Personal View

Mirror neuron dysfunction in autism spectrum disorders

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Article info

Article history:
Received 6 July 2009
Accepted 17 January 2010

Keywords:
Autistic disorder
Autism spectrum disorders
High functioning autism
Inferior frontal gyrus
Inferior parietal lobule
Mirror neurons
Mu rhythm

Abstract

Autism spectrum disorders (ASDs) are developmental conditions characterized by deficits in social interaction, verbal and nonverbal communication and obsessive/stereotyped patterns of behaviour. Although there is no reliable neurophysiological marker associated with ASDs, dysfunction of the parieto-frontal mirror neuron system has been suggested as a disturbance linked to the disorder. Mirror neurons (MNs) are visuomotor neurons which discharge both when performing and observing a goal directed action. Research suggests MNs may have a role in imitation, empathy, theory of mind and language. Although the research base is small, evidence from functional MRI, transcranial magnetic stimulation, and an electroencephalographic component called the μ rhythm suggests MNs are dysfunctional in subjects with ASD. These deficits are more pronounced when ASD subjects complete tasks with social relevance, or that are emotional in nature. Promising research has identified that interventions targeting MN related functions such as imitation can improve social functioning in ASDs. Boosting the function of MNs may improve the prognosis of ASDs, and contribute to diagnostic clarity.

1. Introduction

Autism spectrum disorders (ASDs) are pervasive, developmental, neurological conditions which adversely impact behaviour in three key domains: social interaction, verbal and nonverbal communication, and obsessive and/or stereotyped patterns of behaviour. Abnormal or impaired social interaction is characterized by deficits in joint attention, reciprocity, imitation, empathy, relationships, as well as hyperactive/impulsive behaviour and social anxiety. Communicative deficits in language include odd prosody, failure to understand metaphors or statements with implied meaning, idiosyncratic use of words and delayed speech development. Obsessive interests and stereotyped patterns of behaviour including an intense interest in a particular subject matter, preoccupation with small details as opposed to global functioning, inflexible adherence to non-functional routines and rituals, and abnormal motor and sensory functioning. Although presentation varies considerably across individuals, these core characteristics are defined as deviant relative to the individual’s developmental level.

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM IV-TR), describes two major ASDs: Autistic disorder (AD) and Asperger's syndrome (AS). Although subject to ongoing debate, AS is diagnostically differentiated from AD on the basis of normal language development, defined as expression of single words by age 2 years and communicative phrases by age 3 years. Where intellectual functioning is not impaired (IQ > 70–85) in AD, the condition is termed high functioning autism (HFA). A meta-analysis of 43 studies estimates the prevalence of autism (AD and HFA) to be approximately 0.13% of the population, and AS 0.03%.

To date, an important issue confronting clinicians and researchers is the absence of definable and reliable, neurophysiological markers to the disorder. Diagnosis is made on the basis of behavioural symptoms, which reduces diagnostic clarity and limits the capacity to identify these conditions early and accurately. In 1999, two research groups independently suggested that a network of visuomotor cells known as mirror neurons (MNs) may contribute to some of the key symptoms that characterize autism.

2. Mirror neurons

MNs are activated by the performance or observation of object or goal directed actions. What distinguishes MNs from other motor neurons is they not only discharge when an individual performs a particular action (such as reaching for a piece of food), but also...
when an individual watches somebody else perform a similar action (such as a friend reaching for a piece of food).\textsuperscript{8}

Studies in primates have identified a MN system consisting of the ventral premotor cortex (area F5) and inferior parietal lobe (IPL).\textsuperscript{9} Although MNs have not been directly observed in humans, there is indirect evidence that MNs may exist in homologous areas. These are the ventral premotor cortex, IPL, and inferior frontal gyrus (IFG; which corresponds to the pars opercularis).\textsuperscript{10} This network has been named the parieto-frontal mirror system.\textsuperscript{9} A large body of evidence using fMRI has identified activity in these regions when observing motor actions such as grasping an object.\textsuperscript{11–16}

3. Mirror neuron dysfunction in autism

3.1. Initial theory

Prior to the discovery of MNs, a theory was penned that suggested a deficit in self-other matching contribute to autism.\textsuperscript{17} This ability involves forming and coordinating mental representations of the self and others. Understanding others behaviours and social rules is achieved by extracting patterns of similarity between the self and other. It has now been acknowledged that this theory of autism is similar to the key role of MNs. Disruption of MN functioning may contribute to this self-other matching deficit.\textsuperscript{7} However, it is unlikely that this alone would account for the entire presentation of autism. We argue here that MN function may constitute a neurophysiological marker of autism.

MN deficits were first thought to be linked to autism due to their purported role in behaviours and abilities that are commonly disturbed in autism. The first studies of MNs by Rizzolatti and his colleagues identified their key function as most likely facilitating understanding of motor actions.\textsuperscript{9} Because the same pattern of MNs are activated when performing or observing an action, primates can recognize the goal of a motor act performed by others.\textsuperscript{6} More recent evidence suggests that this execution/observation matching system may have evolved conjointly with other networks to allow for more complex functions in humans. These include, imitation, empathy, theory of mind and language,\textsuperscript{18} all of which can be disturbed in autism.

3.2. Imitation and empathy

The ability to imitate the actions of others is commonly disturbed in autism.\textsuperscript{19} Neuroimaging studies in normal individuals have furnished evidence of a role for MNs in motor imitation. One study used repetitive Transcranial Magnetic Stimulation (rTMS) to disrupt function in particular cortical areas during imitative tasks. The authors identified a significant increase in error rate during imitation when either the left or right pars opercularis was activated.\textsuperscript{20} In other words, disruption of an area believed to be populated with MNs led to a decrement in imitative performance. Other studies support the hypothesis that MN areas are involved in imitation.\textsuperscript{21–23}

Empathy refers to the ability to understand and vicariously experience the emotional state of others. Empathy is linked to imitation, and is commonly disturbed in autism.\textsuperscript{24} Those with autism have more difficulty interpreting others emotions such as discriminating between a sad and happy face.\textsuperscript{25}

Anatomical studies have revealed connectivity between the dysgranular field of the insula and the frontal and parietal MN areas.\textsuperscript{26} Further, insula neurons with mirror-like properties have been identified. Utilizing fMRI on 14 healthy males, overlap of activity in the insula was found whilst subjects inhaled a foul smelling odorant (execution condition), and when they watched a video of someone emotionally expressing disgust (observation condition).\textsuperscript{27} Two other studies have found similar concordance of neural activity between the performance and observation of disgusting stimuli.\textsuperscript{28,29} A study in which subjects had to identify or imitate faces depicting six emotions (happy, angry, sad, surprise, disgust and fear) also found increased activity in MN areas.\textsuperscript{30}

Although this research base provides evidence for mirror-like activity, the methodology of correlating brain activity to a task does not necessarily prove whether MNs are involved.

3.3. Theory of mind

MN have been linked to theory of mind (TOM) abilities. TOM requires an inference of what other people are thinking, and allows people to evaluate the behaviour of others within the context of their mental states. This includes their goals, desires, emotions and opinions.\textsuperscript{4} Impaired TOM is a prominent cognitive theory of autism, with a large body of research identifying TOM deficits among those with autism.\textsuperscript{31–33} The possibility that MNs have a role in TOM has yet to be directly tested. However a theoretical link has been made. Proposed more than a decade before the discovery of MNs, this theory suggests people use their own mental representations to predict and comprehend the mental processes and behaviours of others.\textsuperscript{34} Indirect attempts to support this claim have been undertaken with limited success to date,\textsuperscript{35} yet these have not directly assessed the hypothesis that MNs are involved in TOM. Nonetheless, recent research has identified MNs can selectively respond to specific intentions in both monkeys and humans, indicating that they are involved in the internal representation of another.\textsuperscript{36,37}

3.4. Language development and communication

A more speculative link has been made between MNs and language development. A broad range of language deficits can occur in autism, and form part of the diagnostic criteria.\textsuperscript{18} Communicative MNs have been discovered in the lateral region of area F5 of Macaques (homologous to Broca’s area).\textsuperscript{39} These cells respond to performed or observed actions with communicative intent such as tongue protrusion or lip-smacking.

Additionally, MNs with audio properties in Macaques have been identified.\textsuperscript{40} A substantial number of MNs fired in response to a goal directed action (such as breaking a peanut) and also to the sound itself with the action out of sight. It has been speculated that MNs that match observed and executed actions with communicative significance provided a basis for gestural communication.\textsuperscript{41}

4. The case against mirror neurons

Despite this promising research base, numerous criticisms have been made toward the study of MNs in humans. Firstly, MNs have yet to be directly observed in humans.\textsuperscript{42} Secondly, MNs make up a small minority of observed cells in Macaques (approximately 6%; yet the distribution in humans remains unknown),\textsuperscript{3} which means interpretation of homologous areas in humans is not exclusively measuring suspected MN activity. Thirdly, it has been suggested that an exclusive MN explanation of imitation is too simple for such a complex ability.\textsuperscript{43} Fourthly, movement selectivity (a key characteristic of MNs) has not been adequately assessed in humans.\textsuperscript{44} It is worth noting these issues raised are predominantly methodological in nature.

5. Evidence for mirror neuron dysfunction in autism

5.1. Electroencephalograph (EEG)

One method to investigate MN activity in humans is via EEG. The mu wave measures large amplitude oscillations of the synchro-
nized activity of sensorimotor neurons.55 Whenever a voluntary movement is made, these sensorimotor neurons are desynchronized by input from pre-motor neurons (an area believed to house MNs), which blocks the mu wave. Of interest, it has been found that the mu wave is also blocked or suppressed when a person observes another individual performing a voluntary motor action.46 Thus, it has been proposed that when an individual watches someone else perform a motor action, the mu wave is blocked due to input from pre-motor MNs.45

If MNs are in some way abnormal in those with autism, it could be hypothesized that those with autism may lack the normal mu response (that is, that mu wave suppression will be absent or reduced when persons with autism observe a goal directed motor action, but not when completing the action itself). A recent study utilized this methodology to compare a group with HFA (N = 10) to controls (N = 10).35 EEG measures were taken whilst subjects watched a bouncing ball (control condition), a hand moving (observation condition), or moving their own hand (execution condition). Control subjects showed significant mu wave suppression during observed and performed hand movements, whilst HFA subjects only showed significant suppression during performed hand movements. This provides indirect evidence that MN activity was reduced in the HFA group, as sensorimotor activity was not suppressed by (assumed) MN activity during observation.45 This finding has recently been replicated.47

A similar finding has been made with a slightly more elaborate design.48 Subjects with HFA (N = 14) and age matched controls (N = 15) were required to observe a videotaped model perform simple hand movements and facial expressions. Following the single trial of each gesture, they were required to imitate that action. Compared to controls, those with HFA poorly completed the imitated actions. Similarly to past MN research using the mu wave,6,47 suppression was significantly reduced in those with HFA in the observation condition. Moreover, poorer imitation skills were correlated with reduced mu suppression in those with HFA. This was particularly the case for facial expressions compared to motor tasks (r = 0.63). This result suggests that abnormal MN activity in those with autism is more pronounced for tasks with social relevance.

A recent study has considered the possibility that MN tasks with social relevance are more likely to be disturbed in autism.50 These authors tested whether familiarity with the person performing a basic motor act (social relevance) had any influence on mu suppression. Subjects observed a video of a stranger, a parent or their own hand performing a motor action. The control group showed significant suppression for all three conditions, with slightly less suppression to a stranger’s hand. Interestingly, the ASD group showed significant suppression when observing their own or a parent’s hand, but not when observing a stranger’s hand. This finding suggests MN activity was only disturbed in the ASD group when the material was deemed to be socially unfamiliar (a stranger). However, interpretation of this result is problematic. It may be that the preserved MN activity toward familiar people is due to other brain regions that modulate MN activity. A stranger may simply be insufficiently stimulating to an individual with autism.

There are two important points that need to be made regarding EEG research as an indicator of MN activity. First, abnormal mu suppression by EEG has not always been established in samples of persons with autism.50 Second, the mu rhythm is an indirect indicator of possible MN activity. Because it is measuring desynchronization of sensorimotor neurons by the pre-motor cortex, it is an indirect inference that this reflects MN activity.

5.2. Functional magnetic resonance imaging studies

Functional MRI (fMRI) has been used to investigate mirror neuron functioning in autism. Typically, the blood oxygen level depen-
more sensitive deficits, such as slower processing of motor actions due to a disturbed self-matching mechanism.

6. Conclusions and future directions

In summary, there is evidence that brain regions believed to house MNs can be structurally and functionally disturbed in individuals with autism. Although it is premature to interpret findings with such a small research base, the current evidence suggests that MN disturbance is pronounced when information is of a social and emotional nature, or requires discrimination of different items (such as motor acts, or facial emotions). Abnormalities in MN areas have been strongly correlated to social deficits in autism.51–53 Similarly, MN deficits among those with autism have been found to only be present when the person performing the action was unfamiliar to them,48 or when discriminating between different facial emotions.51

A relatively recent hypothesis is that autism is characterized by faulty connectivity between brain regions in the cerebral cortex.55 Overall reduced connectivity between the frontal and parietal lobes has been identified; where the human MN system is believed to reside.56 This may mean that for certain abilities in particular autistic patients, faulty connectivity is responsible for disturbance in the MN system. This would help explain the mixed findings on the role of MN areas in autism, as the disturbance would depend on the specific damage to connectivity. We don’t argue that MNs will account for all the symptomatology in autism, rather that they are a possible neurophysiological marker. Theoretical integration of the under-connectivity and MN theories, in addition to investigation of other networks implicated in autism (such as the default mode network)57 may provide a more thorough account of autistic symptoms.

Deficits in the parieto-frontal MN system characterized by abnormal connectivity may be the first reliable neuro-anatomical marker associated with autism. This may pave the way for targeted treatments that look to improve functioning in autism. MN functioning in healthy individuals is plastic, and can be developed or enhanced through sensorimotor learning tasks.58 Moreover, recent evidence suggests that interventions focusing on imitation skills can be effective in developing specific skills in autistic children. Teaching autistic subjects imitation skills can improve their language, joint attention and pretend play skills.59 Moreover when adult experimenters imitate the behaviours of autistic children, it can lead to an improvement in joint attention, vocalization and smiling.60 Although the efficacy of these effects was not assessed long term, these studies provide evidence that learning tasks which involve MNs can lead to an improvement in autistic symptoms.

It is unlikely that MN deficit is responsible for all symptoms of the disorder (such as routine and ritualistic behaviour). However, if it is proven MN activity (in conjunction with other motor and sensory systems) is necessary for particular abilities such as imitation, diagnostic clarity will be improved. With greater understanding of the networks MNs belong to, it may be identified that MN deficit in autism is subsumed by a broader deficit.

References