FACULTAD DE MEDICINA
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# MIRROR NEURONS AND ITS IMPACT ON NEUROLOGICAL DISEASES

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## 1. ABSTRACT

Mirror Neuron System (MNS) is a neural network composed by visuomotor neurons located in several brain areas whose most relevant characteristic is the capacity to integrate visual and motor information so that individuals experience observed situations as if they would be participating on them. This allows them to fully understand the action they are observing and also the intentions behind that given action. This sensorimotor integration happens in an automatic way that means that higher functions areas are not involved in the process.

The discovery of this type of neurons is one of the most important events in Neuroscience in the last decades, giving a new way of understanding some processes in which mirror neurons could take part, from action understanding to emotion recognition or language and speech evolution.

Knowing how it behaves and its main properties, MNS deficits have been hypothesized to be the cause of some of the core sypmtoms found in some disorders, more specifically behavioural conditions, and what is even more important this mechanism could become a treatment target to develop new therapies to approach these conditions.

Key words: MNS, mirror neurons, empathy, ASD.

## 2. INTRODUCTION

For ages human beings have been trying to figure out how people are able to know what the others are thinking, or even what they are going to do next. Today's Neuroscience attempts to explain us the physiological reasons behind these facts and many more related with the so called Mirror Neuron System (MNS). Mirror neurons (MNs) basically allow us to understand other people acts and feelings so we can adapt our behaviour according to the situation we are living. It can be said that MNS creates a network that connects people [1,2]. The MNS is considered to be one of the most relevant and revolutionary discoveries in Neuroscience during the last decades [3].

Mirror neurons were firstly described by Rizzolati and colleagues in 1996, in the University of Parma [3]. They were studying monkeys' brains when they discovered a particular type of visuomotor neurons in the premotor area of the monkey. At the beginning, the main interesting fact about them was that they were able to discharge both in monkey's action execution and when the monkey was watching similar actions being done by someone else (human or monkey). So, at first, researchers thought that they were dealing with an imitation system but later on many studies have been carried out about the topic, finding that mirror neurons are and form much more than an imitation system.

In the last years many important points came out about these visuomotor neurons: the existence of a complex MNS involving different areas of the human brain, and its important role in several functions such as action understanding, action execution, imitation learning, empathy and social interaction. Although studies about the topic just began a few decades ago, Rizzolati thinks that mirror neurons will do for Neurology and Psychology what DNA did for Biology [4].

About its exact location, in the monkey the MNS was pinpointed in the inferior frontal gyrus (IFG, also known as area F5), the inferior parietal lobule (IPL) and superior temporal sulcus (STS). In humans, fMRI has been widely used to locate MNS, suggesting that it is mainly located in the inferior frontal cortex and superior parietal lobe [3,5]. In order to confirm the existence of MNS in humans, different neurophysiological techniques had to be done. In the last few years, intracranial depth electrode recording of single neurons activity verified the existence of human MNS.

Taking into account the properties of the MNS, the understanding of how it really operates is believed to have a great impact on the future of clinical medicine, as the failure of MNS is thought to be one of the causes of the symptoms related with social impairments seen in Neuropsychiatric disorders such as the Autism Spectrum Disorders (ASD) or Schizophrenia.

Another field in which mirror neurons are involved is creating new motor memories, which can be useful in rehabilitation after a stroke. These findings open the opportunity to use the knowledge about MNS as a therapeutic target for these conditions. Till now, the field in which more concrete MNS directed techniques have been assessed is post stroke rehabilitation therapy.

## 3. OBJECTIVES

The aim of the review is to give a general view about what Science already knows on mirror neurons. Through these lines, we will try to explain how they behave, their main physiological characteristics, in which processes they are thought to be involved and the impact that this finding could have in the present and future of some neurological diseases such as Autism Spectrum Disorders, Schizophrenia, Post-stroke recovery or Phantom limb pain.

## 4. DISCUSSION

### 4.1. THEORETICAL BACKGROUND: PHYSIOLOGICAL BASIS OF MIRROR NEURONS.

One of the most interesting discoveries in Neuroscience in the past few years has been the MNS, a mechanism that unifies action perception and action execution. Before Rizzolati and colleagues found MNS, it was thought that the understanding of actions done by others relied on inferential reasoning, which means higher order association areas in the brain. According to this previous thought, understanding someone else's actions and intentions was possible thanks to elaborated cognitive mechanisms, which compared new acquired information with previous data stored. In fact, this probably happens when the observed motor act is really complex and difficult to interpret but not always [4].

The MNS function could be basically explained like this: an individual observes actions being done by others, this information is processed in the visual system, and the actions seen are directly, which means without higher cognitive mediation, mapped into the observer's motor representation of that same actions. The income of a neural pattern similar to the one already present during the observer's own motor action will make possible for him to understand the action and intention of the other person [4].

Action understanding and imitation learning are key factors for human beings and other primates in order to survive [1,4]. Without knowing and understanding the intentions of the others social behavior and organization would be impossible and as mentioned, humans are able to learn new skills by imitation, which is the basis of human culture.

Mirror neurons are a particular type of visuomotor neurons firstly discovered in the ventral premotor cortex of the macaque monkey, known as area F5, which corresponds to human Broca's area [1,2]. These neurons were seen to have the property of discharge when the monkey is performing a particular action (motor act) and when that monkey sees another individual (monkey or human being) doing the same or a similar action. The MNS is bilateral and includes large portions of the parietal and premotor cortex of the monkey. *(Figure 1).*

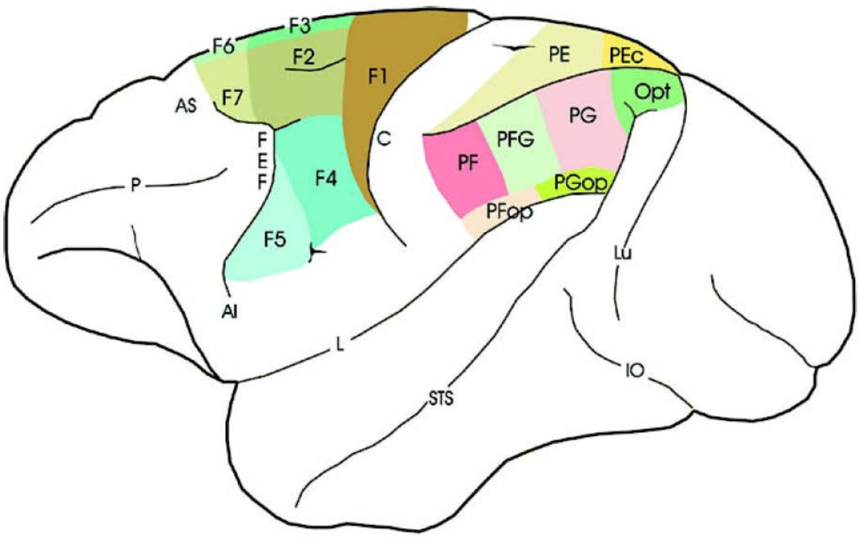



**Figure 1.** Lateral representation of the monkey brain, showing the motor areas of the frontal lobe and the areas of the posterior parietal cortex. For nomenclature and definition of frontal motor areas (F1-F7) and posterior parietal areas (PE, PEc, PF, PFG, PG, PF op, PG op, and Opt). AI, inferior arcuate sulcus; AS, superior arcuate sulcus; C, central sulcus; L, lateral fissure; Lu, lunate sulcus; P, principal sulcus; POs, parieto-occipital sulcus; STS, superior temporal sulcus. From reference 1.

The similarity needed between the observed and the executed motor act (already mapped in the observer's brain) in order to light up a concrete mirror neuron is different from one mirror neuron to another, but it mostly depends on the common goal they share [4]. It is important to note that these neurons in monkeys do not discharge in response to the presentation of food or to the presentation of other objects (non goal-directed actions are known as pantomime).

Therefore, MNS is a complex neural system that unifies action perception and action execution, transforming specific sensory information into a motor code [6]. This system has been studied in monkeys and humans through direct and indirect neurophysiological techniques that go from recording single neurons activity to the use of transcranial magnetic stimulation (TMS), electroencephalography (EEG), magnetoencephalography (MEG), and brain imaging techniques (PET, fMRI):

- Transcranial magnetic stimulation (TMS) creates a strong localized transient magnetic field that induces current flow in underlying neural tissue, causing a temporary disruption of activity in small regions of the brain [6].

- Positron emision tomography (PET) is an "in vivo" imaging technique used for diagnostic examination that involves the acquisition of physiological images based on the detection of positrons, which are emitted from a radioactive substance previously administered to the patient [4].

- Magnetoencephalography (MEG) is a non-invasive technique that allows the detection of the changing magnetic fields that are associated with brain activity on the timescale of milliseconds [4].

- Functional Magnetic Resonance Imaging (fMRI): this technique allows the "in vivo" study of human brain actions, measuring and mapping which areas are functionally involved in concrete tasks.

In humans, areas with mirror mechanism properties are mainly composed by two cortical networks, one formed by the ventral premotor cortex, the inferior parietal lobe and the caudal part of Broca's area, and the second one formed by the insula and the anterior cingulate cortex [7, 8]. The most important visual input to the MNS comes from the posterior part of the superior temporal sulcus (STS). Data suggests that the MNS's frontoparietal network, the most studied one, is in charge of converting sensory inputs into motor representations, allowing us to understand motor actions and intentios of the others [1], while the MNS's composed by the insula and the anterior cingulate gyrus would convert observed feeling expressions into visceromotor responses similar to those responses seen when a person is directly feeling emotions, giving the observer a direct feeling of what another person is experiencing. This plays a role in emotion understanding and empathy [7].

Other networks containing mirror mechanism are involved in coding non goal-directed acts and in converting heard phonemes in motor acts able to generate them, this could be the basis of language evolution.

### 4.1.1 Mirror neurons in monkeys

As mentioned before, mirror neurons were firstly seen in macaque ventral premotor cortex (area F5) and so far, they have been identified in two areas in the cortex: the posterior part of the inferior frontal cortex (PMv) and the anterior part of the inferior parietal lobule (IPL) [9]. Neurons lighting with the observation of actions have also been seen in the cortex of the superior temporal sulcus (STS), they have complex visual properties and some of them activate with the sight of motor acts done by others [4]. However, they lack motor properties, which define mirror neurons, and cannot be considered part of the MNS.

These two areas set up an integrated frontoparietal mirror neuron network that is included in the system of parietofrontal circuits in charge of organizing motor acts in the monkey [5]. Therefore, this MNS connecting IFC and IPL is one of the many neural networks reaching the frontal lobe from the parietal areas whose function is related with sensorimotor integration [9]. Frontal motor areas have representations of the different body parts, and they receive sensory inputs (visual and somatosensory) from the parietal lobe. It is important to anatomically locate the MNS to understand its functions. This sensorimotor integration was studied in monkeys with a network controlling grasping (*Figure 2).*

This grasping network is formed by area F5 and the parietal area in the anterior part of the intraparietal sulcus (AIP). Three different categories of mirror neurons were seen to be taking part in this grasping sytem: visual dominant neurons that light up when the monkey sees a graspable object and a grasping move, visuomotor neurons, which have a more intense activation when grasping and get activated also with the sight of a graspable thing, and motor dominant neurons that fire when observing a grasp action but do not light up with the sight of a graspabe object [1,9].

Visual dominant neurons are seen only in the parietal part of the network (AIP) and they are not considered mirror neurons, and motor dominant and visuomotor mirror neurons are mostly located in the premotor cortex (area F5); mirror neurons fire when observing object-oriented actions done by another person. This finding means that the parietal cortex sends sensory information to area F5, where the information and intention of grasping is processed. In the upper part of area F5 hand actions are represented and, in the lateral part of F5, most are related to mouth actions [10].

The main function of the frontoparietal mirror system is to comprehend actions executed by another individual in an automatic mode, which means that higher association areas are not needed [5]. When a monkey watches another individual (human or monkey) performing an action, mirror neurons that code for that action are fire in the observer's premotor cortex which cause motor representation of the action observed, converting the visual stimuli into motor knowledge [1]. Frontoparietal mirror sytem matches the action seen to the monkey's own motor repertoire (*Figure 3).*

It was then thought that if mirror neurons play a key role in action understanding they should also be triggered when a monkey cannot directly see an action being performed but has enough hints to know what was happening and create a mental representation of it. To test this hypothesis other experiments were done, they showed that more than half of area F5 mirror neurons were able to discharge also when the monkey could not directly see the action done but had enough visual hints to understand that a concrete action was being carried out. Some mirror neurons discharged even with sounds that help the monkey to create the mental representation of the action, these neurons showed to be audio-visual motor neurons. This means that premotor mirror neurons fire when the monkey sets up an internal representation of a motor action even when the monkey cannot directly observe the action [1].

More recent studies about the frontoparietal MNS in monkeys indicate that mirror neurons are part of more complex functions than action understanding; more concretely it has been showed that hand related areas in the IFL code in a different way whether the same motor act has different final goals, for example grasping to eat, grasping to throw or grasping to place. It has been proposed that this frontoparietal MNS organization is the basis to understanding the goal of the whole observed motor act before it is concluded and then anticipate and predict what is going to happen next.

To be activated mirror neurons need a visual input with an interaction between a biological effector, the hand in the cases explained, and an object. Observating an object alone or another individual making non-object directed actions do not fire mirror neurons in macaques and this type of actions, as said before, are called "pantomime" [1]. Data available proves that the frontal and the parietal motor areas mostly code for actions with specific goals instead of simple movement of body parts;

most of the mirror neurons are differently activated depending on the goal. This criteria was used to classify premotor mirror neurons into categories: “grasping neurons”, “holding neurons”, “reaching neurons” [9]. Both IPL and premotor cortex (F5) are organized in motor chains. In one experiment, grasping neurons were observed in two processes, in one condition the observed monkey was grasping food to eat, in the other condition the observed monkey was grasping food to put it into a container, results showed that the intensity of the response in the so called grasping neurons was different (*Figure 4).* This motor chain organization seems to be important to provide fluidity to action execution as they facilitate the activity of these downstream neurons.

In area F5 two types of mirror neurons were described according to their congruency. Those mirror neurons that, to be fire, do not need the sight of exactly the same action that they code are named as “broadly congruent” representing two thirds of F5 mirror neurons and mirror neurons that require that the same observed action and executed action are similar in terms of goal (e.g., grasping) and way of achieving the goal are named as “strictly congruent”, representing one third of area F5 mirror neurons [1,5].

Talking about mouth representation in area F5, two classes of mirror neurons have been found depending on the visual stimuli needed to be triggered: communicative and ingestive mirror neurons. Communicative mirror neurons represent 20% and get activated with communicative gestures (e.g., lip smacking), ingestive mirror neurons represent 80% and they light when observating ingestive actions such as grasping food or sucking. Although there is a lot of controversy about the issue, some studies suggest that during evolution, some communicative movements developed from ingestive motor actions, which would mean that mouth mirror neurons in F5 would reflect a process of corticalization of communicative functions [1,5].

The capacity of being able to learn new skills from observing someone doing them, also known as imitation, is possible thanks to sensorimotor integration. Humans and some primates like apes are able to learn by imitation. In monkeys, learning by imitation is still under debate and there is not direct data correlating mirror neurons activacion with imitation, that is the reason why it is believed that the original and primary function of mirror neurons is action understanding [9, 11].

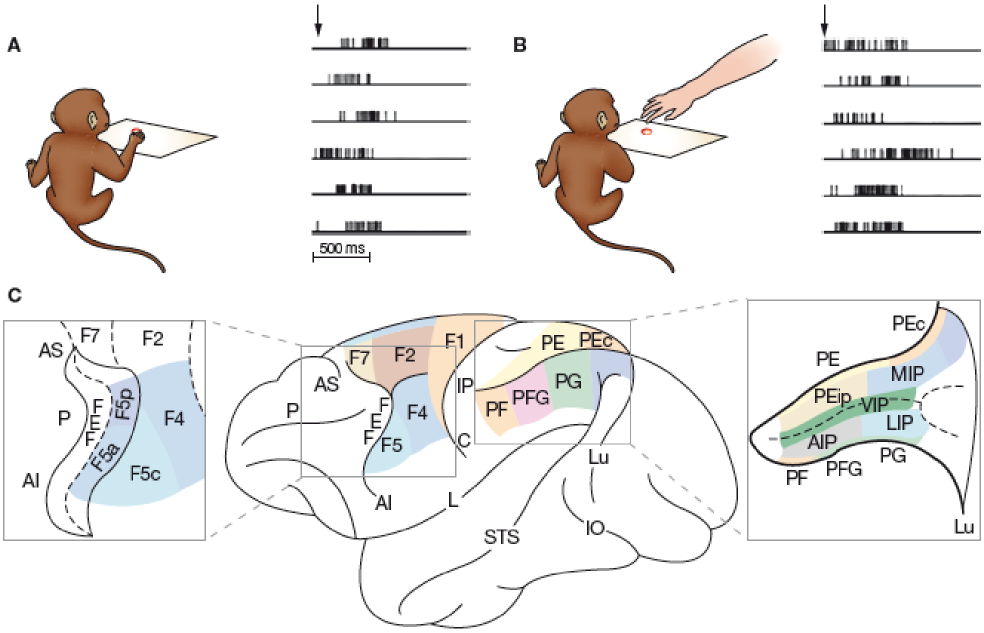



**Figure 2.** A cytoarchitectonic map of the monkey cortex and an example of a mirror neuron. The upper part of the figure shows the activity of a mirror neuron recorded from area F5. The neuron discharges both when the monkey grasps an object (**A**) and when it observes the experimenter grasping the object (**B**). (**C**) The cytoarchitectonic parcellation of the agranular frontal cortex and the parietal lobe. PE, PEc, PEip, PF, PFG and PG are parietal areas. An enlargement of the frontal region shows the three parts of area F5: F5c, F5p and F5a. The mirror neurons are typically found in F5c. The inset on the right shows the areas buried within the intraparietal sulcus. Abbreviations: AI, inferior arcuate sulcus; AIP, anterior intraparietal area; AS, superior arcuate sulcus; C, central sulcus; FEF, frontal eye field; IO, inferior occipital sulcus; IP, inferior precentral sulcus; L, lateral sulcus; LIP, lateral intraparietal area; Lu, lunate sulcus; MIP, medial intraparietal area; P, principal sulcus; STS, superior temporal sulcus; VIP, ventral intraparietal area. From reference 4.

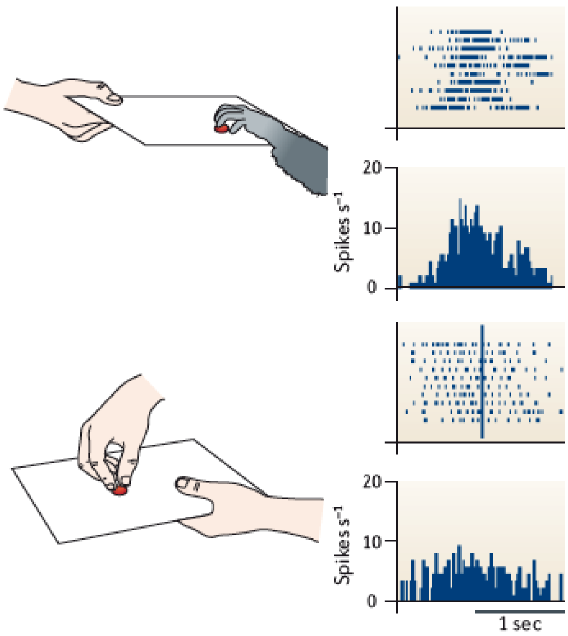



**Figure 3. Mirror neurons in area F5.** The recordings show neural discharges of a mirror neuron in area F5 of the macaque inferior frontal cortex when the monkey grasps food (top) and when the monkey observes the experimenter grasping the food (bottom). Observe how both tasks elicit strong neural responses in area F5. From reference 9.

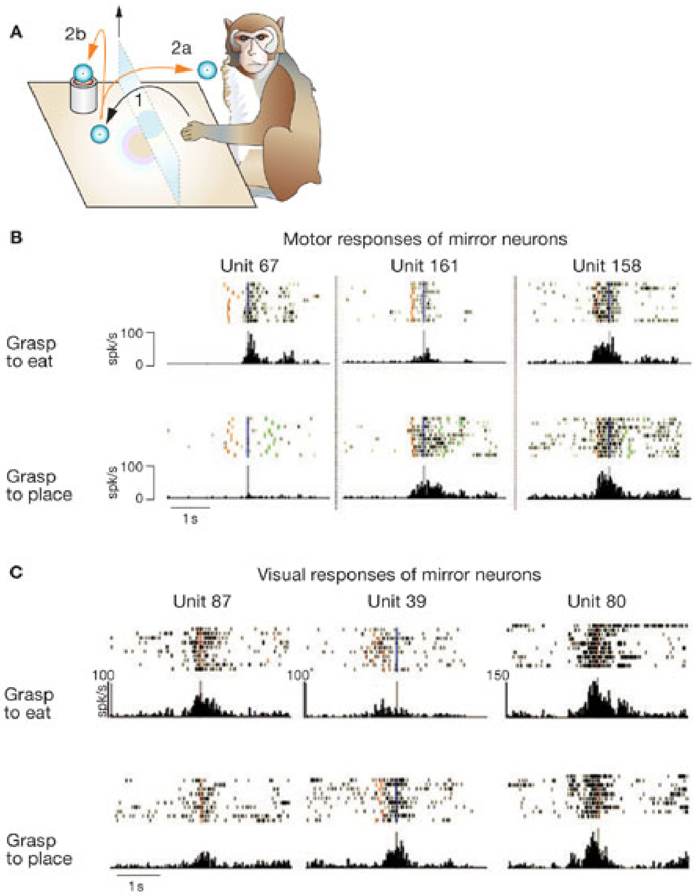



**Figure 4. Action-constrained neurons in the monkey IPL.** (**A**) Apparatus and paradigm used for a task designed to demonstrate action-constrained neurons. The monkey starts from the same position in all trials, reaches for an object (1) and brings it to the mouth (2a) or places it into a container (2b). (**B**) Activity of three IPL neurons during the motor task in conditions 2a (grasp to place) and 2b (grasp to eat). Histograms are synchronized with the moment when the monkey touched the object to be grasped. Unit 67 fires during grasping to eat and not during grasping to place. Unit 161 is selective for grasping to place. Unit 158 does not show any task preference. (**C**) Visual responses of IPL mirror neurons during the observation of grasping to eat and grasping to place performed by an experimenter. Unit 87 is selective for grasping to eat, unit 39 is selective for grasping to place and unit 80 does not display any task preference. Abbreviation: IPL, inferior parietal lobule. From reference 4.

### 4.1.2 Mirror neurons in humans

The evidence of the existence of a MNS in human's motor cortex is based on studies using non-invasive electrophysiological tests and neuroimaging techniques [9]. Electroencephalography (EEG), Magnetoencephalography (MEG), Transcranial stimulation (TMS) or brain imaging techniques as PET or functional MRI (fMRI) have demonstrated the existence of two cortical networks with the properties of mirror neurons in humans; one formed by the parietal lobe, the premotor cortex and the caudal part of the inferior frontal gyrus or frontoparietal mirror system, and the other one formed by the insula and the anterior cingulate cortex known as limbic mirror system [5].

The frontoparietal mirror system is essencial in understanding other people's actions and the intentions behind that actions, it is also thought to be important in observational learning, while the limbic mirror system is more related with recognition of emotions and empathy.

MNS in humans is a wider and more complex visuomotor system than the one we explained in the monkey. The differences between both mirror systems might also explain some functional implications as we will see later [12].

Some experiments have been carried out to study the anatomical representation of the observed motor action in the frontoparietal mirror system. They mainly studied goal-directed actions (also known as transitive actions) and showed that they are coded in the ventral premotor cortex showing a somatotopic organization; mouth acts are coded ventrally, legs are located dorsally and hand actions in the middle. Referring to the inferior parietal cortex, goal-directed acts are represented in the intraparietal sulcus and in the IPL convexity, mouth acts rostrally, hand and arm motor actions caudally, and leg motor acts more caudally and dorsally, mostly corresponding to the MNS areas in the monkey [5, 9]. Non object directed motor acts are represented in the posterior part of the supramarginal gyrus, extending into the angular gyrus. The sight of actions performed using tools, activates the hand region but in the most rostral part of the supramarginal gyrus, ventral to the area of representation of hand grasping. Both the frontal and the parietal areas show a somatotopic organization.

It is thought that the only motor actions capable of activating the MNS are the ones already present in the motor repertoire of the person observing, an study in which mouth motor acts done by humans, dogs and monkeys were presented to humans showed that the IFG and IPL neurons fire only when the action was already present in the observer motor repertoire, for example biting in order to eat, but the same neurons were not activated when the motor act was not included in the motor repertoire of the human, for example barking. It also showed that the intensity of the activation was related with the motor skill that the human presented for that concrete action, the more skilled the person is for one concrete action, higher activation is achieved. Another study on that issue concluded that initial dancers showed a more intense activation as they were being motor trained, this could have a role in post stroke recovery.

The two main differences between human and monkey MNS are, first, intransitive actions (pantomime) activate human MNS and this does not happen in monkeys, that are only fired when observating goal-directed acts. Second, human mirror neurons code also for the simple movements determining an action and not only for the whole action as the monkey system does. These two properties are believed to have a very important role in humans' ability to imitate other people actions [1, 4].

### 4.1.3 Mirror Neuron System Anatomy

Different brain imaging techniques have been widely used to determine the exact location of mirror areas.

The human parietofrontal mirror network accomplishes the same functions mediated by the homologous system in the monkey, understanding both the aim of a motor action donde by others and the intentions behind, so it was expected to be located in similar areas than the one in the monkey [6]. Ample brain imaging studies demonstrate that the MNS in humans is a complex system extended over the occipital, parietal (superior, inferior and the intraparietal sulcus) and temporal visual areas, plus three cortical regions predominantly motor: rostral part of the IPL, the lower part of the precentral gyrus and the posterior part of the IFG. Studies show that the inferior parietal region correspond to PF and PFG in monkeys. About the frontal lobe, the ventral premotor cortex (PMv) and the dorsal premotor cortex (PMd), it seems that the arcuate sulcus and the pars opercularis of IFG (area 44) are the homologous regions for area F5 in monkeys. [5, 13] (*Figure 5).*

Area 44 in humans, besides speech representation, has motor representation of the movements performed with hands and the same is for area F5 in the monkey; observation of neck and proximal arm movements activate the PMv, and hand and mouth movements activate area 44. Data suggests that human PMv corresponds to area F4 in the monkey and human area 44 is the homologue of area F5 in the monkey.

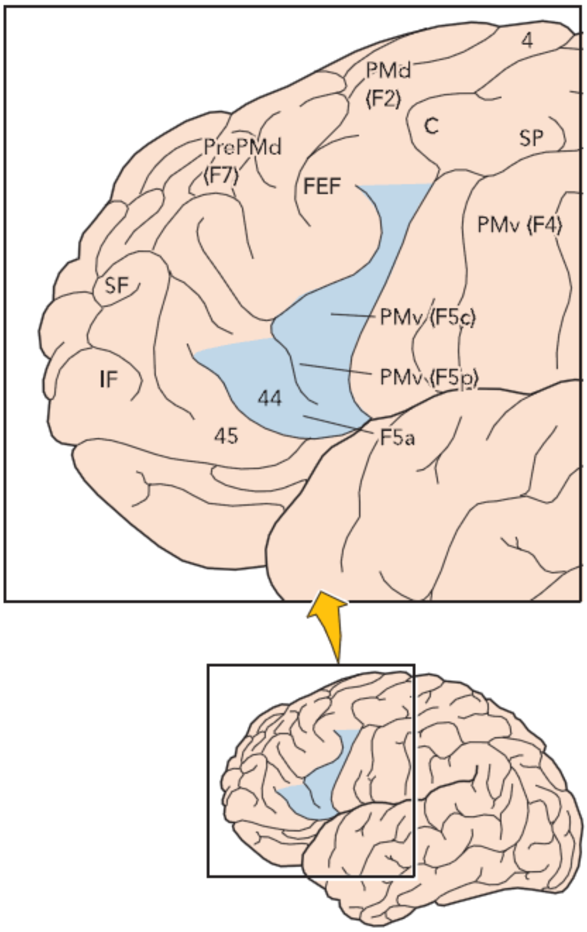



**Figure 5.** Lateral view of human cortex with an enlarged view the frontal lobe cytoarchitectonic subdivision according to Brodmann. The areas in yellow show areas responding to the observation and execution of hand motor acts. *Top*: enlarged view of the frontal lobe. The possible homology between monkey and human premotor cortex are indicated. C, central sulcus; IF, inferior frontal sulcus; FEF, frontal eye field; PMd, dorsal premotor cortex; PMv, ventral premotor cortex; PrePMd, predorsal premotor cortex; SP, upper part of the superior precentral sulcus. From reference 6.

In an interesting and useful study to locate mirror neurons areas in humans, human healthy volunteers were presented with videos showing actions done with different parts of the body: the mouth, arm/hand, and leg/foot, both transitive actions (goal-directed) and intransitive actions (non goal-directed) were played. These situations of motor action observation were contrasted with the sight of static pictures of the face, arm/hand and leg/foot. [14]

The results were as follows: the sight of goal directed mouth movements activated bilaterally the lower part of the precentral gyrus and of the pars opercularis of the IFG plus two activation in the parietal lobe, one in the rostral part of the IPL (corresponding to area PF), and the posterior part of the same lobule. On the other hand, the sight of intransitive actions fires the same premotor areas but they do not fire any spot in the parietal lobe. So it can be said that the observation of goal directed actions activate frontal and parietal areas but non goal-directed actions do not activate parietal areas. The human mirror system areas show somatotopical organization and this somatotopy is the same also found in monkeys. [15]

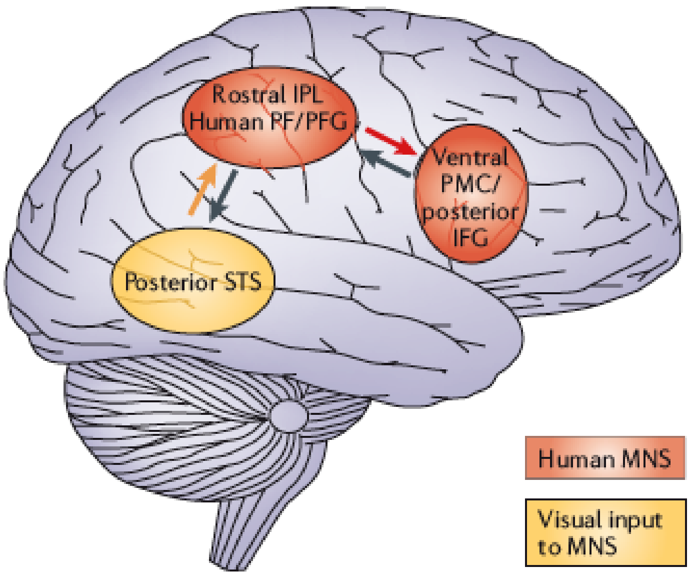



**Figure 6.** Schematic representation of the frontoparietal mirror neuron system (MNS) (red) and its main visual input (yellow) in the human brain. An anterior area with mirror neuron properties is located in the inferior frontal cortex, encompassing the posterior inferior frontal gyrus (IFG) and adjacent ventral premotor cortex (PMC). A posterior area with mirror neuron properties is located in the rostral part of the inferior parietal lobule (IPL), and can be considered the human homologue of area PF/PFG in the macaque. The main visual input to the MNS originates from the posterior sector of the superior temporal sulcus (STS). Together, these three areas form a 'core circuit' for imitation. The visual input from the STS to the MNS is represented by an orange arrow. The red arrow represents the information flow from the parietal MNS, which is mostly concerned with the motoric description of the action, to the frontal MNS, which is more concerned with the goal of the action. The black arrows represent efference copies of motor imitative commands that are sent back to the STS to allow matching between the sensory predictions of imitative motor plans and the visual description of the observed action. From reference 9.

### 4.1.4 Mirror-Neuron System properties: action understanding

Mirror mechanism and its sensorimotor integration play a role in action and intention understanding, action imitation, emotion feeling and probably speech evolution [6].

In everyday social living it is essential to interpret the behaviors of the others around us, this MNS help us to understand the action itself and the intention behind that action. How the mirror system does this has been widely studied, studies from Gallese and Caggiano [16, 17] determining that when we observe someone doing an action, our MNS builds an internal representation of that action in our own motor repertoire, converting sensory inputs into motor patterns similar to the ones that get activated when we perform that action ourselves. This fact implies that the motor act observed is experienced as the observer was actually performing that action, wholly comprehending from the inside its meaning. Motor acts that do not belong to the motor repertoire of the observer do not activate the motor areas (no motor involvement) and are just interprent on a visual basis. The acts that activate the motor system evoke motor resonance that converts the visual inputs into neural patters and knowledge. This all is done without the inferences of higher cognitive associatons. As previously explained, mirror neurons code the action but also the specific aim of the action (grasp to eat, grasp to push it away), this means that the monkey will be able to predict, depending on the contex, what is going to happen next, that is the same as intentions [1, 16, 18].

Depending on the crongruence needed to activate the cell, mirror neurons can be classified in two groups: “strictly” congruent and “broadly” congruent cells [9]. Strictly congruent mirror neurons activate when observing an action that is identical to the executed one (grasping with the thumb and the index). In broadly congruent mirror neurons identical acts are not needed to activate de cell but they have to share a common goal (grasping with the hand or grasping with the index and the thumb). Different activation depending on the goal of an action is thought to be crucial in action understanding as it demonstrates abstract interpretation of observed acts. [9]

Another experiment on this issue showed another remarkable characteristic of the mirror neurons: the intensity of discharge in one concrete cell is different depending on the intention of the motor act, this was tested in monkeys comparing the response in the IPL when grasping food with the underlying intention of eating and grasping food with the intention of placing it in a box [19]. The results were that two thirs of the cells activated more when grasping to eat and when observing someone else grasping to eat, the remaining cells showed the opposite, becoming more active when grasping to place in a box or when observing someone else grasping to put in a box. These results show how the MNS not only builds abstract representation of motor acts but also it interpretates and maps the intention of the action, which could be the basis of empathy.

Therefore, mirror cells have two important qualities, they get activated differently according to the goal and intentions of an observed action no matter how it is achieved and they have selectivity for different motor outcomes according to Gallese studies in 1996 [16].

In 2002, Kohler explained the possibility that MNs code also abstract actions [20], in his study he discovered certain neurons in area F5 that become activated when directly watching a transitive action and, what is more important, they also become activated when the monkey hears a sound clearly related with that action, without any visual input. For example, these mirror neurons light when the monkey sees a peanunt being broken and also when the monkey hears the soubd of a peanut being broken without any sight. These neurons were called audiovisual mirror neurons and with his study Kohler demonstrated that certain mirror neurons have also the capacity of coding abstract actions. This is also relevant because implies that there is an auditory input to the MNS, essential in the hypothesis that the MNS is the basis of neural patterns for language [21].

Another experiment related with this was tested by Caggiano and colleagues in 2009 [22]; recording single cell activity in monkeys, they showed how some mirror neurons activate not mattering how far the action was done from the monkey but, and this is more interesting, some of the mirror neurons fire only when the actions where performed near the monkey, in its peripersonal space in which the monkey was able to interact with the object and action. This means that the MNS is able to differenciate the peripersonal from the extrapersonal actions, thus evaluating others behaviors [4, 22].

Moreover, a class of motor neurons that fire during the sight of motor actions done by others and giving the observer the experienced aspects of the action supports an essential way to connect related acts. How this action-understanding, that links perception, cognition and motor control is achieved was clarified by Rizzolati and Craighero in 2004 [1] that showed how premotor, parietal and primary motor cortex are connected to perceive, build and execute specific goal-directed actions being the basis of understanding intentions behind actions. As mention before, other studies also tested how some mirror neurons in humans also activate with intransitive, meaningless actions.

As Broca's area is the human homologous of the monkey area F5, studies showed how the activation of this area is higher while observing mouth actions as Iacoboni proposed in 1999 [16]. Knowning the characteristics of Broca's area, it was also studied whether people that presented lesions in the posterior part of the IFG (Broca's area) showed impairments in speech production and articulation (as motor area) but also impairments in speech comprehension as corresponds with the MNS deficits [11, 16], most of the studies showed how these patients had trouble in speech production and comprehension [16, 23]. Furthermore, mouth representation in the mirror motor system, especially for those movements in which the final intention is communicate, supports the hypothesis of mirror neurons being the basis of empathy as most of the feelings are expressed through facial acts.

To sum up, mirror neurons resonating in motor areas when we observe a goal-directed action is highly relevant to daily life, this way we have a direct experience and understanding of the observed actions and intentions behind that actions allowing us to continuously interpretate others behaviours so we can adapt ours.

### 4.1.4 Mirror Neuron System properties: action imitation

When MNS studies began in the 1990's using fMRI, PET and TMS to evidence the existence of the MNS they did not test imitation [6, 9]. The mirror system that we described so far is involved in action and intention understanding but we mentioned that MNS is the basis of other important functions for humans such as imitation. It was not until the last years of the 1990's when scientists studied the link between MNS and imitation using fMRI [6, 9].

Knowing that mirror neurons activate more during action execution than during action observation and assuming that when we imitate we, at the same time observe and execute, it could be suggested that mirror cells would be more intense activated while imitating [9]. One fMRI study was performed in humans in order to prove this hypothesis, showing that when imitating (finger movements in the case of the study), two human brain areas show higher response intensity, the pars opercularis of the IFG and the rostral part of the parietal lobe [11] (*Figure 6).* In the last 15 years there has been a great interest in comprehending imitation and its neurobiology [24].

Imitation is the capacity to learn new motor skills from seeing them done, which means acquiring by observation, new motor actions [24]. This has an essential role in human behavior development, learning, social cognition, and trasmission of knowledge and culture [24]. Imitation requires the capacity to convert sensory inputs into motor representations. The hypothesis relating imitation and MNS suggests that imitative learning is a resonance mechanism in which the observed motor act is directly mapped in the internal representation of the same act, matching both motor acts [6].

Iacoboni and colleagues showed that the activation of the MNS was more intense while imitating [24, 25]. The circuit in charge of imitation coincides with the one discharging in action imitation, being composed of three parts: the posterior part of the STS, the IPL and the posterior part of IFG and adjacent ventral premotor cortex [24].

Since the first years of MNS study in humans it was relatively clear that the human network has a property not seen in monkeys, its capacity to be active with non goal-directed actions also known as intransitive or meaningless [6, 9]. TMS studies evidence that the sight of goal-directed and non goal-directed increase the motor evoked potentials recorded in the obrserver's arm and hand muscles in charge of producing the motor acts observed. The evidence of the MNS also responding to meaningless acts has a great importance in imitation [26].

The underlying mechanism involved in imitation learning seems to be more complex, being the result of different processes: decomposition of the whole motor action in basic motor components of the action to be learnt by imitation and converting them into motor representations (this activates PF, PMv and pars opercularis of IFG) and organization of these motor acts in temporospatial patterns identical to the ones observed [11, 24, 25]. There is evidence that the first part is done by the MNS but the other one is done by the premotor cortex and more concrete area 46 that puts together all the information, recombining the motor elements and building a new pattern [5].

So the information processing in imitation learning is as following explained: the posterior part of the STS processes the observed motor act visual input and sends this information to the IPL, posterior part of the IFG and ventral premotor cortex (vPMC), these areas form the MNS activated in action observation, action execution and simple imitation. This MNS would decomposed the observed motor act into basic motor representations of the whole action in the observer's brain and send the motor pattern of the action to be learnt by imitation back to the STS. In the STS the motor pattern, the visual input of the observed act, and the planned imitative act are put together what is known as "matching process". If the match is successfully done the action will be executed but if the match is not good there will be a correction of the motor act planned. The basic motor representation will be recombined in the premotor cortex to finish with the learning by imitation process.

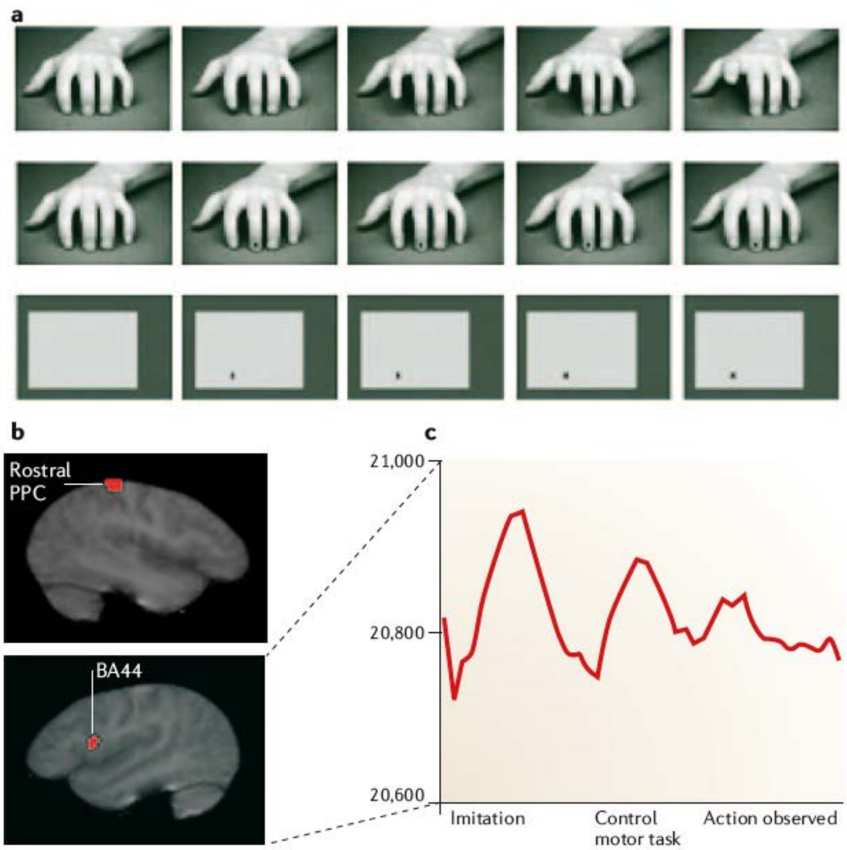



**Figure 7. The human mirror neuron system and imitation:** fMRI study of imitation of finger movements showing two human cortical areas with the predicted pattern of activity for mirror neuron areas. **a)** Participants observed or imitated the lifting of the index or the middle finger (top). In visual control conditions they observed a cross appearing on the index or middle finger of a static hand (middle), or appearing on the left or right side of a grey rectangle (bottom). In motor control conditions, partipants lifted the index or middle finger in response to the appearance of the cross. **b)** The two areas showing the predicted pattern of higher activity for the control motor task compared with action observation, and highest activity during imitation, were located in the inferior frontal cortex (Brodmann's area 44; BA44) and in the rostral part of the posterior parietal cortex (PPC). **c)** Blood-oxygen-leveldependent (BOLD) fMRI activity in signal intensity rescaled by smoothing measured in BA44 shows the predicted pattern of activity for mirror neuron areas. From reference 11.

## 4.2. MIRROR NEURONS AND HUMAN EVOLUTION

### 4.2.1 Language

Many studies try to link MNS with language evolution, concluding that mirror neurons could be the origin of neural networks concerned with language in the human brain [1]. This hypothesis is mainly supported by anatomical facts: the homology between Brodmann area 44 in inferior part of the frontal lobe in humans and area F5 in the monkey brain, an area that is strongly linked with speech [16, 26]. However, there is still a lot of disagreement discussing if human language comes from animal sounds or gestures [6].

Liberman and collaborators defend the Motor Theory of speech perception (MT) [28, 29], for them, the most important characteristic of speech is that it activates the motor patterns of the heard sound in the person listening, proposing that there is a MNS transforming heard sounds (phonemes) in motor representations of the sound. There seems to be no doubt about the potential role of this system in language but it is still under debate how much it is implicated in the understanding of words meaning.

The motor theory of language suggests that the objects of language perception are the gestures, instead of acoustic sounds, similar to what it happens with action understanding in MNS [6]. Thus, this theory proposes that speech was developed from gestural motor acts, being related with imitation and the capacity of MNS in humans to be triggered with non goal-directed actions [30]. According to this hypothesis, during speech evolution, the gesture motor acts had to be converted into abstract sounds, as gestures and the meaning of the words are not related, which implies that arm / hand and speech gestures were put together sharing neural patterns. Some fMRI and TMS studies have support this motor theory as they show how motor speech areas are activated when perceiving speech, but it is not clear if this activacion is really necessary to understand the speech. Other studies showed that arm / hand motor representation areas in the cortex activate when a person is speaking and also reeding, linking hand and mouth motor acts.

Differently, in the monkey's brain we explained before how a special type of mirrors were found in area F5, able to activate motor representation of an action when the monkey hears a sound related with a motor action even if the monkey does not receives a visual stimuli (breaking a peanut, tearing paper); these neurons are know as audiovisual mirror neurons and evidenced the existence of auditory imputs activating motor areas [20]. The main difference with MNS is that monkey's neurons code only for goal directed actions and are not enough to build an intentional speech network [6].

Thus, it was hypothesized that in humans word meaning should have emerged when linking sounds with non goal-directed motor acts (pantomime). At the beginning of speech evolution, probably the understanding of the words happened in a way similar to the monkey: mouth ingestive sounds activated audio-visual mirror cells related with ingestive acts; later on evolution imitation improved, being the humans able to create sounds that were characteristic of a concrete mouth action without performing the action, being the basis of an auditory mirror network that finally was independent from the audio-visual network. The premotor cortex would be the area in charge of building sounds without motor acts and echo-neurons, motor mirror neurons that activate when producing sounds and hearing sounds, appeared. Broadman area 44 (Broca's area) is the evolution resulting area where phonemas, semantic, ingestive motor acts and hand acts are all recombined [6].

MNS is a particular higher motor system, and higher order motor systems are prone to be bilateral so it would be logical to think that MNS would be bilaterally represented [9]. TMS experiments studying action obvservation and imitation support the hyphothesis that the MNS activation is mainly bilateral. However it is known that language is a left lateralize network. As suggested, language originally comes from action observation and imitation MNS, but this needs to explain the lateralization issue. To study this a TMS experiment tested how was the motor activation in both hemispheres when people were listening to action sounds, showing that it happened only in the left human brain. This suggests that left brain motor areas are activated with visual and auditory inputs while right brain motor areas are activated only with visual stimuli. The evolution from a visual MNS to a multimodal MNS is supposed to have determined left lateralization of speech functions [6, 9, 31].

### 4.1.2 Emotion recognition

Although still under debate, fear, sadness, anger, disgust, happiness and love seem to be the basic emotions, as they are present in human beings in spite of race [6].

Disgust has been one of the most studied emotions and brain imaging techniques showed that when humans are exposed to smells or tastes that disgust us two areas of the brain get activated: the amygdala and the insula. The insula has two functionally different parts, the anterior part comprising the agranular and the anterior disgranular insular, and a posterior part including the posterior disgranular and the granular insula. Gustatory and olfactory inputs are sent to the anterior part and seem to control visceroautonomic responses. Besides, STS sends visual inputs to the anterior part of the insula. On the other side, the posterior functional part is linked with premotor, somatosensory and auditory areas. [26, 32, 33] This suggests that the insula is not only a sensory area and to prove this theory, electrical stimulation studies were done, showing that the stimulation of the insula in the monkey and in humans evokes body movements together with autonomic visceromotor responses.

Wicker and collaborators [34] demonstrated with brain fMRI how the sight of faces expressing disgust also lights the anterior insula, and investigated if these activated areas were the same that the ones activated when feeling disgust. To test this, volunteers were exposed to disgusting and pleasant smells directly and then they were showed a video where pleople were exposed to disgusting and pleasant smells. When directly feeling disgust three areas fired: insula, amygdala and the anterior cingulate cortex. The sight of people expressing disgusting feelings activated the insula and anterior cingulate cortex but do not fire the amygdala. With this, they evidenced that some neurons in the insula and anterior cingulate cortex behave like mirror neurons becoming active in expressing feelings and in observing others expressing feelings. Evidence in pain field demonstrated a mirror network similar to the one operating in disgust.

It is important to note that even though activation of visceromotor structures seems to be the basis for emotion recognition, this does not means that cognition indirectly recognizes emotions, but the cognitive emotion recognition is different from the one controlled by the insula and the anterior cingulate cortex, being the second one the only that builds a link of shared feeling between the observer an the person observed.

### 4.3. DEFINITION OF EMPATHY: MIRROR NEURON SYTEM AND SOCIAL INTERACTION

Not understanding how another person feels about us is a scary situation, as we do not know the intentions or if the other individual wants to hurt us [35].

Both, imitation and action understanding seem to be essential for developing social cognition what suggests that mirror mechanisms are also the key in understanding others emotions. But for comprehending emotions the limbic system is also necessary. In the brain, the frontoparietal MNS and the limbic system are anatomically linked by the insula which probably means that the frontoparietal MNS, the insula and some limbic areas (cingulate cortex) are involved in empathy [9, 35].

When we observe someone expressing feelings we share common states, being able to understand what the other is feeling and predict what will happen next. This connection allows the individual to adapt his behavior and react to the situation that he is living.

Preston and de Waal in 2001 proposed that observation and imagination of emotional expressions activate representations in the observer (first hand experience) together with autonomic and somatic responses [36]. MNS would be the neural mechanism of empathy.

Empathy, described as the ability to share the feelings of others, is essential for us as we live in society. Empathy occurs when the observation of emotional expressions in another person evokes shared states in us. The difference between empathizing and sympathy or compassion is that while empathy with a person that is suffering pain give us a direct feeling of pain, sympathy and compassion just give us the feeling of need to help or caring about that person [37, 38]. To understand the neurobiology of empathy, theory of mind (TOM) has been proposed. TOM says that we are capable of comprehend our own and other people's emotional states letting us predict others behaviors [39]. One example of disorder related with impaired TOM is ASD.

TOM proposes MNS as the network allowing people to create fast, shared mental states that let us evaluate actions without cognitive mediation, representing the observed feeling state as if it our own mental state. Secondly a more complex cognitive system would take part creating higher reasoning about those feelings. There is some neurophysiological evidence that supports this idea. When we talked about mirror neurons properties, we mentioned that they code the motor action and also the intentions behind that motor action, being activated in a different way whether the intention was grasping to eat or grasping to put in a box. This fact would be highly relevant to understand the intentions related with others actions [9].

As previously explained, human imaging studies showed how feelings observed in others activate areas also fired in our own emotional states, specially anterior insula and cingulate cortex. This evidences that empathy is based on affective shared states of direct and observed expression of feelings, allowing us to predict behaviours and adapt ours to different social situations [37].

Evidence of TOM comes mostly from studies using fMRI confirming that observing others expression of feelings, activates brain areas that are also activated when we experiment those feelings in first hand, supporting the hypothesis of shared states, these areas are the anterior insula and anterior cingulate cortex [35, 36]. Since the first fMRI experiments that mainly focused on pain and disgust many feelings have been studied: fear, sadness, anger, anxiety, and even more complicated feelings such as social exclusion or embarrassment. We will now explain how this system works for pain [40], as is one of the most well studied emotions.

When we directly experience a painful stimuli, several areas in the brain fire: premotor and prefrontal cortex, primary and secondary somatosensory cortex, insula, anterior cingulate cortex, thalamic and brain stem regions (periaqueductal gray), amygdala and cerebellum [37]. Somatosensory areas and posterior insula are related with the sensory and discrimintative features of pain stimuli. An interesting study was performed [41, 42]: volunteer couples were selected and they were individually applied pain stimuli, the activated areas were shown to be the ones named above. Then, females were able to see the facial expression of her partner in pain; in this latter situation there was activation of the anterior insula, anterior cingulate cortex, brain stem and cerebellum. While insula is thought to integrate and represent emotional states, anterior cingulate cortex is more related with the motivational and action part of the emotional state. Anterior insula and cingulate cortex with limbic and subcortical regions compose a network that evaluate the content of stimuli (internal and external) to control and regulate context behaviors.

Therefore it can be said that in order to adapt to different social contexts certain requierements are needed: affective sharing, self-recognition of own feelings and self-other distinction. This is important because if we assume that understanding our own feelings is necessary to comprehend others emotions, alteration of these networks will make impossible to understand other people’s states, and social cognition will be severely impaired [1,9].

## 4.4. ROLE OF MIRROR NEURONS IN NEUROLOGICAL DISEASES

When mirror neurons, able to get activated when performing and action and also when observating another individual doing a similar action were described, a new neurophysiological mechanism appeared and with it apparently some disorders related with impairments in social cognition could be explained [9]. It is important to point out that the MNS is not an independent system and it is now clear that most cortical areas organizing motor outputs show somehow response to motor observation. This means that when there is a deficit in MNS the impairment caused is not selective as it could be expected from other brain areas [5].

Once that we explained the neurophysiological characteristics of mirror neurons, and knowing that these neurons are essential for imitation and consequently for social understanding and social behavior, it was proposed that MNS deficits could be related with diseases that present social cognition dysfunction. An impairment of MNS activity would not allow understanding others' behaviors, leading to social deficits.

ASD is until now, the most studied condition related with MNS impairment, being widely tested using different approaches. People with autism usually evidence lack of empathy, deficits in imitation and self-awareness, features that are linked with MNS [9]. Through the following pages we will review ASD, and another important disease that also shows great impairments in social behaviour such as Schizophrenia [43].

Another aspect that is already linked with MNS is post stroke rehabilitation, as MNS could play an important role in creating new rehabilitation techniques inducing cortical plasticity to improve the outcomes of these patients. These new techniques would be based on action observation.

## 4.5. AUTISM SPECTRUM DISORDERS (ASD)

ASD is the term used to classify several heterogeneus neurodevelopmental conditions characterized, according to the Diagnostic and Statistical Manual V (DSM V) [44], by anomalies in two key domains: social communication, and repetitive and/or stereotyped patterns of behaviour. Some clinical features that we can find in these patients are: strong deficits in reciprocal social cognition that determines poor social interaction, deficits in communication, and restricted, repetitive and sterotyped patterns of behavior or interests. Difficulties in social cognition involve lack of attention, ability to imitate, empathy and social anxiety; communication deficits include odd prosody, lack of understanding implicit meanings in sentences and altered speech development; and stereotyped patters of behavior or interests is visible in strong interest in some concrete fields, rituals, unability to understand global function and inflexibility [9, 45, 46, 47, 48].

The prevalence of ASD is 1 in 150 chlidren (1-2% of population) [48] and it includes a wide range of phenotypes from high-functioning conditions to children with strong mental deficits. Nowadays, the diagnosis is still made according to its behavioural presentation.

ASD affects many nervous structures, from the brain cortex to the cerebellum and brainstem. However, although the neuropathophysiology of ASD is still unclear, it is strongly believed that some of ASD symptoms such as social cognition impairment, communication deficits or poor emotion recognition are related with MNS dysfunction in this social isolating condition [45, 47]. In 1999 two different scientific groups, suggested that MNs could be a neural substrate for understanding actions of other people, creating a connection between ASD and MNS [47] and, to date, although still little, there is growing evidence to support the idea that MNS areas are structurally or functionally impaired in people with autism [9]. This link firstly established in 1999 between aberrant development of mirror properties and ASD could be used to develop new ways of rehabilitation based on motor and cognitive strategies. Development of approaches targeting MNS is particularly important because at present, there are not many evidence-based interventions that enhance significant improvements in social communication in individuals with ASD [49].

Leo Kanner in Baltimore in 1943 and Hans Asperger in Wien in 1944 described for the first time and nearly simultaneously this syndrome, and that is why this condition is also known as Kanner-Asperger disease [50].

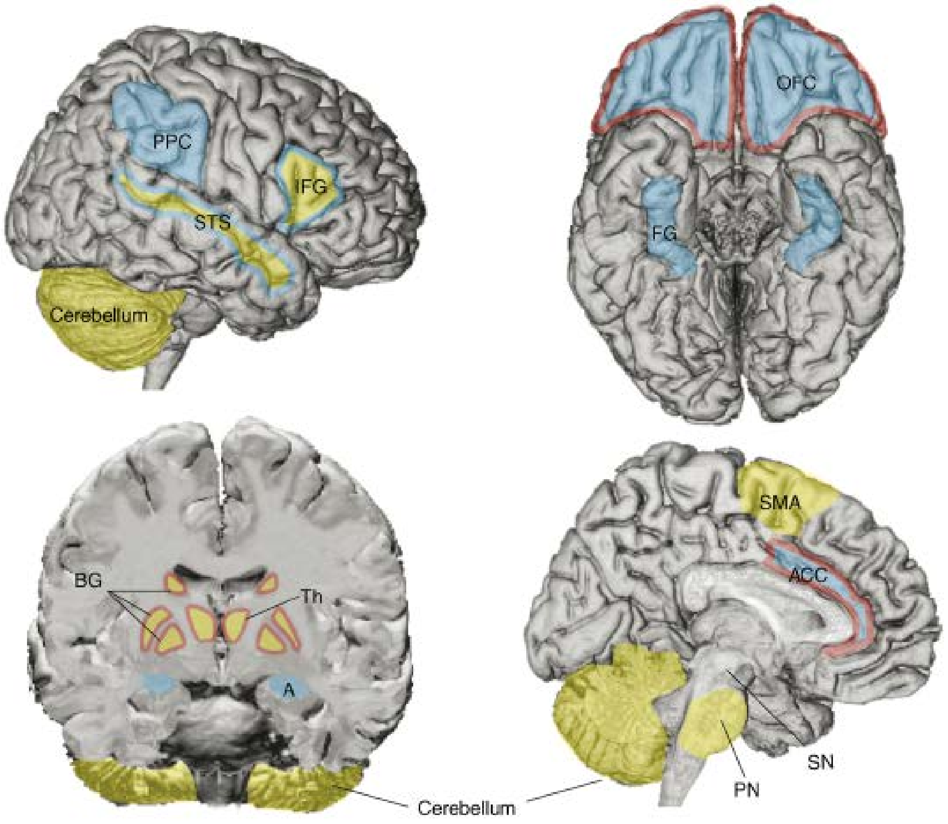
Kanner described autisim associating three core items: impairments in reciprocal social interactions; abnormal use of language; and repetitive and ritualized behaviors [51, 52]. Hans Asperger, in his children clinic, observed a particular type of infants among those with intellectual disabilities (mental retardation) whose characteristics were different from the others: they showed lack of social communication (verbal and non verbal), lack of affective contact with the others, fascination for some objets and repetitive behaviors. At the same type some of these children had extraordinary abilities in some fields such as memory or numbers. He concluded that, unlike the other children with intellectual disabilities, this particular group seemed to have impairments in some intellectual areas but not in others [51, 52].

Moreover, ASD presents co-morbid neurological disorders: the prevalence of mental retardation in idiopathic autism is 60%, epilepsy appears more often and anxiety is also very common, being related with their incapacity to understand the world happening around them [46].

Referring to the onset in ASD there is heterogeneity: some children present syptoms of developmental delay in the first 18 months of life, however, 25%-40% of infants with autism initially show a nearly normal development until 18–24 months, when they regress into an autism indistinguishable from the early onset one [46].

Anatomically, different brain regions have been studied with TMS and fMRI and are thought to be involved in the core ASD symptoms: social interaction includes regions of the frontal lobe, parietal lobe, superior temporal cortex and amygdala; language function is more related with Broca's area in the inferior frontal gyrus, parts of the supplementary motor cortex, Wernicke's area and superior temporal sulcus; repetitive and stereotyped patterns of behavior involve frontal cortex and caudate nucleus [46] (*Figure 7).*

Some experiments suggest, although is not really clear, that brain enlargement is found in children with autism, this enlargement is in terms of white matter, not gray matter. The most important increases have been found in the frontal lobes. Studies also suggest that amygdala enlargement would be related with more severe anxiety and worse social and communication skills and caudate nucleus enlargement would be related with more repetitive behaviors. There is still a lot of controversy in this field.




| Social impairment | Communication deficits | Repetitive behaviors |
|---|---|---|
| OFC – Orbitofrontal cortex<br>ACC – Anterior cingulate cortex<br>FG – Fusiform gyrus<br>STS – Superior temporal sulcus<br>A – Amygdala mirror neuron regions<br>IFG – Inferior frontal gyrus<br>PPC – Posterior parietal cortex | IFG- Inferior frontal gyrus (Broca's area)<br>STS – Superior temporal sulcus<br>SMA – Supplementary motor area<br>BG – Basal ganglia<br>SN – Substantia nigra<br>Th – Thalamus<br>PN – Pontine nuclei cerebellum | OFC – Orbitofrontal cortex<br>ACC – Anterior cingulate cortex<br>BG – Basal ganglia<br>Th – Thalamus |

*TRENDS in Neurosciences*

**Figure 7**. **Neuroanatomy of autism:** brain areas that have been implicated in the mediation of the three core behaviors that are impaired in autism: social behavior, language and communication, and repetitive and stereotyped behaviors. From reference 46.

### 4.5.1 Mirror Neuron System in ASD

Before the discovery of MNS, the most accepted theory about ASD was that it was caused by an unability to match self and others representations, but the neurophysiological process underlying was not clear [45].

MNS is formed by neurons able to fire with visual, motor and auditory inputs coming from others, this means that they can '"mirror"' others actions and behaviors being an integration system of what we see, hear and do, allowing us to recognize the goals and intections behind a motor action [53]. Therefore, MNS has been proposed to have an important role in action understanding, imitation, empathy, theory of mind and speech [45]. Taking into account its integration properties, in infants, mirror neurons are proposed to let them learn from other's actions and understand actions and intentions, by mapping those actions into their own motor representations. Through this, the kid has a first-hand experience of that action and is able to predict the action itself and the mental state of the observed person as TOM proposes, comprehending the person being observed aims, desires and beliefs [45]. In ASD children, MNS is thought to be dysfunctional, which is known as "broken mirror hypothesis" [43] and this potentially causes different deficits that include imitation learning, communication and social cognition disorders, but it is also important to clarify that MNS is unlikely to cause all the symptoms in ASD.

Research using fMRI, TMS, and EEG provide indirect evidence that MN constitute a fronto-parieto network in humans; these regions are the ventral premotor cortex (vPMC), the IFG, the IPL and the STS [48]. More recent depth electrode research on humans suggests neurons with mirror properties are located in supplementary motor areas and medial temporal areas, in addition to the anterior cingulated cortex. Nowadays, the ASDs are still diagnosed according to symptoms, but since studies about MNS began, a marker correlating mirror neurons activity was searched. This marker seemed to be mu rhythm in EEG [48].

Mu rhythm is caused by the spontaneous electrical activity in sensorimotor cortex, being its frequency between 8 and 13 Hz [50]. When we perform a movement, sensorimotor neurons are desynchronized by premotor cortex suppressing the mu rhythm, as premotor cortex is known to have mirror neuron activity. This mu suppression could be also predicted to happen when observing a motor action, and it actually happens. This is why mu suppression is nowadays considered a marker of mirror mechanism activity, which indirectly means that if MNS is properly working; when we observe, hear or perform actions, the mu frequency range will be suppressed in EEG [50]. As MNS in ASD is hypothesized to be dysfunctional, children with autism would not present normal mu suppression when observing someone performing an action [45, 48]. Some experiments show how mu rhythm suppression does not happen (or is reduced) in children suffering from ASD when they are observing an action being done by someone else (the difference with normal volunteers is more intense when observing actions with emotional or social implications) [39, 54, 55]. There are also few studies providing contradictory results. It can be predicted that in order to try to improve abilities and funcionality in ASD, a target element has to be the MNS.

These mu rhythm experiments also demonstrated how children with ASD (and also the comparing normal developing kids) have greater mu rhythm suppression when observing actions done by a relative (parents) [55], revealing that mu suppression depended on the familiarity of the observer with the observed, which suggests that improvements in social cognition and communication skills can be achieved with therapies in which ASD children interact with their families.

Besides EEG, several studies including fMRI, TMS and MEG suggest that MNS could work unproperly in children with ASD [45].

MRI has been used to measure the size of MNS areas and other relevant areas in social cognition. Studies comparing ASD people with normal volunteers showed thinner gray matter in the pars opercularis, IPL and superior sulcus in ASD [50]. Another ample used method to study mirror neurons in autism is fMRI, the blood oxygen level dependent (BOLD) in mirror areas is measured and compared in ASD and normal volunteers when observing people performing goal-directed actions. While observating and imitating facial expressions showing basic emotions, there is evidence of reduced BOLD response in regions believed to have MN properties in ASD compared to typically developing volunteers [48]. *Figure 8* shows the result of one of these studies in which high-functioning children with ASD were compared with normal developing volunteers when observing and imitating emotional face expressions. Results showed weaker activation of the MNS in ASD children and the intensity of the activation was inversely related to symptom severity.

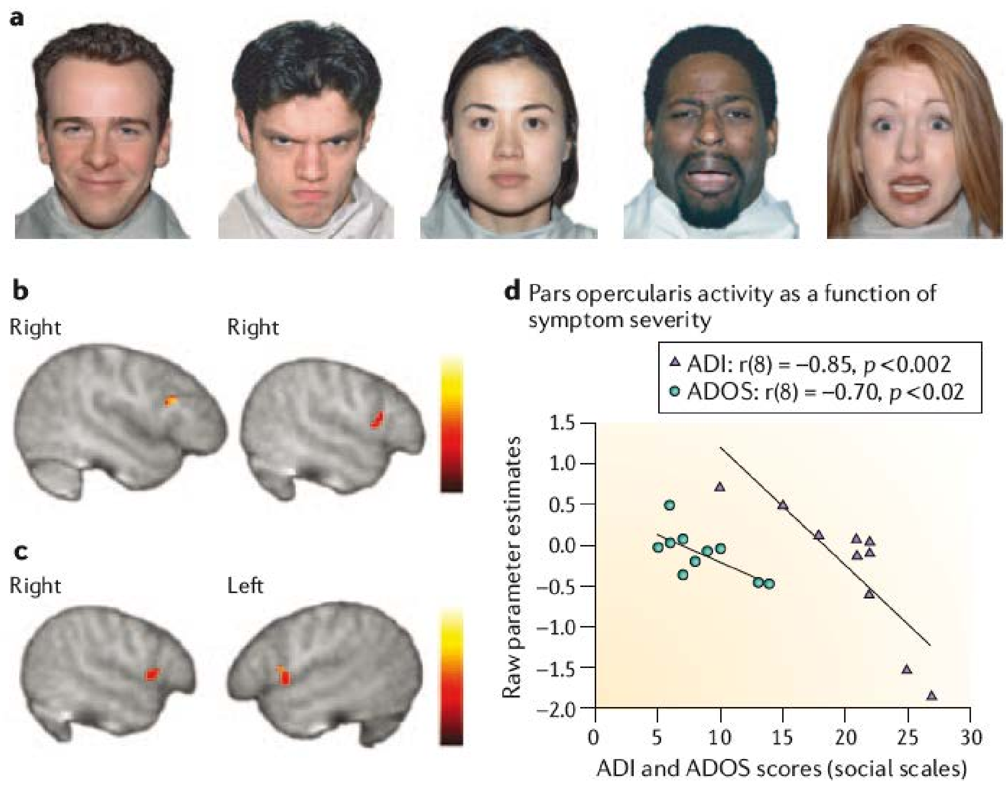



**Figure 8. The human mirror neuron system and autism.** Typically developing children and children with autism were studied with functional MRI while they observed or imitated facial emotional expressions (a). Compared with typically developing children, children with autism demonstrated reduced activity in the frontal mirror neuron system (MNS) area located in the pars opercularis of the IFG. Moreover, this activity correlated with the severity of disorder as assessed by widely used clinical scales, the Autism Diagnostic Observation Interview (ADI) (b) and the Autism Diagnostic Observation Schedule (ADOS) (c), such that the higher the severity of disease, the lower the activity in the MNS. From reference 56.

Little evidence is still available about dysfunction of MNS in ASD, but the current evidence shows MNS impairment (funcion and structure) in ASD patients. This was more intense when the actions observed involved social interaction or emotional states, and less intense when interacting with relatives [50, 56]. MNS in healthy people shows plasticity and its properties can be increased with MNS targeted sensorimotor tasks or imitation, this can also happen in ASD. Some studies already done showed how enhancing MNS in ASD through imitation learning could improve autistic core symptoms.

As previously explained, imitation is the most important way of learning that children have in order to get new skills and it is also a key point to develop social cognition, understanding other people's intentions, desires and goals [9, 57]. The discovery of mirror neurons, distinguished from other motor neurons by discharging both when an individual performs an action and when an individual watches another performing a similar action and thus being able to unify perception and execution, represented a mechanism that could explain among others imitation, and that is supposed to be essential in early social, communicative and affective development [48]. Lack of capacity to imitate is a core symptom in autism, and empathy is also linked with imitation. Impairment in self-other awareness has been proposed as a possible cause for these imitation deficits defining also other issues such as problems with communication, theory of mind related capacities or failure to have empathy in social interactions. TOM proposes that we understand others mental states as they activate inner mental representations in our brain, and this way we can understand others goals and desires [57].

In this sense, frontoparietal MNS is essential to create self-other recognition. TMS and fMRI studies showed how frontoparietal right structures overlapping with MNS get activated when recognizing our own face, compared with recognizing other faces, so frontoparietal MNS is thought to be important in self-other awareness being a basic fact in social functioning. Studies evidence that MNS is already functioning during the first living months, one-year-old kids (humans and monkeys) can imitate facial and hand movements and also predict the goal of an action performed by another person, and these studies also showed how activity in the MNS is related with the level of empathic response and social behavior skills. This correlation is also seen in adults [58].

Using TMS, disfunctionally corticospinal motor facilitation during action observation has been seen in autistic individuals. Moreover, ASD children, do not imitate other people in a mirror way when observing them face to face. This fact is probably due to a deficit in the ability of the mirror mechanism to superimpose another person's movements on one's own [58].

MEG studies show that the activation in the temporal circuit for imitation is delayed in patients with Asperger's syndrome compared with volunteers, probably related with a connectivity failure between the MNS regions and their visual inputs. There is also evidence of disordered functional connectivity between visual and inferior frontal mirror neuron areas and between frontal and parietal areas in patients with ASD [56, 58].

Another interesting study in ASD field compared the EMG activity of the mylohyoid muscle (used in mouth opening) in ASD and in normal developing children while observing another person grasping food for eating and grasping paper to put it in a box

[59]. Final results showed how observation of food grasping activated mylohyoid muscle in typically developing children but not in ASD, suggesting that mirror system is not activated in ASD while observing others motor acts. This involves that immediate understanding of the action and its associated intention is not possible in these individuals. The results also showed how both types of children could recognize what the observed person was doing, but children with ASD could not recognize why the act was done, interpreting the intention from the semantic of the object, for example when an ASD person sees a person with scissors, no matter how the scissors are grasped, they always attibute the "cut" intention to the action. This implies that ASD children interpretate others behaviors according to the normal use of the objects instead of the behaviour of the person with that object, lacking the capacity to understand others intentions [56, 59].

All together, these data supports the hypothesis that MNS dysfunction is a core deficit in autism, and that activity in mirror neuron areas during social mirroring could be an effective biomarker of the impairment of patients with ASD. Recent studies of the MNS in autism and the connection between the MNS and imitation suggest that action imitation could be used as a potential way of treatment in children with ASD. Furthermore, behavioural experiments already seem to support this hypothesis. In one study, two groups of children with autism interacted with an adult, and the adult imitated the actions of the children in only one group. Children in the group whose actions were imitated had a higher tendency to initiate social interactions in a later session compared with the group of children that had only a normal interaction with the adult, with no imitation [60, 61].

Another ASD therapy approach is music making (singing or playing instruments), as this is an activity that implies brain areas overlapping with MNS regions. Knowing the role that MNS is thought to play in understanding the intentions behind and action and social communication, a treatment targetting MNS may have significant clinical potential. Music making implies multimodal stimulus involving visual, auditory, somatosensory, and motor information; then used to execute motor actions, and listening to music involves emotional feelings which can be also positive for ASD patientes as they lack abilities to process emotions. Listening and playing music could help children with autism in interacting with others through acquiring motor, language and social skills [49].

## 4.6. SCHIZOPHRENIA

Evolutionary biologists categorize schizophrenia as a disorder of the social brain; the reason is that schizophrenic patients present disturbances in several social abilities such as social cognition, emotional recognition and social perception of others. MNS discovery opened a new field of study in the neurobiology of disorders affecting the social brain including schizophrenia [60].

The neural mechanisms behind are not well defined yet, but over the last decade MNS disfunction has been proposed to be the cause of some of the symptoms in this condition for example social cognition symptoms, ego-boundary defitics and negative symptoms [35, 43]. Although the available evidence relating MNS and schizophrenia is still in its infancy, there is some evidence to support this fact.

Until now, most of the testing experiments showed how mirror neuron activity is decreased in people with schizophrenia compared with healthy controls, and another key point seems to be that the more severe negative symptoms in a schizophrenic patient, the less MNS activity they have [35, 43]. Patient characteristics: age, gender, duration of the illness and education, did not influence the MNS response. Furthermore, studies that showed reduced mirror neurons activity also showed more important deficits in social skills and imitation. This means that schizophrenic patients might have an impairment in firing their MNS which produces functional dissociations between action observation or imagination and action representation, resulting in deficits in self control and misattribution of agency (ego-boundary disturbances) caused by their inability to understand the internal state of others [50].

Some studies try to connect the pathophysiology and neuropsychology of autism and schizophrenia. Although some symptoms are pathognomic of each specific disorder, and clinically, it is not difficult to discriminate autism from schizophrenia, there is growing evidence that the broader phenotypes of these diseases may overlap. Some of the clinical features that are common to both conditions are odd thinking and speech, inappropriate affect, behavior and appearence, lack of social cognition and social anxiety. The main difference is the presence of paranoid ideation in schizophrenia [50].

Future experiments studing MNS and its relation with schizophrenia are necessary to comprehend the neurobiology behind this disorder and improve the diagnostic validity of this complex and heterogeneous disorder, as well as, provide new targets for treatment research [43].

Some studies are starting to also focus on other psychiatric conditions such as mania. These initial findings propose that a possible MNS disinhibition may take part in symptom severity of mania. Future studies should test if mirror neurons activity is increased during symptomatic mania and if it could also be related with other syptoms happening in this condition such as overfamiliarity, impulsivity and disinhibited behaviors [63].

### 4.7. POST STROKE RECOVERY

Humans have the remarkable capacity to learn motor skills from imitation. In order to achieve that, several interacting elements are necessary: efficient sensory information, decision-making and selection of motor acts, and the implementation of both predictive and reactive control mechanisms. Therefore learning is strongly determined by the neural representations of motor acts and motor memories [64].

Observation learning is an important source of motor knowledge, when mirror neurons were discovered, a new mechanism of observation learning was proposed, as MNS is known to be an integrational sensorimotor system [64, 65].

Studies provide evidence that watching another person performing a concrete action activates motor representation of that action in the observer and it has been demonstrated that we can learn new motor skills by observing others [65, 66]. So mirror neurons play a role in action understanding as well as in the mirror modulating the motor behavior of the observer [11]. The mechanism involved in imitation learning has been studied in an fMRI study in which normal volunteers were asked to imitate guitar chords played by another guitar player, brain areas activations were mapped during observation and execution of the chord [67]. The results showed that during new motor pattern formation, there was a strong activation of the MNS, more concretely the IPL, the vPMC, and the pars opercularis of the IFG.

More recent experiments [64] showed that we could also learn how to compensate for movement disbalances through action observation, which also allows the observer to predict errors. The observer is proposed to create predictions about motor acts results, comparing these predictions with the ones already available and using the error to generate an internal model to compensate perturbances. Furthermore our capacity to predict actions outcomes depends on how skilled we are in that concrete action. For example, basketball players are better at predicting the result of a basket shot.

This action modulation function is the basis for the imitation of simple motor acts and for learning through imitation. What is important from a clinical point of view is the demonstration that the mirror neurons are involved in creating motor memories [64, 68]. Evidence of this role in building new motor memories came from TMS studies, showing that when volunteers observed and performed an action, the learning of that motor act was potentiated comparing with learning through motor training alone [64, 68]. This implies that action observation and action imitation facilitate the building of motor memories. This fact could have an important role in motor neurorehabilitation therapies.

When a patient suffers a stroke, motor representations in his brain are modified according to the afferent inputs, experiences and learning processes; as the affected area of the body will be immobile, there will be a decreased in sensory and motor inputs what implies a motor representations reorganization, and a decreased in grey matter in the somatosensory cortex and M1 in the opposite brain hemisphere [69], and EEG in post stroke patients shows less suppression of the mu rhythm in the affected hemisphere compared to the unaffected hemisphere, negatively correlated with lesion extent within the inferior parietal cortex [70].

Neuroplasticity is the continuous remodelating process that optimizes neural functioning [69]. Current neurorehabilitation therapies work through inducing long-term plasticity in the motor cortex in two ways: depressing activity on the healthy side or increasing activity on the affected side [64, 70]. The suggested possibility that plasticity can also be induced in the motor cortex through action observation (activating motor representations of those movements) has already been tested.

A study with people with stable paretic limb caused by stroke in the middle cerebral artery divided these people in two groups [5]. The first one repeated upper limb movements after watching the same action being done in a video and the other group was the control group. They were asked to do the same movement without any visual input. Results showed how the first group had better functional outcomes compared with the control group, demonstrating that matching observation and execution significantly increases and improves plasticity in the motor cortex.

MNs also seem to be the basis of “mirror therapy” used to improve function in patients after stroke. Patients are asked to perform motor acts with their healthy limb and watch the reflect in a parasagittal mirror, this gives a visual illusion of movement of the paretic limb and seems to build cortical plasticity, matching seen and executed actions improving the functional outcomes in patients after stroke.

So it can be said that the basic characteristic of Penfield homunculus (somatotopy and unique representation) are questioned with this MNS model [69]. The presence of multiple motor representations in the primary motor area and in the parietal lobe interconnected by frontoparietal circuits, which are widely overlapped, form a complex organization. Both features support the recovery of functions after brain injury. Regarding the movement organization, it is possible to predict the relevant impact through the understanding of actions and intentions of others, which is mediated by the activation of mirror-neuron systems. The implementation of cognitive functions (observation, image of the action and imitation) from the acute treatment phase allows the activation of motor representations without having to perform the action and it plays an important role in learning new motor patterns.

### 4.8 PHANTOM LIMB

After limb amputation, some patients have a vivid phantom limb that sometimes associates severe pain and immobilization. As fMRI experiments in humans showed, there are also mirror neurons for touch; when a person is being touched his sensory touch neurons will activate, but also when a person sees another person being touched [5].

The reason why we cannot actually feel the touch when observing others being touched is that the amount of mirror neurons activated when observing are not enough to reach the threshold of conscious experience. Another possibility to not to directly feel when observing another person being touched is receiving a signal informing that actually we are not touched. Knowing this an approach to phantom limb pain used to decrease that sensation is a vertical mirror in which the patient places his limbs symmetrically on each side of the mirror (the normal limb in one side, and the amputee in the other), giving the impression through the reflection that the patient has two limbs. This way, when the patient moves his healthy limb, his amputee limb also feels like being moved, and in some cases the pain is improved [70, 71].

## 6. CONCLUSIONS AND KEY ISSUES:

The Scottish philosopher David Hume wrote in his book, *A Treatise of Human Nature* (1740), what follows: "The minds of men are mirrors to one another, not only because they reflect each other's emotions, but also because those rays of passions, sentiments and opinions may be often reverberated, and may decay away by insensible degrees".

Today's Neuroscience discovered that this is actually true; mirror neurons form complex neural networks that act like bridges connecting people's acts and feelings making it possible to understand each other through directly converting sensory inputs into a motor code, what has been proved to take part in many cognitive functions from action understanding to empathy, imitation learning or language evolution. We can then conclude:

- MNs are a special type of visuomotor neurons that convert sensory inputs into motor representations.

- Firstly described in monkeys, MNS in humans formed complex systems extended over the occipital, parietal (superior, inferior and the intraparietal sulcus) and temporal visual areas, plus three cortical regions predominantly motor: rostral part of the IPL, the lower part of the precentral gyrus and the posterior part of the IFG.

- When we observe an action, our MNS builds an internal motor representation of that action in our own motor repertoire, converting sensory inputs into motor patterns similar to the ones that get activated when we perform that action ourselves.

- MNs are able to code observed actions and also the specific intention of that actions. Thus, the motor act observed is experienced as if we woud be actually performing that action, wholly comprehending its meaning from the inside.

- This all is done without the inferences of higher cognitive associatons.

- MNS basically allows us to understand acts and feelings so we can interpret the context, predict what is going to happen and adapt our behaviour to the situation.

- Certain mirror neurons have the capacity of coding abstract actions and non goal-directed motor acts. This implies that there is an auditory input to the MNS, essential to support the Motor Theory of language hypothesis, suggesting that the MNS could be the basis of neural patterns for language.

- Some neurons in the insula and anterior cingulate cortex have mirror properties, becoming active both when expressing feelings and when observing others' body expressions. This evidences that empathy is based on affective shared states.

- The neuropathophysiology of ASD is still unclear, but it is strongly believed that some of ASD symptoms such as social cognition impairment, communication deficits or poor emotion recognition are related with MNS dysfunction.

- MNS activation deficits are present in ASD, they are more intense when the actions observed involve social interaction and emotional states, and less intense when interacting with relatives.

- MNS could be a target in developing new treatment strategies for ASD patients; till now there are little but encouraging results.

- In other social cognition related disorders such as Schizophrenia, further evidence is needed.

- Mirror-based therapies improve functional outcomes in patients after stroke and in patients with phantom limb pain.

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