannot distinguish whether the mirror neuron impairment is the primary dysfunction or a consequence of anatomical or functional impairments in other brain regions. A lower level explanation of our results is that the differences found in mirror neuron activity are the result of impaired visual processing of biological motion. This would result in less activity in visual areas thought to be critically involved in biological motion perception such as the

superior temporal sulcus (Castelli et al., 2002; Frith, 2001). There may also be deficits even earlier in visual processing as evidenced by assessments of low level dorsal stream visual processing (Bertone et al., 2003; Spencer et al., 2000).

Another possible explanation may be dysfunctional input from social/attentional networks. For example, individuals with ASD have been shown to have impairments in frontal brain regions thought to be involved in social attention. (Castelli et al., 2002). Given that mirror neurons are one part of a broader network (Fagg and Arbib, 1998; Oztop and Arbib, 2002) which may be modulated by multiple systems throughout the brain, an alternative interpretation of our results is that the MNS in individuals with ASD may be functional, but receiving dysfunctional input from other brain regions. Again, future research using higher resolution EEG and fMRI could further investigate these questions.

In summary, numerous converging lines of evidence suggest that the MNS is involved in processes such as imitation, language, theory of mind, and empathy. As ASD is defined by behavioral deficits in many of these areas, there is reason to believe that impairments in the MNS may play a role in the social and communicative deficits associated with ASD. Future research should focus on the independent contributions of frontal and parietal mirror neurons, as well as the contribution of lower-level processing deficits. If supported by such future studies, pathology of the MNS and associated networks may prove to be critical in helping us to understand the neural basis of autism and related disorders.

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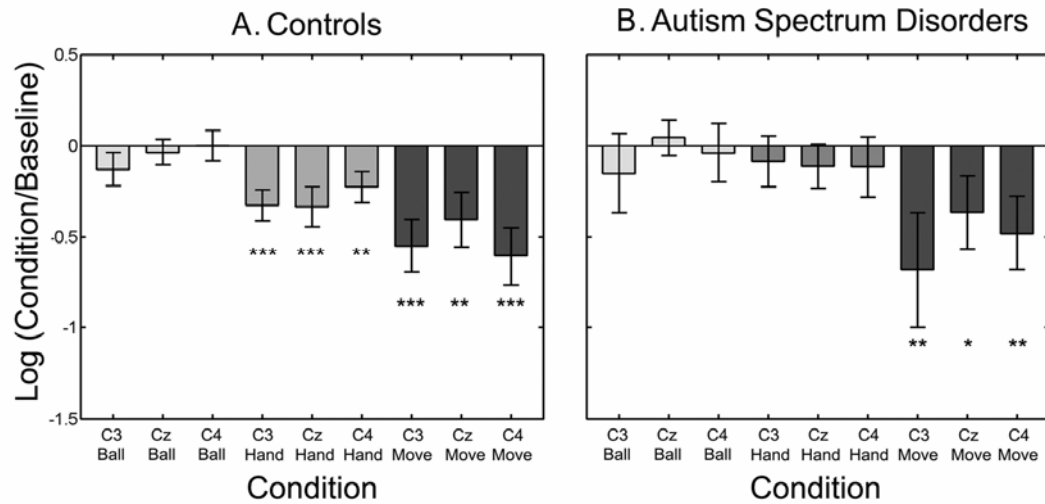


Figure 2.1 Mu suppression in control and ASD participants Bars represent the mean log ratio of power in the mu frequency (8-13 Hz) during the watching balls condition (light gray), watching hand movement condition (medium gray) and moving own hand condition (dark gray), over the power in the baseline condition for scalp locations C3, CZ and C4 for typically developing individuals (a) and individuals with ASD (b). Error bars represent the standard error of the mean. For all values, a mean log ratio greater than zero indicates mu enhancement; a mean log ratio less than zero indicates mu suppression. Significant suppression is indicated by asterisks, * $p < .05$, ** $p < .01$, *** $p < .005$.

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Chapter 3

Abstract

In an early description of the mu rhythm, researchers noted that it was blocked when an individual identified himself with an active person on the screen, suggesting that the mu wave (and perhaps the MNS) may be modulated by the degree to which the individual can relate to the observed action. Additionally, multiple studies suggest that the MNS is impaired in individuals with Autism Spectrum Disorders (ASD). The current study investigated the degree to which the MNS is sensitive to two manipulations aimed at varying the degree to which the observer is able to identify with the action on the screen: social versus nonsocial actions, and the familiarity of the individual performing the action. Data were collected while participants viewed six videos: (1) Bouncing Ball: baseline, (2) Non-interacting: three individuals tossed a ball up in the air to themselves, (3) Social Action: three individuals tossed a ball to each other and occasionally off the screen toward the viewer, (4) Stranger: an unfamiliar experimenter performing a grasping action, (5) Familiar: the child's guardian or sibling performing the same action, (6) Own: the participant performing the same action.

The mu wave was not sensitive to social action as compared to nonsocial action. Neurotypical children showed suppression to both stimuli, whereas children with ASD showed no suppression during either condition. The mu wave did however, appear to be sensitive to familiarity of the individual performing the action. Both neurotypical participants and those with ASD showed greater suppression to familiar individuals compared to the stranger. This finding suggests that the MNS may respond to observed actions in individuals with ASD under specific conditions.

3.1 Introduction

The original studies of mu suppression, conducted over 50 years ago (Gastaut and Bert 1954) predict not only the existence of mirror neurons (neurons in the motor system that respond to performed as well as observed movement), but also their sensitivity to socially relevant information. In their report, Gastaut and Bert write “the relation between the blocking of the rhythm and the image of the boxers in action is unquestionable” and “It [the mu rhythm] disappears when the subject identifies himself with an active person represented on the screen” (p. 439). Thus the degree of suppression of this rhythm appears to be related to the degree to which the observer relates to the image on the screen.

Although it is widely accepted that the MNS is selective for animate stimuli (Rizzolatti and Fadiga, 1998) and proposed to be involved in many aspects of social cognition (for a review see Gallese, 2004), the degree to which the MNS or the mu wave is sensitive to socially-relevant information such as the degree of social interaction or the person’s subjective connection with the stimulus on the screen remains unclear. Additionally, if individuals with autism have impairments in understanding social interaction and connecting with others in a social manner, it is unclear whether their MNS impairment may be partially alleviated through the use of more socially relevant stimuli.

Two previous studies have investigated the question of sensitivity of the premotor MNS to social interaction in typical adults. The first, conducted by Iacoboni et al. (2004), finds differences in the degree of activity in the inferior frontal gyrus

(IFG) when an observer watches a scene depicting two individuals interacting as compared to a scene depicting one individual engaging in everyday activities. However, as these scenes differed in complexity, content, and degree of social interaction, it is hard to discern which stimulus property the IFG was sensitive to.

Another study, conducted by Oberman et al., (2007) measured mu wave suppression in response to stimuli matched for low-level visual properties such as complexity and content, but with various degrees of social interaction between the individuals on the screen and the viewer. Specifically, they report that the mu wave was maximally suppressed to a video of three individuals passing a ball to one another and occasionally tossing the ball out toward the viewer (including the viewer in the social activity) and minimally suppressed to a video of the same three individuals tossing a ball up and down to themselves. The finding that the system is most active (resulting in the greatest amount of mu wave suppression) when the stimulus is not only social but also interactive is consistent with the anecdotal report by Gastaut and Bert (1954) that the blocking of the mu wave occurs when an individual “identifies himself with an active person represented on the screen” (p.439). The sensitivity of the human MNS to socially relevant information may explain how an action recognition system in the macaque may have evolved to mediate more complex social skills such as TOM, empathy and language in the human, as has previously been suggested (Ramachandran, 2000; Rizzolatti and Arbib, 1998).

The current study seeks to extend these previous findings and explore the modulation of the mu rhythm in neurotypical children and children with ASD. In addition to using social stimuli as used in the previous study, this study also included

videos of the participant performing an action as well as a familiar person (i.e. parent, guardian or sibling) performing the same action to test the hypothesis that the degree of mu suppression is modulated by the degree to which the child “relates” to the image on the screen. It is hypothesized that typically-developing children will show greater suppression to the social as compared to the non-social stimuli (replicating the finding in adults) as well as greater suppression to the observation of themselves and the familiar individual’s actions as compared to a stranger performing the same action. Children with ASD, however, may be insensitive to the degree of social interaction, while still showing a response to the observation of themselves or a familiar individual’s actions as compared to a stranger’s actions.

3.2 Methods

3.2.1 Participants

Thirteen children with autism spectrum disorders and 13 typically developing children participated in the study. All participants in the study were male. Participants ranged in age from eight to 12 years. All participants had normal hearing and normal, or corrected to normal, vision.

ASD participants were recruited through Valerie’s List, a listserv of families and professionals in the autism community. Children with ASD were diagnosed by a licensed clinical psychologist or medical doctor not associated with this research. This diagnosis was verified through administration of the Autism Diagnostic Observation Schedule – Generic (ADOS-G, Lord, et al., 2000) in the laboratory by an individual specifically trained in administering this test. Based on the results of these assessments

and clinical judgment, seven of the 13 children met criteria for *Autistic Disorder*, and the remaining six met criteria for *Autism Spectrum Disorder*. All participants were considered high-functioning, defined as having age appropriate verbal comprehension abilities and an Intelligence Quotient (IQ) greater than 80 as assessed by the research team.

Neurotypical control participants were recruited from the San Diego area. All control participants scored within the normal range on a standardized test of intelligence (see Procedure below), had no neurological or psychological disorder, and were matched on chronological age and gender with a participant in the ASD group. Participants were given age-appropriate assents and the parent/guardian provided written consent for his/her child's participation. This project was reviewed and approved by the University of California, San Diego (UCSD) Human Research Protections Program.

3.2.2 Cognitive Testing

Standardized assessments of cognitive and language skills were administered to all children. The Weschler Abbreviated Scale of Intelligence (WASI) (Weschler, 1999) was used to assess intellectual functioning, and a revised Movement Imitation Test (De Renzi, 1980) was administered to provide a measure of imitation skills. The mean standardized scores and standard errors for each group are presented in Table 3.1.

3.2.3 EEG Stimuli

For the EEG task, participants were presented with six 80-second videos (See Figure 3.1). Four of the videos were previously used in other studies in our laboratory (Stimuli 1-2: Oberman et al., 2005; Stimuli 3-4: Oberman et al., 2007). The stimuli consisted of: (1) Bouncing balls: two light gray balls (32.9 cd/m^2) on a black background (1.0 cd/m^2) moved vertically towards each other, then touched in the middle of the screen then moved apart to their initial starting position. (2) Stranger: a video of an unfamiliar individual opening and closing the right hand. (3) Social action: three individuals tossing a ball to one another and occasionally throwing the ball off the screen, seemingly toward the viewer, as if the viewer were part of the game. (4) Nonsocial: three individuals tossing a ball up in the air to themselves. (5) Familiar: a video matched to the action in the stranger's hand condition in all respects except that the hand was that of the parent, guardian, or sibling of the participant. (6) Own: a video matched to the action in the stranger's hand in all respects except the hand was that of the participant.

3.2.4 EEG Procedure

Video stimuli were presented on a 14 inch computer screen. All videos were presented at a viewing distance of 96 cm. The ball, stranger, familiar, and own hand stimuli were matched on movement trajectory and speed. All conditions were presented twice in order to obtain enough clean EEG data for analyses and the order of the conditions was counter-balanced across participants.

Data were collected in an electromagnetically and acoustically shielded chamber, with the child sitting in a comfortable chair. Brief breaks were taken between videos. To ensure that the participants attended to the video stimuli, they were asked to engage in a continuous performance task. Between three and six times during the 80-second video, the stimuli stopped moving for a period of one to two seconds. As a measure of attention to the task, participants were asked to count the number of times the stimuli stopped and report the number of stops to the experimenter at the end of the block.

3.2.5 EEG Recording and Analysis

The same recording and analysis parameters as the study presented in the previous chapter were utilized in the current study.

Mu suppression was calculated by creating a ratio of the power during the experimental conditions (social, non-social, stranger, familiar, and own action conditions) relative to the power during the ball condition. The ball condition was chosen as a baseline as multiple studies have shown no mu suppression to this stimulus (Oberman et al., 2005; Oberman et al., 2007; Pineda & Oberman, 2006). In addition, the ball condition contained directional movement, was matched for low-level visual properties to the stranger, familiar and own videos and contained a continuous performance task to ensure the participant was paying attention to the stimulus. A ratio was used to control for variability in absolute mu power as a result of individual differences such as scalp thickness and electrode impedance, as opposed to mirror

neuron activity. Since ratio data are inherently non-normal as a result of lower bounding, a log transform was used for analysis.

3.3 Results

3.3.1 Cognitive Testing

The Weschler Abbreviated Scale of Intelligence (WASI) was used to assess intellectual functioning. Two-tailed t-tests conducted on the full-scale IQ score, the Verbal IQ score and the Performance IQ score revealed no significant group differences in any of these measures (all p s >0.20). Additionally, the children with ASD had normal intelligence, as evidenced by a mean full-scale IQ above 100. Scores on the Movement Imitation Test, however, did show a group effect. The test was broken into four subscales (1. Actions with Objects, 2. Actions without objects, 3. Meaningful Gestures, and 4. Non-meaningful gestures). The control group performed significantly better than the ASD group on all subscales of the test, except meaningful gestures (1. $t(24) = -2.18, p < 0.05$, 2. $t(22) = -2.40, p < 0.05$, 3. $t(24) = -1.57, p > 0.10$, 4. $t(24) = -2.21, p < 0.05$). Though the ASD group showed a relative impairment in imitation, this impairment was not significantly correlated with any of the EEG measures described below (all p s >0.10).

3.3.2 EEG Behavioral Performance

All participants performed with 100 percent accuracy on the continuous performance task. We therefore infer that any differences found in mu suppression are not due to differences in attending to the stimuli.

3.3.3 EEG Mu Suppression

3.3.3.1 Social versus Nonsocial Stimuli

Power in the mu frequency at scalp locations corresponding to left and right hemisphere sensorimotor cortex (C3 and C4) during the observation of social and non-social stimuli was compared to power during the observation of the ball condition by forming the log ratio of the power in these conditions for both groups (Figure 3.2). Although data were obtained from electrodes across the scalp, mu rhythm is defined as oscillations measured over sensorimotor cortex, thus only data from C3 and C4 are presented.

A 2 (Social vs. Nonsocial) by 2 (left vs. right hemisphere) by 2 (ASD vs. Control) mixed model factorial analysis of variance revealed no significant main effect of social content ($F(1,96) = 0.02, p > 0.89$), hemisphere ($F(1,96) = 0.06, p > 0.81$), or diagnosis ($F(1,96) = 1.32, p > 0.25$).

T-tests comparing mu suppression during each of the experimental conditions to zero showed significant suppression from baseline in the control group in both hemispheres during both the social and nonsocial observation conditions (Social: C3 $t(12) = -5.32, p < 0.0001$, C4 $t(12) = -3.40, p < 0.01$; Nonsocial: C3 $t(12) = -1.77, p < 0.05$, C4 $t(12) = -2.70, p < 0.01$). The ASD group did not show significant suppression during either the social or the non-social observation conditions. The failure to find suppression in the ASD group was not due to differences in baseline mu power (C3 $t(24) = 1.19, p > 0.20$, C4 $t(24) = 1.28, p > 0.20$).

Since the mu frequency band overlaps with the posterior alpha frequency band (recorded from O1 and O2) and the generator for posterior alpha is stronger than that for mu, it is possible that recordings from C3 and C4 might be contaminated by this posterior activity. As all conditions involved visual stimuli and the eyes were open throughout the study, we would not expect a systematic difference between conditions in posterior alpha activity. Additionally, by eliminating the first and last 10 seconds of each block, and including a continuous performance task during all conditions, we reduced the possibility of confounds such as changes in attention affecting our mu power results. Consistent with this, other than C3 and C4, no electrodes showed a consistent pattern of suppression in the frequency band of interest. These results suggest that the modulations of mu rhythms observed in C3 and C4 were not likely to be mediated by posterior alpha activity or differences in attentional demands between the experimental conditions.

3.3.3.2 Familiar vs. Unfamiliar Stimuli

Power in the mu frequency at scalp locations corresponding to left and right hemisphere sensorimotor cortex (C3 & C4) during the observation of a stranger's action, a familiar individual's action and the participant's own action was compared to power during the observation of the ball condition by forming the log ratio of the power in these conditions for both groups (Figure 3.3).

A 3 (Stranger vs. Familiar vs. Own Action) by 2 (left vs. right hemisphere) by 2 (ASD vs. Control) mixed model factorial analysis of variance revealed a significant main effect of degree of familiarity ($F(2,144) = 2.95, p < 0.05$). Follow-up t-tests

revealed a linear trend with the own action condition showing the greatest amount of suppression ($M = -0.26$) followed by the familiar individual's action ($M = -.23$) with the stranger's action showing the least amount of suppression ($M = -0.13$). Though there was not a significant group by familiarity interaction, this linear trend appears to be largely driven by the ASD group's significant suppression to the familiar and own action conditions. There was no significant main effect of hemisphere ($F(1,144) = 0.50, p > 0.48$) or diagnosis ($F(1,144) = 0.38, p > 0.54$).

T-tests comparing mu suppression during each of the experimental conditions to zero showed significant suppression from baseline in the control group at each electrode during all three experimental conditions (Stranger: C3 $t(12) = -2.94, p < 0.01$, C4 $t(12) = -1.83, p < 0.05$; Familiar: C3 $t(12) = -5.45, p < 0.001$, C4 $t(12) = -3.71, p < 0.01$; Own: C3 $t(12) = -3.56, p < 0.01$, C4 $t(12) = -3.28, p < 0.01$) and no significant difference between the three conditions (both $ps > 0.5$). Consistent with the finding in the previous chapter, the ASD group did not show significant suppression during the observation of a stranger's action (C3 $t(12) = -1.34, p > 0.10$, C4 $t(12) = -.11, p > 0.45$). However, the observation of a familiar individual's actions did result in significant suppression in the ASD group (Familiar: C3 $t(12) = -2.16, p < 0.05$, C4 $t(12) = -2.75, p < 0.01$; Own: C3 $t(12) = -2.66, p < 0.01$, C4 $t(12) = -5.09, p < 0.0001$) In addition, t-tests comparing suppression during the stranger condition to suppression during the familiar and own conditions revealed greater suppression during the familiar condition ($t(12) = -1.98, p < 0.05$) and own condition ($t(12) = -2.65, p < 0.01$) as compared to the stranger condition for the ASD group (Figure 3.4).

Consistent with the previous section, other than C3 and C4, no electrodes showed a consistent pattern of suppression in the frequency band of interest during the observation of these stimuli.

3.4 Discussion

The results of this study suggest that the degree of social interaction in the stimulus does not modulate the suppression of the mu wave in children. Neurotypical children showed only slightly less, though not significant, suppression to non-social actions as compared to social actions. More specifically, both social and nonsocial actions significantly suppressed the mu wave in this group. The presence of social interaction with the stimulus also did not appear to affect the lack of suppression in the ASD group. If anything, they showed slightly greater (non-significant) suppression to the non-social stimuli as compared to the social stimuli. The lack of modulation based on social interaction in the neurotypical group was unexpected based on a previous study conducted in our lab (Oberman et al., 2007). The inability to detect a difference in this case may have been a result of the smaller sample size (the previous study had a sample of 20 adults) making it difficult to detect a small effect. Additionally, the participants in the previous study were adults, while this study's participants were children. The lack of modulation based on social interaction may be a difference in the selectivity of the MNS between children and adults.

The familiarity of the stimulus, however, did appear to affect the degree of suppression in both groups. Both the neurotypical and ASD group showed greater suppression to actions performed by a familiar individual or themselves as compared to

the unfamiliar individual. This resulted in significant suppression (to the same degree as the neurotypical group) in the ASD group to the observation of actions by familiar individuals as well as themselves.

The finding that the MNS is most active (resulting in the greatest amount of mu wave suppression) when the observed actor is familiar to the participant is consistent with the anecdotal report by Gastaut and Bert (1954) that the blocking of the mu wave occurs when an individual “identifies himself with an active person represented on the screen” (p.439). Additionally, the finding that the children with ASD show suppression to the observed action when it is performed by a familiar individual suggests that the previous reports of impaired mu wave suppression (Oberman et al., 2005) may have been a result of the observed action being performed by a stranger.

This is the first study to show mu wave suppression to observed actions in children with ASD. It is also the first study to investigate the MNS in individuals with ASD using stimuli where the actor performing the observed action is familiar to the participant. This is not, however, the first study to suggest that the MNS is sensitive to the familiarity of the stimuli. In a study conducted by Calvo-Merino and colleagues (2005), participants, who were expert dancers, watched either familiar or unfamiliar styles of dance movements. FMRI was recorded and regions comprising the human MNS, namely inferior frontal gyrus, parietal cortices and superior temporal sulcus, showed increased BOLD signal during the observation of familiar styles of dance movements, as compared with unfamiliar styles matched for low-level visuomotor properties. In the Calvo-Merino et al. (2005) study, however, it was the style of dance, not the person performing the action, that was familiar to the observer. In the current

study, the actions were identical; it was simply the person performing the action that was familiar. Thus, the MNS may be sensitive to both the familiarity of the style of the action as well as the familiarity of the actor.

An additional finding that speaks to the importance of stimulus familiarity in ASD is that the typical neural response to faces, previously thought to be absent in this population (Hubl et al., 2003, Pierce et al., 2001, and Schultz et al., 2000), is found to be intact when photos of familiar individuals are used. In a study conducted by Aylward et al. (2004) participants with autism were presented with familiar faces and cars and showed a comparable degree of activity in the FFA to neurotypical individuals. In another study conducted by Pierce and colleagues (2004) ASD participants were presented with both stranger and familiar faces and showed greater fusiform activity in response to familiar faces than stranger faces.

Combined with previous findings showing other brain regions thought to be dysfunctional may be modulated by familiarity, the current finding of mu suppression to actions performed by a familiar individual suggests that the reported dysfunction in both the MNS and other regions of the brain may reflect an underlying impairment in identifying with and assigning personal significance to unfamiliar people. This may manifest itself as a dysfunction in systems that are modulated by the ability to identify with, or assign personal significance to, a stimulus such as the MNS or FFA.

Thus, to say that these systems are nonfunctional may not be completely accurate. If these systems only activate to stimuli that the observer identifies with, perhaps typically developing individuals identify with all people, resulting in activation of these areas in response to all people, while individuals with ASD only identify with

themselves and certain familiar individuals. This is somewhat a chicken and egg problem when looking at children age 8-12. It is possible that a dysfunctional mirror neuron system leads to a deficit in relating to unfamiliar people. It is also possible that a deficit in relating to unfamiliar people leads to a dysfunction in the mirror neuron system. These two possibilities will be further addressed in chapter five.

Although mu wave suppression is considered a valid index of mirror neuron activity in neurotypical populations and ASD populations (Muthukumaraswamy et al., 2004; Oberman et al., 2005; Oberman et al., 2007), owing to the low spatial resolution of EEG it is difficult to differentiate between activity selective to the premotor MNS and activity in other regions that are part of a larger action observation/execution network that may modulate the activity in the premotor MNS (Muthukumaraswamy and Johnson, 2004; Muthukumaraswamy et al., 2004). Further investigations with higher spatial resolution techniques, such as fMRI and high-resolution EEG, may be able to dissociate between these two sources of activation and confirm at what stage of processing the information regarding familiarity, relation to self and personal significance is processed. This will tell us more about the other systems which may be underlying the observed dysfunction in the premotor MNS as well as other regions of the brain.

One unexpected result in this study was the lack of correlation between the mu wave suppression and imitation scores in either the control or the ASD group. One of the first theorized functions of the MNS was for imitation (see Iacoboni, 2005 for a review). If mu wave suppression is a valid index of MNS activity and the MNS is

suggested to underlie the ability to imitate, then one would expect a correlation between activity in this system and imitation scores.

One recent study, conducted by Bernier et al. (in press) reports a correlation between their measure of mu wave suppression and an imitation scale in adults with ASD. As the age, stimuli, EEG analysis procedure and imitation task was different in this study than the current study, it is unclear which factor may have led this group to find a correlation while the current study did not. Additionally, neurofeedback training studies targeting mu suppression find that while participants improve on mu suppression to observed actions following this training, there does not appear to be a resulting improvement in imitation ability (Pineda, personal communication). Thus, the relationship between mu suppression and imitation has yet to be conclusively determined. It is possible that the MNS plays a large role in the early development of the ability to imitate and match other people's actions to one's own motor representation, with compensatory mechanisms mediating imitation later in life. The development of the MNS in both neurotypical and clinical populations is a topic that has yet to be properly addressed.

In conclusion, this study finds that observation of actions performed by familiar individuals results in mu wave suppression in individuals with ASD, while stranger's actions, do not. This is the first study to show "normal" mu wave suppression during action observation in individuals with ASD. The finding that the MNS in ASD may not be completely nonfunctional bodes well for therapeutic interventions aimed at improving the functioning of the MNS. Perhaps if one could improve the ability in children with ASD to identify himself or herself with the observed unfamiliar person

through behavioral or neurofeedback training, one could improve the functioning of the MNS and alleviate some of the behavioral deficits associated with a poorly functioning MNS.

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Table 3.1 Results from Cognitive Testing Means and standard deviations (in parentheses) for each of the experimental groups, and the results of statistical comparisons between groups, are presented. Statistical results are based on one-tailed t-tests.

Cognitive Test	ASD	Neurotypical	Significance Level
WASI-Full Scale	102.8 (15.8)	112.5 (17.3)	NS
WASI-Verbal	99.9 (21.7)	110.6 (15.4)	NS
WASI-Performance	106.5 (15.3)	111.7 (19.6)	NS
Imitation With Objects	62.2 (17.3)	77.4 (12.9)	p<0.05
Imitation Without Objects	73.6 (11.6)	83.4 (11.4)	p<0.05
Meaningful Gestures	81.0 (7.9)	87.0 (11.2)	NS
Nonmeaningful Gestures	65.9 (17.1)	79.7 (14.6)	p<0.05

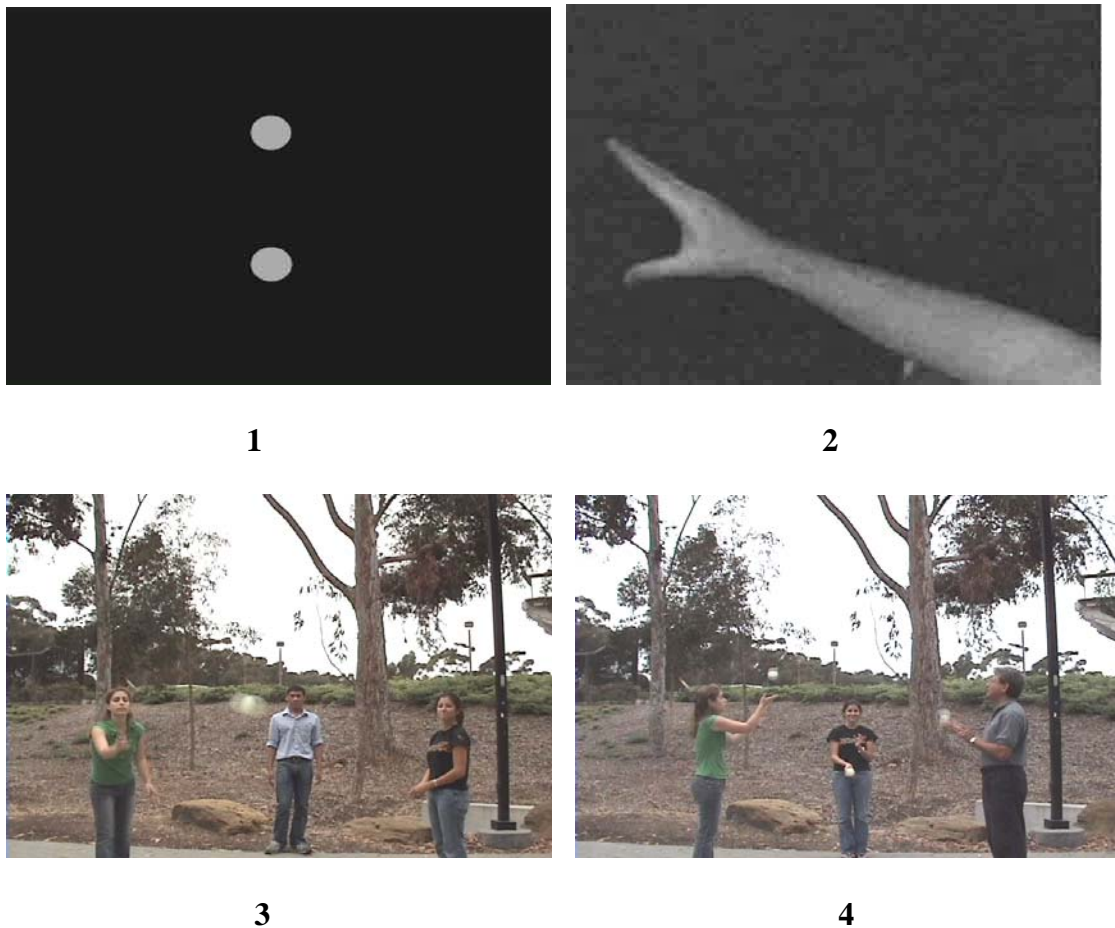


Figure 3.1 Stimuli for Studies described in Chapter 3 Stimulus 1 (Bouncing Balls) was used as a baseline for both studies. Stimulus 2 (Stranger) was used in the second study described in this chapter. Also used in the second study were videos of the participant performing the same action as well as a relative (parent, guardian, or sibling) performing the same action (not shown above). Stimuli 3 (Social) and 4 (Nonsocial) were used in the first study described in this chapter.

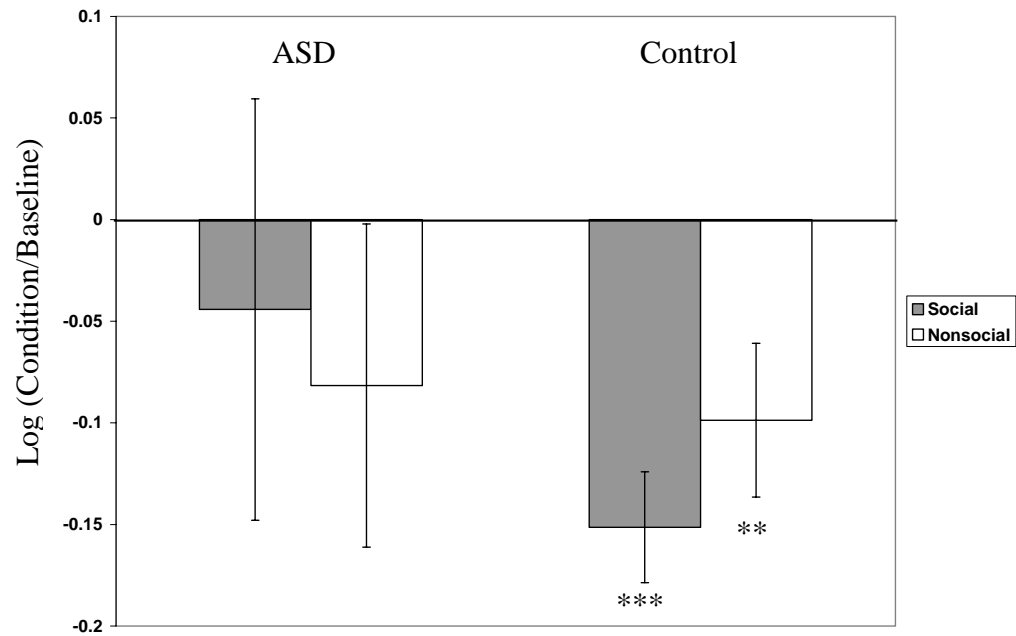


Figure 3.2 Mu suppression to Social and Nonsocial Stimuli Bars represent the mean log ratio of power in the mu frequency (8-13 Hz) during the social (gray bars) and nonsocial (white bars) conditions, over the power in the bouncing ball condition for scalp locations C3 and C4 for individuals with ASD and typically developing individuals. Error bars represent the standard error of the mean. For all values, a mean log ratio greater than zero indicates mu enhancement; a mean log ratio less than zero indicates mu suppression. Significant suppression is indicated by asterisks, ** $p < .01$, *** $p < .001$.

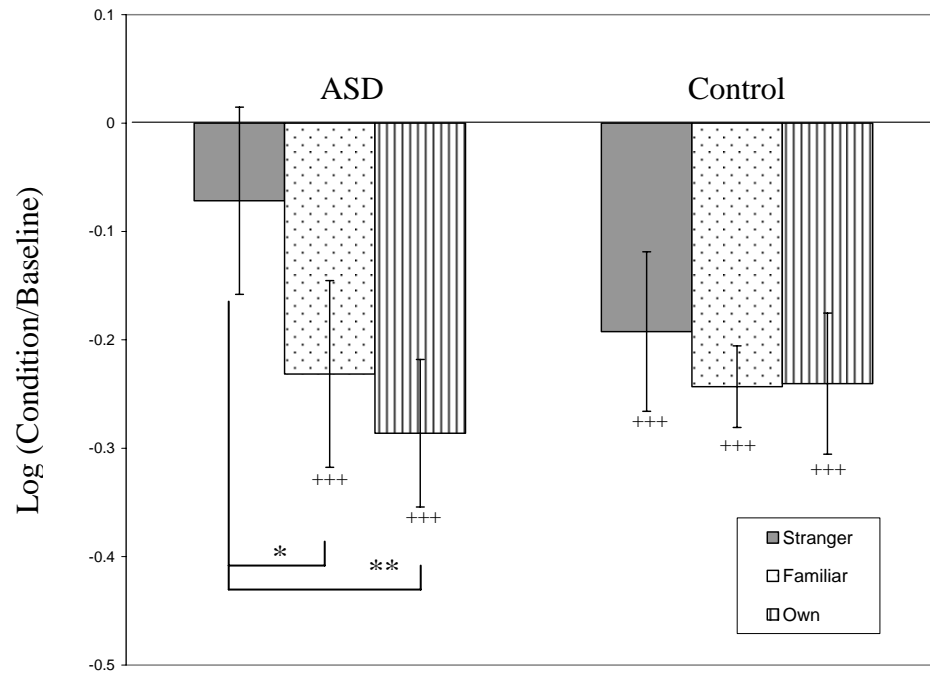


Figure 3.3 Mu suppression to observed actions performed by an Unfamiliar individual, a Familiar Individual and the Participant himself Bars represent the mean log ratio of power in the mu frequency (8-13 Hz) during the stranger (gray bars), familiar (polka-dotted bars) and own (striped bars) conditions, over the power in the bouncing ball condition collapsed across hemispheres for individuals with ASD and typically developing individuals. Error bars represent the standard error of the mean. For all values, a mean log ratio greater than zero indicates mu enhancement; a mean log ratio less than zero indicates mu suppression. Significant differences in suppression is indicated by asterisks, * $p < .05$, ** $p < .01$, Significant suppression from 0 is indicated by plus signs, +++ $p < 0.001$.

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Chapter 4

Abstract

The spontaneous mimicry of facial expressions has long been reported. It has been suggested that facial mimicry plays a role in social skills such as emotion recognition and emotional empathy, both skills in which individuals with autism spectrum disorders often have behavioral deficits. The current study investigated facial mimicry in children with autism spectrum disorders as well as matched control participants by measuring electromyography (EMG) from multiple facial muscles while participants viewed static photographs of individuals displaying expressions of happy, sad, fear, anger, disgust and neutral expressions. Though ASD participants showed comparable activity to the control group in the appropriate muscle groups, this activity had a greater latency occurring on average over 150 ms later than the control group. This greater latency is discussed in light of the current literature on the importance of temporal factors in social interaction.

4.1 Introduction

The ability to create representations of other's states is not only necessary for action observation and imitation, but clearly is an important precursor to understanding others' thoughts and emotions. In fact, "simulation mechanisms" or the ability to recreate another's internal state within one's own cognitive or limbic systems have been suggested to underlie both theory of mind (TOM) and empathy abilities.

Simulation theorists propose that TOM is simply an outgrowth of the ability to interpret others' actions through simulation. By creating an internal simulation, individuals can "step into the mental shoes of another person" and understand the thoughts, emotions, and intentions behind their behaviors (see Gordon, 1986; Heal, 1986; Goldman, 2000 for reviews). Simulation theories simply require that the observer reflect back on his own experience and use that knowledge to infer the mental state of the other individual. These theories are supported by brain-based studies finding mirror neuron system (MNS) activity in response to the goal or intention of an action and regions of the brain that respond both when participants are asked to reflect on their own mental state and when they are asked to infer the mental state of another individual (Gallese et al., 1996; Iacoboni et al., 2005; Ochsner et al., 2004).

Although not traditionally discussed in reference to the simulation view of TOM, the "Mary" scenario provides an excellent example for the necessity of reflection on self-knowledge for the understanding of internal states of others. Jackson (1986) suggests a thought experiment based on the idea of whether Mary, a color blind neuroscientist who knows everything about the physiological processing of color but has never experienced it herself, would really "know" what it is like to see red. Jackson

proposes that the “theory/experience gap” would preclude Mary from understanding the internal qualia, or mental content, of the experience of seeing red. This theoretical scenario demonstrates the importance of an individual’s own experiences in the understanding of others’ mental states. Further, one can draw a parallel between understanding the internal qualia of seeing red and understanding the internal state of another. Under this thought experiment, simply having the cognitive “theory” of what others may think or feel in a certain scenario would not be sufficient for TOM. Similar to Mary, oftentimes individuals with autism can be taught rules regarding what individuals may think or how they may feel in a certain situation. However, they will often still have difficulty really “knowing” the other’s mental state, not because they do not have their own representation (like Mary), but rather because they have difficulty relating their own representation to that of others.

Similar to the simulation theory of TOM, empathy by definition incorporates a “simulation” of an observed person’s internal state. The term empathy was originally introduced by Theodore Lipps (1903), and he used it to describe the feeling one gets when watching an acrobat walking on a suspended wire. Lipps writes, “I feel myself inside of him.” This concept was further elaborated by Edith Stein in her book “On the Problem of Empathy” (1912/1964, English Translation). Stein proposes that empathy is not simply the understanding of other’s feelings or emotions in a cognitive or theoretical manner. Rather, empathy is a function of one individual experiencing the same feelings as another individual through an appreciation of similarity. Most recently, Preston and DeWaal (2002) proposed the Perception-Action Model of Empathy, which states that the attended perception of an individual’s state

automatically activates the observer's representations of the state and situation. Further, the activation of these representations automatically primes or generates the associated autonomic and somatic responses unless inhibited.

Strong empirical evidence exists for the role of simulation in the ability to empathize with others' emotions. When participants are presented with stimuli of others displaying emotional facial expressions, typically-developing individuals will automatically (without instruction to do so) mimic the facial expression of the stimuli (Bush et al., 1989; Dimberg, 1982, Dimberg and Lundqvist, 1988). This mimicry occurs even when the stimuli are presented subliminally (Dimberg et al., 2000). The spontaneous facial mimicry response has been proposed to facilitate recognition and empathy for the observed emotion through a process of internal simulation of the corresponding facial expression (Lipps, 1907; Niedenthal et al., 2001; Pietromonaco et al., 1981; Wallbott, 1991).

In addition to spontaneous mimicry, one can also voluntarily produce a matching expression to an observed expression. However, this occurs much later (over 1000 ms post stimulus) as compared to the spontaneous response (between 500 and 900 ms post stimulus) (McIntosh et al., 2006) and is thought to be mediated by conscious cognitive processes, leading to the suggestion that a voluntary mimicry response is generated by a different underlying neural system than spontaneous mimicry (Matsumoto & Lee, 1993; Tassinari & Cacioppo, 2000).

Many researchers have suggested that spontaneous mimicry plays a role in recognition of facial expressions and social skills including emotional empathy (Chartrand and Bargh, 1999). Two recent studies have directly investigated the role of

mimicry in recognition of facial expressions, showing that manipulations that block an individual's ability to use spontaneous facial mimicry decreases his/her ability to identify emotions (Niedenthal et al., 2001; Oberman et al., in press).

In the study conducted by Niedenthal et al. (2001), participants were asked to hold a pen sideways in their mouths, between their teeth and lips, preventing facial mimicry. Performance of the experimental group was compared against a group of participants who were free to move their faces naturally. Both groups were asked to identify the point at which a morphed face changed from happy to sad and vice versa. Participants who were prevented from using facial mimicry detected the change later in both directions than those who were able to move their face freely, indicating that the disruption of facial mimicry may lead to impaired recognition of emotional facial expressions.

In the study conducted by Oberman et al. (in press), participants were asked to bite on a pen in such a way that the cheek, mouth, and nose muscles were consistently activated. Participants were then asked to classify an expression as representing either happy, sad, fear, or disgust while performing this bite manipulation, chewing on gum, and in two control conditions. The bite manipulation interfered most with recognition of happiness suggesting that facial mimicry differentially contributes to recognition of specific facial expressions.

While these studies support a relationship between spontaneous mimicry of facial expression and emotion recognition, and theoretically empathy has been conceived as a result of both external and internal mirroring (Lipps, 1903), a missing step exists in this theoretical account. If empathy is a result of internal and external

mimicry, it would follow that, individuals who are more empathetic should produce more facial mimicry than those who are less empathetic. In order to investigate this question, Sonnby-Borgstrom et al. (2003) compared spontaneous facial mimicry in individuals who scored high and low on an emotional empathy scale (QMEE). Highly-empathetic individuals displayed EMG activity consistent with mimicry of the presented facial expressions at both automatic (56 ms) and controlled (2350 ms) exposure levels. Low-empathetic individuals did not display mimicry at any exposure level. Thus, this study supports the role of simulation in emotional empathy.

As would be expected from the facial mimicry research, fMRI conducted while people observe emotional facial expressions in others activates a similar network as imitation of those same expressions. Notable areas in this shared network include inferior frontal cortex, superior temporal cortex, insula and amygdala, all of which not only showed increased activity in both observe and imitate conditions as compared to rest, but also showed more activity in the imitate condition as compared to the observe condition (Carr et al., 2003). This study argues for overlapping regions of premotor cortex that respond both when participants are asked to interpret emotional facial expressions and when they observe hand actions.

Recent studies provide evidence for the role of simulation and mirror neuron dysfunction in the manifestation of empathy deficits in ASD. For example, an EMG study conducted by McIntosh and colleagues (2006) found that individuals with ASD, unlike typically-developing individuals, do not spontaneously selectively activate corresponding muscles in response to visually presented emotional facial expressions. In this study, adults with ASD and neurotypical adults viewed pictures of happy and

angry facial expressions. In the spontaneous mimicry condition, participants were instructed to “watch the pictures as they appear on the screen.” In a second condition, voluntary mimicry was measured by instructing the participants to “make an expression just like this one.” EMG electrodes placed over the cheek and brow recorded muscle activity. Despite displaying a normal pattern of voluntary mimicry, results from this study suggest that, unlike the age, gender, and verbal IQ matched control group, participants with ASD do not spontaneously selectively activate congruent facial muscles. Rather, they indiscriminately activate both congruent and incongruent muscles, showing no selectivity. Taken together with Sonny-Borgstrom’s finding that spontaneous mimicry correlates with empathy skills, these findings provide support for the simulation hypothesis of autism proposed previously.

A recent study by Dapretto and colleagues (2005) provides a possible neural basis for this lack of mimicry and empathy deficits in ASD by showing a lack of mirror neuron activity to the observation of facial expressions. Ten high-functioning children with ASD and ten typically-developing individuals were presented with faces expressing five different emotional expressions (happy, sad, angry, fear, and neutral) and were asked to either observe or imitate the expression while in an fMRI scanner. Despite performing equally well on the imitation task, individuals with autism did not show any activation during either the observation or imitation tasks in the premotor mirror neuron region. Typically-developing participants on the other hand, showed strong activation during both tasks in this area. Results from this study support the involvement of this region in empathy and facial mimicry in typical individuals and provide a possible explanation for deficits in these skills in individuals with ASD.

In order to further clarify the abnormalities in facial mimicry to emotional facial expressions seen in ASD, the current study implemented a design based on studies by McIntosh and colleagues (2006) and Sonby-Borgstrom and colleagues (2003). Participants were asked to view emotional facial expressions at fast (25ms), medium (75ms), and slow (1000ms) exposure levels while facial EMG measures were taken. They were then asked to voluntarily mimic the facial expressions.

4.2 Methods

4.2.1 Participants

The same 26 children that participated in the studies in chapter three also participated in these studies. All participants in the study were male. Participants ranged in age from eight to 12 years. Children with ASD were diagnosed by a licensed clinical psychologist or medical doctor not associated with this research. This diagnosis was verified through administration of the Autism Diagnostic Observation Schedule – Generic (ADOS-G, Lord, Risi, Lambrecht, Cook, Leventhal, et al., 2000). All participants were considered high-functioning, defined as having age appropriate verbal comprehension abilities and an Intelligence Quotient (IQ) greater than 80 as assessed by the research team.

4.2.2 Cognitive Testing

Standardized assessments of empathy were revised from their original versions from a 1st person viewpoint to a 3rd person viewpoint and the parent/guardian of the child was asked to evaluate how well the scale items described their child. The Basic Emotional Empathy Scale (Mehrabian, 1996) and the Empathetic Concern Scale of the Interpersonal Reactivity Index (Davis, 1980) were used to assess empathy, while the Perspective-Taking Scale of the Interpersonal Reactivity Index (Davis, 1980) were used to assess theory of mind skills. The mean standardized scores and standard errors for each group are presented in Table 4.1.

4.2.3 Stimuli

Stimuli consisted of 192 photos of facial expressions used with permission from the Mac Brain Stimulus Set (<http://www.macbrain.org/faces/index.htm>). Stimuli were presented on a 15-in monitor located approximately 80 cm away from the participant and measured approximately 10 x 10 cm in size. Stimuli were presented at three exposure levels (25ms, 75 ms, and 1000 ms). Order of presentation of stimuli and exposure level was randomized. For 1000 ms prior to the stimulus presentation, a fixation cross appeared in the center of the screen to signal to the participant to pay attention to that portion of the screen, where a stimulus would appear.

4.2.4 Procedure

Consistent with earlier studies of facial mimicry (Dimberg, 1982; McIntosh et al., 2006), this study involved two blocks. In the first block, participants were asked to

watch facial expressions presented on a computer screen and classify them as expressing happy, sad, angry, fear, disgust, or neutral. Performance on this task was collected and analyzed for accuracy. During the second block, participants were explicitly told to make the same expression as they saw on the screen then classify it as they had done in block one. During this block the stimulus remained on the screen for 1000 ms to ensure that the participant had ample time to perceive the stimulus.

4.2.4 EMG Data processing

In order to obtain EMG information, pairs of 4-mm silver/silver-chloride electrodes were placed on the left side of the participant's face. Two adjacent electrodes, referenced to one another, were placed over the zygomaticus major, corrugator, medial frontalis, orbicularis oris, and levator muscle groups respectively. An additional ground electrode was placed in the upper portion of the forehead. The impedances of all electrodes were reduced to less than 15 k Ω . The location of the electrodes and recording technique conformed to the standards for EMG recording (Cacioppo et al., 1990).

The acquisition of EMG signals was controlled by a Biopac Amplifier and Acqknowledge software package manufactured by Biopac Corporation. The signals were immediately amplified by a factor of 150 at the headbox located near the participant and by a factor of 500 at the amplifier. The signals were filtered on-line with a low pass of 500 Hz and a high pass of 10 Hz and sampled at 2048 Hz. The samples were then integrated and rectified. Average values were obtained for each

100ms interval beginning at 1000 ms pre-stimulus onset and ending at 2000 ms post-stimulus onset, creating 30 100 ms interval values per trial.

4.2.5 EMG Data Cleaning and Reduction

The signals were screened for movement and electrical artifacts. Trials containing artifacts were removed prior to analysis by a blind coder. Artifacts were found in less than 5% of the trials. After removal of artifacts, the data were logarithmically transformed, which reduces the impact of extreme values. The data were then standardized (i.e., expressed as Z scores) within participants and muscle sites, which attenuates the undue impact of highly reactive individuals on group scores and allows for meaningful comparisons across sites.

Once data were converted to Z-scores, baseline values for each trial were obtained by calculating the average EMG activity in the time window from 500 ms to zero ms prior to stimulus presentation. Baseline-corrected activity was then calculated for each 100 ms interval from 100 ms post-stimulus to 2000 ms post-stimulus. Finally, to obtain one value for every 100 ms interval of each trial type, trials of the same emotion and stimulus presentation length were averaged.

4.2.6 Analysis

Several measures were obtained from the raw data. In order to quantify the amplitude of the response, a peak was defined as the highest value occurring between 300 and 1900 ms followed by a reduction in activity of a minimum of 0.1 Z. The latency of this response was defined as the 100 ms interval in which the peak occurred.

Finally, in order to quantify the overall response during the typical automatic and voluntary time frames, both an average and an integral of the response within the window of 300 ms to 900 ms (automatic time window) as well as 1000 ms to 2000 ms (voluntary time window) was calculated. These windows were chosen based on previous literature defining response latencies for spontaneous and voluntary facial mimicry (Dimberg et al., 2002; McIntosh et al., 2006).

Proper mimicry not only involves the activation of the muscle matching the observed expression, but also the lack of activation of inconsistent muscles. Thus, in addition to calculating the above values for the appropriate muscle (Happy – zygomaticus major, Angry – corrugator, Sad – orbicularis oris, Fear – medial frontalis and Disgust – levator) two contrasting muscle groups (Happy – corrugator and Angry – zygomaticus major) were also analyzed in order to confirm that the activation was selective to the appropriate muscle.

Group differences in EMG activity during each exposure level and during the voluntary mimicry condition were analyzed using a between-subjects analysis of variance. Standardized tests of empathy (the Empathetic Concern Scale from the modified interpersonal reactivity index (IRI) and the Balanced Emotional Empathy Scale (BEES)) were also analyzed for group differences.

4.3 Results

4.3.1 Cognitive Testing

A modified version of the Balanced Emotional Empathy Scale (BEES) (Mehrabian, 1996) and Empathetic Concern Scale from the Interpersonal Reactivity

Index (IRI-EC) (Davis, 1980) were utilized to quantify empathy skills in participants. The Perspective Taking Scale of the IRI (IRI-PT) was utilized to quantify theory of mind abilities. Two-tailed t-tests conducted on these measures revealed a significant effect of group with the neurotypical group showing a higher degree of empathy and theory of mind than the ASD group (BEES: $t(24) = 24.84$, $p < 0.0001$, IRI-EC: $t(24) = 19.27$, $p < 0.0002$, IRI-PT: $t(24) = 36.71$, $p > 0.0001$). Though the ASD group showed a large impairment in empathy and theory of mind, this impairment was not significantly correlated with any of the EMG measures described below (all $ps > 0.10$).

4.3.2 EMG Behavioral Performance

There was no group difference in accuracy on the behavioral task (all $ps > 0.2$). Chance performance on this task would be 17% (1 out of 6), yet even at the fastest speeds, performance in both groups was above 60%.

The observe and mimicry blocks, were first analyzed separately, then a comparison between the latency of responses in the two blocks was performed. Mixed model factorial analyses were performed for both blocks. During the observe block, a 2 (Group: ASD, Neurotypical) by 2 (Emotion: Happy, Sad, Fear, Disgust, Anger) by 3 (Speed: Fast, Medium, Slow) mixed model factorial analysis of variance was performed on 6 outcome measures: peak amplitude, average activity within the automatic time window, average activity within the voluntary time window, integral of activity within the automatic time window, integral of activity within the voluntary time window, and peak latency.

4.3.3 Observation Block

For peak amplitude in the appropriate facial muscle, there was a significant main effect of emotion ($F(4,357) = 8.83, p < 0.0001$). Subsequent t-tests revealed that the observation of an Angry face resulted in significantly greater peak amplitude than a Fear, Disgust, or Sad face (all $ps < 0.01$). The observation of a Happy face resulted in significantly greater peak amplitude than a Disgust or Sad face (both $ps < 0.01$). The observation of a Fear face resulted in a significantly greater peak amplitude than a Disgust or Sad face (both $ps < 0.05$) (Figure 4.1).

For latency, there was a significant main effect of group ($F(1,357) = 13.35, p < 0.001$) with the ASD group showing a greater latency to respond than the neurotypical group (Figure 4.2). There was also a significant main effect of speed ($F(1,357) = 4.19, p < 0.05$). Subsequent t-tests revealed a linear trend with the Fast speed resulting in the shortest latency, followed by the Medium speed, with the slow speed resulting in the greatest latency.

The effects for the average activity and integral of the activity in the appropriate facial muscle in the automatic time window were similar to that of the peak effect. There was a main effect of emotion for both of these outcome measures (Average: $F(4,357) = 7.67, p < 0.0001$; Integral: $F(4,357) = 7.91, p < 0.0001$). Subsequent t-tests revealed that the observation of a Happy face resulted in significantly greater average activity and integral of the activity in the automatic time window than a Angry, Fear, Disgust, or Sad face (all $ps < 0.05$). The observation of an Angry face resulted in significantly greater average activity and integral of the activity than a Disgust or Sad

face (both p s < 0.05). The observation of a Fear face resulted in a significantly greater average activity and integral of the activity than a Disgust face ($p < 0.05$) (Figure 4.3).

For the voluntary time window there was a main effect of emotion and speed for both the average and integral outcome measures (Emotion, Average: $F(4,357) = 2.80$, $p < 0.05$; Integral: $F(4,357) = 2.75$, $p < 0.05$) (Speed, Average: $F(4,357) = 3.75$, $p < 0.05$; Integral: $F(4,357) = 4.05$, $p < 0.05$) Subsequent t-tests revealed that the observation of a Happy face resulted in significantly greater average activity and integral of the activity in the voluntary time window than a Fear, Disgust, or Sad face (all p s < 0.05). The observation of an Angry face resulted in significantly greater average activity and integral of the activity than a Disgust face ($p < 0.05$) (Figure 4.4). Additionally, there appeared to be a linear trend with the Fast speed resulting in the least average activity and integral of the activity in the voluntary time window, followed by the Medium speed, with the slow speed resulting in the greatest average activity and integral of the activity during this time window.

When activity in the corresponding muscle (Zygomaticus-Happy, Corrugator-Angry) was compared to activity in the noncorresponding muscle (Zygomaticus-Angry, Corrugator-Happy) there was a main effect of correspondence on outcome measures of peak, as well as average and integral of activity during both automatic and voluntary time windows for both groups (all p s < 0.001) (Figures 4.5, 4.6 and 4.7 respectively). Subsequent analyses on automatic and voluntary time windows revealed that although both groups showed a difference in activity between corresponding and noncorresponding muscles across these windows, the ASD group showed no difference in activity between the noncorresponding muscle and baseline activity (all p s > 0.20)

while the neurotypical group actively suppressed activity in the noncorresponding muscle as compared to baseline (all p s < 0.01).

4.3.4 Mimicry Block

There was no significant main effect of group or emotion, nor was there an interaction between the two for peak amplitude or latency during the mimicry block. Unlike the observation block, the majority of participants in both groups did not show any spontaneous mimicry response during this block. Thus, during the automatic time window, there were no effects of group or emotion and no interactions between the two for either the average or the integral of activity. The voluntary time window, however, did result in a main effect of group for both the average and integral of the activity (Average: $F(1,120) = 6.62$, $p < 0.01$; Integral: $F(1,120) = 6.28$, $p < 0.05$) with the neurotypical group showing greater activity in this time window than the ASD group (Figure 4.8).

When activity in the corresponding muscle (Zygomaticus-Happy, Corrugator-Angry) was compared to activity in the noncorresponding muscle (Zygomaticus-Angry, Corrugator-Happy), during the mimicry block, there was a main effect of correspondence on outcome measures of peak, as well as the average and the integral of activity during both automatic and voluntary time windows for both groups (all p s < 0.003) (Figures 4.9, 4.10 and 4.11 respectively).

4.3.5 Observation vs. Mimicry Block

There was no significant correlation between the latency of responses during the mimicry block as compared to the slow speed observation block for any emotion in either group, indicating that voluntary mimicry and spontaneous mimicry responses are separable in both groups.

4.4 Discussion

There were two main findings revealed in this study that deserve further discussion. First, across both groups, Happy and Angry emotional expressions showed the greatest peak and overall spontaneous and voluntary mimicry activity while Sad and Disgust were least mimicked. Second, though the ASD group showed comparable peak and overall activity across two time windows, the initiation of this activity was significantly delayed as compared to age and gender-matched neurotypical individuals.

These findings both support and extend the previous literature on emotional facial mimicry in neurotypical individuals as well as individuals with ASD. The finding that Happy and Angry expressions were the most strongly mimicked expressions is consistent with the suggestion that these expressions may depend on facial simulation mechanisms (Oberman et al., in press), while simulation of other emotions such as disgust and sadness may draw on different types of somatosensory resources. For example, recognition of disgust might involve simulation of interoceptive states (e.g., feeling nauseous) and recruit somatic maps in the insula (Wicker et al., 2003) whereas recognition of sadness might involve simulation of more postural components and draw more on physical body schema (Reed, 2002). Additionally, Ekman (2004) suggests that

the expression of happiness is less restricted by cultural display rules, thus creating a particularly strong pairing between perception and action. Furthermore, one of the main elicitors of anger is the observation of anger in someone else (Ekman, 2004). These factors may have also contributed to the relatively large degree of mimicry of these expressions. The relative role of simulation of specific external and internal aspects of emotion in recognition of different expressions represents an exciting direction for future research.

In addition to the effects of emotion, group effects were seen in the latency of the spontaneous mimicry response. In the previous study by McIntosh et al. (2006) the ASD group showed an overall equivalent degree of activity occurring at approximately the same latency as the control group, however there was no evidence of selectivity of the corresponding muscle (i.e. no difference between activity in the corrugator and activity in the zygomaticus major during the observation of happy expressions and vice versa). In contrast, the current study found differences in latency and evidence for selectivity of the corresponding muscle in the ASD group.

Methodological differences between the two studies may account for these inconsistencies. In the study conducted by McIntosh et al (2006) participants were simply told to “Watch the pictures as they appear on the screen”. Thus, perhaps the addition of a behavioral task was sufficient to produce a significant (though delayed) mimicry response. Additionally, the previous study examined only the time window extending to 800 ms post stimulus onset. Given the average peak latency for the ASD group in the current study fell at approximately 1150 ms post stimulus, perhaps an extended window would have revealed a delayed response in their study.

The finding of a difference in latency of response between the ASD and neurotypical group has significant relevance for the behavioral deficits in social functioning in the ASD group. It has been suggested that temporal coordination of behavior (i.e. processing socially relevant information in a timely manner and responding in appropriate latencies) is “the bedrock of all social interaction” (Crown et al., 2002). Specifically, studies demonstrate that temporal properties are important in interpersonal perception (Crown, 1982), communication of personality traits (Feldstein, 1982), communication of mood (Natale, 1978), empathy (Welkowitz & Feldstein, 1969, 1970), perceived interpersonal relatedness (Crown, 1984; Welkowitz & Feldstein, 1969), understanding of intentions (Baldwin, 1993; Tomasello, 1999), and theory of mind abilities (Blakemore et al., 2003). Additionally, the ability to coordinate timing in social situations appears to be present as early as four months of age (Jasnow et al., 1988), suggesting that early impairments in this ability could lead to deficits in the above mentioned behavioral skills thought to depend on functional temporal processing.

The abnormal latency of response to social stimuli in ASD has been previously noted by Feldstein and colleagues (1982) as well as Rizzolatti (personal communication). A recent study by Rizzolatti and colleagues (personal communication), finds activation of mouth muscles during the observation of someone picking up a piece of food and bringing it to their mouth in neurotypical individuals. Individuals with ASD do eventually show activity in their mouth muscles, but this response is significantly delayed as compared to the control group. In the study conducted by Feldstein and colleagues (1982), 12 individuals with autism participated in two interactions, one with an experimenter and one with his or her parent.

Conversations involving the participant contained significantly longer intraspeaker pauses by the autistic participant as well as longer interspeaker pauses during a change of speakers. Additionally, the autistic participants never achieved what is referred to as temporal synchrony, the ability to match the length of pauses with a speaking partner.

The neural mechanisms underlying spontaneous facial mimicry and temporal processing are not currently known, but one candidate system for facial mimicry is the MNS (McIntosh et al., 2006; Oberman et al., in press). Consistent with this, the premotor MNS activates to the observation of emotional facial expressions in neurotypical adults (Carr et al., 2003), but does not activate to the observation of emotional facial expressions in individuals with ASD (Dapretto et al., 2005). Thus, perhaps the delay in latency seen in this study is a result of the use of a compensatory mechanism for facial mimicry in this group.

The specific impairment in latency, rather than overall activity, or specificity of activity may be related to recent studies suggesting abnormal functional connectivity in individuals with ASD. Specifically, recent studies have found a reduction in long-range axons, through the use of Diffusion Tensor Imaging (DTI) in children with ASD (Barnea-Goraly et al., 2004) and an increase in local cortico-cortical connections as measured by volumetric studies indicating white matter hyperplasia (Carper et al., 2002). During social interactions, these impairments might lead to a reduced ability to send signals from visual cortices in the occipital and temporal lobes to frontal cortices necessary for initiating appropriate responses to stimuli, along with an increase in local “noise” resulting in delayed processing of stimuli.

Though processing delays of 100-200 ms may not affect certain skills such as mathematics or memory, social interaction requires fast efficient processing as verbal and nonverbal cues are often only presented for a fraction of a second. Thus, it is the skills that depend on efficient temporal processing (interpersonal perception, communication of personality traits, communication of mood, empathy, perceived interpersonal relatedness, understanding of intentions, and theory of mind abilities) that will be behaviorally impaired in children with ASD.

Another neural system that may account for the greater response latency in ASD is the cerebellum. As previously mentioned, the cerebellum has been identified as one of the main regions of abnormal development in individuals with ASD (Courchesne, 1997). Additionally, Ivry and colleagues (Ivry, 1996; Ivry et al., 2002) have suggested that the exact type of cell, the Purkinje cell, which has been shown to be deficient in ASD, is critical for tasks that involve explicit temporal representations on the order of a few hundred milliseconds. A fundamental function of the cerebellum is thought to be interpretation and integration of incoming sensory signals and coordinating these incoming signals with motor output (Ito, 2002; Ivry & Keele, 1989). A recent study by Gowen and Miall (2005) finds specific deficits in motor tasks that require coordinating sensory input with appropriate motor output. They suggest that these behavioral deficits may reflect dysfunction in the cerebellar timing systems. Courchesne (1997) suggests that abnormalities in the cerebellum could lead to maldevelopment of several other neural systems which receive direct input from the cerebellum, including the limbic system, parietal cortex, and motor control systems. Thus, dysfunction in the

cerebellar timing systems and their connections with the rest of the cortex may account for some of the latency delays seen in the spontaneous mimicry task.

In summary, consistent with previous findings, we show abnormal spontaneous mimicry in individuals with ASD. Specifically, the ASD group showed greater latency to respond to observed facial expressions. Unlike a previous study looking at facial mimicry in ASD, we find that despite this delayed response, that the specificity and amplitude of the response does not differ from neurotypical individuals. This finding relates to recent theories implicating abnormal functioning of the MNS, abnormal temporal processing, as well as abnormal anatomical and functional connectivity in this population.

Based on the findings presented in chapter 3, future studies investigating facial mimicry in this population should include photographs of the participant as well as a familiar individual in order to determine whether abnormal mimicry would persist when the participant is more familiar with the individual expressing the emotion. Ekman (2004) suggests that emotions may be elicited by witnessing the expression of an emotion in another individual only if the observer feels connected to or identifies with that person. Perhaps typical individuals show spontaneous mimicry in response to all human expressions while individuals with ASD may only show normal responses to individuals they feel personally connected to.

Acknowledgements

I would like to acknowledge the significant contributions of my supervisors on this research, V.S. Ramachandran and Piotr Winkielman. I would also like to thank the families who participated in the study. I would like to acknowledge Charmi Shah, Rachel Spradley, Tim Machado, Jennifer Rabelo, and Matt Ascutto for assistance with programming, data collection and data analysis.

Table 4.1 Results from Cognitive Testing Means and standard deviations (in parentheses) for each of the experimental groups, and the results of statistical comparisons between groups, are presented. Statistical results are based on one-tailed t-tests.

Cognitive Test	ASD	Neurotypical	Significance Level
Basic Emotional Empathy Scale (BEES)	-10.04 (33.62)	51.00 (28.62)	p<0.0001
Interpersonal Reactivity Index (IRI)-Empathetic Concern Scale	10.85 (7.12)	20.62 (3.71)	p<0.0002
Interpersonal Reactivity Index (IRI)-Perspective Taking Scale	3.54 (4.07)	13.26 (4.27)	p<0.0001

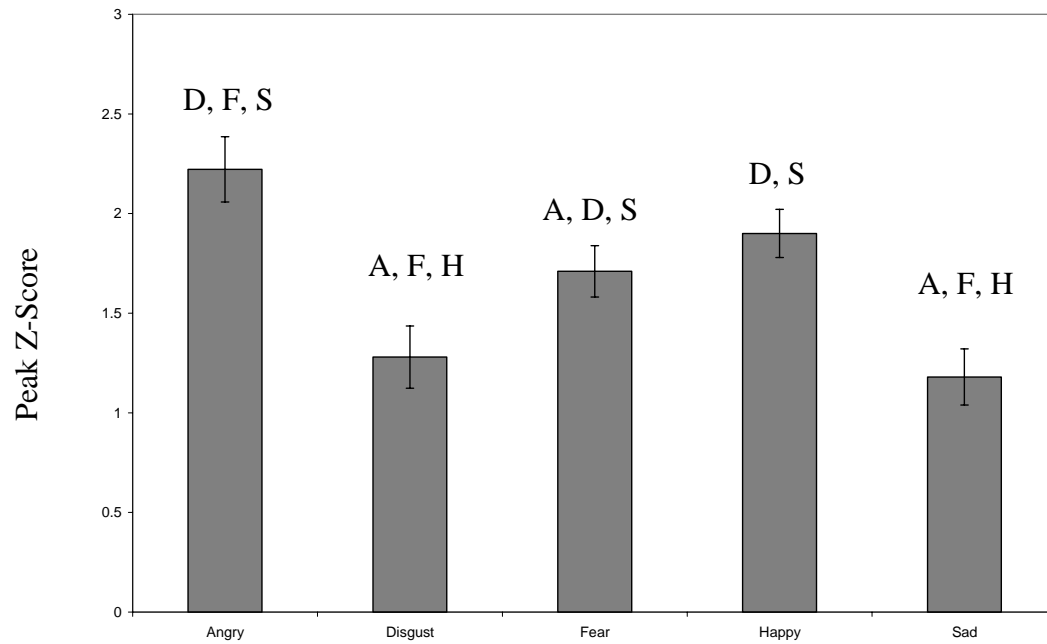


Figure 4.1 Peak Amplitude across Participants for the 5 emotional expressions
Bars represent the mean Z score determined to be the peak for each category of emotion. Error bars represent the standard error of the mean. Significant differences ($p < 0.05$) in peak amplitude are indicated by the letters A, D, F, H, and S representing significant difference from Angry, Disgust, Fear, Happy, and Sad respectively.

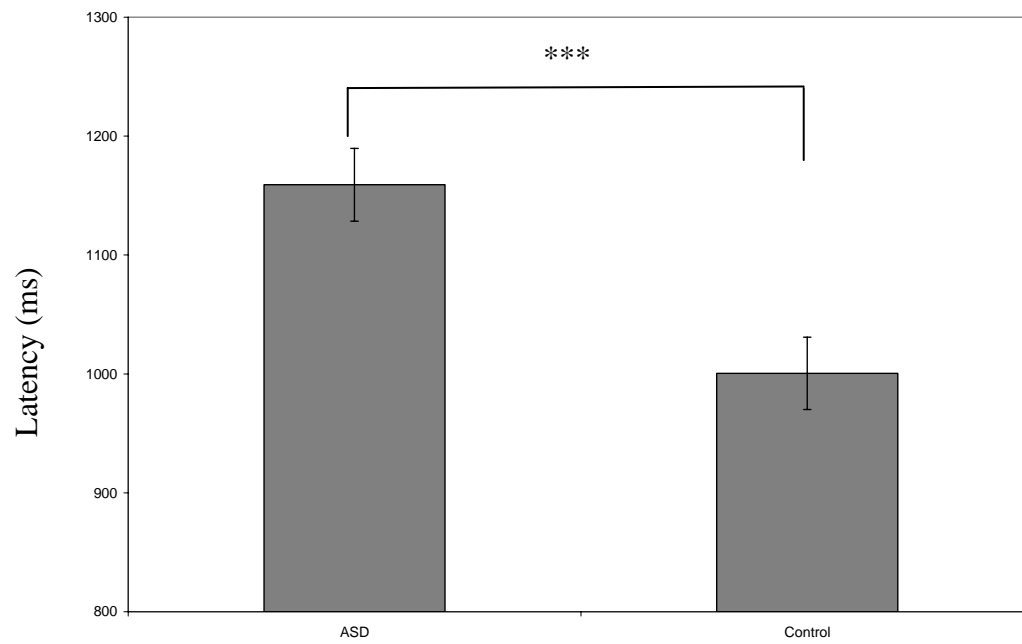
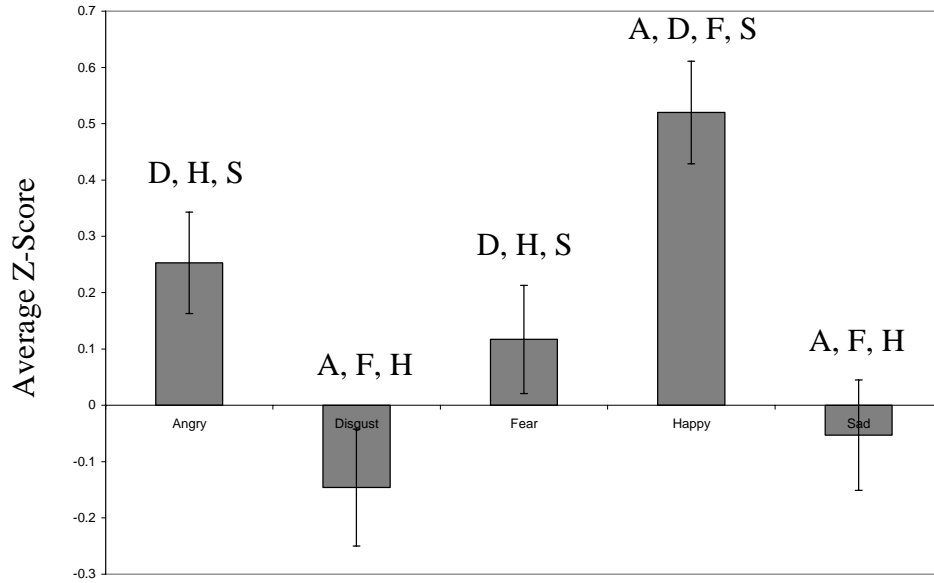


Figure 4.2 Peak Latency for each group Bars represent the average latency of EMG peak in milliseconds for each group. Error bars represent the standard error of the mean. The significant difference in peak latency is indicated by asterisks, *** $p < .001$.

A. Average



B. Integral

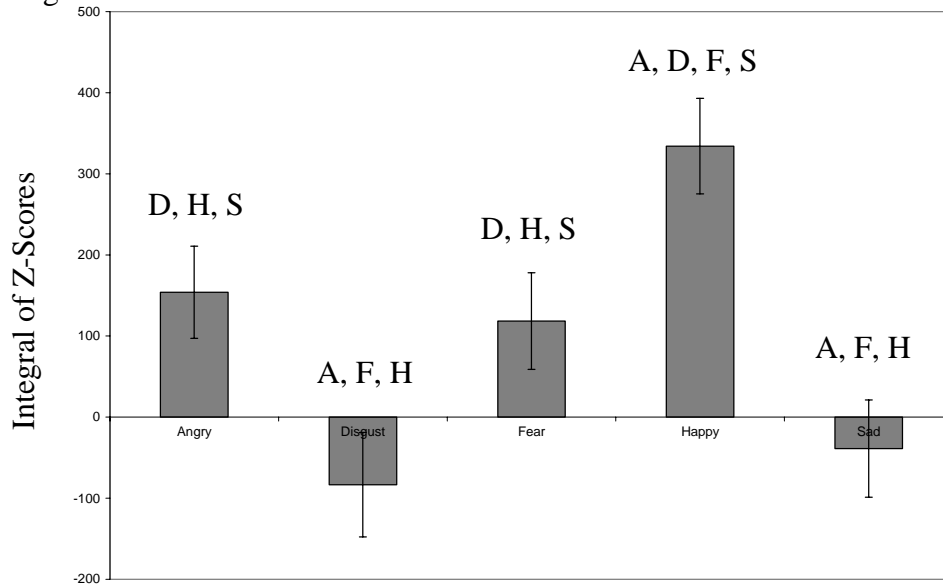
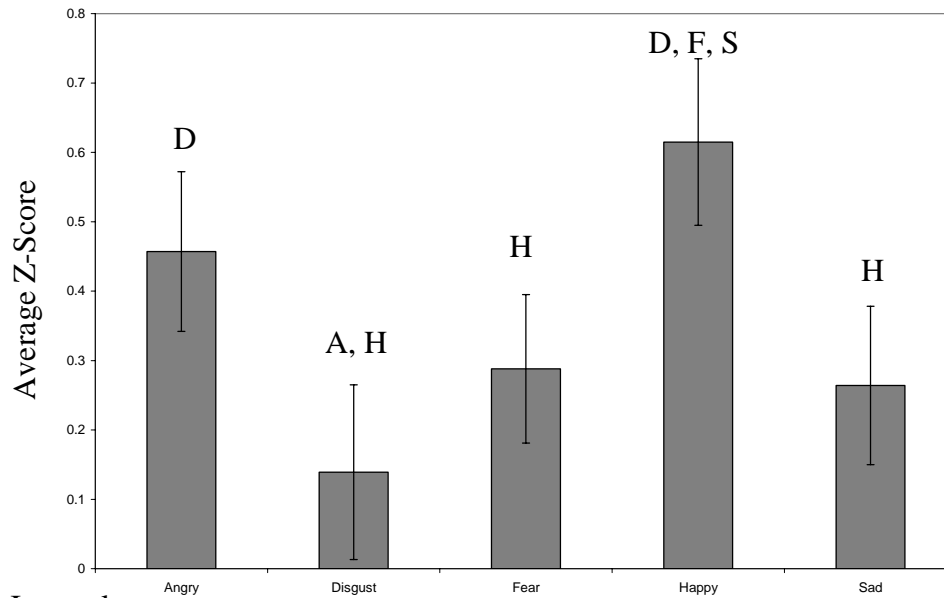


Figure 4.3 Average and Integral of EMG activity during the Automatic Time Window Bars represent the Average (A) and Integral (B) of the Z scores over the time window of 300-900 milliseconds for each category of emotion. Error bars represent the standard error of the mean. Significant differences ($p < 0.05$) in EMG activity are indicated by the letters A, D, F, H, and S representing significant difference from Angry, Disgust, Fear, Happy, and Sad respectively.

A. Average



B. Integral

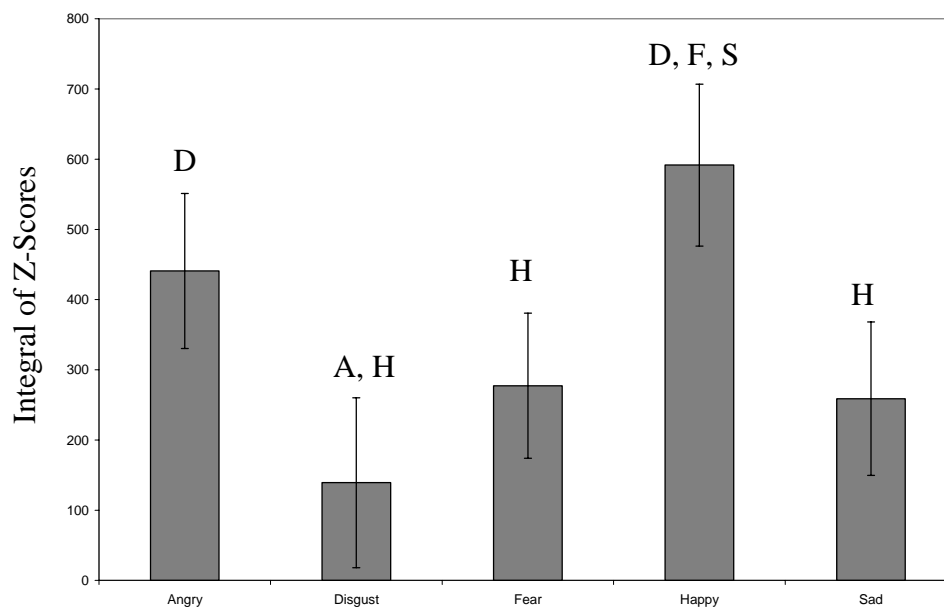


Figure 4.4 Average and Integral of EMG activity during the Voluntary Time Window Bars represent the Average (A) and Integral (B) of the Z scores over the time window of 1000-2000 milliseconds for each category of emotion. Error bars represent the standard error of the mean. Significant differences ($p < 0.05$) in EMG activity are indicated by the letters A, D, F, H, and S representing significant difference from Angry, Disgust, Fear, Happy, and Sad respectively.

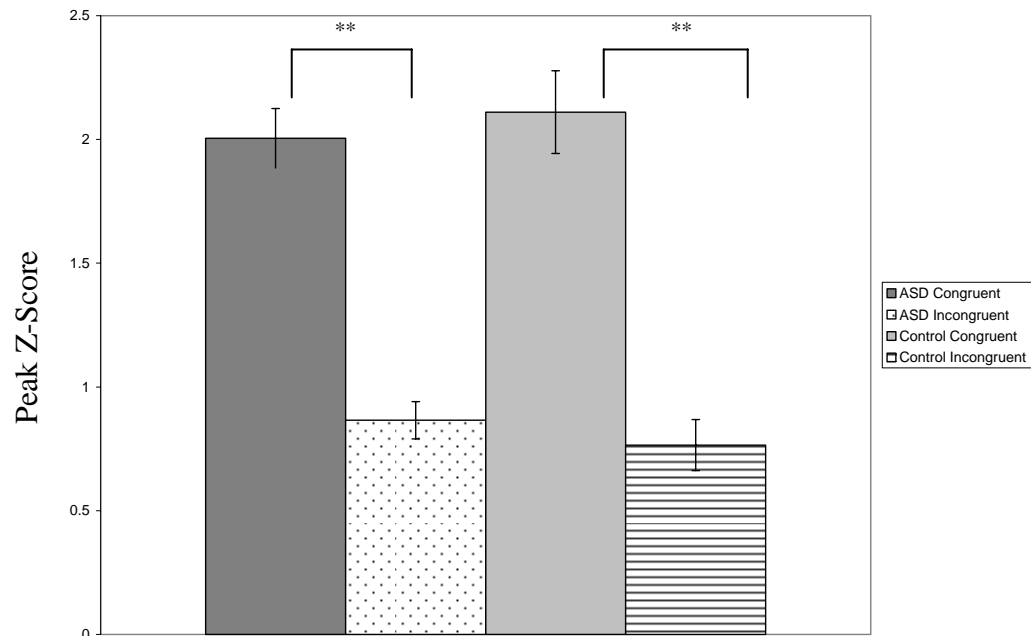
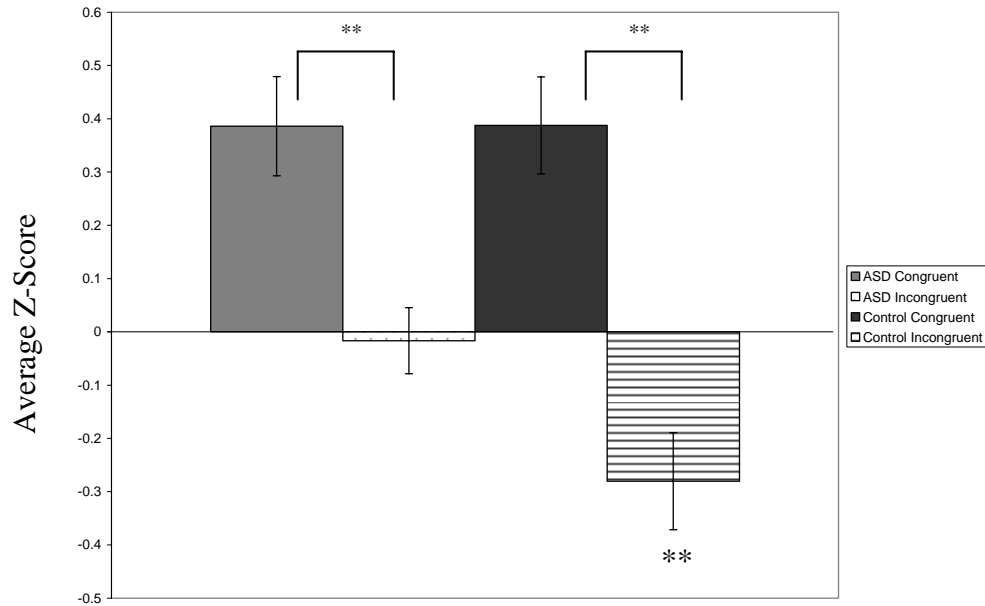


Figure 4.5 Comparison of Congruent and Incongruent Peak amplitude Bars represent the mean Z score determined to be the peak for Congruent muscle activity (Zygomaticus Major-Happy, Corrugator-Angry) and Incongruent Muscle Activity (Zygomaticus Major-Angry, Corrugator-Happy). Error bars represent the standard error of the mean. Significant differences in peak amplitude are indicated by asterisks, *** $p < .001$.

A. Average



B. Integral

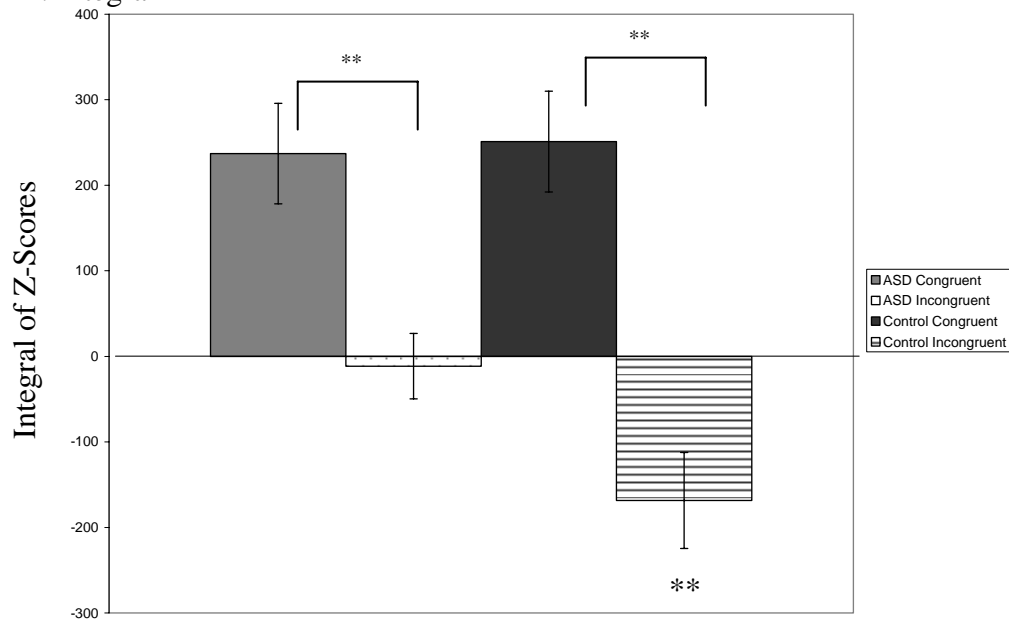
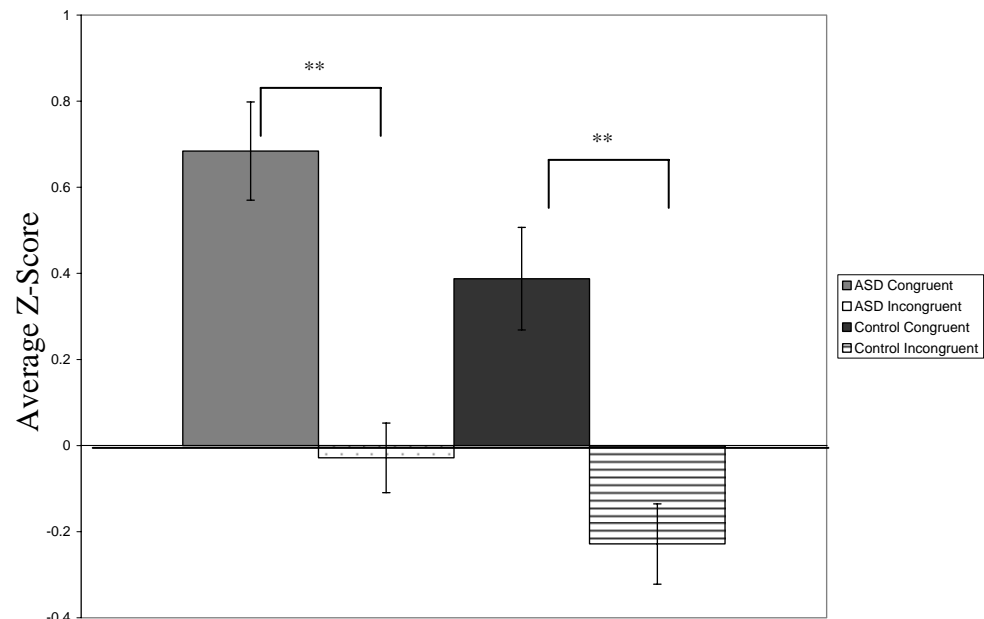


Figure 4.6 Comparison of Congruent and Incongruent Average and Integral of activity during the Automatic Time Window Bars represent the average (A) and Integral (B) of the Z scores over the time window of 300-900 milliseconds for Congruent muscle activity (Zygomaticus Major-Happy, Corrugator-Angry) and Incongruent Muscle Activity (Zygomaticus Major-Angry, Corrugator-Happy). Error bars represent the standard error of the mean. Significant differences in activity are indicated by asterisks, ** $p < 0.01$. Significant reduction in activity is indicated by an asterisk, * $p < 0.05$.

A. Average



B. Integral

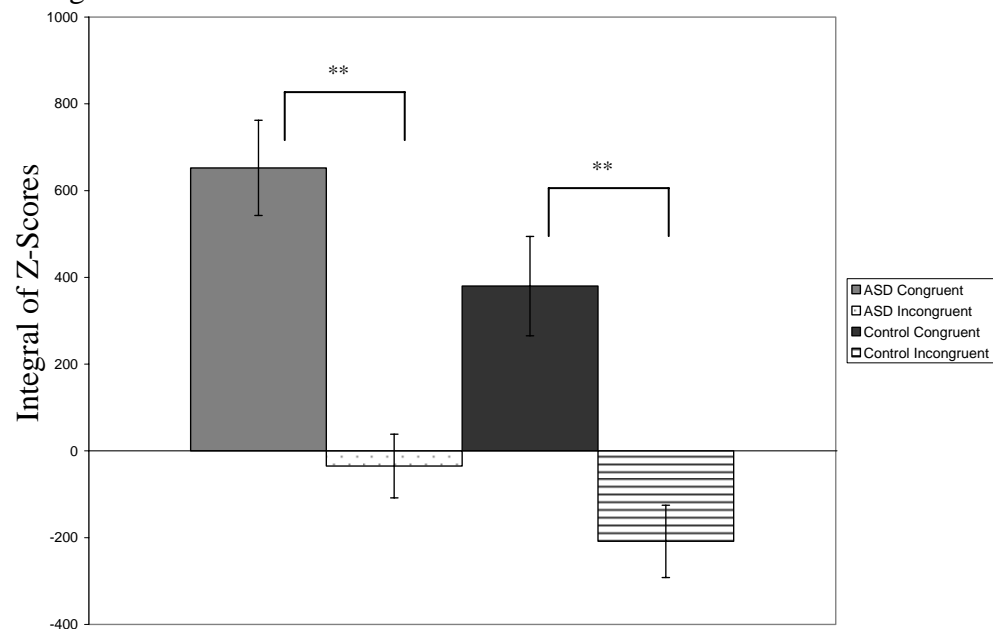
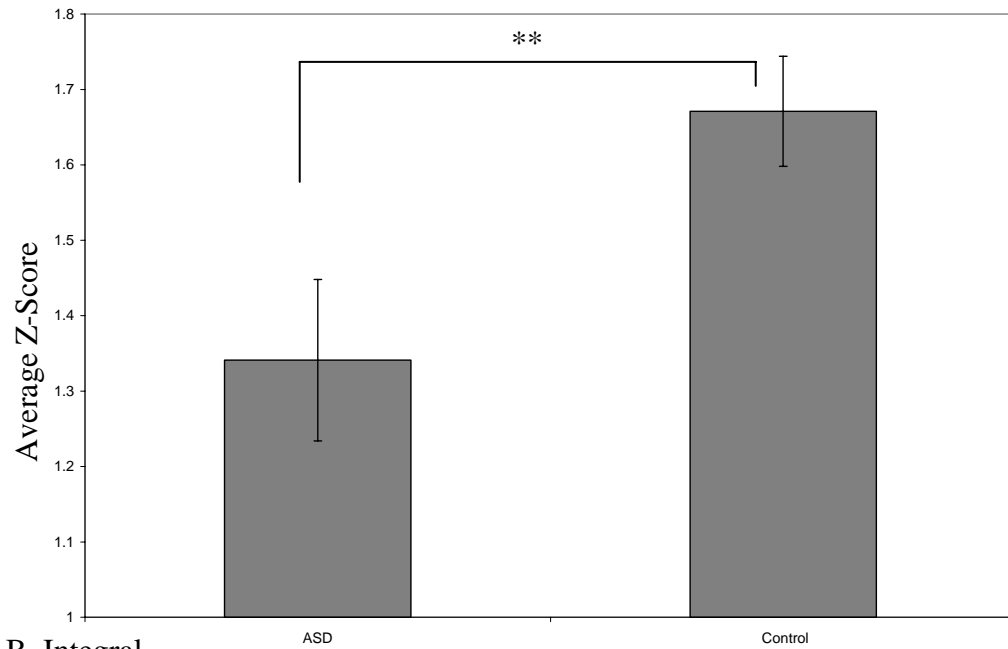


Figure 4.7 Comparison of Congruent and Incongruent Average and Integral of activity during the Automatic Time Window Bars represent the average (A) and Integral (B) of the Z scores over the time window of 300-900 milliseconds for Congruent muscle activity (Zygomaticus Major-Happy, Corrugator-Angry) and Incongruent Muscle Activity (Zygomaticus Major-Angry, Corrugator-Happy). Error bars represent the standard error of the mean. Significant differences in activity are indicated by asterisks, ** $p < 0.01$. Significant reduction in activity is indicated by an asterisk, * $p < 0.05$.

A. Average



B. Integral

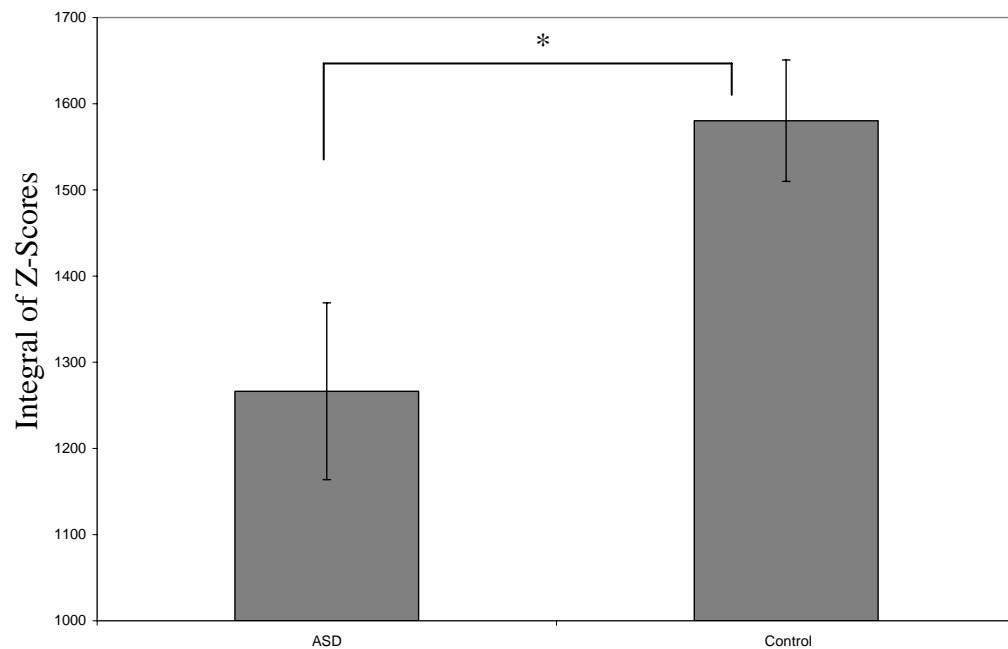


Figure 4.8 Average and Integral of EMG activity during the Voluntary Time Window of the mimicry block for each group Bars represent the average (A) and integral (B) of the Z scores over the time window of 1000-2000 milliseconds for each speed. Error bars represent the standard error of the mean. Significant differences in activity are indicated by asterisks, * $p < 0.05$, ** $p < .01$.

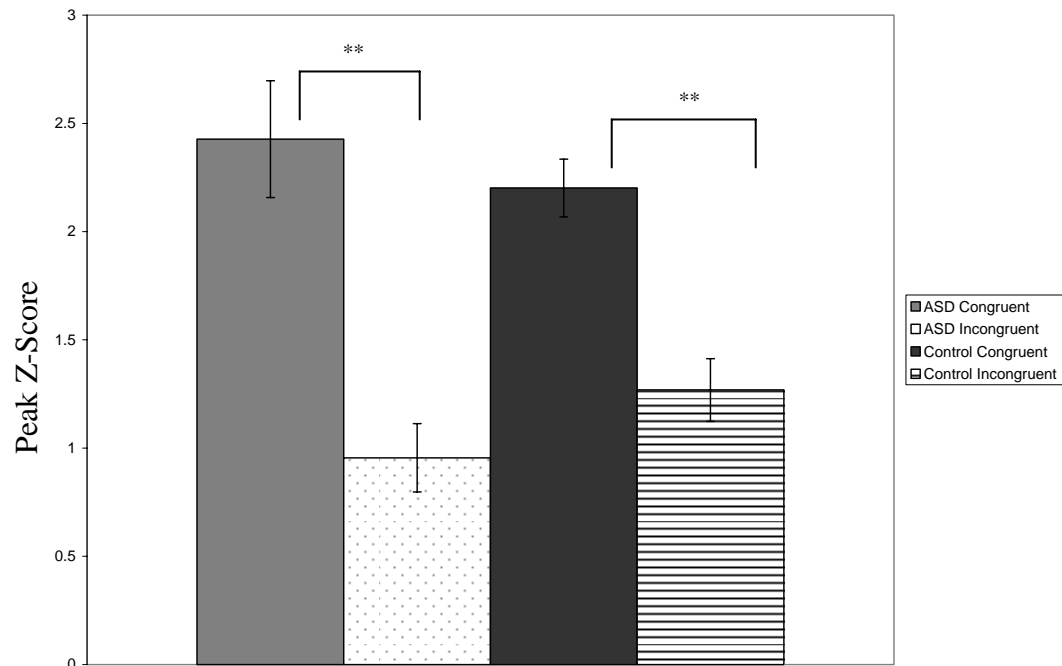
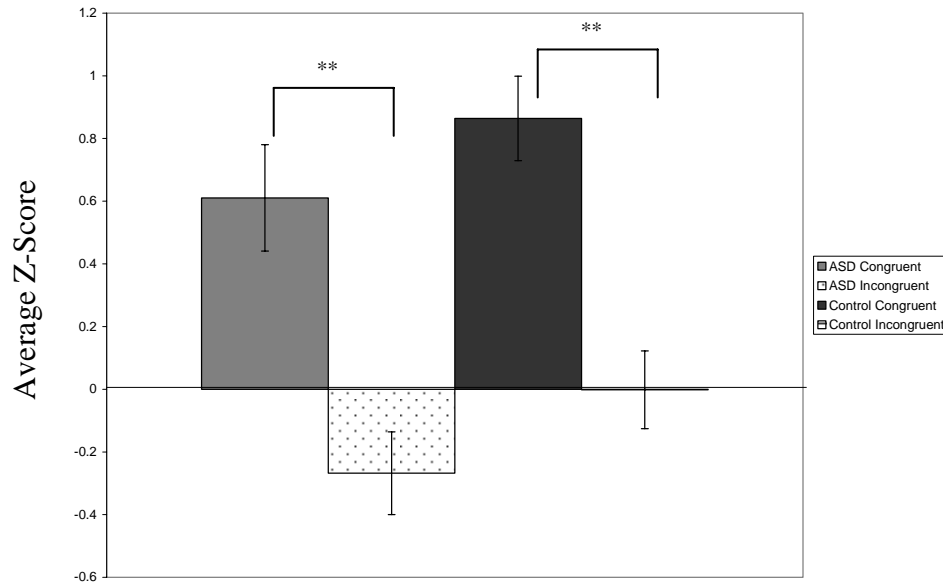


Figure 4.9 Comparison of Congruent and Incongruent Peak amplitude for the Mimicry Block Bars represent the mean Z score determined to be the peak for Congruent muscle activity (Zygomaticus Major-Happy, Corrugator-Angry) and Incongruent Muscle Activity (Zygomaticus Major-Angry, Corrugator-Happy). Error bars represent the standard error of the mean. Significant differences in peak amplitude are indicated by asterisks, *** $p < .001$.

A. Average



B. Integral

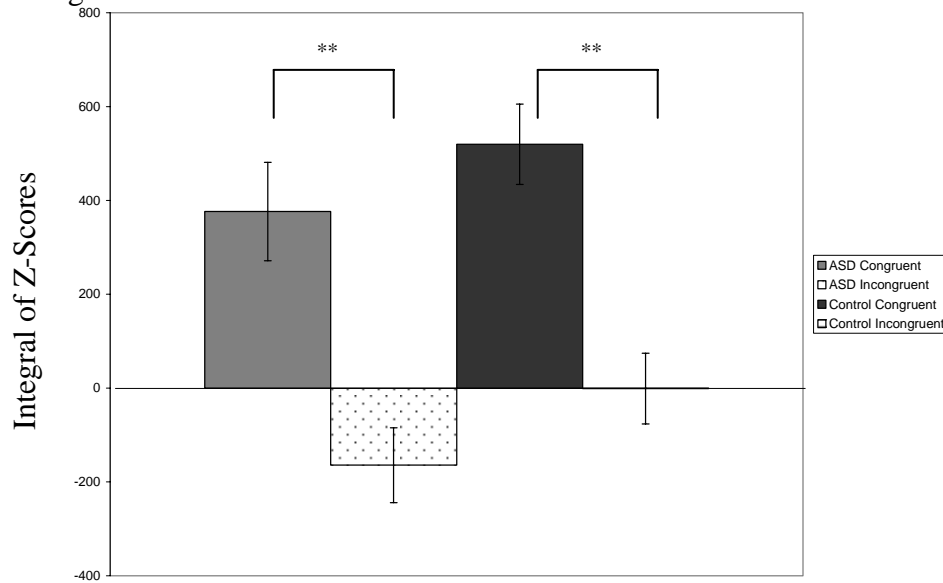
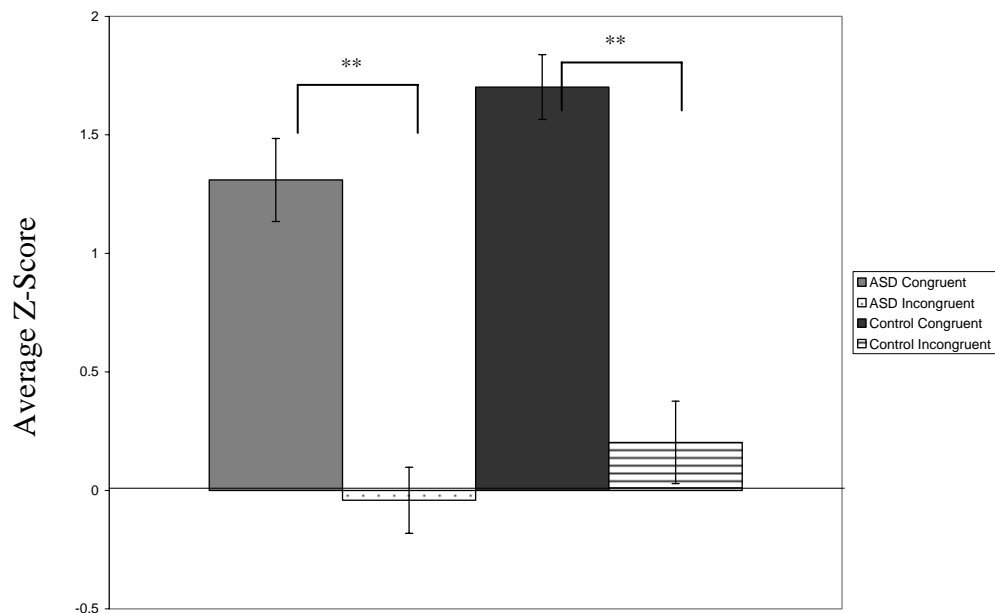


Figure 4.10 Comparison of Congruent and Incongruent Average and Integral of activity during the Automatic Time Window of the Mimicry Block Bars represent the average (A) and Integral (B) of the Z scores over the time window of 300-900 milliseconds for Congruent muscle activity (Zygomaticus Major-Happy, Corrugator-Angry) and Incongruent Muscle Activity (Zygomaticus Major-Angry, Corrugator-Happy). Error bars represent the standard error of the mean. Significant differences in activity are indicated by asterisks, ** $p < 0.01$.

A. Average



B. Integral

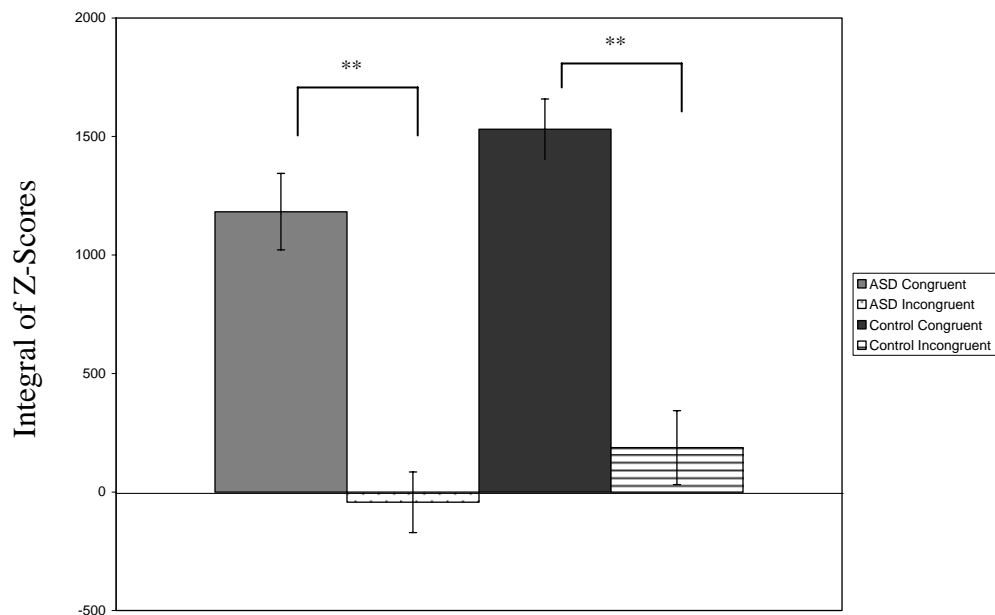


Figure 4.11 Comparison of Congruent and Incongruent Average and Integral of activity during the Voluntary Time Window of the Mimicry Block

Bars represent the average (A) and Integral (B) of the Z scores over the time window of 1000-2000 milliseconds for Congruent muscle activity (Zygomaticus Major-Happy, Corrugator-Angry) and Incongruent Muscle Activity (Zygomaticus Major-Angry, Corrugator-Happy). Error bars represent the standard error of the mean. Significant differences in activity are indicated by asterisks, ** $p < 0.01$.

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Chapter 5

The three experiments discussed in the previous chapters were conducted in an effort to examine the functioning of simulation systems including the MNS in individuals with ASD. The first of these experiments utilized the EEG mu rhythm as an index of the MNS. The purpose of this experiment was to establish whether individuals with ASD would respond with the characteristic blocking of the mu rhythm during observation and performance of human actions. The results indicate that the MNS does not function normally in these individuals as evidenced by a lack of mu wave suppression during the observation of human actions.

To follow-up on this finding, we sought to further characterize this dysfunction by examining whether this lack of suppression was present for all human actions or was modulated by social or experience-based factors. This study found that the presence of social interaction did not significantly modulate the suppression in either group. While neurotypical participants showed significant suppression to both social and nonsocial stimuli, children with ASD did not show significant suppression to either. The second part of this study included the presentation of videos of actions performed by a stranger, a family member, or the child's own actions. Replicating and extending the study presented in chapter two, children with ASD did not show suppression to the observation of a stranger's action. However, the observation of a family member's and their own actions did result in significant suppression in this group.

Finally, the third study investigated spontaneous mimicry of facial expressions. Despite showing a normal amplitude and specificity of response, the response in the ASD group was delayed an average of 150 ms compared with that in the neurotypical group. This finding was discussed in the context of the previously described studies as well as recent findings in neuroscience.

Together, the data collected in these studies provide important insights into the role of simulation systems in the etiology of ASD. The results from this series of studies not only suggest that these systems are dysfunctional, but characterize the dysfunction. Though operating at suboptimal levels, results from the studies described in the third and fourth chapters suggest that these systems are not completely nonfunctional and may respond to therapeutic interventions.

One must always consider that any one brain region or system is not functioning in isolation of other brain regions or psychological processes. Thus, the finding that the MNS in an individual with ASD does not respond to an action performed by a stranger is certainly evidence of dysfunction (as the MNS responds to all human actions in neurotypical individuals). However, the findings from the study described in the third chapter suggests that perhaps the MNS responds to all human actions in neurotypical individuals because these individuals are able to relate to all humans. In fact, there is evidence that the MNS in neurotypical individuals also responds to inanimate “anthropomorphic” stimuli such as robots (Oberman et al., in press) and animated geometric shapes (Martin and Weisberg, 2003). Temporal properties in these stimuli may provide the basis for the observer’s ability to “relate” to these stimuli. Thus, the human MNS may not be limited to animate actions (as previously suggested), but rather

may include actions that the viewer is capable of relating to. Just as the MNS would not respond in a neurotypical individual to a ball bouncing up and down (because a neurotypical individual cannot relate to a ball's bounce), perhaps the MNS in a child with autism does not respond to a stranger's actions because he/she cannot relate to that person.

This ability to "relate to" the observed action may simply be a process in which the observed action is matched on some level with an action in the observer's motor repertoire. This proposed matching mechanism likely exists in both the human and monkey MNS, explaining why both systems are sensitive to actions within the observer's motor repertoire. However, the typical human MNS may be more flexible to include actions performed by inanimate, but "anthropomorphic" stimuli. Hence, the subjective experience of "relating to" animated geometric shapes (Martin & Weisberg, 2003). The MNS of an individual with ASD, however, may have a restricted range of stimuli that it responds to perhaps partially as a result of temporal processing impairments (as described below). As the participants in the current studies were over the age of eight, it is hard to dissociate whether the child with ASD's inherent lack of ability to relate to others lead to the MNS impairment or whether a MNS impairment lead to his inability to relate to others or a combination of both. Further research into the development of the MNS in neurotypical infants and infants at risk for ASD may be able to dissociate these two possibilities.

Figure 5.1 provides a model designed to account for the findings in the previous chapters and lead to new hypotheses to be tested in future studies. This model begins with what should be expected in the neurotypical individual (Figure 5.1a). Specifically,

as a result of typical neural development these individuals have both efficient processing of social stimuli and a functional mirror neuron system. The efficient processing of social stimuli facilitates the development of typical social behaviors including TOM, empathy, and the ability to relate to others. The functional development of the MNS allows for internal simulation of social stimuli, which further facilitates typical social behaviors. In addition, the ability to relate to others modulates the functioning of the MNS, creating a positive feedback loop.

Figure 5.1b shows how this same series of processes may be impaired in an individual with ASD. In a child with ASD, abnormal neural development leads to longer latency to process social stimuli as well as a dysfunctional mirror neuron system. This longer latency to process social stimuli leads to deficits in social behaviors which critically depend on efficient temporal processing including TOM, empathy, and the ability to relate to others. The dysfunctional development of the MNS leads to impaired internal simulation of social stimuli and further impairments in social behaviors. The same loop that facilitated social behaviors in neurotypical individuals, now leads to a negative feedback loop leading to qualitative impairments in social interaction in children with ASD.

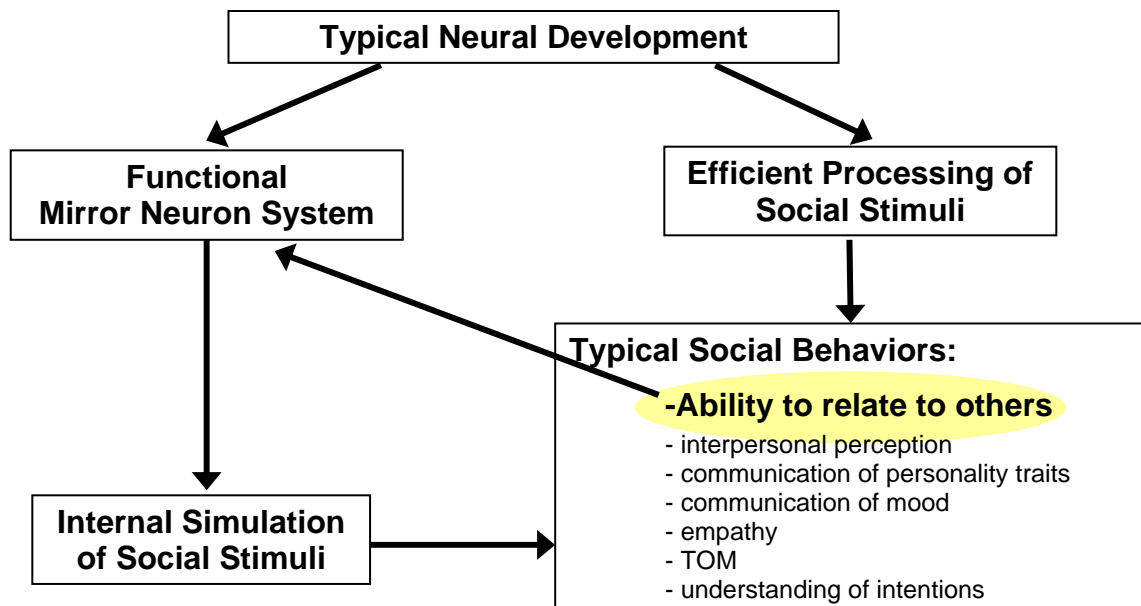
As future studies further characterize the impairments in the MNS and other simulation systems, therapeutic interventions can be developed that take advantage of the factors that are found to modulate the functioning. For example, if a child with ASD shows mu suppression to the observation of a family member's actions and their own actions, but not a stranger's actions, playing on his/her strength of responding to familiar individuals, a MNS neurofeedback training paradigm could be designed to

transition from actions performed by a character who resembles the participant to one who looks like a family member, and finally to a stranger. If a dysfunction in the MNS is leading to some of the behavioral impairments in ASD, then training this system to respond to unfamiliar individuals may lead to behavioral improvements. Preliminary studies along these lines are currently underway (Pineda, personal communication).

Another therapeutic intervention which could be designed based on the findings presented in the EMG study would involve adjusting the connectivity patterns such that long-range connections are increased and unnecessary short-range connections are pruned, resulting in more effective transmission of the signal. Transcranial Magnetic Stimulation (TMS) is a candidate therapeutic technique capable of changing neural connectivity patterns. Studies using TMS to investigate neural plasticity in ASD and potentially change the connection patterns in these children are currently underway (Pascual-Leone, personal communication).

The primary goal of the studies presented in this dissertation is to explore the underlying neural mechanisms that lead to the behavioral impairments that characterize ASD and similar disorders. The knowledge gained from studies of the neural basis of autism provides valuable targets for development of therapies designed to treat the underlying cause of the problem rather than the symptoms. Forty years ago children with ASD would have been institutionalized and the parents blamed for their child's condition. Because of studies such as the ones described here, ASD is now recognized as a disorder caused by abnormal neurodevelopment. Within the next forty years, undoubtedly, therapies such as the ones described above will lead to massive improvements in the quality of life of children with ASD.

a. Typical



b. ASD

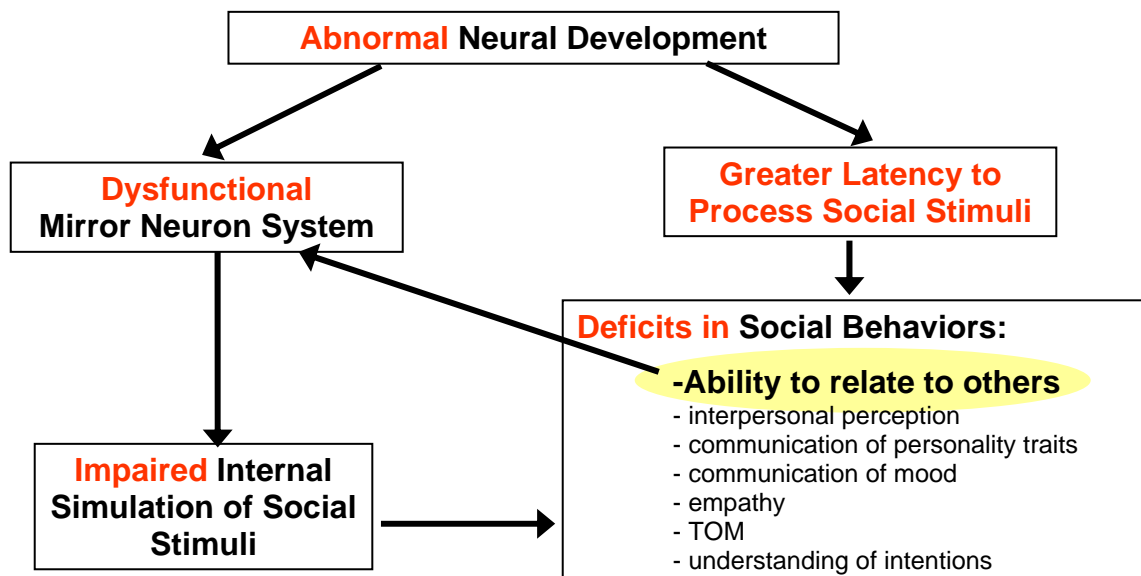


Figure 5.1 Model of Role of Simulation Systems in Social behaviors in (a) Typical and (b) ASD populations.

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