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What is True About the Mirror Neuron System; Reflecting on Previous Evidence Regarding Mirror Neuron Function, Empathy and Autism Spectrum Disorder

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Abstract

Mirror neurons (MNs) are cells that fire during both action execution and observation. It has been researched extensively and the mirror neuron system was hypothesized to be involved in many processes such as action understanding, imitation, intention understanding, speech perception, and even empathy. However, there is an ongoing debate about whether there is enough evidence to make these assumptions. This paper critically reviews MN function, especially looking deeper into the role of MNs in empathy and whether dysfunction in this system could lead to autism spectrum disorder. The literature seems to agree on the function of MNs in action understanding and imitation, but there is mixed evidence about their function in intention understanding and speech perception. Although functional neuroimaging techniques indicate a role for MNs in empathy, the reliance on this evidence is heavily debated. These techniques do not provide information on a cellular level and are rather correlational instead of causational. Single-cell studies provide more insight into individual neurons but are challenging to perform in humans. Lesion studies provide causational evidence, but the evidence is rather mixed around the role of MNs in empathy. Ultimately, it is important to keep in mind that empathy is a complex, multidimensional phenomenon, with probably multiple neural mechanisms underlying it. In addition, there is much disagreement about “the broken mirror theory”. This theory states that dysfunction in the mirror neuron system results in autism spectrum disorder, and interpretation of mixed evidence varies among neuroscientists. In the end, there is no substantial evidence to conclude the relationship between MN dysfunction and autism but can be concluded that MNs are involved in empathy, although a causal role remains unclear and should be further explored.

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1 Introduction

32 years ago, mirror neurons were initially described in macaque monkeys by Di Pellegrino and colleagues (1992), who found specific neurons that fire not only during action execution but also during observation of the same action (like a mirror). Four years later, the same research group gave the neurons their evocative name; mirror neurons (Gallese et al., 1996). Subsequent neuroimaging techniques have confirmed the existence of mirror neurons in humans, implicating their involvement in action understanding, imitation, and even social behavior (Rizzolatti and Craighero, 2009). Given the importance of social interactions in human health and survival, understanding the neural mechanisms underlying social behavior is crucial, yet it remains limited (Young, 2008). Not surprisingly, the discovery of mirror neurons sparked a lot of interest among researchers, leading to interesting claims and newspaper headlines, such as “*Cells that Read Minds*” in 2006 by Blakeese, or “*What Makes Humans Social*” in 2008 by Lehrer, and finally, Ramachandran claimed in 2009 that “*mirror neurons will do for psychology what DNA did for biology*” (Heyes and Catmur, 2021). Of course, the whole discovery of mirror neurons was exciting since it led to a new way of reflecting on our actions and understanding others. Mirror neurons may even explain the puzzling phenomenon of empathy and a deficit in them may underlie autism spectrum disorder. However, these relationships are not well established due to limited empirical evidence and methodological challenges. Therefore, it is necessary to review previous papers about mirror neurons critically, especially those about the role of mirror neurons in empathy.

2 What is empathy?

Empathy is a complex social phenomenon and there is no one exact definition. Neuroscientists view empathy as the matching of emotions of two people; an ‘agent’ and a ‘target’, wherein the agent’s response matches that of the target (“I feel what you feel”) (Heyes, 2018). Humans not only perceive basic emotions (sadness, anger, joy, etc.) but also more complex ones like guilt, love, and embarrassment (Singer, 2006). But what is empathy precisely? This is also a complex question in philosophy. Is it a way of understanding others, or is it just a feeling? These two might seem similar, but there are differences in the way the agent adopts the target’s emotions. There are four (slightly) different ways to emphasize; emotional contagion, perspective-taking, affective empathy, and sympathy. Firstly, emotional contagion. This is an emotional state caused by observing someone else’s affective state. It is a form of perception (“I see you cry, now I feel sad”). Simply, it is catching the feeling of someone else. This paper will mention several papers that use emotional contagion as a measure of empathy. Secondly, perspective-taking. This is a psychological understanding by mentally placing oneself in another’s position. However, there are numerous ways to psychological understanding, either with or without emotional sharing. Psychological understanding without personal involvement (like sharing emotions) is also called theory of mind, and can not be used interchangeably with empathy, which does entail emotional sharing between agent and target. Thirdly, affective empathy involves perceiving and sharing another’s emotions more broadly. The agent can acquire information about the target’s situation and assume their emotional state. Sometimes affective empathy leads to more self-focused emotional responses instead of other-focused ones. It might become confusing whom the emotion is experienced for; self or other. Questions arise whether this state is still empathy or more personal distress. Lastly, the focus on empathy can be on the general well-being of the other person, rather than their immediate emotions. We experience sympathy (also known as empathetic concern) when our emotional response matches the other person’s welfare (for example, I feel bad for you because you did not get that

long-awaited promotion) (Maibom, 2020). This lack of a universal definition of empathy makes it challenging to measure empathy levels, and even in literature various perspectives coexist.

Heyes (2018) introduces the dual system model of empathy, suggesting that empathy is produced by two systems; empathy1 and empathy2 (see figure 1). Empathy1 represents an innate and automatic response present from early human development and is observed across various animal species. This response is triggered by both motor activation (premotor cortex, inferior parietal lobe, and posterior superior temporal sulcus) and somatic activation (anterior insula and anterior cingulate cortex). This automatic response often becomes the input for empathy2. In contrast, empathy2 emerges later in life and involves controlled processes by meta-cognitive and cognitive factors that contribute to empathic understanding, which is a trait potentially unique to humans (Heyes, 2018). Where does empathy1 come from? It is an innate mechanism to match emotions to the stimuli (target), shaped by evolutionary forces. Natural selection favored genes promoting empathy in early mammals where parental care and social behavior in a group were crucial for survival (Heyes, 2018). However, as the environment became more complex, especially in the human social milieu, adaptation became increasingly challenging. This possibly led to the development of more complex neural networks, such as mirror neurons (Mafessoni and Lachmann, 2019). In this review, multiple papers use emotional contagions interchangeably with empathy. They refer to empathy1, where someone emotionally responds to someone else (like facial expression recognition), but this is different from the cognitive part of empathy, where there is real empathetic understanding.

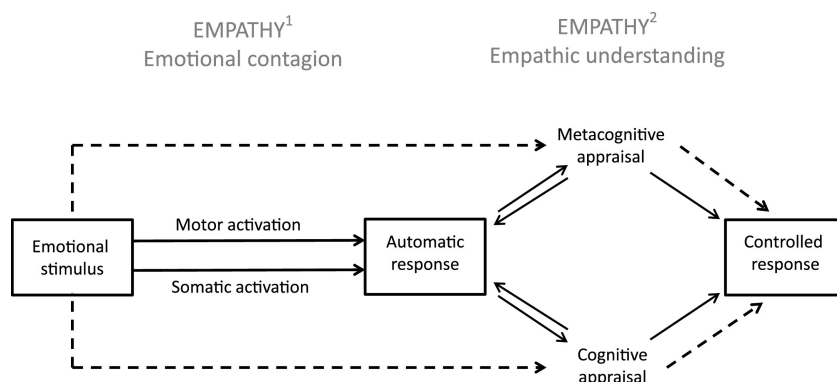


Figure 1: The dual system model of empathy by Heyes (2018)

Neuroimaging studies have aimed to localize brain regions associated with empathy and many areas throughout the brain were associated with any form of empathy. For example, it was found that people with stronger feelings for empathy had increased activity in the insula, inferior frontal gyrus, medial frontal regions around the cingulate cortex, the thalamus, caudate, amygdala, putamen, and primary somatosensory area S1 (figure 2). Since non-invasive neuroimaging studies are often used, these findings are correlational in nature and do not imply causation. This is because these studies measure increased activity during an action, which could indicate engagement in that area, but does not say whether that activity is necessary to perform that action. The brain regions mentioned before lie too deep in the brain to perform noninvasive neuromodulate studies (studies that indicate a causal relationship between brain structure and action), because without surgery other areas could be affected. (Keysers and Gazzola, 2009). However, Paradiso et al. (2021) used paradigms in which empathy-related phenomena can be measured in rodents and primates. As mentioned before, empathetic understanding may be unique to humans (or the cognitive ability to perceive other people's thoughts, or empathy2), but emotional contagion (empathy1) is much more widespread and can be (indirectly) observed

through different behaviors (Heyes, 2018). For example, a rat freezes when witnessing its cage mate receiving an electric shock. However, discussion remains on whether this reaction occurs because the rat is scared of the shock itself or because it empathizes with their cage mate. By reviewing neuromodulation data, it was concluded that the anterior cingulate and the amygdala play a crucial role in emotional contagion (Paradiso et al., 2021). This mechanism evolved homologous across species in evolution, and the proposed function is to detect danger in the group environment. Additionally, emotional contagion appears to be stronger between familiar animals than between novel animals (Han et al., 2019).

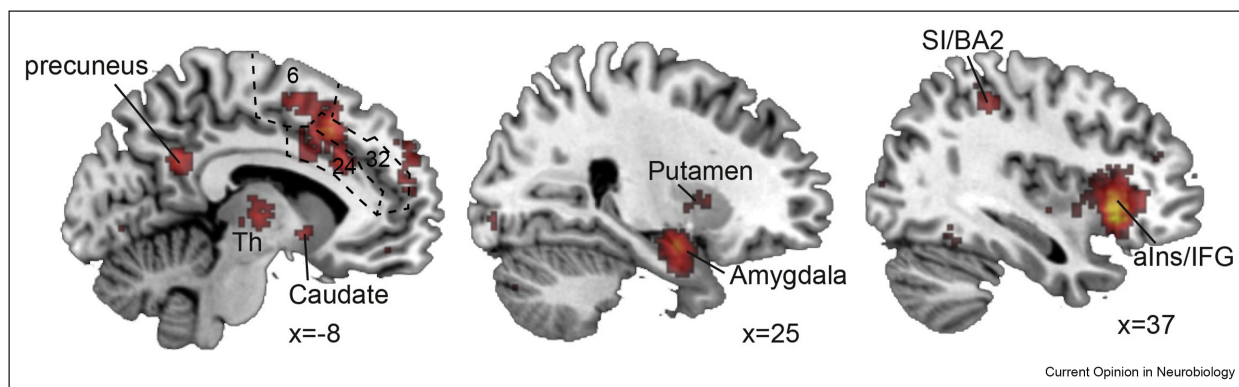


Figure 2: Results of a meta-analysis performed by Paradiso et al. (2021). This figure shows brain regions identified to play a role in empathy (uniformity test). Numbers represent the approximate position of three distinct cortical midline structures (including supplementary motor cortex and cingulate cortices that have homologs in nonhuman primates and rodents). Abbreviations; Ba, Brodmann area; Th, thalamus; aIns, anterior insula; IFG, inferior frontal gyrus; S1, primary somatosensory area.

3 What are mirror neurons?

A mirror neuron (MN) is a specialized sensory-motor cell located in the brain, which activates not only when an individual performs an action, but also when they observe someone else performing the same action. It ‘mirrors’ the other (Knoblich and Sebanz, 2014). Mirror neurons have both sensory and motor properties distinguishing them from most other neurons that typically have singular functions. In addition, it is found that mirror neurons respond not only to visual stimuli but also to auditory cues (these MNs are called audio-visual mirror neurons) (Keysers et al., 2003).

The proposed functions of mirror neurons include a range of cognitive processes, such as action understanding, imitation, intention understanding, language, and empathy. However, it is important to note that these functions are likely interconnected. For instance, action understanding may occur first, and is likely to be followed by imitation. Furthermore, dysfunction in the MNS is hypothesized to lead to several disorders like schizophrenia and autism spectrum disorder (Minichino and Cadenhead, 2016). Nevertheless, controversies and uncertainties about these functions persist and will be addressed later in this paper.

3.1 Mirror neurons in monkeys

Originally, mirror neurons were discovered in the rostral part of the inferior premotor cortex (area F5) of macaque monkeys, later they have also been found in the inferior parietal lobule (IPL). These two areas are collectively known as the classical areas of motor and sensory processing (Acharya and Shukla, 2012). However, Tkach et al. (2007) performed a single-cell

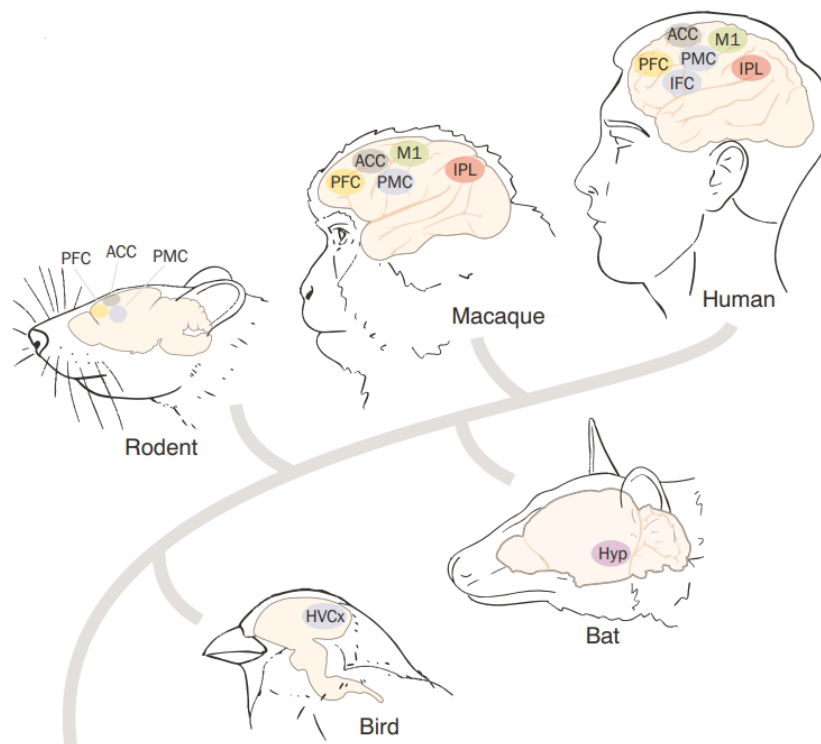


Figure 3: Bonini et al. (2022) visualized the locations of mirror neurons in several species and brain areas. Similar colors for different areas indicate possible homologies across species.

study to demonstrate MN functioning beyond these classical areas, including the primary motor cortex. MNs can respond to observed actions and visually represented objects, as well as actions performed with a tool and nonbiological moving objects (Albertini et al., 2021). In monkeys the neurons are classified into two types; strictly congruent and broadly congruent. Around 30% of the area F5 neurons are strictly congruent, meaning that they fire when a monkey performs a particular action, and when a monkey observes the same movement (for example precision grasping). The other 60% respond to a wider range of stimuli. For example, a cell responds when the monkey holds an object, and the same cell also fires when it observes someone else holding or grasping for that object. (Kilner and Lemon, 2013). Monkey MNs respond to both hand and mouth movements, with hand movement for grasping, holding placing, and finger movements (Di Pellegrino et al., 1992), and mouth movements are associated with eating (chewing or sucking) or communicating (lip smacking, or lip and tongue protrusion) (Ferrari et al., 2003).

3.2 Mirror neurons in rodents

The mirror neuron system is not only limited to primates. This was established by Carrillo et al. (2019), who identified emotional MNs in the rat anterior cingulate cortex (ACC). They showed that these neurons exhibit activity both when a rat experiences pain from a footshock, and when it witnesses another rat in pain. Furthermore, when the ACC is deactivated, the rat's response to observing the other rat's pain reduces. Rodent studies have been important in advancing research on the mirror neuron system and empathy because they are social mammals and are easy to use in behavioral tests. Viaro et al. (2021) further confirmed the presence of emotional MNs in the rat's ACC. They used Long-Evan rats which is a strain that has a highly

developed visual system. The visuomotor responses in the motor cortex of the rat, which are involved in both executing and observing goal-directed actions, suggest the existence of a similar neuronal mirror network as observed before in monkeys.

3.3 Mirror neurons in birds

The mirror neuron system is also present in songbirds; neurons within the telencephalic nucleus of the hyperstriatum (HVC) demonstrate activity both when a bird sings and when it listens to another bird's song (figure 3) (Prather et al., 2008). Furthermore, the HVC is connected to two neural pathways; a song motor pathway and an anterior forebrain pathway. The first plays an essential role in song production and the second to copy a tutor song. This area is believed to be analogous to Broca's area in the human brain, which is associated with learned vocalizations. (Mooney, 2014). Interestingly, songbirds that receive lesions in the HVC region show impairment in recognizing songs of other birds of the same species (Brenowitz, 1991) and impaired development of song production in juvenile male zebra finches (Bottjer et al., 1984). These findings suggest the role of MNs in song learning and communication among birds. Moreover, these discoveries have led to the belief that speech production in humans may also involve the MNS.

3.4 Mirror neurons in humans

After the first discovery of MNs in macaque monkeys, researchers tried to identify similar MN networks in humans as well. The first study was performed in 1995, using transcranial magnetic stimulation to target brain regions analogous to the macaque area F5, namely the premotor cortex (PMC) (Fadiga et al., 1995). Subsequent neuroimaging studies confirmed mirror-like properties in this area in humans as well. The PMC together with the inferior frontal gyrus (IFG) are indicated as the main nodes for the human mirror neuron system. This is however not direct proof of the existence of MNs in humans, because these brain areas could consist of clusters of neurons responding to either action execution or observations. It should be noted that some papers refer to mirror neuron systems (MNS), instead of individual mirror neurons. Later, Mukamel et al. (2010) provided evidence for the existence of MNs in humans by conducting single-cell studies on pre-surgical patients. Additionally, the presence of the human mirror neuron mechanism is supported by the observation of mirror motor evoked potentials (MEPs) during action observation, indicating increased excitability corresponding to the observed movement (Catmur et al., 2011). Furthermore, studies revealed that action imitation occurs involuntarily upon observing an action. Humans particularly show automatic imitation in hand, arm foot, and mouth movements (Heyes, 2011). Studies have shown that disruption of the IFG interferes with automatic imitation. MEP and automatic imitation are regarded as evidence of a human MNS (Cook et al., 2014). Where it is thought that mirror neurons fire in monkeys merely when there is a goal object present (e.g. food), they respond to a wider action range in humans (Goldman, 2006). Like monkey MNs, studies with humans have also localized MNs outside the classical areas, including the dorsal premotor cortex, superior parietal lobule, cerebellum (Molenberghs et al., 2012), supplementary motor area, and medial temporal lobe (Mukamel et al., 2010).

4 Mirror neuron function

Since their discovery, a lot has been hypothesized about the function of these special neurons, initially proposed by the research group that identified them. These functions include action

understanding, intention understanding, imitation, and empathy (Gallese et al., 2004). In addition, Rizzolatti and Arbib (1998) suggested a role for MNs in language development. However, there are conflicting beliefs regarding the specific function of MNs. In the following section, action understanding, intention understanding, imitation, and language will be shortly discussed. Later in this paper, the role of mirror neurons in empathy will be discussed in more detail.

4.1 Action understanding

The first proposed MN function is action understanding in 1996 (Gallese et al., 1996). This hypothesis suggests that simply observing a movement would be limited to visual perception, but when the motor system is activated, the visual cue is transformed into a motor movement. However, this process may not provide information about the intrinsic value or goal of the action (Rizzolatti, 2005). Indeed, multivoxel pattern analysis shows that MNs display a concrete representation of an observed action, rather than abstract concepts like the goal of the action. For example, the focus tends to be on the general action itself, like opening a bottle, rather than the overarching goal of “to open” (Wurm and Caramazza, 2019). Additionally, Thompson et al. (2019) reviewed that MNs contribute to action understanding at lower-level processes, such as action identification, but may not play a significant role in higher-level processes like determining the intention or goal behind an action.

4.2 Intention understanding

Intention understanding refers to the ability of an observer to discover the intention behind an actor's movements. It has already been demonstrated that, in most cases, an observer can discover an actor's intention based on their movement kinematics (Ansuini et al., 2014). However, the role of MNs in intention understanding remains a subject of debate. Catmur (2015) suggests that there is not enough evidence to establish the contribution of MNs to intention understanding. As mentioned above, Thompson and colleagues (2019) are in line with this perspective. They affirm the role of MNs in action understanding rather than intention understanding. On the other hand, Iacoboni et al. (2005) has concluded otherwise. They showed that using fMRI, the activity of the right IFG increased after observing a movement in context (suggesting an intention or meaning behind an action, like eating). This activity was not seen when the action was performed without a context (suggesting action understanding, but not the intention behind the action).

4.3 Imitation

The MNS copies the neural activity of another's motor actions, logically, this could imply the mechanism behind imitation. Indeed, imitation is one of the most accepted roles of the human MNS. Rizzolatti et al. (2001) proposed that MNs are involved in imitation, and this theory is supported by various studies. For instance, experiments using transcranial magnetic stimulation have demonstrated that disrupting the IFG (a classical area associated with MNs) leads to difficulties imitating finger movements (Catmur et al., 2009; Heiser et al., 2003). Furthermore, another research was conducted that looked at intentionally not imitating participants. Using fMRI, they measured activity after a match (imitation) or mismatch stimulus-response (participants had to counter-imitate the observed action). The findings revealed distinct activation patterns between imitation and counter-imitation. Predominantly MN areas were activated during imitations, whereas more parietal frontal networks responded during counter-imitation. This indicates preparatory inhibition of imitation during counter-imitation.

They concluded that adaptive behavior is the result of an interplay of mirroring and executive control processes. This is important in complex human interactions since people have the options to imitate, avoid doing so, do the complementary, or choose an alternative option (Campbell et al., 2018).

4.4 Speech perception

Neuroimaging data has shown activation of the premotor cortex during speech perception, indicating a mirroring system behind language perception (Cogan et al., 2014). Nuttall et al. (2017) found increased motor evoked potentials after a motor-distorted speech (a tongue depressor was applied) and also after speech in a noisy environment compared to natural speech in quiet conditions. This indicates that motor mirroring improves speech perception, particularly in a noisy environment. However, some lesion studies could not find impaired speech perception after PMC lesions. Thus, even though the PMC is involved in speech perception, it is not critical and speech can be perceived without it (Hickok et al., 2008).

5 The role of mirror neurons in empathy

The ability to infer the mental state or emotional status of other people is crucial in social interactions, particularly for humans. Humans have developed a heightened ability to interpret such signals. Quickly after the discovery of MNs, researchers proposed their involvement in social cognition, including empathy (Gallese et al., 2004). In the following years, there has been much focus on this aspect in both psychological and neuroscientific research. In 2009, the MNS was even proposed to be the biological basis of social cognition (Pineda, 2009). Subsequently, studies demonstrated overlapping brain activity during the processing of one's own emotions and when empathizing with others. For example, Carr et al. (2003) found activation of premotor areas after imitation and observation of emotions, using fMRI. In addition, Leslie et al. (2004) found mirroring activation in the right ventral premotor area when passively observing facial expressions. This finding suggests a neural mirroring system in the right hemisphere (particularly the right hemisphere since it is responsible for emotions) that underlies empathy. Yet it should be noted that these studies search for mirror-like activation during empathy, and they show similar activation patterns in the brain during action execution and observation. This notion applies to multiple studies in this field, as will be discussed later in this paper.

After their discovery in monkeys, research into the function of MNs has predominantly focused on humans (60%), as they may provide a neurological understanding of some human features that are not well understood (like emotions). Human research is done in either healthy or clinical subjects or theoretical studies (32%) (figure 4). However, studies done in humans are often indirect, using noninvasive techniques (Bonini et al., 2022). Such techniques have some limitations, and there is ongoing discussion about their reliability. In addition, much of this research tends to overlook the complexity of empathy, like the multitude of neural mechanisms involved in all types of empathy. Often, studies try to attribute it to one specific neurological mechanism.

Studies using noninvasive neuroimaging techniques in humans often support the role of MNs in empathy. The most famous techniques are functional magnetic resonance imaging (fMRI), transcranial magnetic stimulation (TMS), magnetoencephalography (MEG), and electroencephalography (EEG). In the next section, these four techniques will be reviewed.

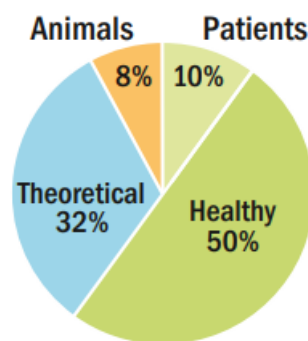


Figure 4: Pie chart, obtained from a review from Bonini and colleagues (2022). ‘Healthy’ and ‘patient’ include noninvasive experiments on humans. ‘Theoretical’ includes meta-analyses, review articles, computational models, and opinion articles. ‘Animals’ means neurophysiological and behavioral experiments on animals.

5.1 Functional Magnetic Resonance Imaging

Functional Magnetic Resonance Imaging (fMRI) is a widely used noninvasive neuroimaging technique that measures brain activity by detecting changes in blood flow. It allows full brain coverage with good temporal and spatial resolution (Glover, 2011). In an early study by Carr and colleagues (2003), fMRI was used to explore the interaction between MN areas and emotional brain centers. They found overlapping brain regions activated during both the observation and imitation of facial emotional expressions, with premotor areas showing activation after observation of these expressions. For the results of this study, see figure 7 in Appendix A. Another indication of emotional contagion is the feeling of disgust, which is an emotional response usually triggered by something repulsive. Wicker et al. (2003) investigated the neural response after inhaling an odorant producing a strong feeling of disgust. In addition, they looked at the response after observation of others experiencing this same feeling of disgust (participants were offered a movie showing the emotional facial expression of disgust). The main finding was that the anterior insula and the anterior cingulate cortex (ACC) were activated during the observation of another’s feeling of disgust, indicating a mirroring of the observer’s emotion. Structural connectivity studies, such as those conducted by Takeuchi et al. (2013), have shown a correlation between white matter volume in MN areas (IFG and IPL) and empathy levels (empathy was assessed by the Empathy Quotient questionnaire). While these findings suggest a role for MNs in empathy, inconsistencies in brain area activation and their specific functions persist. Fan et al. (2011) performed a whole-brain quantitative meta-analysis of fMRI studies investigating the function of MNs on empathy. The results indicate no consistent activation of MN regions; It suggests that the MNS is not centrally involved in empathy per se, but that they might have a supporting role.

5.2 Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) is based on electromagnetic induction, wherein a magnetic pulse passes through the scalp and skull, inducing an electrical current in the underlying tissue. It is a noninvasive tool for brain stimulation (Śliwińska et al., 2014). One kind of TMS is cortico-spinal facilitation. The first TMS study regarding MNs was done by Fadiga and colleagues (1995). The premotor cortex contains MNs, which fire during action observation. This firing makes the PMC more excitable, which can be observed by TMS (stimulation) of the cortico-spinal motor system. This can be measured by motor-evoked potentials (MEPs). Indeed, larger MEPs have been observed when the subject’s motor cortex is stimulated by

action observation (compared to the control group). Concerning empathy, TMS indicates a similar motor response when experiencing pain yourself and observing pain in someone else. Avenanti et al. (2005) demonstrated that watching videos of individuals experiencing pain led to inhibition of MEPs in the corresponding motor area, with the degree of inhibition correlating with self-reported empathy levels. A second way to use TMS is the virtual lesion method, where repetitive stimulation of brain regions suppresses its activity. This way researchers can investigate the causal role of that brain area on behavior. Knoch et al. (2006) utilized this approach to disrupt the right dorsolateral prefrontal cortex (DLPFC), leading to a reduction in individuals' willingness to reject unfair monetary offers from other players. This indicates that after TMS treatment, there was a behavioral change of increased selfishness (and less resistance to economic temptation) since people put self-interest above social and moral norms (not accepting unfair offers). This change is not seen when disrupting the left DLPFC, indicating that the right DLPFC plays a role in prosocial behavior.

5.3 Electroencephalography and magnetoencephalography

Electroencephalography (EEG) and magnetoencephalography (MEG) are noninvasive neuroimaging techniques used to measure oscillatory activity in the brain (EEG uses electrical activity and MEG measures the magnetic field produced by electrical activity in the brain). These methods provide insight into the temporal dynamics of the brain, whereas, for example, fMRI localized activity (Proudfoot et al., 2014). Sato et al. (2015) investigated participants observing dynamic facial expressions of fear and happiness or a dynamic mosaic. They found a hierarchical and bidirectional neural mechanism processing such dynamic facial expressions. It was shown that the visual and motor-related cortices are active in turn, indicating that the brain first manipulates visual representations before utilizing motor representations for processing and interpreting dynamic facial expressions. However, it remains unclear whether motor representations are necessary for emotion recognition. Both EEG and MEG studies have shown that central sensory-motor regions oscillate in the 10-20 Hz range, and desynchronize during action performance and observation. This desynchronization (meaning a reduction in oscillatory power) is due to mu rhythm suppression, which operates at an 8-13 Hz frequency range and provides a good parameter for mirror neuron activity and also for empathy (Christov-Moore et al., 2014). Yang et al. (2009) looked at mu rhythm suppression and the perception of pain in others and compared males to females. They found increased mu rhythm suppression when observing pain, and this effect is more pronounced in women than in men. The data figure of this study can be found in figure 8 in Appendix B.

5.4 Critical comments regarding non-invasive neurological imaging in humans

The idea that the MNS is the main mechanism behind empathy has often been affirmed by researchers. However, merely human-centered research and one-sided evidence have started a debate around the reliability of evidence supporting empathy as a function of MNs. Numerous review studies claim that there is insufficient empirical evidence to solely attribute empathy to mirror neurons (Lamm and Majdandžić, 2015; Heyes, 2018). In humans, we have to rely on non-invasive studies. However, these techniques have some limitations: they fail to provide information on a cellular level and are correlational in nature.

In general, psychological phenomena are often misunderstood by biological or clinical studies. Neuroscientists tend to assign neural events for psychological phenomena wrongly, assuming causation while we don't know the exact mechanism behind it. For example, localization of psychological function and the role of genetics in psychopathology are often misjudged.

Mistreating psychology is a common mistake in neuroscience, as Miller (2010) describes in his article. It is thus important to critically evaluate papers studying psychology and biology.

5.5 The first limitation; the lack of evidence for single-cell properties

Firstly, neuroimaging techniques measure mass neural activation and not single-cell firing. In the case of mirror neurons, brain regions could show both motor and sensory responses, which could be attributed to MNs but could also indicate colocalization of both sensory and motor neurons together. Studies should be careful in implicating mirror neurons after observing sensorimotor responses in brain areas. (Grill-Spector and Malach, 2001). Still, brain areas with mirror properties do not have to be better or worse than individual neurons with mirror functions. Both can fulfill mirror functions, such as action understanding, imitation, and empathy. Still, it is important to gain knowledge about single cells, since it leads to a better understanding of the molecular mechanisms behind them and provides a potential target for medicine. In addition, it is important to realize that when an article refers to a 'mirror neuron system', it refers to a brain area with mirror properties, not to single mirror neurons. Thus the MNS and MNs can not be used interchangeably.

Single-cell recordings provide more insight into individual neurons instead of larger brain areas, and could potentially identify individual mirror neurons in the brain. For example, electrocorticography (ECoG) was performed in epileptic patients to measure activity between viewing and grasping in single neurons. This study visualized temporal-spatial patterns of individual mirror neurons (Perry et al., 2017). Other studies using single-cell intracortical EEG (iEEG) recordings in presurgical patients have already indicated the presence of MNs in humans (Mukamel et al., 2010). However, this study is one of the few that looked at the role of MNs in empathy as well. They recorded extracellular activity in 21 patients during facial emotion expression and hand-grasping actions. Besides performing facial expressions, they also observed the same facial expressions of someone else. MNs were observed in the SMA, hippocampus, parahippocampal gyrus, and entorhinal cortex (see figure 9 in appendix C). Although single-cell recordings are used in MN research, they are not typically employed in studies directly examining the role of MNs in empathy in humans, partly due to limitations associated with this technique. Firstly, the availability of suitable patients for such studies is limited, as hospitals typically have a few implantations a year, and the time to perform experiments on patients is limited. Furthermore, the experiment takes place in a clinical environment, potentially introducing background noise and other confounding factors (Quiroga, 2019).

5.6 The second limitation; evidence is correlational rather than causal

Neuroimaging techniques are merely correlational by nature, showing responses co-occurring with empathy rather than proving the direct effects of brain areas on empathy. More causal studies, such as lesion or neurostimulation studies can be used alongside. The virtual lesions method of TMS (as mentioned above) is a noninvasive lesion technique that implies causation, but it has difficulties in reaching brain areas deeply located under the cortical mantle. Still, this technique is promising for further use in the future (Lamm and Majdandžić, 2015). Lesion studies can reveal areas of the brain that are critical for a specific task, proving a causal relationship (Hillis, 2013). A good example of a lesion study is the work of Shamay-Tsoory et al. (2004). They investigated the impairment of affective and cognitive empathy in patients with focal brain lesions. They compared cognitive and affective responses among patients with localized prefrontal lesions (n=36), patients with parietal lesions (n=15), and healthy control subjects (n=19), and found significantly impaired empathy responses in patients with prefrontal lesions compared to those with parietal lesions and the control group. However, when the lesions

were located in the right hemisphere, empathy was impaired in both lesion groups. In this example, lesion studies support conclusions from most functional imaging studies, but there is widely mixed evidence.

Besides, it is important to critically review lesion studies as well. In humans, lesions in the human brain can result from disease, injury, or neurosurgical treatment, thus they are not experimentally controlled (possibly the damage is more or less severe than expected). Additionally, lesions vary between patients in size, etiology, laterality, and age of onset. Lesions after neurosurgical treatments are most experimentally controlled, but often sample size is rather small. Additionally, the human brain will try to recover, for example by promoting reorganization of that area. There are a lot of different factors influencing how the brain adapts after a lesion, including time after damage, etiology (stroke versus tumor), and location of damage (Vaidya et al., 2019).

In her paper, Hillis (2013), reviews multiple lesion studies performed in humans highlighting their strengths and limitations. She also addresses conflicting results between experiments. Yet, she is confident to conclude that the right inferior frontal cortex and orbitofrontal cortex (both parts of the prefrontal cortex) are critical for emotional contagion and that the right prefrontal cortex is generally engaged in affective empathy.

To study the causal function of a brain area more precisely, experimental lesioning can be induced in rodents. This was done by Carrillo et al. (2019). As explained before, researchers look at the freezing behavior of rats after experiencing a shock and observe another rat receive the same shock. The ACC fires both when receiving a shock and observing others receiving the same shock, and this study found that deactivation of the ACC reduces freezing after experiencing and observing the shock. This implies that the mirror neurons located in the ACC are responsible for emotional responses after experiencing pain and witnessing another rat's pain. Another advanced technique that can be used in animal models is optogenetics. This technique allows researchers to manipulate neurons or clusters of neurons with precision in time and space. Light is used to control the activity of genetically modified cells that respond to the light. Suzuki et al. (2015) used optogenetics to prove the presence of MNs in marmosets (they were the first to indicate MNs in nonhuman primates other than macaque monkeys) and Roberts et al. (2012) used this technique to impair imitative learning in songbirds. Animal studies allow researchers to experimentally manipulate the animal's brain, but they must be cautious about concluding the same function in the human brain, especially in the case of empathy.

5.7 Empathy as a complex multidimensional response

It is important to remember that empathy is a complex multidimensional phenomenon, as described before in more detail. Not only is the definition of empathy itself unclear, but its underlying neuronal mechanism is not fully understood. For instance, many studies mentioned in this paper use facial expression recognition as a measurement for empathy (this could indicate affective empathy, but what about cognitive empathy?). But how fair is this, do I empathize with you when I just recognize your sadness? Besides, empathy consists of different psychological processes and may depend on overlapping and interconnected brain networks. Hillis (2013) proposed a functional-anatomical model that integrates both cognitive and affective aspects of empathy, along with the associated brain regions. This model provides a broad framework for the dynamics of empathy. Given this complexity, it is crucial to question the relevance of studies that attempt to prove a relationship between specific regions and the broad phenomenon of empathy.

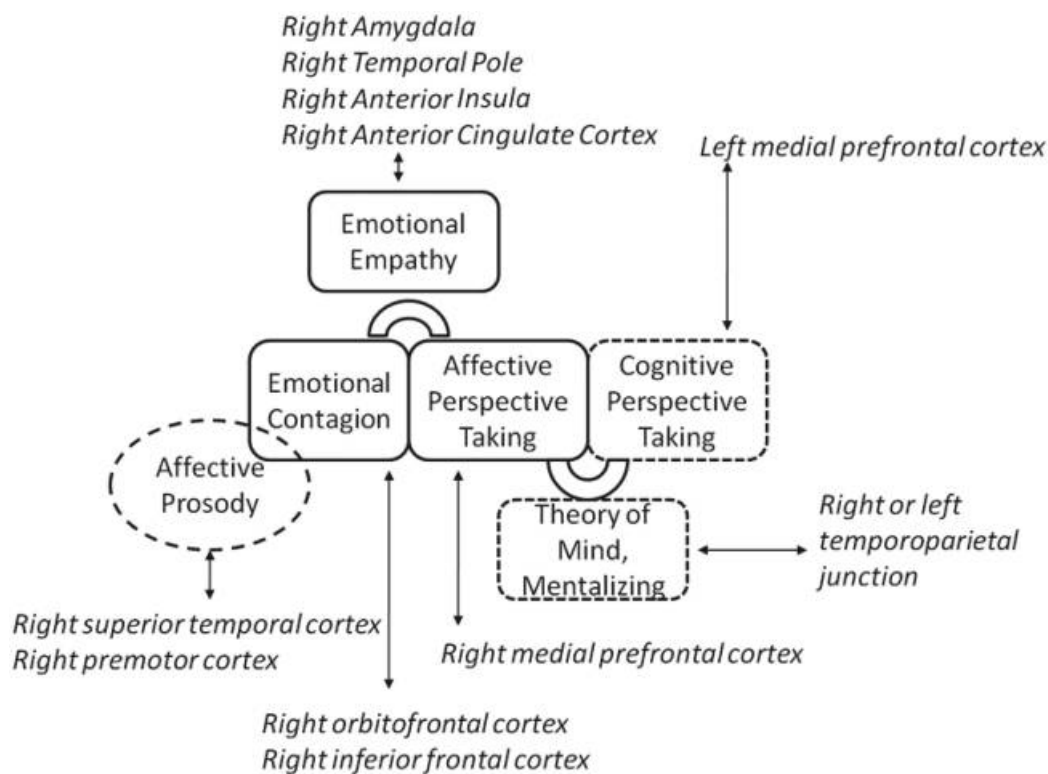


Figure 5: The schematic functional-anatomical model proposed by Hillis (2013), displays proposed cognitive and neural mechanisms underlying empathy (in solid borders), proposed cognitive processes (in dashed borders), and associated brain regions. Interestingly, this model is comparable with the Dual System Model of empathy by Heyes (2018), as described before.

6 Mirror neuron dysfunction and Autism Spectrum Disorder

Just like any neural network, abnormalities in the development of the MNS can lead to significant consequences. Deficits in MNs have been linked to Autism Spectrum Disorder (ASD). This association seems logical, given that individuals with ASD experience challenges with social interactions, communication, imitation, theory of mind, and empathy, functions associated with the MNS (Oberman et al., 2005). However, as we have seen before in research in the field of MNs, there is a huge disagreement about the relationship between ASD and MN dysfunction (Heyes and Catmur, 2021).

6.1 What is Autism Spectrum Disorder?

ASD is characterized by impaired social interactions and the presence of early emergence of restricted and repetitive behaviors or interests. It is influenced by strong genetic components and arises from early altered brain development. However, there is no reliable biomarker, thus diagnoses are made based on behavior (Lord et al., 2018). People suffering from ASD often encounter challenges in various aspects of life, including functioning at school or work. Because there is a wide variety in type and severity of symptoms, it is known as a “spectrum” disorder (Khalil et al., 2018). In the Statistical Manual of Mental Disorders (DSM)-5 criteria for ASD are specified based on two domains: social communication and/or restricted, repetitive, or unusual sensory-motor behaviors. Table 1 in Appendix D shows an overview of the DSM-5 criteria for ASD which is provided by The American Psychiatric Association (Lord et al., 2018).

6.2 The broken mirror theory

It has been hypothesized that the MNS is dysfunctional in ASD, which is also known as the “broken mirror theory”. Williams et al. (2001) was the first to investigate this relationship and propose that early development failures in the MNS are the cause of a cascade of further developmental impairment, resulting in autism. Subsequent studies focus merely on imitation impairment in individuals with ASD. Indeed, a few years later, Oberman and colleagues (2005) tested this by measuring mu suppression in ten high-functioning individuals with ASD. Subjects were tested in four conditions; watching a movie of a moving hand, moving their own hand, watching bouncing balls, and visual noise. They found a lack of suppression in the ASD group during observed hand movements, but not during movement of their own hand, which indicates dysfunction of the MNS but not other motor systems. On the other hand, Gordon et al. (2020) did not find such an effect. They investigated automatic imitation (AI) in 42 individuals with ASD and 50 typical developing (TD) control subjects. Participants had to perform finger movements according to certain cues on a screen, which could be either congruent or incongruent (they had to either imitate or counter-imitate the cue). Accuracy rate (%) and median reaction times were recorded. This study could not find an imitation deficit in ASD.

Another form of imitation is mimicry of facial expressions which happens often automatically (think of the contagiousness of laughter). McIntosh et al. (2006) found that individuals with ASD did not automatically mimic facial expressions compared to TD participants (using facial electromyography). However, they did not find these differences when looking at voluntary mimicry, indicating impairment of basic automatic social-emotion processes, but not with voluntary or controlled mimicry.

Besides imitations, the broken mirror theory proposes dysfunction in the MNS resulting in impaired action perception, empathy, and social decision-making in ASD as well. For example, Boria et al. (2009) looked deeper into action understanding. A picture showing hand-object interactions was presented to children with ASD and TD, and they were asked what the goal was (e.g. grasping) and what the intention was (e.g. grasping for drinking). In some cases, the observer grip was congruent with the function of the object, and in some cases, it was used solely to move but not use that object. It was found that children with ASD can identify the goal of the action, but they made errors when the action was used to move the object. This suggests that they have difficulties in intention understanding others only through motor cues.

In their paper, Khalil and colleagues (2018) reviewed several studies with mixed evidence and theories regarding this subject. Based on their review, they came up with a multilayer neural network underlying autism, taking the heterogeneity of ASD into account. In this model, MNs form the first layer, transforming information to a higher layer network responsible for reasoning (figure 6).

The interpretation of mixed evidence varies among different neuroscientists. Whereas Khalil et al (2018) conclude sufficient evidence to support the involvement of MNs in ASD, another review by Hamilton (2013) concludes otherwise. Indirect evidence (EEG, MEG, TMS, EMG, and eye tracking techniques) yielded mixed results with weakly localized measures. better localized fMRI studies showed only some differences using emotional stimuli instead of non-emotional hand action stimuli. In the end, Hamilton and colleagues (2013) did not consider this evidence to be sufficient to prove the broken mirror theory of ASD to be true.

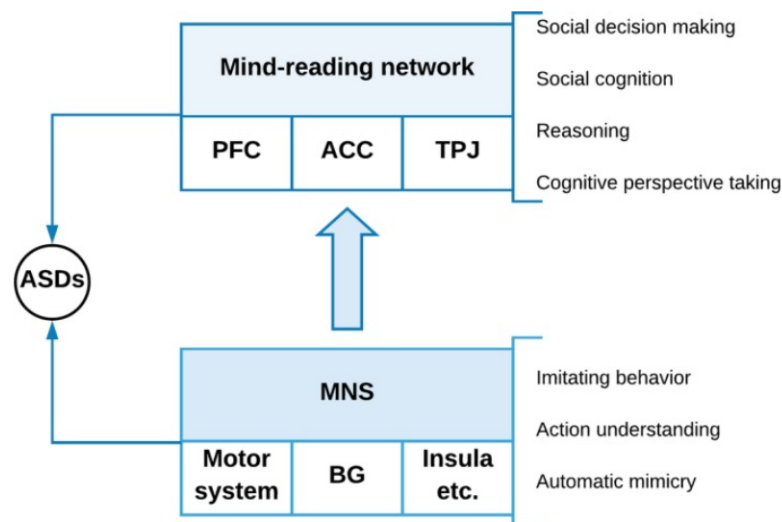


Figure 6: Schematic representation of a multilayer neural network underlying mechanism by Khalil et al. (2018). The MNS includes the first layer of neural processing, involving the motor system, the basal ganglia (BG), and the insula. Higher-order neural processes include reasoning about others' mental states, a "mind-reading network", involving the prefrontal cortex (PFC), the anterior cingulate cortex (ACC), and the temporoparietal junction (TP).

7 Discussion

Since their discovery, mirror neurons received a lot of attention in the psychological and neuroscientific world. In this paper, MN function was critically reviewed, especially the role of MNs in empathy was thoroughly evaluated. It can be concluded that sufficient evidence confirmed the function of MNs in action understanding and imitation. However, there is no solid proof to attribute intention understanding and speech perception to MNs. It was also hypothesized that MNs are the underlying mechanism behind empathy. Empathy itself is a complex, multifaceted, undefined phenomenon, and the discovery of MNs provided a good explanation for this phenomenon. However, there is an ongoing debate about whether this is empirical evidence for this assumption. Noninvasive studies such as fMRI, TMS, and MEG/EEG in humans tend to support the role of MNs in empathy, but the question remains whether this is reliable or not. Because these techniques do not provide information about single neurons and are correlational instead of causal. Alternative studies could be single-cell recordings (ECoG or iEEG) and lesion studies. Only one study examined single MNs and empathy and found similar activation patterns in single MNs during facial expression imitation and observation. Lesion studies provide mixed evidence on this topic. Besides, these techniques also have limitations. Single-cell studies are challenging to perform in humans and lesion studies are not well experimentally controlled when performed in humans. Overall, neuroimaging studies agree on the involvement of the MNS in empathy, but both single-cell and lesion studies provide mixed evidence. It should be noted that empathy cannot be easily ascribed to a specific brain area or neural network, but it is likely to be an interplay of multiple circuits, specific to the different dynamics of empathy. For example, the effects of neurons or brain areas can be due to their interaction with other brain structures. The same is true for the role of MN dysfunction in Autism Spectrum Disorder. The Broken Mirror Theory was quickly proposed by literature, but different studies yield mixed results, and how these results are interpreted varies by different views.

Given the abundance of neuroimaging techniques supporting the engagement of MNs in empathy, we can conclude that MNs play a role in empathy. But whether there is a causal

relationship, or whether MNs are necessary for empathy, remains unclear. Moreover, it is always hard to assign a biological mechanism to a psychological response, but combining studies can give us more insight into some processes in the brain that make us social. Future research could combine noninvasive studies to map brain structures in the brain, followed by causal studies (for example by conducting optogenetics in animal models) to see if this brain structure is necessary for empathy. In addition, further studies can be more diverse in assessing empathy, because empathy is not just facial expression recognition and self-reporting is often biased. Regarding MN dysfunction and ASD, there is even more disagreement on this matter, because of the heterogeneity of ASD and individual variety (a wide spectrum of symptoms) compounds the problem. Although some studies indicate a relationship, concrete conclusions cannot be drawn. In the end, the mirror neuron system is an intriguing complex neural mechanism with fascinating functions, but we must admit that it is too early to state that “*mirror neurons are what makes humans social*” (Lehrer, 2008) or that mirror neurons are “*cells that read minds*” (Blakeslee, 2006), but they might “*do for psychology what DNA did for biology*” (Ramachandran, 2009) in the future.

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10 Appendix

10.1 Appendix A

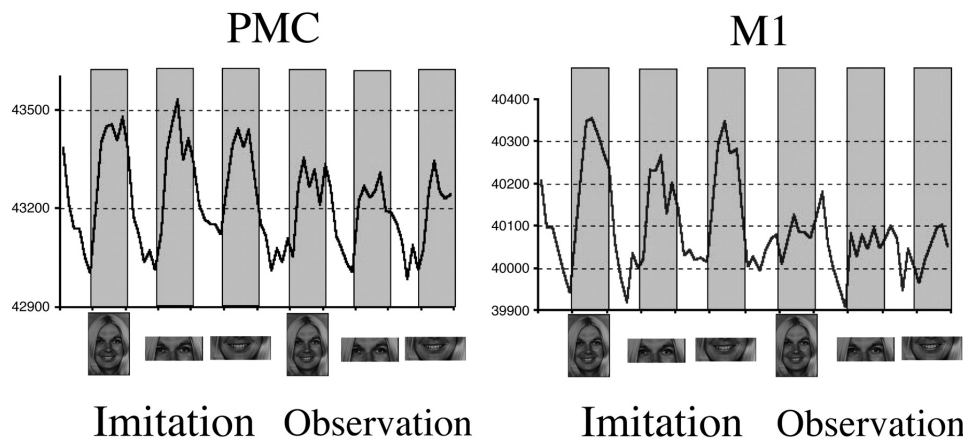


Figure 7: Results from Carr et al. (2003), the figure shows a time-series of activity peaks in the right central (M1) and precentral (PMC) sulcus. Activity occurs not only during imitation but also during observation of emotional facial expressions (activity is more similar in PMC)

10.2 Appendix B

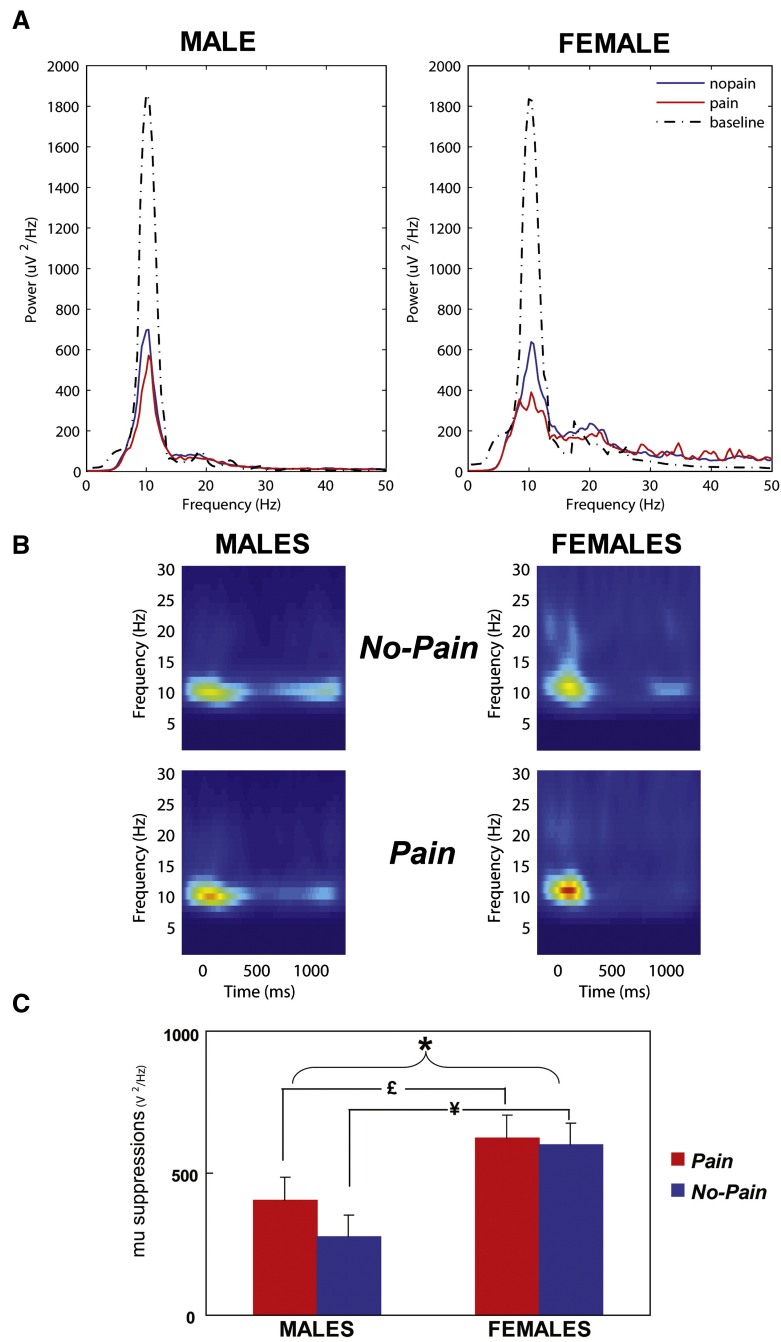


Figure 8: Data figure adapted from Yang et al. (2009). (A) represents the frequency spectrum after a visual stimulus showing either pain or no pain. The baseline is similar across two genders, empathy by mu suppression appears stronger in females than men. (B) Shows the time-frequency spectrum in both groups. (C) Statistical comparison between male and female. Gender effect is significant because females have more mu suppression during observation of others in painful as well as in non-painful situations.

10.3 Appendix C

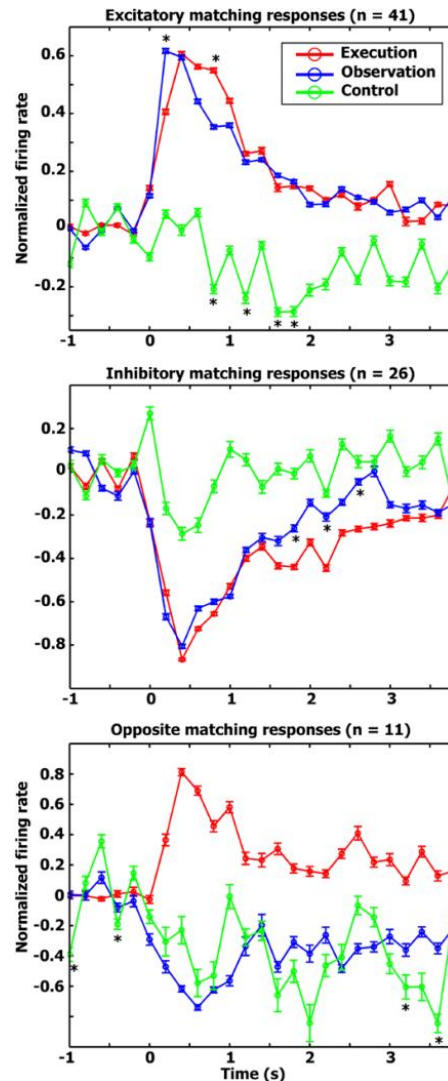


Figure 9: Data figure adapted from Mukamel et al. (2010). The figure shows the average normalized response profile of individual neurons which matched action observation and execution. (A) is an average of 41 excitatory responses (from distinct 33 neurons) during both action execution and observation. (B) The average of 26 inhibitory responses (from 21 distinct neurons) (C). This firing pattern may seem contradictory. It shows the average of 11 response profiles (from 11 distinct neurons) that showed excitation during action execution and inhibition during action observation. Still, this is a mirror neuron pattern since it responds in both situations. Error bars indicate the standard error of the means across all neurons. Asterisks indicate significant differences between the temporal profiles of action execution and observation. The asterisk on the control task indicates that the control conditions are significant from zero. In conclusion, the majority of cells ($n=45$) matched firing during action observation/execution (meaning that response is inhibitory or excitatory during both action execution and observation), while 14 cells had opposite matching responses.

10.4 Appendix D

Section	Description
A	Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history
	<ol style="list-style-type: none"> 1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions 2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication 3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers
B	Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history
	<ol style="list-style-type: none"> 1. Stereotyped or repetitive motor movements, use of objects, or speech (eg, simple motor stereotypes, lining up toys or flipping objects, echolalia, idiosyncratic phrases) 2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (eg, extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day) 3. Highly restricted, fixated interests that are abnormal in intensity or focus (eg, strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests) 4. Hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of the environment (eg, apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement)
C	Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life)
D	Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning
E	These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level

Table 1: DSM-5 Criteria for Autism Spectrum Disorder, adapted from American Psychiatric Association, DSM-5 Task Force (2013).