

The Correlation between a Dysfunctional Mirror Neuron System and Autism Spectrum Disorders

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Frequently explored in macaque monkeys, the mirror neuron system (MNS) has demonstrated much influence over the development of behavioral patterns of animals. Since its discovery in macaque monkeys, research about MNS has extended to the development of humans. Researchers have deduced that the cognitive functions of MNS are essential for daily learning and social interactions such as executing imitation, understanding the actions of others, and expressing empathy. Furthermore, recent research has revealed a potential correlation between the impairment of these MNS functions in individuals diagnosed with an autism spectrum disorder (ASD). As individuals with ASD progress into adulthood, deficiencies in the functions controlled by MNS become more apparent such as socialization and communication. When individuals with ASD perform activities that are regulated by MNS functions, the putative regions of the brain where these functions are localized reveal little to no activity. Additionally, the structural development of these putative regions in ASD individuals is atypical compared to persons without ASD. Particular studies have shown simultaneous activity of another neural system, known as the mentalizing system, with that of MNS in ASD individuals. The abnormal levels of crosstalk between the MNS and the mentalizing system appears to be a direction for further analysis in ASD individuals. This review will mainly explore the relationship between emergence of ASDs from the dysfunction of the individual's MNS.

Abbreviations: MNS – mirror neuron system; ASD – autism spectrum disorder

Keywords: macaque monkeys; mirror neuron system; autism spectrum disorder; mentalizing system

Introduction

Within the last few decades of neuroscience and psychology research, the mirror neuron system (MNS) has intrigued many scientists and become a subject of high exploration. The MNS was first detected in primates, specifically the macaque monkeys, by neurophysiologist Giacomo Rizzolatti and his team of researchers in the 1980s (Rizzolatti et al., 1996). Since then, multiple studies have revealed that the MNS controls several functions essential to one's mental development. These core functions include action observation and understanding, imitation, as well as speech and language (Rajmohan & Mohandas, 2007).

Autism spectrum disorders (ASD) are classified as neurodevelopmental disorders recognized by evident impairments in social communication and behavior, and more specifically, in MNS functions (Perkins et al., 2010).

For years, the etiology of ASDs has been quite ambiguous, but is thought to be the result of various genetic and environmental factors. Unlike other genetic disorders that can be detected in pregnancy, ASDs cannot be detected until after birth and further development. Furthermore, a cure for ASDs is currently unknown (Zaky, 2017). Recently, in the fifth edition of the Diagnostic and Statistical

Manual of Mental Disorders, highly specific diagnostic conditions for ASDs have been established for a definitive diagnosis (CDC, 2018). Conditions such as Asperger's disorder, autistic disorder, pervasive neurodevelopmental disorder, and childhood disintegrative disorder, all of which can range from being mildly to extremely severe, are collectively diagnosed as ASDs. The following conditions for ASD diagnosis can be seen in any child or individual; however, they must persist throughout one's lifetime and impede normal operations to be indicative of an ASD. Firstly, individuals must display limitations in starting conversation, executing emotional and social responses, understanding nonverbal gestures and producing their own, and maintaining relationships (CDC, 2018). Secondly, they must demonstrate any two of the following behaviors: monotony in actions, speech, or object use; stubborn attachment to established routines, kinds of nonverbal or verbal behavior, or familiarity (i.e. aggression towards change); hyperintense obsession with certain interests; overdramatized or indifferent reaction to stimuli within the environment (Martínez-Pedraza & Carter, 2011). The symptoms displayed by ASD individuals manifest from a young age but they are unable to be diagnosed because the individuals do not yet need social skills and therefore, do not display any highly concerning deficiencies in social skill. Diagnosis usually occurs within an individual's adolescence or adulthood as social skills are highly required during these times in life (Lauritsen, 2013).

In order to understand the social impairment of ASD individuals, researchers have examined the mechanics of MNS functions and in general, how information is taken in and processed. One of the main social functions impaired is action observation and understanding (Frith, 2001). This function is necessitated by the translation of visual input, involving motor actions, into a well-rounded comprehension of those actions including the intended goals of them. Then, during imitation, this information is externalized as the individual performs the actions to understand and predict the succeeding actions (Iacoboni et al., 2005). These basic MNS functions continue to evolve into more complex ones such as social communication, empathy, and Theory of Mind, which enables the

recognition and assumption of one's thoughts by gestures and both nonverbal and verbal communication (Rajmohan & Mohandas, 2007).

Once the mechanics of these MNS functions were determined, specific functions could be localized to different areas of the brain to investigate. This information provided a foundation for the study of ASDs. The main regions of interest (ROI) where mirror neuron activity has been found are the pars opercularis (POp) of the inferior frontal gyrus (IFG), temporal and occipital areas, motor cortex areas, and superior parietal lobules (Figure 1) (Rajmohan & Mohandas, 2007; Iacoboni et al., 1999). When visual sensory input is received from the environment and translated into actions or knowledge, these different regions of the brain are sequentially activated. For example, when the MNS engages during performance of imitation, the performer's motor actions are first received by the observer's occipital lobe and progress throughout different regions until the information reaches the motor cortex to be transformed into actions (Rizzolatti & Craighero, 2004). Areas of the brain such as the amygdala (i.e. located within the temporal lobe), premotor face area (i.e. a part of the premotor cortex area), POp of IFG, superior temporal sulcus, and insula (i.e. located within the sulcus separating the frontal and parietal lobe from the temporal lobe) demonstrate activity during observation of facial gestures and then during imitation of them (Figure 1) (Carr et al., 2003).

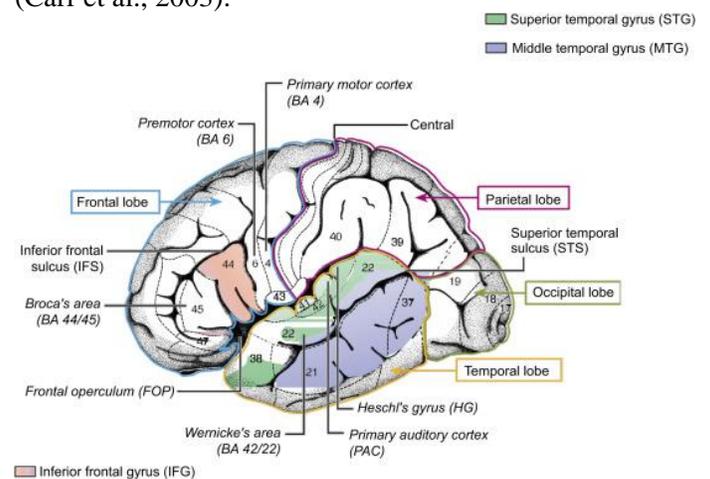


Figure 1: Diagram of the left hemisphere of the brain depicting the main putative MNS ROIs stated above: Pop of the IFG (BA 44 [pink colored area]), temporal and occipital lobes, motor cortex areas (primary motor cortex and premotor cortex area), superior temporal sulcus, and superior parietal lobes (parietal lobe). Used with permission from Friederici AD (2011) and *Physiological Reviews*.

Along with the strong correlation between MNS dysfunction and ASDs, there is other evidence that suggests the involvement of other systems such as the mentalizing system in ASD etiology (Arioli et al., 2018; Fishman et al., 2014; Ruysschaert et al., 2014; Wadsworth et al., 2017). The mentalizing system works adjacently with the MNS in individuals; it enables us to make inferences on the emotions, thoughts, and mental states of others that surround us. In being able to do this, we can predict or determine the actions that others might take and evaluate whether the actions are malicious or benevolent. Therefore, in daily social situations, the viability of this system is crucial (Frith & Frith, 2006).

In individuals whose ASD is confirmed through multiple social communication tests and their resulting scores, various studies have indicated that their ROIs lack activity when MNS tasks are executed (Rizzolatti & Craighero, 2004; Nickl-Jockschat et al., 2015; Couteur et al., 2003; Dapretto et al., 2005; Wadsworth et al., 2017). Understanding the correlation between MNS dysfunction and ASDs may aid in the diagnosis of ASDs earlier in children on a cerebral level, and thus, allow for intervention and treatment early on through appropriate therapies for the individual. This review will explore research conducted over the last five to ten years involving ASDs and corresponding abnormalities discovered in cerebral ROIs where MNS is generally confined. Additionally, this review will consider evidence from recent studies that suggest the contribution of the malfunction of other systems in ASD individuals.

ASD individuals' MNS ROIs lack activity during expression of emotion and empathy

One of the functions of the MNS is imitation. The function of imitation develops into

higher form functions, such as empathy and emotion (Rajmohan & Mohandas, 2007). In individuals with ASDs, the presence of empathy and emotion, which is seen in typically developing (TD) individuals, is absent (Mensi et al., 2018). When ASD individuals appear to express their empathy and emotion, certain regions of the brain are less active than that of others (Rizzolatti & Craighero, 2004). This section will explore putative ROIs of ASD individuals during the expression of MNS functions of emotion and empathy in comparison to TD individuals.

In later stages of development (adolescence and adulthood), ASD individuals, like all other individuals, are expected to express emotion and empathy in certain social situations. However, they are unsuccessful in doing so as shown in various studies (Lauritsen, 2013). ASD individuals are unable to appropriately execute the following process: observe a person's facial expression, understand it, and then imitate it (Dapretto et al., 2005). This may be due to the impairment of the fundamental mechanism of facial processing which is associated with the putative MNS ROIs of visual and occipital areas. During the facial processing of other's faces, ASD individuals display abnormally low activity bilaterally in regions such as the IFG, temporo-occipital lobe, motor areas, parietal and temporal lobes, and the thalamus (i.e. located within the middle of the brain above the amygdala) (Figure 1). Additionally, when ASD individuals are performing facial processing, there is an overlap of activity between the temporo-occipital lobe and the fusiform gyrus. Furthermore, this overlap between the fusiform gyrus and temporo-occipital lobe in atypical facial processing may result in insufficiencies of the MNS processes of imitation and action observation, leading to consequences in the context of social communication (Nickl-Jockschat et al., 2015).

A lack of activity is present in additional ROIs of ASD individuals such as the amygdala and insula of the brain (Adolphs, Sears, & Piven, 2001). During their observation and then imitation of performers' emotional expressions, TD adolescents and ASD adolescents have different levels of activity in

all three of the main MNS regions mentioned above: the IFG, insula, and amygdala (Baron-Cohen et al., 2000). The TD adolescents display normative activity of Pop of the IFG, whereas, the Pop of the ASD adolescents display significantly lower levels of activity (Uddin & Menon, 2009). Therefore, a negative correlation exists between the severity of ASDs in individuals and their levels of Pop activity during emotion-provoking activities. A negative correlation also exists between the activity of the Pop and the social scores provided by the Autism Diagnostic Observation Schedule and Autism Disorder Observation Interview-Revised (i.e. scales used to measure the severity of one's ASD). The higher the social score an individual receives, the higher the severity of their ASD (Couteur et al., 2003). Furthermore, in the negative correlation, as the social score increases, activity in the MNS region Pop decreases (Dapretto et al., 2005).

Along with larger ROI cerebral units, smaller MNS ROIs in ASD individuals such as the gyri of specific lobules exhibit little to no activity. Firstly, in comparison to TD individuals, ASD individuals exhibit insufficient activity in their right inferior parietal lobule, specifically within the right angular gyrus, during imitation of actions (Ha et al., 2015). A negative correlation exists between the autism quotient scores of these ASD individuals and the activity of the right inferior parietal lobule during performance of imitational activities (Rane et al., 2015). As a note, the higher the ASD individual's autism quotient score is, the higher the severity of their form of autism is. Furthermore, this correlation indicates that as the extremity of one's ASD increases, the amount of activity in the right inferior parietal lobule when the individual engages in imitation decreases (Wadsworth et al., 2017).

These relationships between the severity of one's ASD and activity of smaller and larger MNS ROIs during the expression of empathy and emotion indicate a greater correlation between MNS dysfunction and ASDs. The ROIs identified in the previous scientific studies could become the standard ones that are investigated at the time of a suspected ASD in a child in order to potentially diagnose ASD earlier.

Imitation of action observations and understanding intentions in ASD individuals is impaired

The following social skills are impaired in ASD individuals: understanding the intentions of others and imitating the actions they observe of others to facilitate conversation. As a result, ASD individuals perform incompetently in social situations, especially in conversation. In ASD individuals, studies have shown that during their performance of the stated skills, a lack of activity is shown by putative MNS ROIs in comparison to that of typically developing individuals (Kilroy et al., 2019; Gallese & Lakoff, 2005).

When observing ASD individuals perform sensorimotor actions that necessitate the MNS function of action understanding, the individuals are unable to efficiently understand those newly presented sensorimotor actions, replicate them, and further predict the end goals of them (Marko et al., 2015). In a scenario wherein ASD children were asked to replicate drawings only viewing a mirror (i.e. not their hand directly), the children were unable to reproduce certain motor actions, and it was revealed that a large error was present between the drawings of children with ASD compared to those who are developing normally. However, when both groups had a view of their own hands when drawing, no great errors were present (Salowitz et al., 2013). The ASD children's inability to draw from the unfamiliar perspective of a mirror and not their hands demonstrates that their mechanism of understanding and translating newly introduced sensorimotor information into their own actions is impaired compared to the typically developing children. Additionally, the connection between an ASD individual's motor system and prediction of goals is impaired (de Moraes et al., 2017). For instance, a scenario was set up wherein a group of typically developing and ASD individuals observed a demonstrator bring food into their mouth. This observation was meant to spark the action of preparing to open one's mouth to consume the food. However, after both the typically developing and ASD groups observed the

demonstrator bring the food to their mouths for a few rounds, the ASD groups continually failed to understand the ultimate goal of eating food which was represented by their lack of mylohyoid (i.e. muscle located along the throat) activity. On the other hand, the typically developing individuals displayed consistent mylohyoid activity before food was eaten (Cattaneo et al., 2007).

During performance of activities entailing action understanding and corresponding imitation, identified MNS ROIs in ASD individuals do not demonstrate normal activity and are not normally affected (Ha et al., 2015). The putative MNS ROIs of ASD individuals are affected on different levels. Segments of the parietal lobe are affected more greatly than other segments of the brain. Besides being involved in processing language, the parietal lobe is also partially responsible for understanding and interpreting visual motor information (Brownsett & Wise, 2010). Therefore, when engaging in action understanding, ASD individuals show the highest levels of dysfunction in their parietal lobes, specifically the anterior inferior parietal lobule. The occipital cortex, which is one cortex of the brain that controls processing visual information (Galetta, 2017), is another putative MNS ROI that demonstrates unusual activity in ASD individuals (Yang & Hofman, 2016). The impairment of the occipital cortex is sensible during action understanding and imitation as ASD individuals are attempting to process the visuals they observe and translate them into actions (Clery et al., 2013).

Since functions of action understanding and imitation are ones needed early in development, the impairment or viability of these functions should be evident in individuals. Furthermore, as they are seen to be impaired in ASD individuals, these MNS functions alongside ROIs where they are localized should be carefully examined before development into adulthood occurs (Jones, 2009). This examination should occur before adulthood due to the higher level of performance required of these functions for socialization as an adult (Mortimer & Simmons, 1978). In doing this, individuals with highly severe ASDs can be recognized and receive therapies for successful development into adulthood. During activities

entailing action observation and understanding and imitation, activity levels of specific ROIs such as the occipital and parietal lobes and cortices should be recorded (Cross et al., 2009). As seen, the parietal and occipital regions are central areas where the functions stated above are controlled; thus, they should be the regions focused on when assessing ASD individuals.

The structural development of MNS ROIs differs in individuals with ASD compared to TD individuals

As seen, putative MNS ROIs in ASD individuals are impaired functionally, showing a lack of activity during performance of MNS functions. In addition to their functional impairment, MNS ROIs of ASD individuals are also unusual in their structural development in comparison to those of typically developing individuals (Hadjikhani et al., 2006). This demonstrates that dysfunction of the MNS occurs not just mechanically but morphologically as well.

Structural development of putative MNS regions is altered in ASD individuals. Specifically, the cortical morphometry of individuals with ASD differs from that of typically developing individuals (Ha et al., 2015). The largest period of growth in cortical thickness and cortical surface area occurs within the first two to four years when infants are at high risk for ASDs. The total brain volume of ASD individuals exceeds that of typically developing individuals (Hazlett et al., 2017). This abnormally increasing fashion of cortices continues on to adolescence for ASD individuals. Significant contrasts are present between the development of three cortical morphological aspects (i.e. cortical gyrification, which is the index of gyri throughout the cortices, cortical volume, and cortical thickness) of ASD and typically developing individuals. In comparison with typically developing individuals, ASD individuals display atypical increases in size (i.e. for the cortical thickness and cortical volume) and in number (i.e. for the cortical

gyrification) as they grew older; the parameters corresponding with each aspect correlated positively with the ASD individuals' age. The highest levels of cortical thickness of ASD individuals were localized to the superior parietal lobe and the right middle temporal lobe; highest levels of cortical volume were localized to part of the parietal lobe and superior temporal sulcus; highest proportions of cortical gyrification were localized to the Pop, the left superior parietal lobe, and a portion of the superior temporal lobe (Yang et al., 2016). Additionally, throughout an ASD individual's entire lifespan, the cortical thickness of the frontal cortex, in particular, appears to steadily increase. Overall, since various evident MNS ROIs simultaneously increase over time in ASD individuals, a potential connectivity may be taking place between these ROIs throughout the duration of an ASD individual's life (van Rooij et al., 2017).

The structural development of ASD individuals is altered in another way as well: the thickness of certain subcortical regions and gyri thin with age (Sparks et al., 2002; Zielinski et al., 2014). The POP and portion of the parietal lobe known as the supramarginal gyrus demonstrate different correlations in thickness and age between typically developing and ASD individuals. For the typically developing adolescents, a positive correlation exists between the cortical thickness of the left bilateral Pop and right supramarginal gyrus and the age of the adolescents. This correlation infers that for normal structural development, these specific MNS ROIs should increase in thickness. On the other hand for ASD individuals, some ASD adolescents did display unusual structural development as the cortical thickness of particular ROIs thinned with increase in age. However, according to the study that discovered this correlation, the correlation is not substantially supported due to the limited population of ASD individuals found with the mentioned pattern (Chien et al., 2015). Subcortical regions apart of larger MNS ROIs such as the temporal cortical area and parietal lobe also demonstrate smaller volumes. These subcortical regions include: the pallidum, putamen, amygdala, and nucleus accumbens

(van Rooij et al., 2017; Zielinski et al., 2014; Wallace et al., 2010).

The increases in thickness of these cerebral segments are seen to increase within the main time frame of adolescence (Piven et al., 1995). Thus, there should be much attention paid to these different cortices, subcortical regions, and gyri of individuals at infancy who may be at high risk for ASDs and monitored later into development. In particular, the thicknesses of divisions such as the temporal cortex and lobe, and the parietal lobe should be documented closely as they are regions in ASD individuals that are recorded most frequently for having abnormal thicknesses. These structural differences in ASD individuals have not been found to correlate with any abnormal behavior of putative MNS functions; however, thicknesses in the stated ROIs have been limited to ASD individuals opposed to typically developing individuals. Therefore, thickness in those areas may be another potential element of diagnosis for ASDs which can be detected early on in development with technologies such as functional magnetic resonance imaging, positron emission tomography, electroencephalography, and magnetoencephalogram (Xue et al., 2010).

The involvement of dysfunction of MNS in ASD may involve other systems, and gaps may be present within their correlation

The correlation between the dysfunction of the MNS and the emergence of ASDs is strongly supported by an ASD individual's impairment of putative MNS ROIs observed and aberrant structural development of those putative MNS ROIs from infancy into adolescence. This literature review explored concrete evidence of the occurrence of this relationship with groups of ASD individuals and typically developing individuals. Despite the correlation between abnormality of the MNS and origin of ASD, the involvement of dysfunction of MNS in ASD may involve other systems, and gaps may be present within their

correlation. Various studies suggest that interconnectivity between MNS and other neural systems can undermine the correlation of an irregular MNS and ASDs. One of these studies also uncovered the potential incongruent relationship of a dysfunctional MNS and ASDs.

The source of ASDs may not solely be the malfunctioning of the MNS in individuals, but possibly the abnormal level of interconnectivity of both the MNS and mentalizing system, which is another social cognition system that is responsible for functions such as comprehending one's intentions and Theory of Mind (Sperduti et al., 2014). Complementary connectivity between mirror and mentalizing systems is entailed when typically developing individuals observe and process social interactions such as empathy and cooperation between others. The initial information of the actions that are being observed is received by the mirror system and then the meaning of those actions is interpreted by the mentalizing systems. Observations of social interactions and their transformation into useful information by the mirror and mentalizing systems involves the foundational functions of the MNS, such as action observation and intention understanding (Arioli et al., 2018). A positive correlation was established between the crosstalk of the two processing systems (MNS and mentalizing system) and Autism Disorder Observation Interview-Revised scores for individuals with ASD. A higher activity of connectivity between the two systems correlated to a higher degree of severity of ASD (i.e. determined by the higher Autism Disorder Observation Interview-Revised score) (Fishman et al., 2014). Additionally, besides the mentalizing system, the action imitation network is thought to play a role in ASDs. Putative ROIs involved in the action imitation network are activated during activities employing imitation. As the MNS network is also responsible for the social cognitive function of imitation, the ROIs that are involved in imitation overlap with those of the action imitation network (Wadsworth et al., 2017).

Besides the interdependence of several neural systems and ASDs, another gap may be present in the correlation between a dysfunctional MNS and ASD which can also

detract from their substantial correlation. Potential insignificance exists between the correlation of a dysfunctional MNS and ASD. In a series of action observation and imitation activities performed both by ASD and typically developing individuals, their results from the performances failed to prove a significant difference between the activity in the brain measured by mu suppression between the two groups. Both groups displayed similarity in their mu suppressions. For the ASD individuals, a significant correlation between the activity of an area of the brain where MNS functions of observation and imitation are localized to and Chinese social communication scores was not determined; the relationship appeared to be of the norm when compared to that of the typically developing children (Ruysschaert et al., 2014).

Conclusion

In the future, research can aim to extend beyond the causation of MNS dysfunction for ASDs to other systems. Systems besides the MNS such as the mentalizing system should be closely examined in ASD individuals. This should take place because of evident levels of crosstalk recorded between the MNS and mentalizing system. Conducting further ethical experimentations on ASD individuals to examine the simultaneous activity of these other systems and the MNS, could resolve the margin of uncertainty around the link between the roots of ASDs and a faulty MNS. Additionally, certain limitations exist within the relationship between MNS and ASDs that merit further research. One such limitation is the missing correspondence of structural differences to the inhibition of any MNS functions. If evidence can be discovered for this pattern, then the strength of the greater correlation between an atypical MNS and ASDs will be advanced.

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