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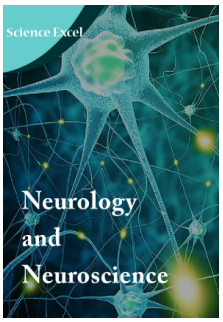

The Role of Mirror Neuron System (MNS) in Autism Spectrum Disorders (ASD)

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Abstract

The Mirror Neuron System (MNS) is a group of specialized neurons that discharge when an individual performs an action or observes another individual performing the same activity. This system is divided into two principal hubs; the premotor area in the frontal lobe and inferior parietal lobule(IPL). Mirror neurons play an essential role fundamentally in human social interaction, such as action observation, imitation, understanding the emotions of others, and a myriad of other sophisticated human behavior and thought processes as well as the theory of mind. Since people with Autism Spectrum Disorders (ASD) have disorders and defects in communication, social interaction, the theory of mind, etc . So it can be suggested that defects in the mirror neuron system (MNS) may be linked to disorders like ASD and also play an essential role in this phenomenon. In this review, we discuss this connection.

Introduction

Mirror neurons were accidentally discovered in monkeys in 1992, and given their evocative name 4 years later [1,2]. The mirror neuron system (MNS) is a network of neurons that discharge both when an individual executes a motor act and when he observes another individual performing the same or a similar motor act. The mirror neuron system is divided into two principal hubs; the Premotor area in the frontal lobe and the inferior parietal lobule (IPL) [3,4]. In general, the superior temporal sulcus (STS) is considered a key area of MNS [5].

Mirror neurons were first discovered in area F5 of the ventral premotor cortex (PMv) in the macaque monkey [1,2,6]. These neurons are selective for the execution of a specific motor act, such as precision grasping. They also activate when the monkey observes another monkey or a human executing the same action.

Some neurons called "canonical neurons" are located in the area F5p (posterior F5) and respond to the presentation of objects, such as when the monkey grasps the object [7,8]. The F5p is also known as a hand-related area that encodes goal-directed actions. Both motor and mirror neurons are located in the dorsal area of F5 (the F5 convexity) (F5c) and they fire during both observation and execution of specific goal-directed actions involving hand and mouth [9].

In macaques, the frontal mirror area of the brain is divided into the lateral surface area 4 (primary motor cortex; M1), the caudal part of area 6 (also a part of M1), medial surface area 6 (supplementary motor area; SMA) and premotor area. The premotor area is divided into caudal part (PMc)—with a direct connection to subcortical areas—and the rostral part (PMr) which indirectly affects motor generation. The F5 area is a part of the parietal-frontal and prefrontal-frontal networks [10].

Kraskov et al. found that pyramidal tract neurons (PTN) in the F5 region were not active during visual observation, but were stimulated and discharged during execution [11]. When was recorded a signal from PTN in the area F1, Vigneswaran et al. found that some pyramidal tract neurons (PTN) are more active during action observation [12].

Early studies on mirror neurons showed that these neurons are engaged in the execution of an action, understanding the intention and purpose of action, and the transformation of visual perception into the action execution. These studies report that the ventral premotor cortex (PMv) is connected to the caudal part of the inferior frontal gyrus (IFG). The inferior frontal gyrus (IFG), also known as Broca's area, is a motor speech-production area for language generation [13,14]. Parts of the mirror neuron system were also discovered

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in the inferior parietal lobule (IPL) of the macaque's brain [15]. Mirror neurons in the inferior parietal lobule (IPL) activate both during observation and execution of complex actions such as grasping an object and placing it in the target location or eating it [16]. The inferior parietal lobule (IPL) receives visual information from the eyes and somatosensory information from the mouth, hands, and arms [17]. This suggests that visuo-motor organization of the IPL likely forms the neural basis of the ability to perceive the action intention of others [18]. Researches reveal that the superior temporal sulcus (STS) also has mirror properties and responds to biological movements [19-21].

STS is responsible for the connection between visual and auditory information and movement. That is, creating an integration between seeing, hearing, and doing [22]. The F5 area is connected to the higher-order visual areas of the STS through the inferior parietal lobule (IPL) [4]. STS is considered a part of the temporal-parietal-premotor pathways and the mirror neuron system (MNS) [23,24]. Experiments comparing execution, imitation, observation, and imagination conditions using various neuroimaging techniques have revealed a network of the MNS [24-27].

The defining feature of mirror neurons is that when the monkey performs an action or witnesses another individual executing that action, they conduct an electric discharge [2,28].

Since their discovery in the ventral premotor cortex (F5) of the macaque monkey, cells with mirror-like properties have been identified in the parietal areas, dorsal premotor cortex (PMd), and even M1 [12,18,29-34].

Therefore, the mirror neuron system (MNS) is located in the parietal-frontal network to coordinate the implementation of visually guided comprehension [35-38]. Mirror cells in area F5 often show similar levels of activity during action execution and observation [2,11]. However, the mirror cells of the M1 area show a decrease in activity and electric discharge during observation compared to the execution of the action [12,39]. While the roles of F5 and M1 regions during the execution of visually-guided grasp have been studied extensively [40-42] a more systematic understanding of the differences between action execution and observation activity in these key areas in the grasping circuitry could provide significant insights into dissociations between the representation of potential actions at the cortical level, and recruitment of descending pathways and muscles for actual action execution [43]. In this regard, recent investigations regarding the mirror neurons of the premotor cortex and the motor cortex have shown that the mirror neurons of the premotor cortex revealed similar changes during action and observation. But such a situation does not occur in the case of motor cortex mirror neurons (M1 area) [44].

Based on these findings, it can be concluded that mirror neurons are involved in a range of actions that are the basis of social behavior, such as observation, imitation, and understanding the feelings of others and in the theory of mind (which will be explained in the following section). Since people with autism spectrum disorders (ASD) also show these symptoms such as deficits in communication/interaction, it seems that MNS defects may play an important role in this disorder. In this research, we discuss this connection.

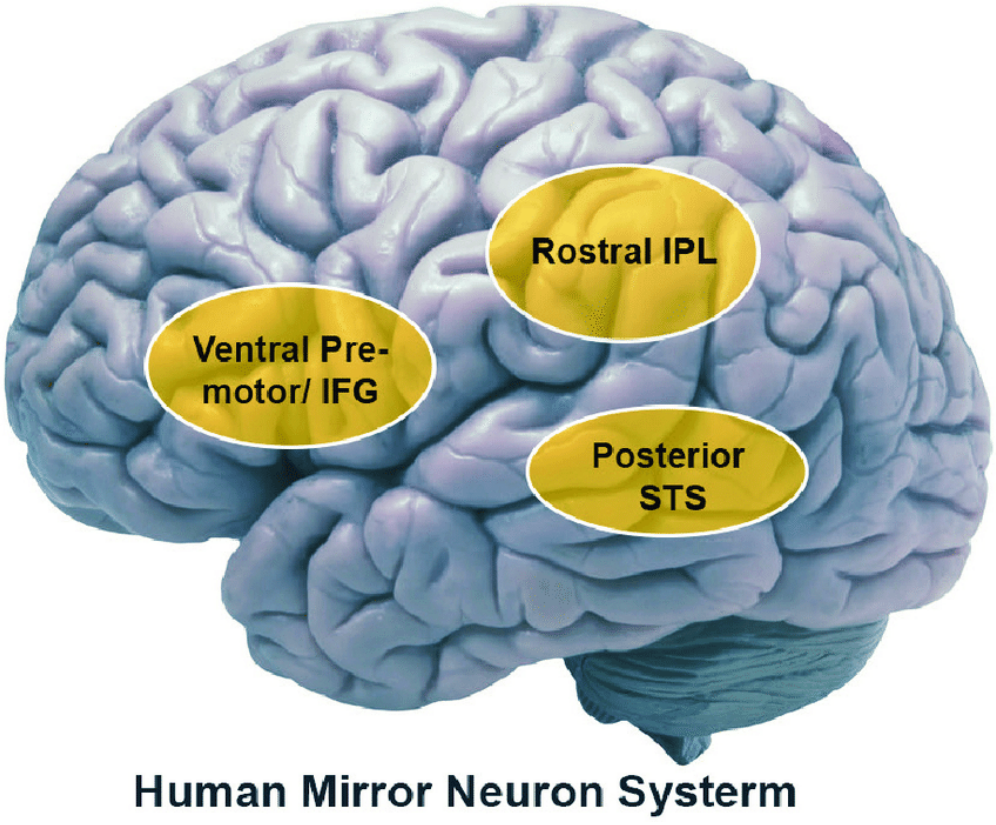

Figure 1. *Figure of the mirror neuron system (MNS) (45)*

Autism Spectrum Disorders (ASD)

Autism spectrum disorder (ASD) was first described in the early 1940s by psychiatrists and pediatricians in different countries. Leo Kanner, an Austrian physician (1943) described eleven children with the characteristics of social isolation, insistence on monotony, delayed speech, or odd language (46). Then Hans Asperger (1944) described four children with the characteristics of abnormal social interactions, special interests, with normal verbal abilities. He called these children the "Little Professors" [47]. Later, Frith (1989) compared these different descriptions of autism spectrum disorders (ASD), and formed the foundation for the conceptualization of autism spectrum disorders [48]..

Autism spectrum disorders are a group of disorders characterized by impairments in communication, social interaction, restricted interests and repetitive behaviors [49]. In the United States, about 1 in 59 children has been identified with autism spectrum disorders (ASD) at the age of 8 [50].

Key and main characteristics of ASD

Social and communication deficits: In DSM-IV (APA,1994) and ICD-10 (WHO,1990) social and communication defects in autism are mentioned as separate symptoms [51,52].The existing diagnostic criteria differentiate communication defects such as severe delays in expressive language from social defects. But research on the behavioral symptoms of ASD shows that several communication defects in ASD such as limited participation in social conversation, problems in mutual conversation with others, and limited gestures include both social factors and communication factors [53].

Moreover, recent studies have indicated that it is more valid and accurate to consider social and communication symptoms together as one, not two separate factors [54,55].

There are several aspects of communication disorders in ASD beyond speech disorders or language delays. people with ASD also often have difficulties communicating nonverbally, such as through hand gestures, eye contact, and facial expressions. Abnormal speech patterns are common in people with ASD, for instance, they don't follow certain grammatical rules. There is also a tendency to use repetitive speech patterns such as stereotyped speech or delayed echolalia [56].

Restricted and repetitive behaviors and interests (RRBs)

Restricted and repetitive behaviors and interests(RRBs) have long been considered one of the core features of autism. According to the DSM-5 criteria for ASD [57], repetitive and restricted interests and behaviors (RRBs) include a very broad category of behaviors such as intense intellectual interests and preoccupations (e.g. having very specific knowledge about vacuum cleaners), adherence to specific and non-functional repetitive behaviors (e.g. insisting on going to school along a certain route), repetitive motor behaviors (e.g. hand waving), and intellectual preoccupations with parts of objects (e.g. looking carefully and paying attention to the wheels of a toy car while rotating).

According to the person's age, many of these examples of repetitive and restricted interests and behaviors (RRBs) are abnormal. However, some young normal children and children with other developmental disorders other than ASD do manifest some of these behaviors during infancy and childhood (58,59,60). For instance, some children with other developmental disorders such as intellectual disabilities without autism show some types of restricted and repetitive behaviors and interests(RRBs) such as sensory interests and unusual complex behaviors. This type of RRBs is known as "lower-order" RRBs, which is related to lower-order intellectual behaviors [61].

Although RRBs could be observed in non-autistic children, these symptoms are significantly more common and severe in children and adolescents with ASD between the age of one to twenty years compared to those with other developmental disorders or normal children and adolescents [59,62,63].

Mental Retardation (MR) and ASD

Although there are frequent claims in the literature that a majority of children with autism are mentally retarded (MR), recent findings have shown that 29-60% of children with autism spectrum disorders are in the normal range of non-verbal IQ [64,65]. There is a great diversity in developmental trajectories and their consequences for children with ASD, however, nonverbal intelligence is one of the best prognostic indicators for this disorder [66,67]. Therefore, information about the cognitive abilities of autistic children plays a crucial role in planning their future (treatment and improvement).

As with nonverbal skills, language abilities vary widely among children and adults with ASD. It was estimated that the majority of autistic children were non-verbal or minimally verbal, but this has changed dramatically with the diagnosis of mild cases of this disorder and also more access to early language interventions.

A study on children with severe ASD demonstrated that about 40% of them showed complex fluent speech and less than 15% were completely nonverbal by the age of 9. These results contradict previous studies claiming that 50% of children with ASD are completely non-verbal [68].

Assessment of social and communication disorders at different language levels, from non-verbal language to fluent and advanced language level, requires expertise with different tools. Moreover, investigating and evaluating social and communication disorders requires a comprehensive understanding of the behaviors related to the autism spectrum. It is important to know that non-ASD people with limited speaking skills use nonverbal forms of communication such as gestures and eye contact to initiate social interactions. Therefore, understanding different types of communication, as well as developmental disabilities, is necessary to identify autistic behavioral patterns and distinguish ASD from other disorders [69].

Imitation

Imitation is a crucial aspect of skill development and one of the important ways of learning and transferring culture, which is strongly related to high-level cognitive functions such as language and the ability to understand our own and others' mental states [70]. Impaired imitation in children with autism was first reported in the early 1950s [71]; however, these findings had little impact on autism research for years. After the recent article of Rogers and Pennington, interest and attention to imitation deficits in autistic individuals has expanded [72]. In addition, recent findings and discoveries in neuroscience have revealed ideal neural mechanisms for imitation.

Although neural circuits underlying imitation in humans are not well studied in individual neurons, they are investigated by techniques such as EEG, magneto encephalo graphy (MEG), transcranial magnetic stimulation (TMS) ,changes in blood flow,

blood oxygenation, positron emission tomography (PET), and functional magnetic resonance imaging (fMRI), which measure the integrated activity of a large group of cells.

Another method is studying neural mechanisms of imitation through neurological samples from patients with brain lesions in-vitro or in-vivo, which examines a large number of neurons. The classic approach is the neuropsychological study of imitation deficits in patients who have suffered brain lesions either naturally or as a result of surgical removal. A more recent approach is to use repetitive transcranial magnetic stimulation (rTMS) which can generate transient lesions in the stimulated brain areas and examine the resulting behavior [73].

ASD and Theory of Mind

There is a lot of evidence demonstrating that people with ASD also exhibit disorders related to the "theory of mind". This theory is defined as the ability to attribute mental states to others and oneself to explain and predict behavior [74]. Attributing mental states is the process of perceiving and interpreting other people's behavior in terms of their mental states, which is considered a natural way by which we understand the social world. Among existing cognitive models of ASD, the theory of mind (ToM) has had a significant influence on research and treatment [75]. Impairment in ToM ability is often seen in children with autism. Inefficient "mind reading" affects the development of social, communication, emotional and imitation skills. Many therapeutic interventions include teaching skills related to the theory of mind. Such interventions often provide psychoeducational problem-solving therapies related to the individual's perspective. Studies have shown that people with ASD can be trained to pass basic theory of mind tasks. These training are conducted through various methods such as computer feedback, peer-to-peer training, and group programs [75-79].

The primary dysfunction of the mirror neuron system (MNS) causes the defects observed in the theory of mind of people with ASD [80]. The mirror neuron system (MNS) plays a crucial role in observing and imitating actions, as well as in understanding the emotions of others. Neurophysiological and neuroimaging studies revealed that MNS is located in the Pars opercularis area, a part of the inferior frontal gyrus (IFG), and the posterior parietal cortex area [4,81-84].

A controlled study by Dapretto et al. (2006) investigated MNS activity during imitation and observation of facial emotional states in children with ASD using fMRI. No MNS activity was observed in the pars opercularis area of the IFG in the autism group compared to the control group [80].

In this regard, Williams et al. (2006) showed that MNS activity is inversely correlated with social dysfunction. Functional brain abnormalities such as reduced MNS activity were associated with impaired imitation in adolescents with ASD compared to the control group [85].

These findings suggest that the development of imitation tasks in people with ASD negatively affects the development and expansion of the theory of mind in these people [86].

Mirror neuron hypothesis in autism spectrum disorderss

Since mirror neurons are involved in a wide range of activities underlying social behavior, some researchers have suggested that autism spectrum disorders may be related to mirror neuron dysfunction [87]. There are positive findings providing evidence in support of this hypothesis using different methods.

Some studies have shown anatomical differences in mirror neuron regions between subjects with autism compared to subjects without autism [88]. Other studies have shown EEG differences in fading mu rhythm as a parameter of mirror neuron activity [89,90]. For example, Oberman et al. (2005) reported that in the ASD group, mu wave suppression during execution of the operation was similar to the control group, but during observation of the operation, the attenuation of the mu wave was reduced compared to the control group. However, there was a significant attenuation in the mu wave during both movement observation and movement execution in the control group [89]. Bernier et al. (2007) also reported that in people with autism, the amount of attenuation of the mu wave during movement observation was less than the control group [91]. Martineau et al. (2008) studied 5-7-year-old children with ASD and showed mu wave suppression during action observation in normal children, and not in children with ASD [92].

Hari et al. (2000) used the MEG method during the task of imitation of facial expressions and observed a slight difference in the timing of MEG components in people with autism compared to normal people, especially in the IFG region [93].

Research by Nishitani et al. (2004) using the MEG method showed delayed cortical activity during imitation task in people with ASD [94]. Honaga et al. (2010) also examined the dysfunction of the mirror neuron system in people with autism using the MEG method (95). Williams et al. (2006) showed differences in the activity levels of mirror neuron regions between subjects with autism in comparison with subjects without autism [85].

Moreover, a study by Dapretto et al. (2006) using fMRI on normal children and children with autism spectrum showed that children with ASD showed less activity in the insula and amygdala region and mirror neuron areas while imitating and observing emotional facial expressions [80].

Discussion and conclusion

The mirror neuron system (MNS) is a network of specialized neurons discharge when a person performs an action or observes an action performed by another. The mirror neuron system is divided into two main hubs; the Premotor area in the frontal lobe and the inferior parietal lobule (IPL) [3,4]. In general, the superior temporal sulcus (STS) is considered a key area of the MNS [5]. Studies on mirror neurons have shown that they are actively engaged in the observation and execution of actions, understanding intentions and meaning, transforming visual perception into action, imitation, and also understanding the emotions of others [13,14]. Since mirror neurons play a significant role in a variety of activities underlying social behavior, such as observation of action, imitation, and understanding the emotions of others, and in the theory of mind, some researchers have proposed that autism spectrum disorders (ASD) may be related to dysfunction of mirror neurons. In this regard, we can mention studies of Hari et al. (2000), Nishitani et al. (2004), Oberman et al. (2005), Dapretto et al. (2006), Williams et al. (2006), Bernier et al. (2007), Martineau et al. (2008) and Honaga et al. (2010) [80,85,89,91-95).

Autism was first officially identified as a spectrum disorder in the early 1940s by psychiatrists and pediatricians in different countries. An Austrian physician Leo Kanner (1943) described 11 children with a desire for aloneness, obsessive insistence on persistent sameness, social isolation, monotonous repetitions, language delay, or abnormal speech [46] .Autism spectrum

disorders are characterized by impairment in communication and social interaction, stereotyped ,restricted and repetitive behaviors and interests (RRBs) [49]. Language delays in people with ASD are not compensated by nonverbal communication methods such as eye contact, gestures, and facial expressions. People with ASD have receptive and expressive language impairments. There are also issues and problems related to speech such as abnormal use of pitch, intonation and rhythm. Besides, they have a tendency to use repetitive speech patterns such as stereotyped speech or delayed echolalia [56].

Another association between autistic spectrum disorder and the mirror neuron system (MNS) might result from imitative impairment. "Imitation" is an important way of learning essential to many socio-cognitive abilities such as the transmission of human culture, and is strongly related to high-level cognitive functions such as language and the ability to understand the minds and thoughts of others [70] and as mentioned, mirror neurons play an important role in the imitation process. Studies from the early 1950s have shown that people with autism have certain deficits in the imitation process, which suggests the role of the mirror neuron system (MNS) in autism spectrum disorders [71].

Another finding that highlights the role of the mirror neuron system (MNS) in autism spectrum disorders is the "theory of mind" (ToM). This theory is defined as the ability to attribute thoughts, desires, and intentions to self and others, to predict or explain the behavior and actions. There is a lot of evidence showing that many people with ASD have disorders related to the "theory of mind" (74). Impairment in the ability to understand the minds of others is related to the main symptoms of ASD. Inefficient "mind-reading" affects the development of social, communication, emotional, and imitation skills [75-79]. Data shows that the primary dysfunction of the mirror neuron system (MNS) is the underlying factor for the defects in the theory of mind observed in people with ASD [80]. Thus, this can indicate another role of the mirror neuron system (MNS) in autism spectrum disorders.

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