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THÈSE

EFFET DES LESIONS NEURODEGENERATIVES SUR LE MECANISME DE RESONANCE MOTRICE A L'OBSERVATION D'ACTION

THE EFFECT OF NEURODEGENERATIVE LESIONS ON THE MECHANISM OF MOTOR RESONANCE INDUCED BY ACTION OBSERVATION

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Résumé

Le concept de "cognition incarnée" considère que le schéma classique Perception-Cognition-Action proposant un flux séquentiel de traitement de l'information n'est pas approprié pour comprendre l'effet comportemental des troubles neurodégénératifs et trouver des solutions thérapeutiques innovantes. La découverte des neurones miroirs (NM) a donné un substrat biologique à cette théorie : on pense maintenant que les NM relient les connaissances sur les actions et les perceptions non seulement pour intégrer la perception dans la planification et l'exécution, mais aussi pour soutenir un large éventail de fonctions cognitives, par ex. empathie et langage. En même temps, il est maintenant clair que, dans chaque maladie neurodégénérative, les symptômes cognitifs et moteurs sont représentés le long d'un continuum. Les maladies neurodégénératives liées au vieillissement, comme la maladie d'Alzheimer (MA), la forme la plus courante de démence, sont devenues un enjeu social très important. Comme il n'y a pas de remède pour la MA, les études se concentrent sur la prévention. Une catégorie qui représente maintenant une cible privilégiée est le trouble cognitif léger (TCL), considéré comme une étape intermédiaire entre le vieillissement normal et la MA. Même si MA et TCL ont été caractérisés comme des maladies «cognitives» jusqu'à présent, un lien entre la fonction motrice et le risque de développer la MA a été reconnu.

Le but principal de cette recherche est d'étudier l'intégrité du réseau NM dans la MA, le TCL et le vieillissement normal. La caractérisation de son fonctionnement dans les maladies neurodégénératives serait utile pour une meilleure compréhension de leurs mécanismes fonctionnels et manifestations cliniques. Cela permettrait également d'exploiter le NM dans la réhabilitation des symptômes.

La thèse comprend deux parties : la première inclut une vaste recherche bibliographique destinée à décrire le cadre scientifique qui justifie une telle recherche.

Nous avons d'abord passé en revue les preuves sur l'existence d'un système NM chez les singes et les humains, et ses multiples rôles possibles et après brièvement décrit le tableau clinique des principaux troubles neurodégénératifs, en montrant comment les symptômes cognitifs et moteurs s'entrecroisent. Ensuite, nous avons détaillé les résultats de la recherche documentaire sur les maladies neurodégénératives, NM et cognition incarnée, en les commentant à la lumière de cette théorie.

La deuxième partie de la thèse décrit la procédure expérimentale qui a été réalisée dans le but de la recherche.

Trois groupes appariés de 16 sujets chacun (CA-sujets de contrôle âgées-, TCL amnésique avec atrophie hippocampique et MA) ont été évalués avec une batterie neuropsychologique centrée sur les fonctions liées au système NM, et une tâche IRMf spécifiquement créée pour tester les NM: celle-ci était constituée d'une tache d’observation, où ont été montrés des vidéos d'une main droite saisissant différents objets, et d'une tache motrice où les sujets ont observé des images d'objets orientés pour être saisis avec la main droite, et ont fait le geste correspondant.

Chez les CA, l'analyse de conjonction (comparant l'activation de l'IRMf pendant l'observation et l'exécution) a indiqué l'activation d'un réseau bilatéral fronto-pariétal dans les zones NM « classiques» et du gyrus temporal supérieur (STG), entrée visuelle corticale aux NM. Le groupe TCL a montré une activation similaire, cependant, les zones pariétales ont été moins activées et le STG n'a pas été activé, tandis que l'inverse était vrai pour la zone de Broca droite. Nous n'avons observé aucune activation du réseau fronto-pariétal chez le groupe MA. Dans tous les tests neuropsychologiques (y compris les tests de fonctions attribuées à NM), les sujets MA ont été plus mauvais que les CA, alors que les sujets TCL montraient seulement des troubles de mémoire épisodique et de fluidité sémantique.

Les résultats et leurs implications futures sont finalement discutés. Ils suggèrent que le réseau NM est préservé dans le vieillissement, alors qu'il est impliqué suivant un gradient antéro-postérieur dans le déclin neurodégénératif. Dans la MA, les performances aux épreuves cognitives diminuent et le réseau NM apparaît clairement déficient. La préservation de la partie antérieure du réseau NM dans le TCL pourrait éventuellement compenser la désintégration initiale de la partie postérieure, en préservant les performances cognitives. Encore plus de recherches sont nécessaires pour confirmer cette hypothèse, mais le concept de la cognition incarnée ouvre des voies encourageantes vers des solutions thérapeutiques non pharmacologiques.

Mot clés : Neurones miroirs ; Maladie d’Alzheimer ; Trouble Cognitif Léger ; maladies neurodégénératives ; vieillissement ; Résonance Magnétique fonctionnelle ; Tests neuropsychologiques.

ABSTRACT

The concept of “embodied cognition” considers that the classical Perception-Cognition-Action architecture proposing a sequential flow of processing with clean cuts between all modules is not appropriate to understand the behavioral effect of neurodegenerative disorders and to find innovative therapeutic solutions. In the last decades, the discovery of the mirror neurons (MN) has given a biological substrate to this theoretical perspective: the MN are now thought to link together knowledge about actions and perceptions not only to integrate perception in action planning and execution but also as a neural mechanism supporting a wide range of cognitive functions, e.g. empathy and language. At the same time, it is now clear that in each neurodegenerative disease both cognitive and motor symptoms are represented along a continuum. In the current demographic context, neurodegenerative diseases linked to aging have become a very important social issue. Alzheimer Disease (AD), the most common form of dementia, is a neurodegenerative disease strictly linked to aging. As actually there is no cure, several studies are focusing on prevention. A category which now represents a preferential target of intervention is Mild Cognitive Impairment (MCI), considered as an intermediate stage between normal aging and AD. Even if AD and MCI have been characterized as “cognitive” diseases until now, a link between motor function and the risk of developing AD has been recognized.

The main purpose of this research is to investigate the integrity of the MN network in AD, MCI and normal aging. Characterizing the functioning of the MN network in neurodegenerative diseases would be useful to better understand functional mechanisms and their clinical manifestations. It would also allow to capitalize on these kinds of neurons in the rehabilitation of motor and cognitive symptoms.

The thesis consists of two parts: the first part includes an extensive bibliographic research intended to describe the scientific frame which justifies such a research.

We first reviewed the evidence about the existence of a MN system in monkeys and humans, and its multiple possible roles in humans.

We then briefly reviewed the clinical picture of the main neurodegenerative disorders, showing how cognitive and motor symptoms intersect in all of them.

Next, we detailed the results of literature searching on neurodegenerative diseases, MN, and embodied cognition, commenting them at the light of this hypothesis.

The second part of the thesis describes the experimental procedure which has been performed to evaluate the integrity of the MN network in normal elderly and people with AD and MCI, and its results.

Three matched groups of 16 subjects each (normal elderly-NE, amnesic MCI with hippocampal atrophy and AD) were evaluated with a neuropsychological battery centered on functions thought to be linked to the MN system, and a fMRI task specifically created to test MN: that comprised of an observation run, where subjects were shown videos of a right hand grasping different objects, and of a motor run, where subjects observed visual pictures of objects oriented to be grasped with the right hand, and made the corresponding gesture.

In NE subjects, the conjunction analysis (comparing fMRI activation during observation and execution), indicated the activation of a bilateral fronto-parietal network in "classical" MN areas, and of the superior temporal gyrus (STG), an area thought to provide the cortical visual input to the MN. The MCI group showed the activation of areas belonging to the same network, however, parietal areas were activated to a lesser extent and the STG was not activated, while the opposite was true for the right Broca's area. We did not observe any activation of the fronto-parietal network in AD participants. They performed worse than NE subjects in all the neuropsychological tests (including tests of functions attributed to MN) whereas the MCI subjects were significantly different from the NE subjects only in episodic memory and semantic fluency.

Results and their future implications are finally discussed. They suggest that the MN network is largely preserved in aging, while it is involved following an anterior-posterior gradient in neurodegenerative decline. In AD, task performance decays and the MN network appears clearly deficient. The preservation of the anterior part of the MN network in MCI could possibly supplement the initial decay of the posterior part, preserving cognitive performance.

Even more researches are needed to confirm this hypothesis, the concept of embodied cognition opens encouraging ways to innovative non-pharmacological therapeutic solutions**.**

Key words

Mirror Neurons; Embodied Cognition; Alzheimer Disease; Mild Cognitive Impairment; neurodegenerative diseases; aging; fMRI; neuropsychological tests.

LIST OF ACRONYMS

ACE: Action-Sentence Compatibility

AD: Alzheimer Disease

ALS: Amyotrophic Lateral Sclerosis

aMCI : amnestic Mild Cognitive Impairment

ANCOVA: Analysis of Covariance

ANOVA: Analysis of Variance

AOT: Action Observation Training

BA22: Brodmann Area 22

BA40: Brodmann Area 40

BA42: Brodmann Area 42

BA44: Broca's Area

BA6: Brodmann Area 6

BDNF: Brain Derived Neurotrophic Factor:

BMI: Body Mass Index

BOLD: Blood Oxygen Level-Dependent

bvFTD: behavioral variant of Frontotemporal Dementia

CBD: Corticobasal Degeneration

Cbl: Cerebellum

DBS: Deep Brain Stimulation:

DLB: Dementia with Lewy Body

EEG: Electroencephalogram

EPI: Echo-Planar Imaging

ERD: Event-Related Desynchronization

ERS: Event-Related Synchronization

FCSRT: Free and Cued Selective Reminding Test

FDI: First Dorsal Interosseous

FIRST : FMRIB's Integrated Registration and Segmentation Tool

fMRI: functional Magnetic Resonance Imaging

FMS: Fugl-Meyer Scale

FSL: FMRIB's Software Library

FTD: Frontotemporal Dementia

FuG: Fusiform Gyrus

GLM: Generalized Linear Model

IFG: Inferior Frontal Gyrus

IPL: Inferior Parietal Lobule

IRCCS: Istituto di Ricovero e Cura a Carattere Scientifico

IWG: International Working Group

M1: Primary Motor Area

MCI: Mild Cognitive Impairment

MEPs: Motor Evoked Potentials

MI: Motor Imagery:

MN: Mirror Neurons

MotND: MotoNeuron Disease

MRI: Magnetic Resonance Imaging

NIA-AA: National Institute on Aging and Alzheimer's Association

PD: Parkinson Disease

PDD: Parkinson Disease Dementia

PET: Positron Emission Tomography

PF-PFG: Rostral Inferior Parietal Lobule Area

PPA: Primary Progressive Aphasia

PrCG: Precentral Gyrus

PTMNs: Pyramidal Tract Mirror Neurons

REM: Rapid Eye Movements:

RME: Reading the Mind in the Eyes Test

S1: Primary Somatosensory Cortex

SEPs: Somatosensory Evoked Potentials

STG: Superior Temporal Gyrus

STS: Superior Temporal Sulcus

TMS: Transcranial Magnetic Stimulation

ToM: Theory of Mind

V5: Visual Area

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Glossary

Affordance: The affordances (see Gibson, 1979) of the environment are what it offers the human or animal. Moreover, all transactions that are possible between an individual and their environment. Gibson's general ideas can be viewed as situated/embodied in the sense that he emphasized the importance of the interaction between the agent and the environment for intelligent behavior.

Enaction: In an enactive system, meaning is the result of the organization and history of the system itself. Hence, the organism and the environment have been developed and bound together, through the process of natural drift. In this view, the environment and the organism cannot be separated since they in fact are codetermined in evolution, which is dependent on the perceptually guided activity of the organism and the environmental regularities.

Mirror Neurons: A special kinds of visuo-motor neurons, which become activated both when performing specific goal-directed hand (and mouth) movements and when observing or hearing about the same actions. Since mirror neurons respond to both conditions, it has been argued that the mirror system functions as a kind of action representation, since it links action and perception of action.

Motor cognition: A biological phenomenon instead of a mental one; this notion proposed that it is the body which has the necessary 'knowledge' to perform the task at hand, since the body 'knows how to act' and 'how to perceive' through the history of its phylogenetic and ontogenetic interactions with the environment. For instance, the understanding of a sentence would be essentially achieved through a simulation of action using the same neural systems active in overt behavior.

Motor resonance: The process that matches visual input directly onto observer's motor repertoire (e.g., it has been found that observers undertake motor facilitation in the same muscles as the one used by the observed individual). Considering the motor resonance as the neurobiological underpinning of 'intercorporeality' and simulation theories as the basis of social interaction and mind-reading, motor resonance provides a significant example of more embodied views of social cognition. Compulsive imitation would be the pathological version of the motor resonance.

Theory of mind: Theory of Mind (ToM, or mind reading) can be broadly divided into 'theory theories' and 'simulation theories'. For the theory theorist, ToM is the ability to predict and interpret the behavior of others using folk psychological theory, based on the structure and function of the human mind. In contrast, in the simulation theory, the mind-reading ability is not any sort of theory. Instead, it is an ability to project oneself into another person's point of view; simulating what it is such as to be in the other person's situation. Simulation theory might be a part of, or a precursor to, a general mind-reading capability that allows one to adopt the sensorimotor point of view of other conspecifics in order to predict others' mental states and behavior.

Action Observation Training: A rehabilitation approach, during which the patient is asked to wisely observe actions presented through a video-clip or performed by another person, in order to activate the motor system via the visual input and promote imitative behaviors.

Frontotemporal Dementia: A heterogeneous group of neurodegenerative disorders characterized by frontal and temporal lobe atrophy associated with neuronal loss, gliosis, and dementia. Patients exhibit progressive changes in social, behavioral, and/or language function. In some cases, patients can also show motor signs such as motor neuron disease or parkinsonism.

Behavioral variant of Frontotemporal dementia: The most common clinical form of frontotemporal dementia, this variant presents with personality and behavioral changes often associated with disinhibition or apathy, and lack of insight.

Primary Progressive Aphasia: A progressive form of dementia characterized by the global loss of language abilities and initial preservation of other cognitive functions. Fluent, nonfluent and logopenic subtypes have been described.

Semantic dementia: also known as semantic or fluent variant of primary progressive aphasia, is a progressive neurodegenerative disorder characterized by loss of semantic memory in both the verbal and non-verbal domains. Clinical signs include fluent aphasia with impaired comprehension of word meaning, anomia, and associative visual agnosia . As the disease progresses, behavioral and personality changes are often seen similar to those seen in the behavioral variant of frontotemporal dementia.

Lewy bodies: abnormal deposits of a protein called alpha-synuclein in the brain, contributing to Parkinson disease, Dementia with Lewy bodies (DLB), Parkinson disease dementia (PDD) and some other disorders.

Dementia with Lewy bodies: A neurodegenerative disease characterized by dementia, mild parkinsonism, fluctuations in attention and alertness, REM behavior disorder and neuroleptic hypersensitivity.

Brain-Derived Neurotrophic Factor: A member of the nerve growth factor family of trophic factors. In the brain it has a trophic action on retinal, cholinergic, and dopaminergic neurons, and in the peripheral nervous system it acts on both motor and sensory neurons.

CHAPTER 1 – THEORETICAL FRAME

1.1 The mirror neurons

The Mirror Neurons (MN) are one of the most important discoveries in the last decades of neuroscience. They represent a distinctive class of neurons that discharge both when an individual executes a motor act and when he observes another individual performing the same or a similar motor act (Figure 1). These neurons were first discovered in monkey's brain, in particular in the ventral premotor area F5 (and above all its F5c cytoarchitectural area) and in the inferior parietal lobule -IPL- (Rizzolatti et al., 2014). In humans, brain activity consistent with that of MN has been found in the premotor cortex (posterior regions of the inferior frontal gyrus -IFG-, considered the human homologue of the monkey F5; Kilner et al. 2009; Ferri et al., 2015), and in the IPL (Rizzolatti, et al. 2001; Rizzolatti & Craighero, 2004; Rizzolatti, 2005; Chong et al., 2008; Arnstein et al., 2011; Molenberghs et al., 2012; Iacoboni et al., 2001; Mukamel et al., 2010; Kilner e Lemon, 2013; Cook et al., 2014). The presence of MN activity was additionally signaled in the primary motor cortex (M1; Fadiga et al., 2005) and even in the hippocampus (Mukamel et al., 2010). fMRI experiments showed that a parietofrontal network is activated during observation and execution of hand grasping acts (Grèzes et al., 2003), as well as during observation of grasping acts made with tools (Peeters et al., 2009). This network is remarkably similar in monkeys and humans. MN discovery received a lot of attention from specialists (not only neuroscientists, but also psychologists and philosophers) and in the scientific and public media. Apart from action understanding (Rizzolatti et al., 1996; Gallese & Sinigaglia, 2011) and imitation (Iacoboni et al., 1999; Bonini e Ferrari, 2011), MN are now thought to be responsible for myriad of other sophisticated human behavior and thinking processes. For instance, the discovery of MN has given a biological complement to the simulation theory, that is the idea that actions involve both an overt and a covert stage (Jeannerod & Frak, 1999; Jeannerod, 2001). In humans, MN are now thought to have a part in understanding not only other people’s actions but also their emotions (Gallese et al., 2004, Enticott et al., 2008; Corradini & Antonietti, 2013), being therefore involved in empathy (Avenanti et al., 2005) and intention-reading (Iacoboni et al., 2005) and have been also proposed to have a main role in different aspects of language: acquisition (Theoret & Pascual-Leone, 2002), speech perception (Glenberg et al., 2008), speech production (Kuhn & Brass, 2008), and evolutionary language development (Arbib, 2008). Even if there have been criticisms of this point of view (Mahon and Caramazza, 2008), the supposed power of MN to explain a broad range of human phenomenon has been perceived as revolutionary (Ramachandran , 2000; Iacoboni, 2008; Oosterhof et al., 2013) at the point that, in the last years, the exploitation of MN system for rehabilitation has been proposed (Michielsen et al., 2010, 2011; Franceschini et al., 2010; Sgandurra et al. 2011; Small et al., 2010, 2013; Chen et al., 2015). In addition, it has been suggested that MN dysfunction contributes to a number of disorders, above all autism (Dapretto et al., 2006; Nishitani et al., 2004; Williams et al., 2001) and schizophrenia (Arbib & Mundhenk, 2005).

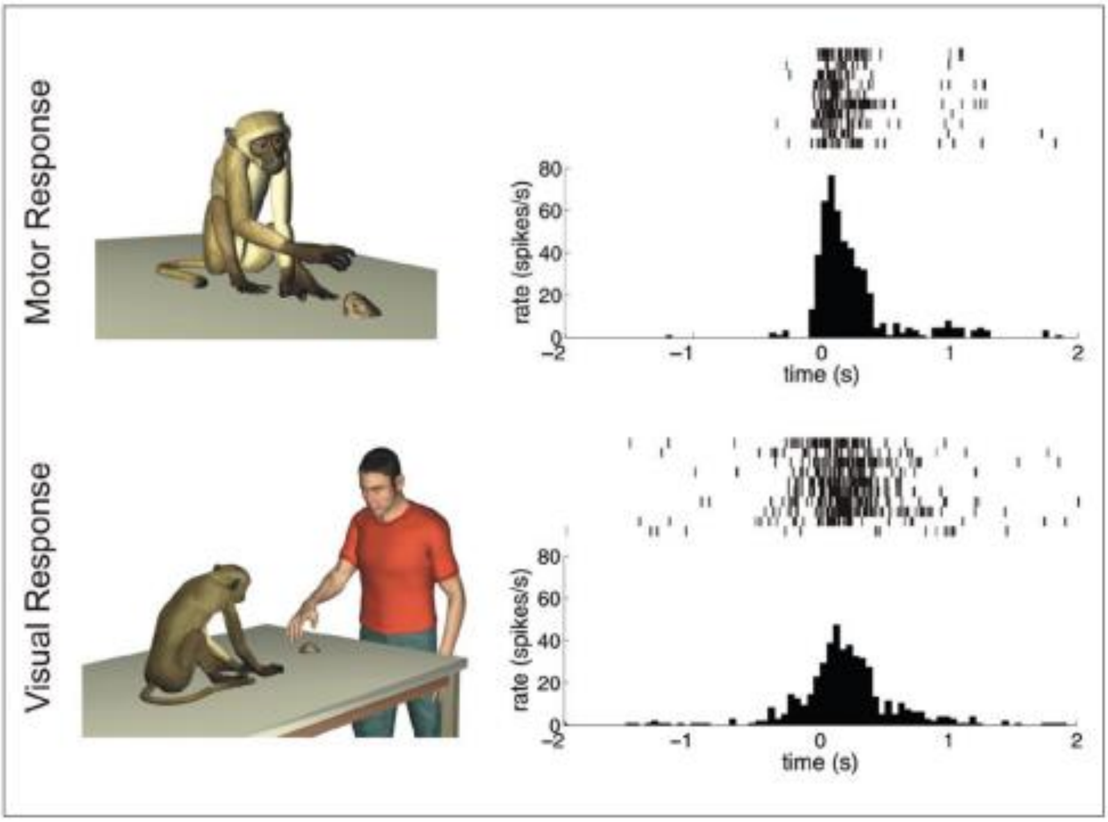

***Figure 1**: Response properties of a **mirror neuron**. Each row in the left column schematically represents the experimental condition. The panels in the right column show the corresponding responses of the same neuron in the form of a raster plot (upper part) and peri-stimulus spike density (bottom part). (top row, right panel) Response of a neuron during active goal-directed motor acts of the monkey (e.g., grasping small objects of different shapes). (bottom row, right panel) Response of the same neuron during the observation of the same goal-directed motor acts performed by the experimenter. In the two raster plots, each vertical bar signifies the occurrence of an action potential, and different lines refer to different trials. In both figures, time t = 0 represents the moment of contact between the monkey's (top panel) or experimenter's (bottom panel) hand with the goal object. (From Casile et al., 2011)*

1.2 The Mirror Neurons system in monkeys and humans

1.2.1 Mirror Neurons in monkeys

The MN were described for the first time 20 years ago in the monkey ventral premotor area F5 (di Pellegrino et al., 1992; Rizzolatti et al., 1996, Gallese et al., 1996), and subsequently in area PF/PFG of the monkey IPL (Gallese et al., 2002; Fogassi et al., 2005; Rozzi et al., 2008; see Figure 2). Their discovery was preceded by a prolonged anatomical and functional investigation of the premotor areas that enabled Rizzolatti's group to highlight a series of unexpected functions of these areas (Gentilucci et al., 1988; Rizzolatti et al., 1988) Among these functions there were the coding of the goal of motor acts rather than movements that form them (Rizzolatti et al., 1988), the responsiveness to objects in area F5 (Murata et al., 1997; Jeannerod et al., 1995) and the coding of the peripersonal space in area F4 (Gentilucci et al., 1988; Fogassi et al., 1996).

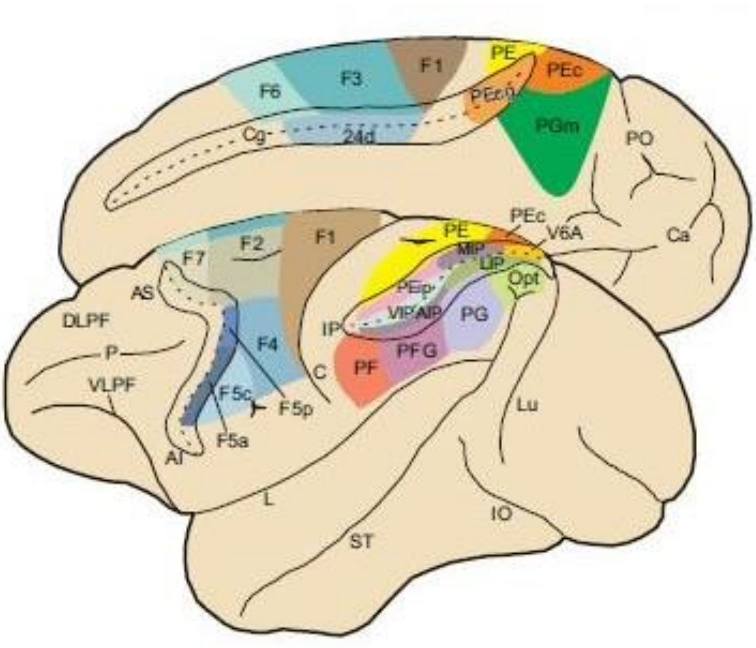

***Figure 2**: Lateral and mesial view of the monkey brain showing a modern anatomical and functional parcellation of the agranular frontal cortex and the posterior parietal cortex along with the localization of F5 and PF and PFG areas (From Rizzolatti et al., 2014)*

At their first description in monkeys, the activity of these cells seemed to be strictly dependent upon the actions having a clear transitive goal (i.e., grasping a piece of food), although premotor MN coding communicative mouth gestures (e.g., lipsmaking), (Ferrari et al., 2003) or intransitive hand movements (Kraskov et al., 2009) have been also described.

In area F5, besides purely motor neurons, two categories of visuomotor neurons were found. One, referred to as 'canonical neurons' (Rizzolatti & Fadiga, 1995), is responsive to the presentation of three-dimensional objects. The other, referred to as 'MN', is responsive to the observation of motor acts performed by others (Rizzolatti et al., 1996; Gallese et al., 1996). The main property of canonical neurons is to match the shape and size of the observed object with a specific type of prehension, whereas the main property of MN is that of matching observation of hand and mouth motor acts with the execution of the same or similar motor acts. This matching mechanism enables the observing individual to achieve an automatic understanding—i.e. an understanding without inferential processing of others' goal-directed motor acts.

Early studies of the field properties of monkey MN–the sensory and motoric conditions in which they fire– revealed three basic types: "Strictly congruent" MN discharge during observation and execution of the same action, for example, precision grip. "Broadly congruent" MN are typically active during the execution of one action (e.g., precision grip) and during the observation of one or more similar, but not identical, actions (e.g., power grip alone, or precision grip, power grip, and grasping with the mouth). “Logically related” MN respond to different actions in observe and execute conditions. For example, they fire during the observation of an experimenter placing food in front of the monkey, and when the monkey grasps the food to eat it. MN do not respond to the presentation of objects alone (di Pellegrino et al., 1992). However, “canonical neurons,” which are active during object observation and performance of an action that is commonly performed on that object, are co-located with MN both in area F5 (Murata et al. 1997) and in the anterior intraparietal sulcus (Murata et al. 2000).

A question posed by the discovery of F5 MN is why the observer does not move during action observation given the activation, in her/his premotor and parietal cortices, of the same neurons that are involved in action. A possible answer has been provided by a study by Kraskov and co-workers (2009). In this study, the authors first identified MN that project through the pyramidal tract, likely to the spinal cord, and then investigated their responses during action production and observation. Half of these pyramidal tract MN (PTMNs) vigorously responded during action production but exhibited a complete suppression of discharge during action observation. Kraskov and coworkers speculated that the suppression of PTMNs’ responses during action observation might serve the purpose of inhibiting, likely at the spinal cord level, self-movements during action observation (Kraskov et al., 2009).

To date, monkey MN have been found that are responsive to the observation and execution of hand and mouth actions. The hand actions include grasping, placing, manipulating with the fingers, and holding (di Pellegrino et al., 1992; Gallese et al., 1996). The mouth actions include ingestive behaviors such as breaking food items, chewing and sucking, and communicative gestures such as lip-smacking, lip-protrusion, and tongue-protrusion (Ferrari et al. 2003).

It was originally reported that F5 MN do not respond if the same action (e.g., grasping) is performed with a tool. However, more recent results showed that after extensive visual exposure of the monkey to actions executed with a tool, a subset of MN in the ventral part of area F5c started responding also to this type of visual stimuli (Ferrari et al., 2005).

Further studies reported additional generalization properties of some F5 MN (Casile et al., 2011) . For example, some of them responded in a similar manner to the same action executed with different effectors (e.g., grasping with the hand and grasping with the mouth) (Ferrari et al., 2003; Rizzolatti et al., 2001), to the sound associated with familiar actions (Kohler et al., 2002), see also the paragraph “*Enhancing the potential of mirror neurons stimulation in rehabilitation”*), and even to partially sealed actions that can be inferred only from their initial motion path (Umiltà et al., 2001).

Subsequently some Authors have shown that the response a subset of IPL MN (i.e., in the cytoarchitectonic area PF and PFG) (Fogassi et al., 2005), during both the observation and execution of a complex grasping act (e.g., grasping to place or grasping to eat), are modulated by the final goal of the action (placing or eating) in which the grasping was embedded (Bonini et al., 2010; Fogassi et al., 2005).

This kind of MN discharge when the monkey grasps a piece of food to eat it, but has a smaller response when the same piece of food is grasped to place it into a box. The same selectivity is present during action observation, that is, the neurons discharge while the monkey observes the experimenter grasping a piece of food to eat it, whereas it remains almost silent when the experimenter grasps the same piece of food to place it into a box. An important feature of these cells is that their activity seems not to be strictly linked to the precise time-deployment of the observed action; indeed, a certain proportion of parietal MN are activated in advance of achievement of the end-goal, e.g., during the initial grasping phase (Fogassi et al., 2005). This anticipatory feature was also shown in a single-cell study where monkey premotor MN fired both when directly seeing hand–food contact and when merely inferring that the observed hand was going to grasp a piece of food behind an occluder (Umiltà et al., 2001). Moreover, specific studies have excluded that the differential response of IPL MN according to the action goal could be due to different kinematic parameters (Rizzolatti & Fogassi, 2014).

Fogassi and co-workers interpreted this pattern of response as an evidence about the possible specific cognitive role of IPL MN of encoding the intentions of others (Fogassi et al., 2005, Figure 3). More recent investigations, however, have shown similar response properties also in F5 MN (Bonini et al., 2010), even if less strong (Rizzolatti & Fogassi, 2014).

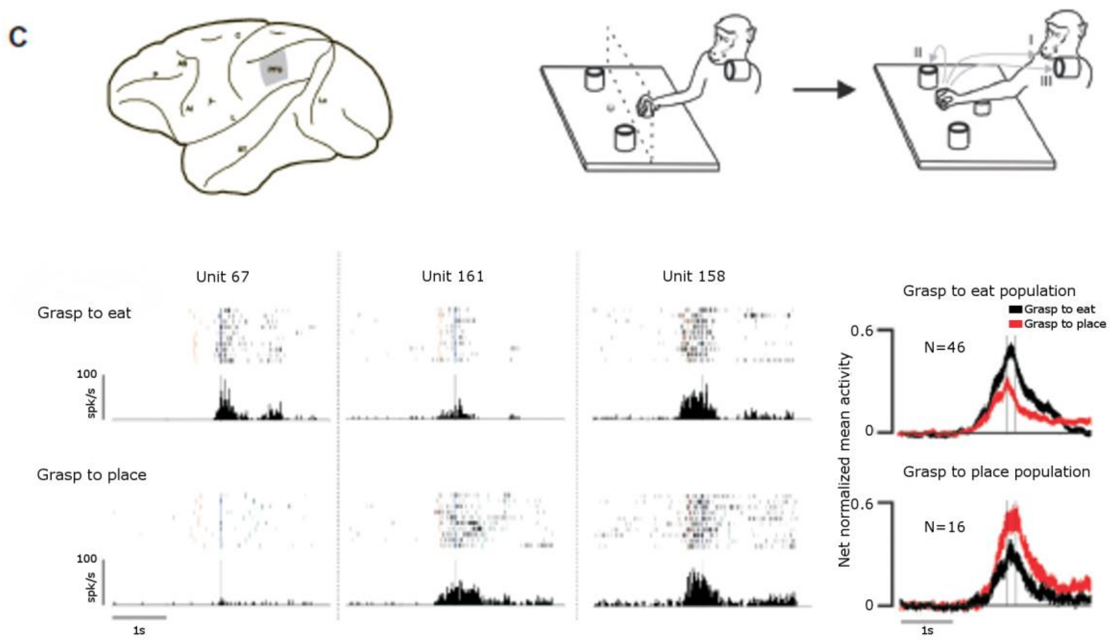

***Figure 3**: Example of motor neuron in PFG modulated by action intention. Top left: lateral view of the monkey brain showing area PFG. Top right: paradigm used for the motor task. The monkey, starting from a fixed position, reaches and grasps a piece of food or an object, then it brings the food to the mouth and eats it (I, grasp-to-eat), or places it into a container (II/III, grasp-to-place). Bottom left: activity of three IPL neurons during grasping in the two actions. Rasters and histograms are aligned with the moment when the monkey touched the object to be grasped. Bottom right: responses of the population of neurons selective for grasping to eat and grasping to place. The vertical lines in the two panels indicate the moment when the monkey touched the object and the moment in which the grasping was completed, respectively. (from Rizzolatti et al., 2014; Modified from Fogassi et al., 2005)*

Additional evidence in favor of goal coding was furnished by experiments in which the monkeys grasped the food with normal or inverted pliers (i.e. pliers which requested opening the hand to grasp the object). MN discharged according to the goal of the action and not to the hand movement (Rizzolatti et al., 1988; Umiltà et al., 2008; Cattaneo et al., 2013; Figure 4). Other data in favor of this are already cited studies in which MN responded in a similar manner to the same action executed with different body parts (e.g., the hand and the mouth) (Ferrari et al., 2003; Rizzolatti et al., 2001) and to the sound associated with familiar actions (Kohler et al., 2002, Figure 5).

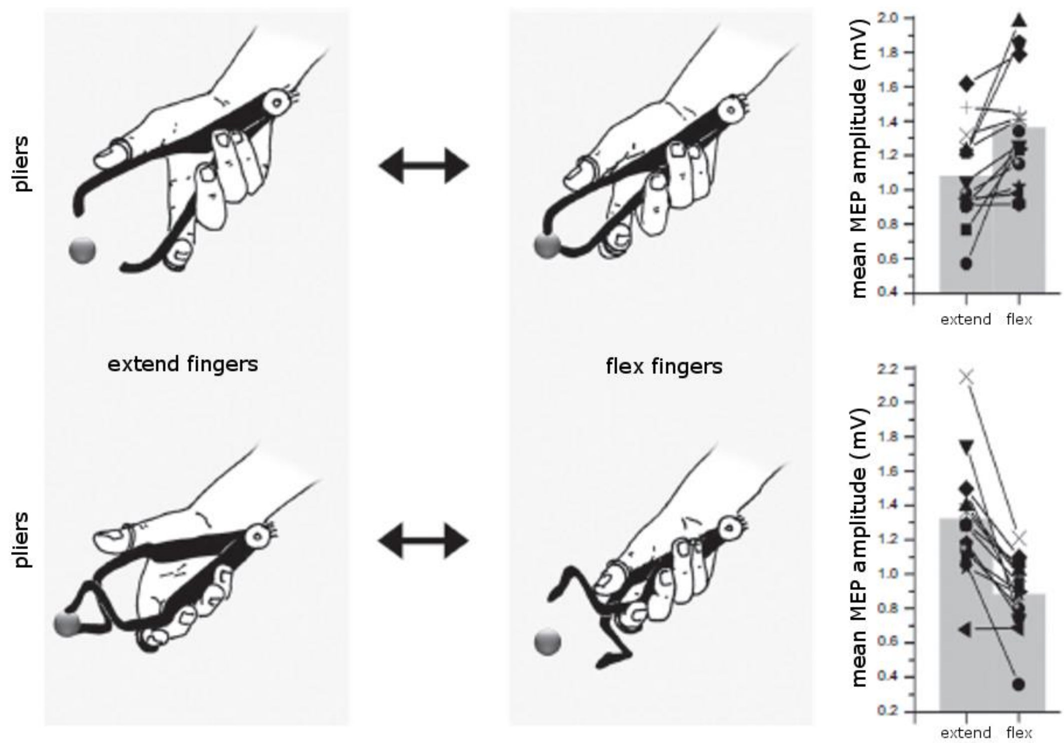

Figure 4*: Evidence for action goal coding by the mirror mechanism. Participants watched the experimenter grasping objects with two types of pliers: direct pliers and reverse pliers (left panel). Finger flexion produced closure of the direct pliers, but opening of the reverse ones (right part of the left panel). Finger extension produced opening of the direct pliers, but closing of the reverse ones (left part of the left panel). The right panel shows MEP amplitudes obtained from the opponens pollicis muscle during the observation of different movement phases. Right panel, top: MEPs during the observation of grasping with direct pliers. Right panel, bottom: MEPs during the observation of grasping with reverse pliers. The observers' motor systems encode the goal of the action, regardless of whether it is achieved by closing or opening the hand. Rizzolatti et al., 2014, modified from Cattaneo et al,. 2013)*

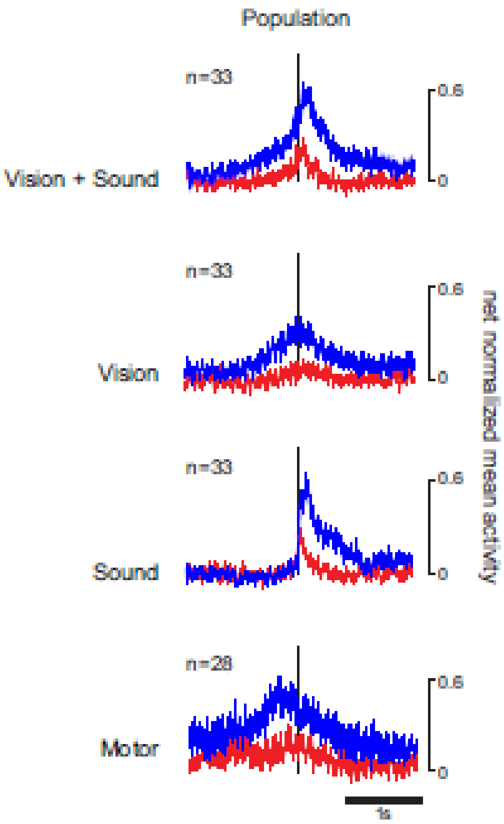

Figure 5*: illustration of findings by Kohler et al., 2002:*

Responses of the population of tested neurons selectively activated by the vision-and-sound, vision-only, sound-only, and motor conditions. Responses to the most effective stimuli are shown in blue, and those to the poorly effective stimuli are in red. Vertical lines indicate the auditory response onset in the population. The y-axes are in normalized units for the population.

Based on the existing studies in monkeys, we can therefore consider that MN modulate their responses according to characteristics of the observed actions that are directly related to motor goals, such as the type of grip or the intention of the actor.

However, other studies suggest that MN integrate in their responses additional pieces of information that are not directly related to the action itself. MN activity can be also modulated by the distance at which the observed motor acts were executed with respect to the monkey that is in the peri-personal space or on the contrary in the extra-personal space of the monkey of the monkey (Caggiano et al, 2009). Half of these neurons code space in a metric (cartesian way), the other half from an operational point of view (i.e. the space is coded according to the possibility of the monkey to reach it; Rizzolatti & Fogassi, 2014: see Figure 6). From a functional perspective, the distance between observer and actor plays no role in understanding action goal. However, it can play a role in selecting possible subsequent behaviors, for example, interacting or approaching behaviors. Thus, the MN system could be part, together with other brain areas, of a system that contributes not only to understanding what others are doing but also in deciding the most appropriate behavioral response (Caggiano et al., 2011).

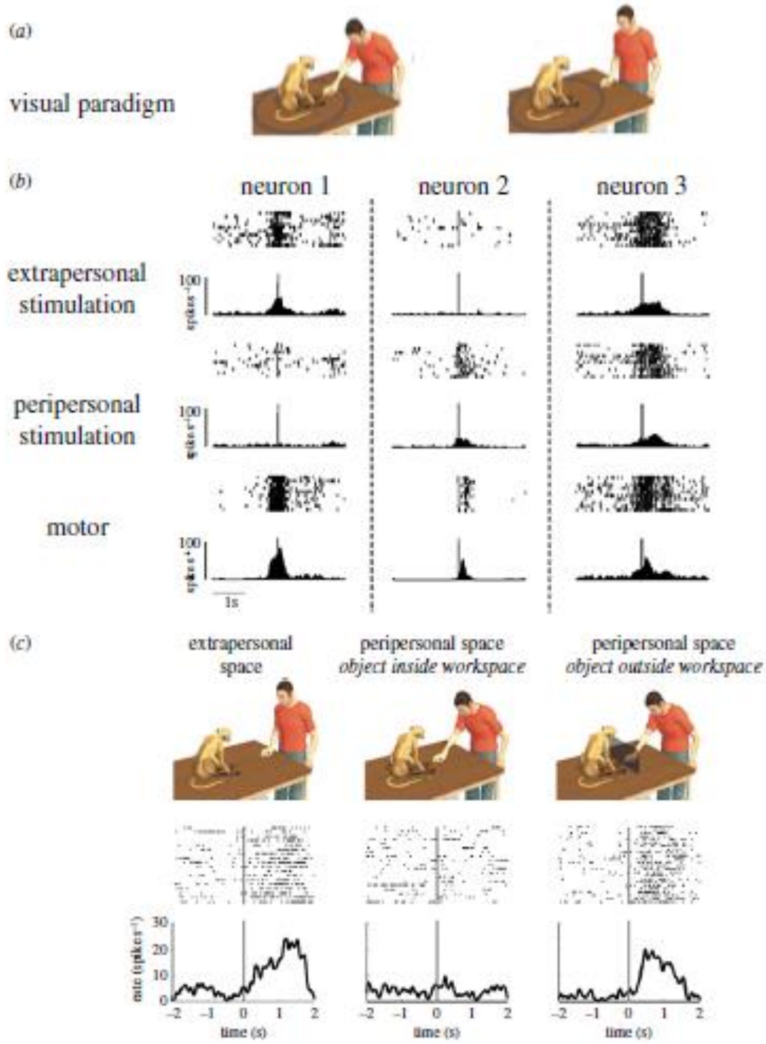

Figure 6**: **Space-selective mirror neurons *(from Rizzolatti and Fogassi, 2014). (a) Schematic view of the visual conditions of the experimental paradigm: the monkey observes an experimenter executing a grasping act in the peripersonal (left) and extrapersonal (right) space of the monkey. (b) Examples of the responses of three mirror neurons during observation of grasping acts executed in the monkey's peri- and extrapersonal space and during monkey execution. Each panel shows the raster plot (top) and the cumulative histogram (bottom) of the neuron responses. Neuron 1 responds more strongly when the observed grasping is performed in the extrapersonal space, while neuron 2 presents a stronger discharge during observation of grasping performed in the peripersonal space. Neuron 3 does not show any space-selective visual response. (c) Operational encoding of the monkey peri- and extrapersonal space. The top part shows the experimental conditions: the experimenter grasps an object in the extrapersonal (left) or in the peripersonal space without (centre) or with (right) a frontal panel impairing the monkey's reach into its peripersonal space. In this latter condition, the object (and the act performed by the experimenter) is metrically in the monkey's peripersonal space, but operationally outside it. The lower panels show the visual responses of a mirror neuron in the three conditions. Before closure with the frontal panel, the neuron was activated only during observation of grasping in the monkey's extrapersonal space. However, after closure, the neuron also responded to observation of grasping performed close to the monkey's body.*

According to another study, the majority of F5 MN seem to visually encode actions in a view dependent manner (Caggiano et al., 2011). In this study, the responses of MN to action observation were studied by presenting the same actions as seen from different points of view, including also the actor's own point of view. The discharges of MN were modulated not only by the action being observed but also by the point of view under which it was observed (e.g., a frontal or a side view) (Caggiano et al., 2011; see also Figure 7). Interestingly, a consistent percentage of MN visually responded not only during the observation of the actions of another individual but also during the observation of the visual representations of the actions seen in a first-person view. This characteristic suggests that MN could be visually activated not only by the actions of others but also by self-generated actions.

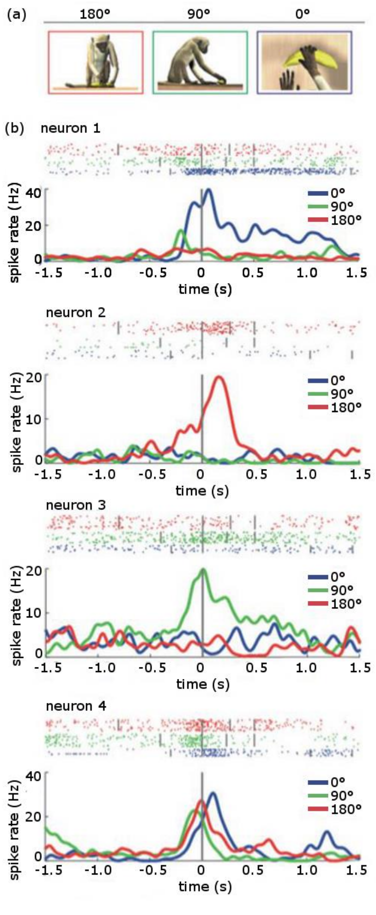

***Figure 7**: **Responses of mirror neurons to grasping observed from three visual perspectives**. (a) Experimental conditions (subjective view: 0°; side view: 90°; frontal view: 180°). (b) Examples of the responses of four mirror neurons during observation of grasping from the three perspectives. Rasters and histograms are temporally aligned (vertical grey line) with the moment at which the observed hand touches the object. Neuron 1 is selective for the subjective view, neuron 2 for the frontal view, neuron 3 for the side view. The activity of neuron 4 discharged equally well for all points of view (from Rizzolatti & Fogassi, 2014)*

The modulations of mirror neuron discharges by the spatial position of the observed action or the point of view suggest an extension of their possible functional role. This finding is relevant for two important implications at phylogenetic and ontogenetic levels. Philogenetically, the mirror neuron system could have evolved to map monkeys' actions onto own motor representations possibly to provide feedback for visually directed graspings (Bonaiuto & Arbib, 2010; Oztop & Arbib 2002;

Casile et al., 2011). According to this proposal, the same system was, later in evolution, exploited to interpret the goal-directed behaviors of others for social interaction and communication purposes.

Ontogenetically, the development and refinement of a successful control strategy for visually guided reaching movements needs also execution of appropriate exploratory behaviors (Von Hofsten, 2004). These self-generated exploratory behaviors serve likely both motor and cognitive purposes. The motor purpose likely consists of the integration of different functional motor circuits and their sensory consequences (e.g., gaze behavior with arm movements and proprioception). The possible cognitive purpose is the development of an internal representation of the space around the infant. The fact that this important cognitive development requires concurrent and coordinated visual and motor experience was demonstrated by Held and Bauer (1967). In their experiments, they dissociated vision and proprioception by preventing newborn macaques from seeing their own arms at birth. When tested at 35 days of age, the subjects exhibited severe impairments in visually guided reaching and grasping despite their preserved capacity to grasp under tactile guidance (Held & Bauer, 1967). This result strongly suggests that the correct development of spatial maps of the peri-personal space for goal-directed hand movements entails the observation of own movements (Casile et al., 2011).

Another interesting property recently discovered about F5 MN is that they are influenced by the value attribution of the grasped object. The vast majority of monkey MN were stronger activated in response to observation of grasping food than of grasping objects without any value for the monkey (Caggiano et al., 2012). It is remarkable that the value an observer attributes to an act is fundamental in choosing the appropriate behavioral response. According to Rizzolatti and Fogassi (2014) this is possible due to the strong connections of the MN frontoparietal circuit with the superior temporal sulcus (STS; Figure 8) -which would provide the higher order visual input necessary to MN functioning- and with the inferotemporal lobe.

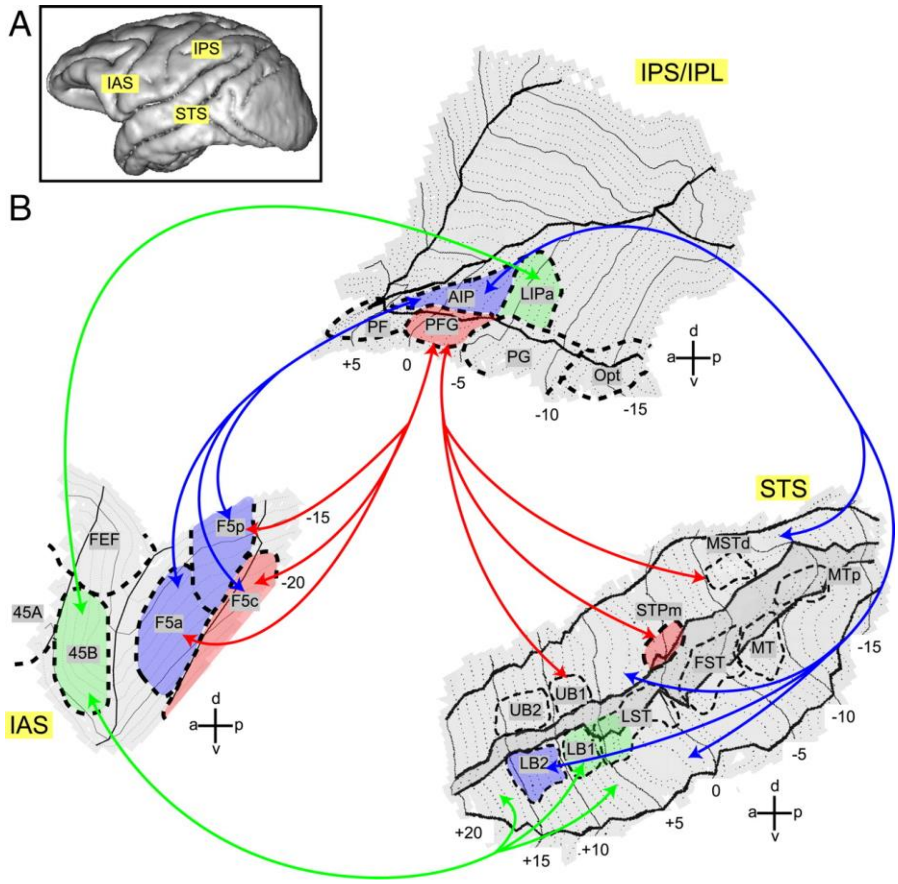

***Figure 8**: **STS-IPL-F5 grasping observation network**.* *A: lateral view of a macaque brain showing locations of three regions involved in action observation. B: flattened representation of STS, IPS/IPL, and IAS (inferior arcuate sulcus). FEF (frontal eye fields); F5c, F5p, F5a. Visual information on observed actions are sent forward from STS through parietal cortex to area F5 along two functional routes: a STPm-PFG-F5c pathway and a LB2-AIP-F5a/p pathway indicated with red and blue arrows, respectively. Area 45B receives parietal input from LIPa and also has direct connections with the lower bank of STS (green arrows). (from Nelissen et al., 2011)*

In the STS of the monkey, there are neurons exhibiting selective responses to human movements either performed by the experimenter in front of the monkey or presented on a computer screen (Perrett et al., 1985). These neurons are sensitive to many characteristics of observed movements. For example, they encode the direction of motion of a walking person with respect to the observer (Perrett et al., 1985), and respond also to human figures presented as static snap-shots, both with arms and legs outstretched and close to the body (Barraclough et al., 2006). They also show a specificity for different body parts (Wachsmuth et al., 1994). In addition to neurons responding to human movements, Perrett and co-workers described also a population of neurons in STS selectively responding during the observation of manipulative behaviors (i.e., hand-object interactions; Perrett et al., 1989). Interestingly, for their relationship with MN, STS neurons have a reduced discharge when the monkey observes hand movements alone miming the action, as well as objects alone with no hand movements elicited (Barraclough et al., 2008). It also deserves a mention the fact that a subset of the monkey STS units selective for human actions are significantly modulated by the sound associated with that action (Barraclough et al, 2005). This finding raises the possibility that STS would not only provide the higher order visual input necessary to MN functioning, but also the auditive one.

1.2.2 Methods, results and implications of Mirror Neurons studies in humans

The MN presence in humans have been studied through neuroimaging (fMRI) and neuropshysiological techniques (EEG, evoked potentials, transcranial magnetic stimulation- TMS), leading to discover neurons with mirror properties in the areas already described (particularly IFG and IPL, the "core MN system"- Pineda, 2008), and to detect cerebral areas strictly connected to the MN system, i.e. STS, insula and the middle temporal gyrus ("extendend MN system"; see later in the chapter for relevant studies; see also Figure 9 and 10).

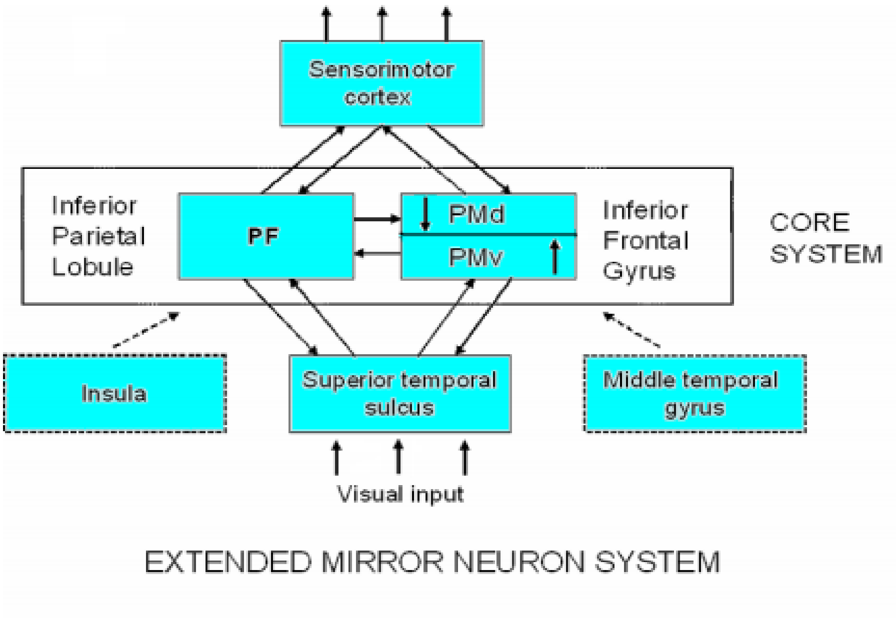

Figure 9*: Schematic of areas in the human brain that contain mirror neurons (inferior parietal lobule and inferior frontal gyrus) and make up the 'core' system. The 'extended' mirror neuron system involves additional brain areas, e.g., insula, middle temporal gyrus, superior temporal sulcus and somatosensory cortex, which connect to the core system and perform transformations on the data critical for mirroring and simulation (from Pineda, 2008).*

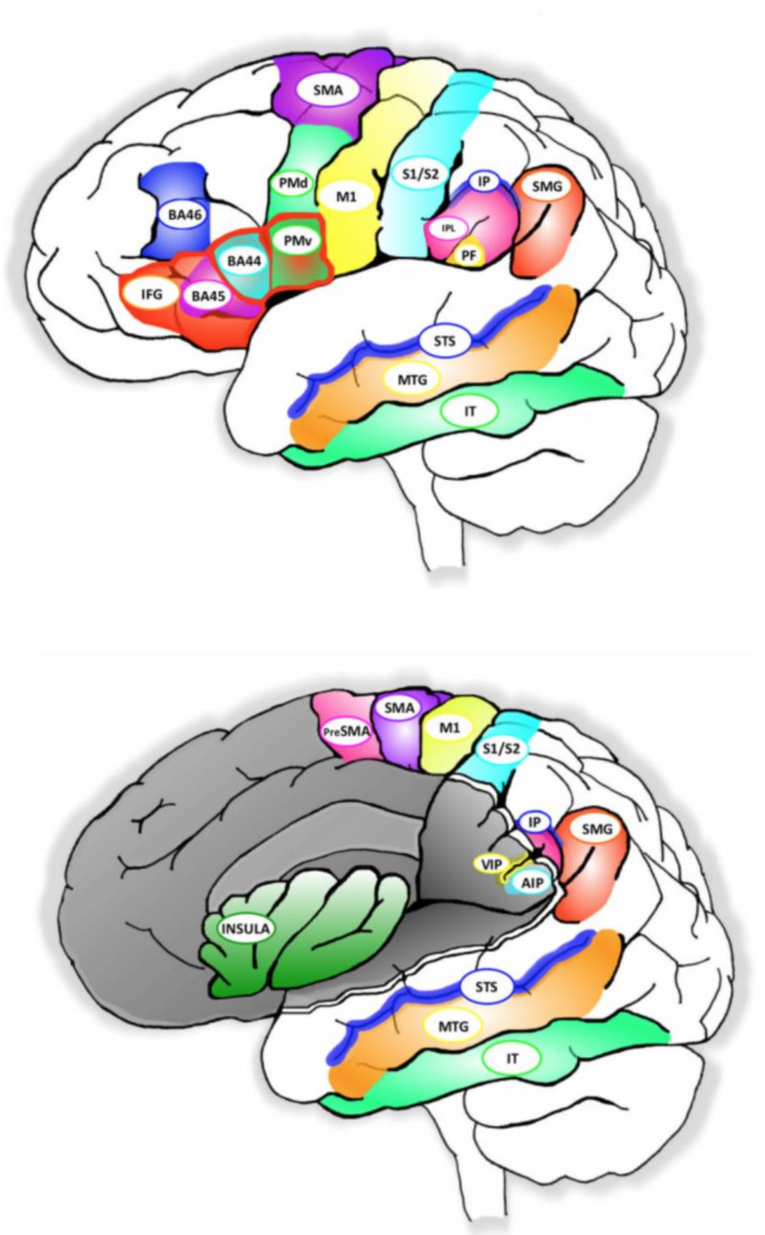

Figure 10*: Mirror neurons areas in humans (Pineda, 2008).*

1.2.2.1 <u>Neurophysiological techniques: EEG, TMS, evoked potentials, neuronal recordings</u>

The reduction of magnitude of the μ rhythm during action observation, observed in several studies, has led to the conclusion that this rhythm indexes a brain system that is functionally comparable to the monkey mirror neuron system (Muthukumaraswamy et al., 2004; Pineda, 2005; Lepage and Théoret, 2006).

The human μ rhythm was first described by Henri Gastaut (Gastaut et al., 1952), and was termed the rolandic wicket rhythm, or the "rythme rolandique en arceau", due to the waves' arch-like or wicket-like shape. At the beginning, it was thought to be a rare rhythm and was associated to pathological significance (Hobson & Bishop, 2017). Later, when it became apparent that μ was not an unusual or particularly pathological phenomenon, new theories emerged about its origin.

Event-related desynchronization or synchronization (ERD/ERS) describes the reduction or increase of a given power band relative to a baseline. ERD and ERS are considered to reflect cortical activation and idling, respectively. (Pfurtscheller & Lopes da Silva, 1999). Using ERD/S, researchers have demonstrated the reactivity of μ to people's own movements and suggested that there may be different types of μ rhythm, which could correspond to different areas of the motor cortex (Pfurtscheller & Neuper, 1994). As well as reacting to participants' own movements, μ is suppressed by observing the movements of others and has been therefore used as an index of MN functioning in humans (Muthukumaraswamy & Johnson, 2004; Muthukumaraswamy et al., 2004). Traditionally, the μ rhythm is considered an EEG oscillation occurring within the standard "alpha" band (i.e., ~8–13 Hz in adults; ~6–9 Hz in children) that is suppressed during the execution and perception of action and is speculated to reflect activity in the premotor and inferior parietal cortices as a result of MN system activation (Fox et al., 2016; see also Figure 11 and 12). However, it is now considered that it has beta (14–25 Hz) components, too (Pineda, 2008).

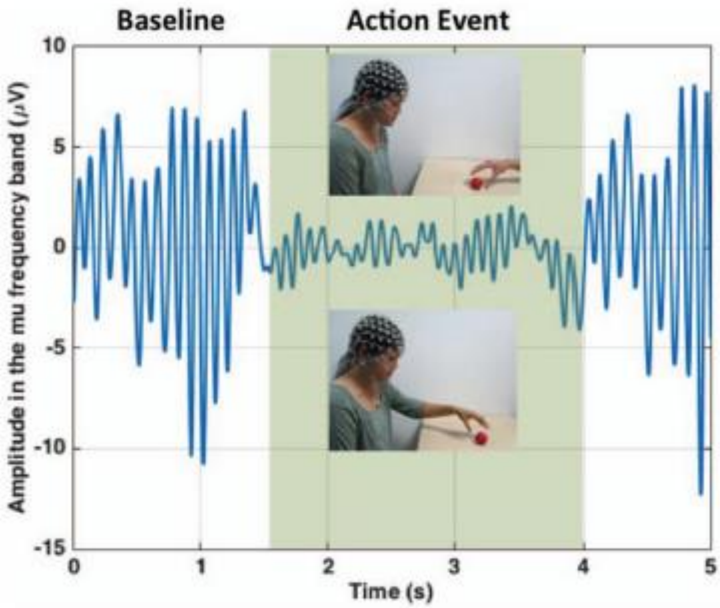

Figure 11 *(from Fox et al., 2016):*

Simulation of mu rhythm desynchronization in the 8- to 13-Hz frequency band. There is a decrease in amplitude in the electroencephalogram from baseline during action observation or execution (action event; highlighted).

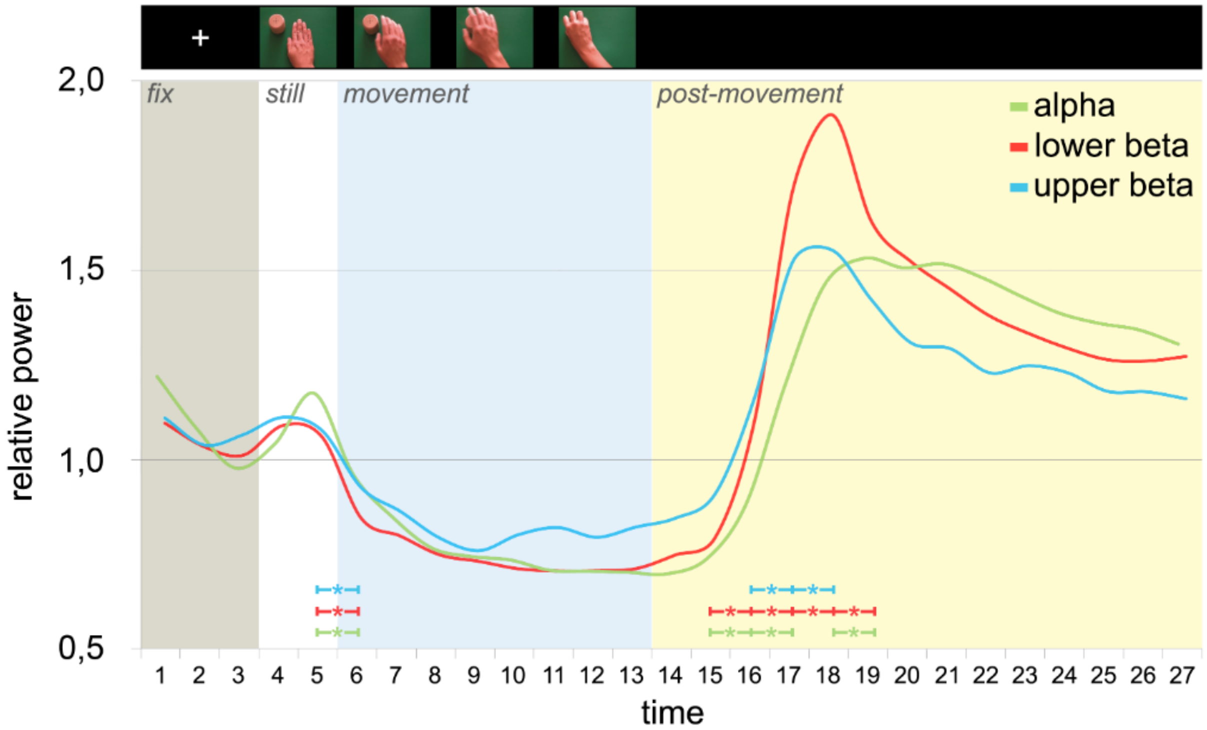

***Figure 12**: EEG rhythms during action observation. The graph shows the EEG power time course for each frequency band: alpha band (8–13 Hz) in green, lower beta (13–18 Hz) in red, and upper beta (18–25 Hz) in cyan. Each epoch (fix, still, movement, and post movement) is labeled by a different color. At the top of the figure, a film strip shows an example illustrating the different epochs of the observed video clips. (Rizzolatti et al., 2014, modified by Avanzini et al. 2012)*

μ suppression studies in humans found that stronger suppression occurred when viewing another's hand in a precision grip (i.e. a grip that could be used on an object) rather than in a neutral, non-grip position, and that object interaction produced greater μ suppression than conditions without object interaction (Muthukumaraswamy & Johnson, 2004; Muthukumaraswamy et al., 2004). It has been proposed that this object effect supports the contention that μ suppression is related to MN activity in humans. As these pioneering studies suggested that μ suppression could be harnessed for research into the human MN system, many more action-observation experiments have been conducted. This line of inquiry was recently reviewed by Fox et al. (2016) in a meta-analysis: Authors concluded that their analysis did show that μ suppression can be used as a proxy for human MN activity. According to their review, results indicates that there is consistent EEG μ desynchronization during action execution and action observation and that these effects occur across diverse experimental conditions that vary in methodology (e.g., type of stimulus observed) and across a variety of actions (e.g., object-directed and non-object-directed). Some authors have also speculated that MN responses to non-object-directed actions are a distinctive property of human MN, and that this difference from other primates may represent a departure from our common ancestors which played an important role in the evolution of language (Rizzolatti & Craighero, 2004)

However, others have contested that μ suppression reflects mirror neuron activity, stating that μ suppression studies have failed to produce robust evidence of the role of MN system due to limitations in methodology: e.g. a few studies report changes in power at site other than the central electrodes, making it impossible to be sure that effects are not being due to changes in power in other areas (Hobson & Bishop, 2016) Coll et al.(2015), reported that μ suppression indexed sensory mirroring but not motor mirroring, a finding that undermines the important connection between action and perception that MN are thought to represent. The validity of μ suppression as a measure of the human MN system is therefore still a topic of debate.

Previous studies have demonstrated that perception of action presented audio-visually facilitates greater MN system activity in humans (Kaplan & Iacoboni, 2007) and non-human primates (Keysers et al., 2003) than perception of action presented unimodally. McGarry et al. (2012) examined whether audio-visual facilitation of the MN system can be indexed using electroencephalography (EEG) measurement of the μ rhythm. Participants observed experimental stimuli unimodally (visual-alone or audio-alone) or bimodally during randomized presentations of two hands ripping a sheet of paper, and a control video depicting a box moving up and down. Audio-visual perception of action stimuli led to greater event-related desynchrony (ERD) of the 8-13 Hz μ rhythm compared to unimodal perception of the same stimuli over the C3 electrode, as well as in a left central cluster when data were examined in source space.

The amplitude of the motor evoked potentials (MEPs) and in general evoked excitability induced by TMS is modulated by action observation training (AOT): this finding has been replicated by several studies (Fadiga et al. 1995; Gangitano et al., 2001, 2004; Fadiga et al., 2005; Avanzino et al., 2015; Celnik et al., 2006; Stefan et al., 2005). When TMS is applied to M1 during passive action observation, the amplitude of the MEPs recorded from the muscles required to execute that action is greater than the amplitude of the MEPs recorded when observing a different action. For example, observing index and little finger abduction movements selectively facilitates the amplitude of MEPs recorded from the first dorsal interosseus and abductor digiti minimi muscles, responsible for index and little finger movements, respectively (Catmur et al. 2011). That action observation selectively increases corticospinal excitability to action relevant muscles is suggestive of “mirror” sensorimotor connectivity. Therefore, although the primary motor cortex (M1) is not classically considered an integral part of the core parietofrontal MN system, TMS studies support the role of M1 in observational learning.

Action observation can also modulate somatosensory evoked potentials (SEPs) in humans (Rossi et al., 2002). In a recent work (McGregor et al., 2016) recorded SEPs associated with median nerve stimulation from primary somatosensory area (S1) before and after AOT (a tutorial video which taught how to reach a target in a force field): SEPs amplitude increased only for participants who observed the video and SEPs amplitude increase was proportional to the amount of learning exhibited by participants after watching at the tutorial video. According to the Authors, S1 plasticity would support motor learning by observing the actions of other people.

The late N30 component of SEPs is known to be modulated by sensory interference, motor action, movement ideation and observation. Cebolla et al. (2014) have proposed a new paradigm in which the observation of another person's hand movement triggers the somatosensory stimulus, inducing the N30 response.

Till now, there has been only one study in which MN have been studied with direct single neuron extracellular recording in humans: Mukamel et al. (2010) described neurons with mirror-like properties in motor supplementary area and in the hippocampus.

Cerri et al. (2015) tested mirror properties of the human Broca's area (BA44). To this aim, they used an fMRI study to assess the activation of brain areas during a fluency task and during the execution and observation of hand and mouth grasping actions as well as nonverbal mouth communicative actions. Subsequently, an intraoperative neurophysiological study on 10 patients submitted to neurosurgery for glioma was designed to investigate whether the electrical stimulation of frontal premotor areas elicited a motor output in hand or mouth muscles. The results challenge the inclusion of Broca's area in the human MN system, because while ventral premotor/BA6 fully and consistently satisfied all the requirements to be considered a MN area, BA44/Broca did not (in particular, no motor response should be elicited by electrical stimulation of this area).

1.2.2.2 fMRI studies

Functional magnetic resonance imaging (fMRI) has caught on to study functional activity in the brain during a behavioral response. Most of these studies make use of blood oxygen level-dependent-(BOLD-) contrast imaging, which involves mapping particular areas of a functioning brain, from the changes in blood oxygen. fMRI recordings require the subject to perform a particular action in order to trigger a dynamic uptake of oxygen into the brain. This is because fMRI recordings are based on the subsequent increase in oxygen demand from the brain tissue upon the execution of a certain stimulus, whether it is motor, sensory or emotional. The images acquired are then superimposed on the neuroanatomical image of the corresponding slices, which facilitated the localization of the sites of recording (Chow et al., 2017; Gore, 2003). BOLD-contrast imaging fMRI has a good enough spatial resolution for the localization of activated brain areas and their delineation from neighboring regions to be visualized. The voxel representing the area of activation is usually defined as covering a few million neurons (Huettel et al., 2009). In addition, the BOLD response lags 1 to 2 s behind the stimulus in order for the vascular system to respond, and in general it peaks at 5 s after the stimulus. A continuation of the same stimulus would downregulate the BOLD response (Huettel et al., 2009; Dale & Buckner, 1997; Kahn et al., 2011). To eliminate noise in the recording, the stimulus must be repeated several times. This process often takes a few minutes to complete, and the results can then be compared across different individuals (Huettel et al., 2009; Rombouts et al., 2008).

fMRI experiments (Peeters, et al., 2009, Grèzes et al., 2003) have shown that a parieto-frontal network, remarkably similar in monkeys and humans, is activated during observation and execution of hand grasping acts. Moreover, this network is also activated during observation of grasping acts made with tools, in line with previous single neurons studies in monkeys (Ferrari et al., 2005). fMRI has identified regions of premotor cortex (both classic BA6 and BA44) and inferior parietal areas that are active during both action observation and execution (Aziz-Zadeh et al., 2006; Buccino et al. 2004; Carr et al., 2003; Grèzes et al. 2003; Iacoboni et al. 1999; Leslie et al., 2004; Tanaka & Inui, 2002; Vogt et al., 2007), even if the more ancient studies have been criticized in term of methodology (e.g.

some of them were lacking of a real execution part to compare with action observation (Turella et al., 2009). Overlapping responses to action observation and execution have been found in single-subject analyses of unsmoothed data (Gazzola & Keysers, 2009), confirming that the foregoing reports are not artifacts of group averaging (Cook et al., 2014).

In humans, both goal-directed actions with the object present and goal-directed pantomimed actions (Buccino et al., 2001; Montgomery et al., 2007) appear to involve the MN system, as do communicative actions. Montgomery et al. (2007) performed a fMRI experiment in which participants viewed, imitated and produced communicative hand gestures and object-directed hand movements. The observation and execution of both types of hand movements activated the MN system (IPL and frontal operculum) to a similar degree. Chong et al. (2008) identified movement-selective MN during observation and execution of actions involving the pantomimed use of objects (Chong et al., 2008).

A fMRI study in humans (Buccino et al., 2001) has shown that the observation of actions performed with the hand, the mouth and the foot leads to the activation of different sectors of Broca's area and premotor cortex. This activation is related to the effector involved in the observed action, following a somatotopic pattern which resembles the classical motor cortex homunculus. Therefore, some authors (Rizzolatti & Arbib, 1998; Buccino et al., 2006; Tettamanti et al., 2005) have claimed that there is a homology between the motor related part of Broca's region, localized in the opercular portion of the inferior frontal premotor cortex (mainly in area 44 of Brodmann) and the monkey area F5 (see Figure 13). As already cited, however, a recent study have raised doubts about the presumed matching between the Broca’s area and F5. (Cerri et al., 2015).

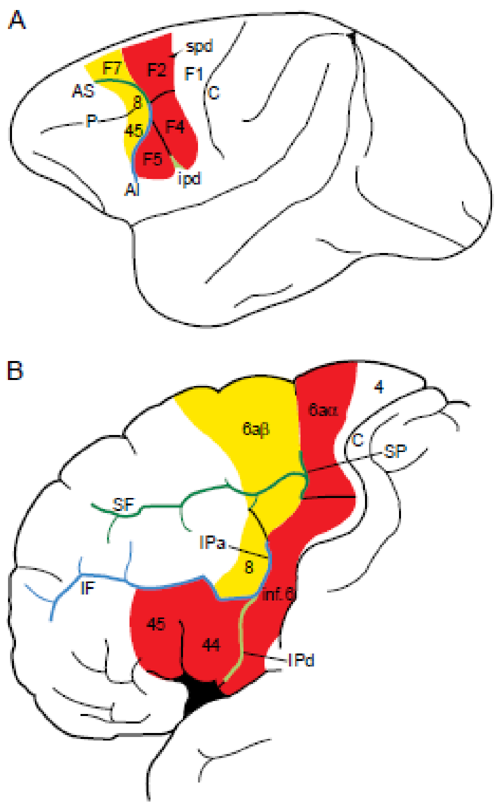

Figure 13: Cytoarchitectonic map of the caudal part of the monkey frontal lobe and possible homologies with human frontal cortex

Similar colors in A and B indicate areas with anatomical and functional homologies. Brain regions colored yellow are areas with anatomical and functional homologies, mostly related to orienting behavior; areas colored red also share anatomical and functional homologies and are mostly related to interactions with the external world. The homology is based on cytoarchitectonics, electrical stimulation and sulci embryology (from Rizzolatti and Arbib, 1998)

As far as more posterior areas of MN human system are concerned, a specific sector of human IPL (left anterior supramarginal gyrus -aSMG-) would be a region unique to hominid evolution as it is specifically activated in humans, but not monkeys, during observation of tool use (Peeters, et al., 2009, Figure 14).

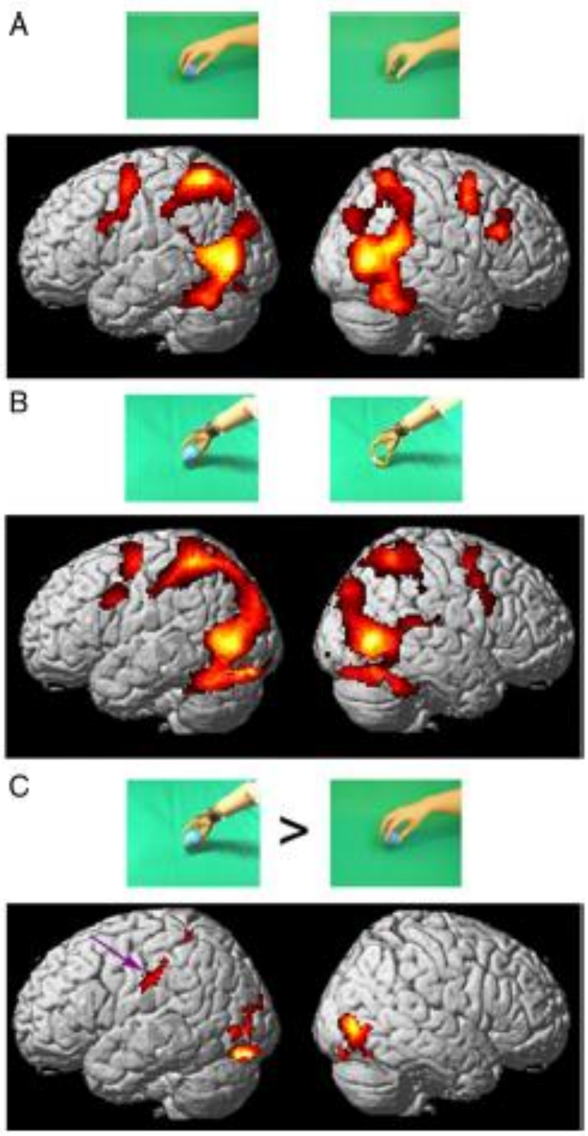

Figure 14*: Results from the work of Peeters et al., 2009*

A*, Cortical regions activated (colored red to yellow) by the observation of hand grasping actions relative to their static controls, rendered on lateral views of the standard (MNI) human brain.*

B*, Cortical regions activated in the contrast observation of mechanical hand actions compared with their static control.*

C*, Cortical regions more active during the observation of grasping performed with a mechanical implement than during the observation of the same action by a hand. The purple arrow indicates the activation in aSMG. Inserts show frames from hand actions and mechanical arm actions.*

Molenberghs et al. (2010), to investigate the role of the MN system in imitation used fMRI to examine patterns of neural activity under four different conditions: passive observation of a pantomimed action, imitation of an observed action, execution of an action in response to a word cue and self-selected execution of an action. They employed pantomimed actions to avoid brain activity associated with object processing that has been found in studies of object directed actions (Buccino et al., 2001). A network of cortical areas, including the left supramarginal gyrus, left superior parietal lobule, left dorsal premotor area and bilateral STS, was significantly active across all four conditions. The STS is strongly associated with activation of MN areas in humans (Saxe et al., 2004), even if most Authors do not consider it a real MN area because it is not constantly activated for action execution (Aziz-Zadeh et al., 2006). As already noted in the description of studies in monkey, STS is considered by these Authors to provide a visual description of the action that is critical for the process of imitation (Nishitani & Hari, 2000; Carr et al., 2003; Miall, 2003) According to another study (Montgomery et al., 2007), STS could be crucial in social communication (Allison et al., 2000). In fact, the Authors found significant activation in the STS and MN system for the observation, imitation and production of both object-directed hand movements and communicative hand gestures. They also demonstrated increased activation in the STS for the production of communicative hand gestures compared to object-directed hand movements.

An extensive quantitative metanalysis (Molenberghs et al., 2012) has analyzed fMRI data from 125 studies. It appears from this review that human MN areas are localized in the inferior frontal gyrus, the ventral premotor cortex, the IPL (which are considered "classical" MN areas and are expected to be part of the MN system based on studies in monkeys) but also in the primary visual cortex, in the cerebellum and of the limbic system (Figure 15). The Authors underline that there are additional activation areas in different studies due to the sensorial modality of the stimulus presentation and that in only 30% of the studies there is an effective comparison between an observation and an execution condition.

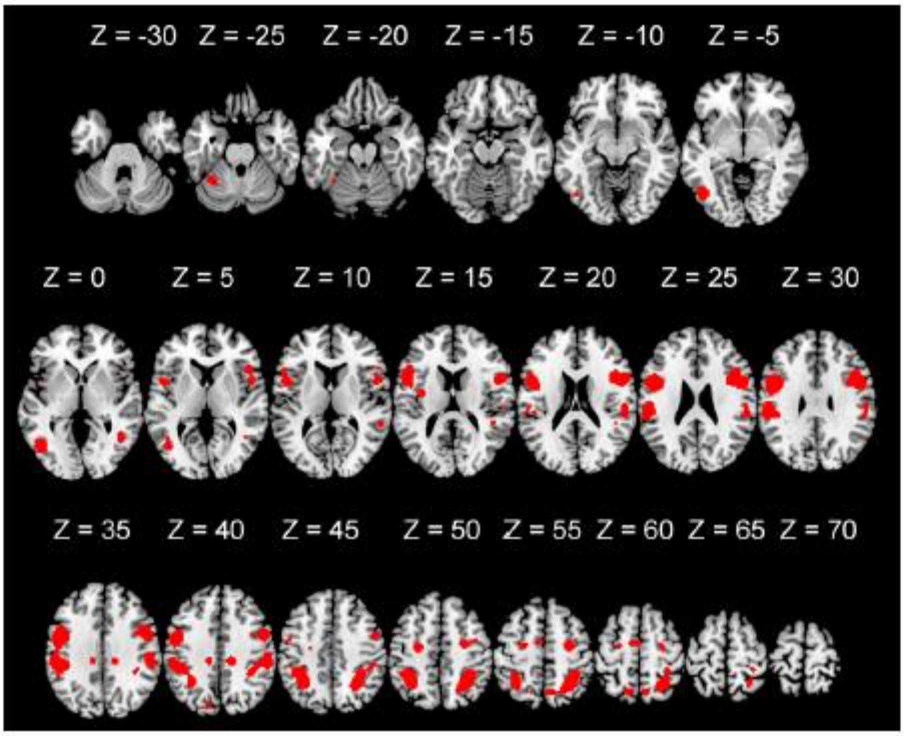

Figure 15*: Molenberghs et al., 2012: Overview of all significant clusters in the quantitative meta-analysis (activation likelihood estimation) analysis of the 125 human fMRI studies in which the authors attributed their findings to mirror system functioning.*

Recently, repetition suppression protocols have been used to provide evidence of mirror populations encoding visual and motor representations of the same action (Cook et al., 2014). These paradigms exploit the logic that repeated stimulus presentation or action execution causes a decrease in neural responses (Grill-Spector et al. 2006). Action observation followed by execution of the same action, or vice versa, elicits repetition suppression in inferior parietal regions (Chong et al. 2008; Lingnau et al. 2009) and in premotor areas (Kilner et al. 2009; Lingnau et al. 2009).

De la Rosa et al. (2016) designed a fMRI study to provide evidence for the location of motor-visual units in humans by attempting to minimize methodological constraints. They wanted to reduce the effect of a priori assumptions about the location of MN by conducting a whole-brain analysis. Specifically, they combined across- modal adaptation paradigm using actions that differed mainly in their object-directedness with a whole-brain analysis for the identification of motor-visual areas. They further checked these voxels for their sensitivity to motor and visual stimulation. The specific location of MN voxels was associated with BA44 and BA45. Thus, this study would demonstrate that part of human IFG, specifically BA 44/45, has BOLD response characteristics very similar to monkey's area F5.

1.2.2.3 fMRI/neurophysiological techniques combined

Some groups have tried to correlate neurophysiological and fMRI data in the study of MN. Braadbaart et al., 2013 used a manual imitation paradigm to look at correlations between μ rhythm and BOLD response by recording sequential EEG and fMRI measures. They found that μ power modulation, defined as μ power changes between conditions, correlated negatively with BOLD response in putative MN areas: right inferior parietal lobe, premotor cortex and inferior frontal gyrus. Thanks to μ suppression they have also identified a range of structures that modulate motor preparation activities and are sensitive to visual input, including but not restricted to the human analogue of the MN system cluster (bilateral cerebellum, left medial frontal gyrus, right temporal lobe and thalamus (Braadbaart et al., 2013).

1.2.2.4 Neuropsychological tests alone or combined with other techniques

Neuropsychological tests have been rarely included in studies on MN (with the exclusion of the aim to evaluate cognitive functions of participants).

A study on patients with stroke (Fazio et al., 2009) selected a population with lesion of the Broca area who were aphasic but not apraxic and not demented. Patients were asked to reconstruct the correct sequence of human actions or physical events (control condition): they exhibited a clear difficulty in action sequencing in comparison with a good performance in sequencing physical events. As Broca area in human has been claimed to be part of the MN system (Buccino et al., 2004; Pobric & Hamilton, 2006), these results suggest an involvement of MN in understanding action meaning.

The same conclusion can be inferred by a fMRI experiment in which participants listened to sentences describing actions performed with the mouth, the hand or the leg. Abstract sentences were used as control condition. Listening to action-related sentences activated a fronto-parietal-temporal network including Broca's area, the premotor cortex, the inferior parietal lobule, the intraparietal sulcus and the posterior middle temporal gyrus (Tettamanti et al., 2005). In another work (Hauk et al., 2004) reading action words referring to face, arm or leg actions differentially activated areas adjacent to respectively motor areas.

Putative contributions of the human MN system to the perception of social information have been assessed by Perry et al. (2010) measuring the suppression of EEG oscillations in the mu/alpha, beta and low-gamma ranges while participants processed social information revealed by point-light video-clips of human motion. Participants were instructed to distinguish the intention, the emotion, or the gender of a moving image of a person. Relative to a baseline presenting a nonbiological but meaningful motion display, all three biological motion conditions reduced the EEG amplitude in the mu/alpha and beta ranges, but not in the low-gamma range. Suppression was larger in the intention than in the emotion and gender conditions, with no difference between the latter two. The suppression in the intention condition was negatively correlated with a measure of empathy (EQ), revealing that participants high in empathy scores manifested less suppression. This result, which is opposite to what expected, has been tentatively explained by the Authors as due to the fact that people higher in empathy do not need to simulate the other's motor acts for such tasks (which may be trivial for them).

Mehta et al. (2014) used two questionnaires to evaluate social cognition in schizophrenia patients: the scores were positively correlated with mirror activity evaluated by TMS (they used TMS paradigms of eliciting MEP- in the right first dorsal interosseous -FDI-while the subjects observed a goal-directed action involving the FDI -actual action and its video- and a static image). The difference in the amplitude of the MEP while they observed the static image and the action provided a measure of MN activity.

Alaerts et al. (2015), in a study on teenagers and young adults affected by autism, demonstrated a positive correlation between a cognitive task (recognizing movements and emotions of a computer-generated silhouette) and resting-state fMRI connectivity of the superior parietal lobule.

Finally, in a study on patients with amyotrophic lateral sclerosis (ALS) Jelsone-Swain et al. (2015) evaluated the integrity of MN system with a fMRI task of observation and execution of actions and a task of action understanding. Patients were also submitted to the Read the Mind in the Eyes (RME) test, which assesses a person's ability to infer the emotions of others by examining pictures of facial eye expressions. Performance in action understanding was positively correlated with a better RME test performance (see also the paragraph 2.2.2.2.1 for further details on this study).

1.2.2.5 Mirror Neurons functions in humans

- *Recognizing actions of others*

The first function attributed to MN in humans has been recognizing actions performed by other people. In a TMS study (Fadiga et al., 1995) subjects were submitted to stimulation during observation of grasping acts, afinalistic movements and static objects observation. Evoked potentials of hand muscles were more marked during grasping observation, even if they were also present during observation of afinalistic movements. The most important point is the fact that evoked potentials were present in muscles exactly involved in the observed act: therefore observing a motor act had stimulated an efferent response conserving the aim of the act.

Another emblematic study has been conducted with fMRI on patients with upper limbs aplasia (Gazzola, et al., 2007; Figure 16): the observation of manual grasping by subjects that never used hands activated MN at the same extent than acts having the same aim and performed by the subjects with the mouth or the foot.

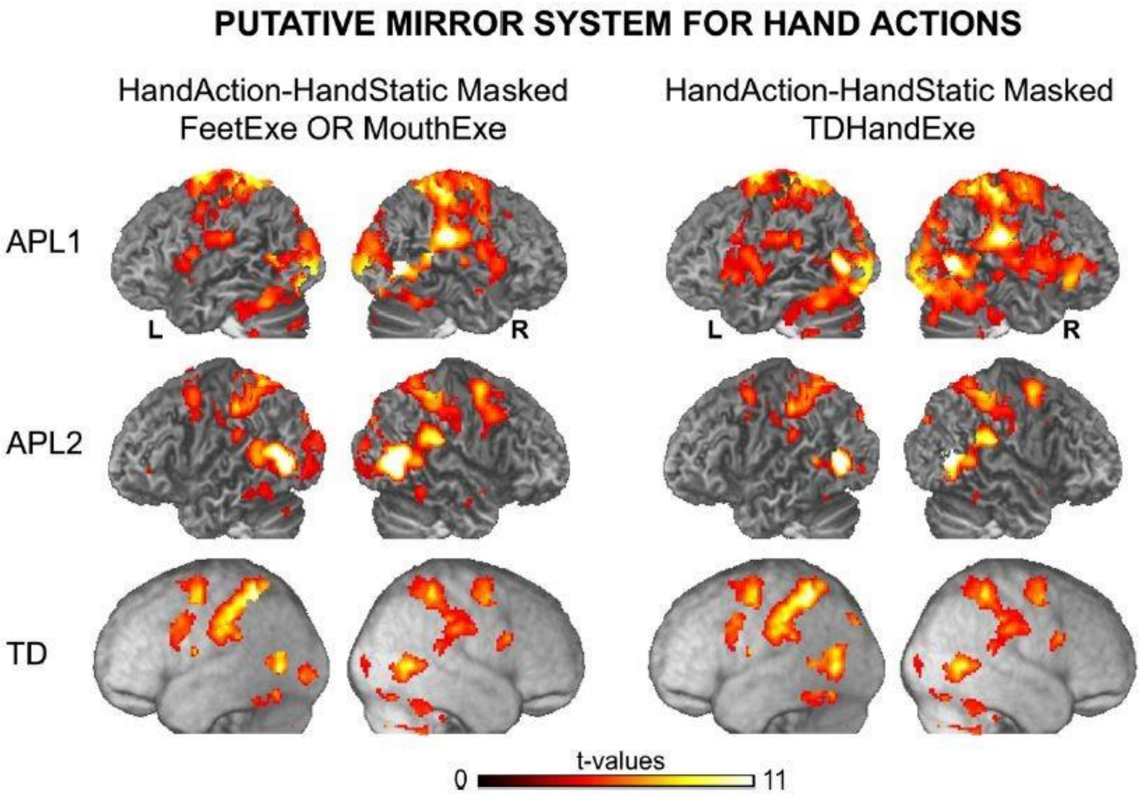

***Figure 16**: from Gazzola et al., 2007: The left two columns show putative hand MN System for aplasic subjects (APL1 and APL2) and typically developed individuals (TD), defined by inclusively masking the visual contrast Hand Action-Hand Static with their Feet Execution or Mouth Execution. The right two columns show the same but defined by masking with TD's Hand Execution.*

- *Interpreting action intention*

The next step in the study of MN function has been to verify whether they were also involved in interpreting the intention embedded in the action. Iacoboni et al. (2005) performed a fMRI study where participants watched three kinds of stimuli: grasping hand actions without a context, context only (scenes containing objects), and grasping hand actions performed in two different contexts. In the latter condition the context suggested the intention associated with the grasping action (either drinking or cleaning: see Figure 17). Actions embedded in contexts, compared with the other two conditions, yielded a significant signal increase in the posterior part of the inferior frontal gyrus and the adjacent sector of the ventral premotor cortex where hand actions are represented. The Authors concluded that premotor MN areas are also involved in understanding the intentions of others.

Figure 17*: Examples of stimuli used in the study of Iacoboni et al., 2005. The ''before tea'' context suggested the intention of drinking (upper row), and the ''after tea'' context suggested the intention of cleaning (lower row). Whole-hand prehension (displayed in the upper row of the Intention column) and precision grip (displayed in the lower row of the Intention column) were presented an equal number of times in the ''drinking'' Intention clip and the ''cleaning'' Intention clip.*

Other studies have confirmed this hypothesis. An American group (De C. Hamilton & Grafton, 2008) conducted a fMRI experiment to study actions with the same motor parameters but different physical outcomes, that is different intentions, e.g. the stimulus was represented by a video with a hand which opened or closed a box with different movements (a box with a sliding lid can be opened or closed by either pushing the lid with a finger or pulling with both finger and thumb). Videos were repeated to study adaptation of the activated areas. A stronger response to novel outcomes than to repeated outcomes was found in regions throughout the expected frontoparietal action circuits (particularly right IPL and the right IFG extending to the inferior frontal sulcus). In these regions, the robust response to novel outcomes was suppressed when the same outcome was repeated on a second trial, regardless of the hand action. This pattern of data suggests that outcomes rather than motor parameters are encoded in neuronal populations within these regions. Therefore, MN system would allow humans to understand the physical consequences of actions in the world and the intentions underlying those actions.

- *Motor imitation and motor learning*

The MN system has been shown to be involved in imitational learning of familiar elementary movements. Iacoboni et al. (1999) demonstrated the activation of the inferior frontal cortex (pars opercularis) and of superior parietal lobule during the observation, spontaneous execution and imitation of a motor task in a fMRI study. The involvement of the pars opercularis of the frontal lobe in imitation has been also confirmed by a TMS study (Heiser et al., 2003)

Molenberghs et al. (2010) investigated the role of the MN system in imitation using fMRI to examine patterns of neural activity under four different conditions: passive observation of a pantomimed action (e.g., hammering a nail); (2) imitation of an observed action; (3) execution of an action in response to a word cue; and (4) self-selected execution of an action. A network of cortical areas, including the left supramarginal gyrus, left superior parietal lobule, left dorsal premotor area and bilateral STS, was significantly active across all four conditions.

Buccino et al. (2004) have also proposed a role of the MN system in the acquisition of new motor skills. In a fMRI study, they recruited subjects which have never played a guitar. Subjects watched a video showing a music teacher which played some chords. After a pause, they had to reproduce chords. Control conditions were represented by: 1) observing the video without reproducing chords; 2) playing accords spontaneously 3) observing a video with a guitar alone, before to imitate; 4) executing movements not related to music, after chords observation. Watching to the video and then imitating was the condition which activated MN system the most, while observation not followed by imitation activated the MN circuit (IPL and the posterior part of the inferior frontal gyrus plus the adjacent motor cortex) at a lesser extent. During the pause, Buccino et al. observed the activation of BA46 in the frontal cortex and of regions of the anterior mesial cortex.

The Authors have advanced the view that in the acquisition of new motor abilities, the familiar elements of the observed novel complex movements would generate resonant activity within the MN system. By this mechanism, the selection of appropriate neuronal activation patterns underlying the intended movement would be greatly facilitated, and the recombination of elementary overlearned movements into movements of greater complexity could be more easily accomplished (Buccino et al., 2004). The activation of BA46 and mesial anterior cortex before MN system activation would suggest a possible control action of these areas on MN during motor learning. BA46 has been classically associated to working memory (Levy & Goldman-Rakic, 2000), but according to other authors would be also responsible for selecting the target of the response (Passingham et al, 2000; Rowe et al., 2002).

In imitation-based motor learning, the formation of lasting motor memories was thought in the past to be provided through the physical practice of movements. According to this new view, in this kind of learning the MN system enables motor learning through facilitating the physical performance of the appropriate training movements. Mattar and Gribble (2005) used kinematic analyses to show that the acquisition of complex motor behaviors is facilitated by previous observation of subjects learning the novel task. Included subjects learned to manipulate a robotic arm through video observation. Other subjects observed a video with a different movement or did not observe the action. Measuring kinematic parameters of the robotic arm and movement accuracy, the Authors demonstrated that it was possible to learn through action observation alone. The same group used a similar protocol with the association of a resting state fMRI study performed before and after motor learning (McGregor & Gribble, 2015). They observed a modification of the medio-temporal visual area (V5), cerebellum and the primary motor (M1) and sensory cortices (S1). According to the Authors, cerebral areas altered after motor learning belong to an action-observation network which also includes the MN system. They also underline that some studies suggest a role for cerebellum in action observation (Calvo-Merino et al., 2006; Gazzola & Keysers, 2009). According to Oh et al. (2013, see Figure 18), "imitation learning is accomplished through a two-phase process combining action observation and imitation, which is voluntarily triggered by the prefrontal cortex (specifically in the rostral part).

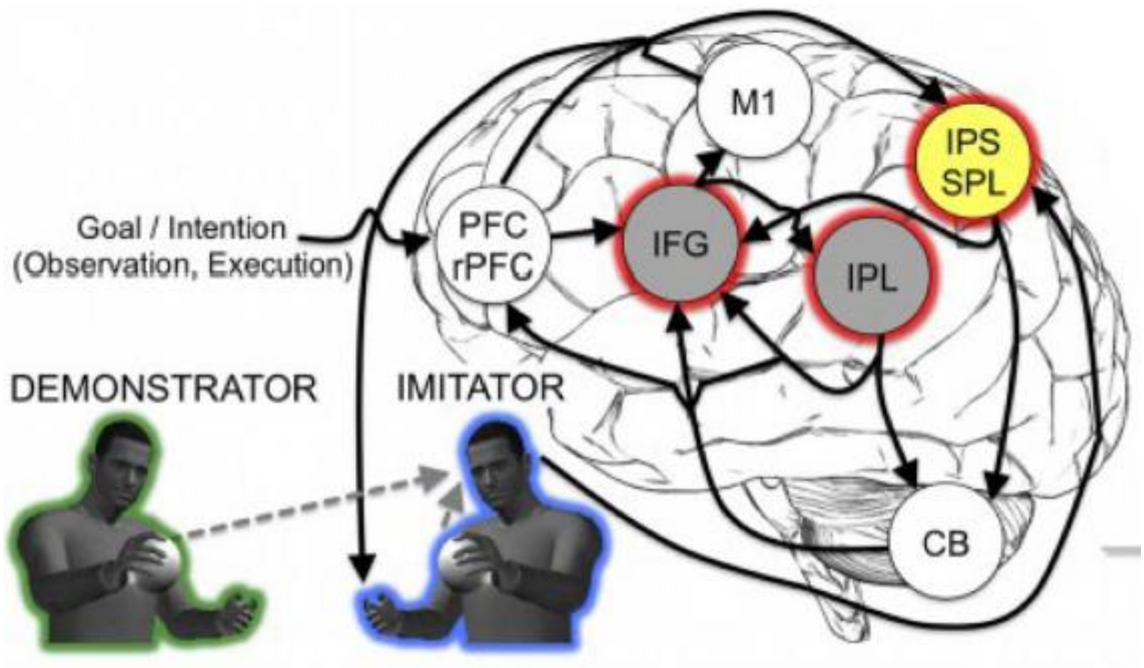

Figure 18*: Model overview for the human MN system based on a model framework incorporating cerebellum, the intraparietal sulcus (IPS) and the superior parietal lobule (SPL), according to Oh et al., 2013. IPS/SPL play a critical role in the transformation between frames of reference, scales, or viewpoints. For the sake of clarity, the STS and its related connections are not shown. The imitator either observes or executes the action based on the current goal/intention. The yellow component (IPS/SPL) generates the neural signal required to process the frame of reference, scaling, and viewpoint transformation. The two gray components (IFG and IPL) indicate the core MN system.*

During the observation phase, the kinematic (i.e., visual information) of the demonstrator is sent to the intraparietal sulcus and the superior parietal lobule, which transforms the visual information into the imitator's egocentric frame of reference, anthropometry, and viewpoint. The transformed observed action updates the IFG by means of mapping from visual to motor representations (i.e., inverse computation), which is then employed to imitate the observed action. Simultaneously, an efference copy of the motor plan is sent to the IPL that would predict the sensory consequences of the corresponding action (i.e., forward computation). Meanwhile, the cerebellum (CB) provides the prediction error for the IFG and the IPL to adjust their internal models".

Stefan et al. (2005) demonstrated that a specific motor memory is formed by observation in M1 (where MN has been also described), one that is like that induced by practicing movements, providing another evidence indicating that the MN system may be involved in generating lasting mnemonic representations of movements, a likely prerequisite of motor learning. After observation of thumb movements directed away from the baseline movement direction, the probability of TMS-evoked movements to fall into the training target zone increased, the acceleration of all TMS-evoked thumb movements was changed toward the direction of the observed movements, and the balance of corticomuscular excitability was altered in favor of the agonist of the observed movements.

- *The simulation theory*

The discovery of MN has given a biological complement to the simulation theory, that is the relatively recent idea that actions involve both an overt and a covert stage (Jeannerod & Frak, 1999; Jeannerod, 2001). The covert stage is a sort of cognitive representation of the future, and includes the goal of the action, the means to reach it, and its consequences on the organism and the external world. Covert and overt stages represent a continuum, such that every overtly executed action implies the existence of a covert stage, whereas the cognitive stage of action does not necessarily turn out into an overt action. The cognitive equivalent of action, in fact, includes a series of behaviorally defined states, which can be conscious or nonconscious: imagined action, prospective action judgments, perceptually based decisions, observation of graspable objects, observation of actions performed by others, and even action in dreams (Jeannerod, 2001). These states can be studied through neuroimaging (fMRI) and neuropshysiological techniques (Vogt et al., 2013).

1.2.3 Embodied Cognition as a link between acting and thinking, Mirror Neurons and cognitive functions

"Embodied Cognition" is a new concept developed in the last two decades, which is strictly linked to the pathway of research previously leading to the simulation theory, and to the idea called "motor cognition": this last theory proposes that thinking is not only manipulating abstract symbol or logico-deductive reasoning, but also includes action simulation (see Jeannerod and Frak, 1999; Jeannerod, 2001; Jeannerod, 2006). In the same vein, the action-perception coupling hypothesis postulates that a part of cognition results from the coupling between action and perception representations, and correspond to implicit action simulation (or "motor resonance") instead of explicit recall of abstract symbols (Jeannerod, 2006; Boulenger et al., 2008; Pulvermüller & Fadiga, 2010; Rizzolatti & Sinigaglia, 2010; Pulvermüller et al. 2014 see also Figure 19 from Uithol et al., 2011 including the concepts of intrapersonal and interpersonal resonace).

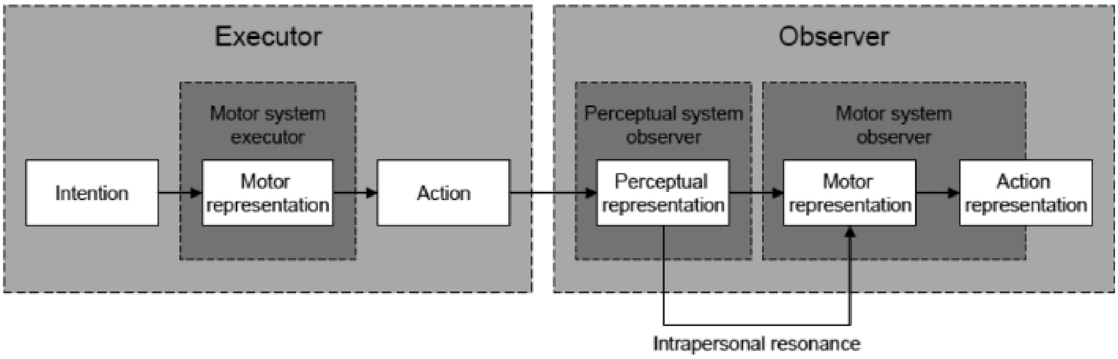

Figure 1. The causal path from action plan in the executor to action representation in the observer and the location of intrapersonal resonance.

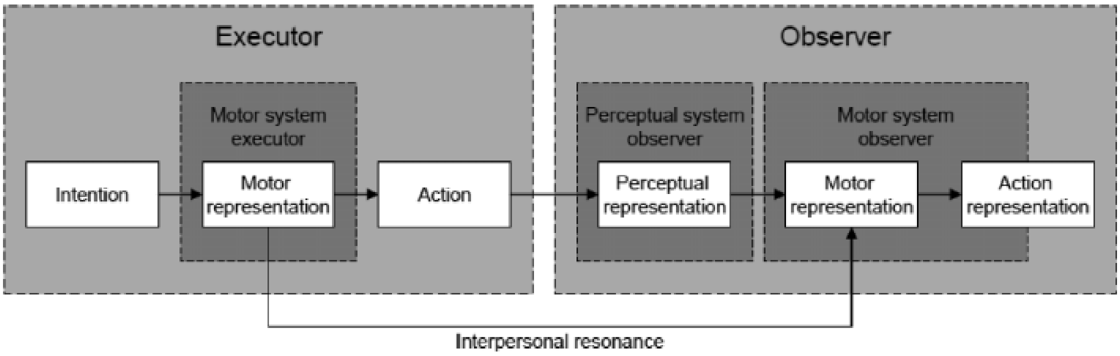

Figure 2. The causal path from action plan in the executor to action representation in the observer as presumed in motor theories of action understanding, and the two parts of the system that take part in interpersonal resonance.

Figure 19*: Intrapersonal and intrapersonal "motor resonance" according to Uithol et al., 2011*

In fact, in the past, psychology and neuropsychology have mainly conceived cognitive abilities as higher-level supervisor functions exploiting perception and action as two separated slave systems: according to this idea, specialized sensors provide sensory input to the cognitive computer for successive peripheral motor implementations (Fodor et al., 1975; Hurley, 2001). This view also specifies the subcomponents of cognition: language perception and production, attention, memory, emotion, and executive functions (decision, planning and conceptual thought). These high-level systems and the two low-level systems (modality-specific perception: visual, auditory, olfactory etc.; motor movement and action) are seen as functionally independent to a degree, although some interaction between them is generally acknowledged. Cognitive neuroscience relates these mental domains to brain structures and led to proposals to map each of the cognitive modules onto one or more brain regions (Pülvermuller, 2014, Figure 20).

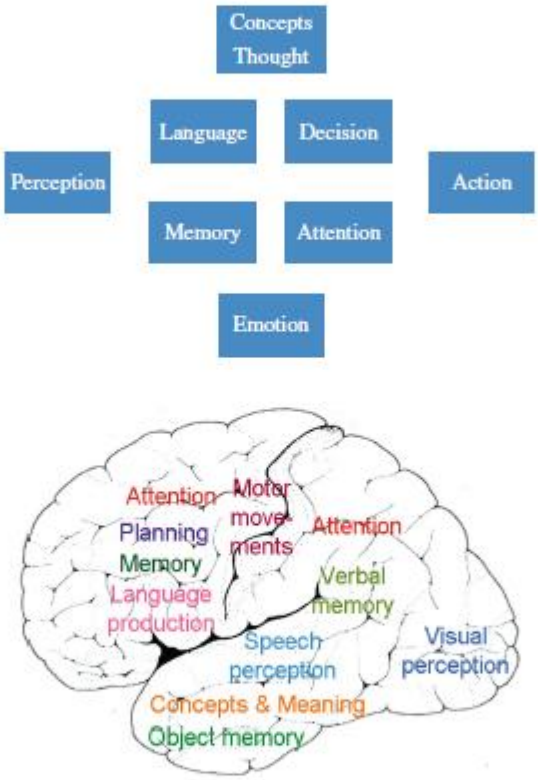

Figure 20 *Brain organization according the « traditional" neuropsychological view (Modified by Pülvermuller et al., 2014):*

The top diagram in the figure presents a plot of major cognitive subdomains.

The bottom panel shows a tentative mapping of cognitive systems onto areas of cortex as it has been suggested in view of evidence from experimental ***neuroimaging*** *and* ***neuropsychological*** *research. Note that several of the displayed mappings are under discussion.*

This view has been characterized as "disembodied cognition" model (Johnson, 2015), where cognition is calibrated on the basis of a definition of intelligence not as a biological property, but as a computational mechanism. In such frame, cognition is made of explicit reasoning and it drives the body using meta-representations. However, it is not free of subjective judgment and is strongly culture-dependent. An instance of this is the notion of "executive function" used in psychology to describe motor planning: a central decision-making system supposed to be located in the frontal lobes and separated from sensorimotor areas (Baddeley and Della Sala S, 1996), elaborates and send abstract instructions to the body actuators located at the end of the process. Following this flow chart independent from any motor subjective constraints, an algorithm transposable on any kind of hardware would pilot the body whatever its individual biomechanical assets. On the other hand, neurophysiology has mainly focused on peripheral phenomena, e.g., muscle activities under reflex control (Magnusson et al., 2008) or more recently limbs' kinematic and kinetic of voluntary movement (Goodman et al., 2017; Nordin et al., 2017), with a limited interest for abstract and private mental representations. Several reasons may explain such divergence. Among them it can be briefly mentioned the over specialization of modern science (see Wehrwein and Carter, 2016) and its academic apartheid: this is characterized by a strong disciplinary division of labor and consequently of methods and experimental models (animal vs human; child vs adult; microscopic vs macroscopic…) that produces very different and sometimes incompatible truths (Kotchoubey et al., 2016).

Nevertheless, inside the multitude of ways to explain human and animal behaviors there is a growing body of experimental evidences suggesting that cognition and action production are strongly dependent and that motor representations are present at each level of cognitive (language, memory, spatial and temporal representations, social cognition) processes (Barsalou, 1999; Wilson, 2002; Noe, 2004; Gallagher, 2005; Wheeler, 2005; Gavazzi et al. 2013). Otherwise, in contrast to the classical "five-sense theory", it is now accepted that perception is an active process: this process predicts sensory feedback instead of collecting independent input via isolated sensory organs passively waiting for external stimuli (Hamilton et al., 2007; Pezzulo and Cisek, 2016).

A rapid inspection of the literature showing the presence of the motor system at all level of cognition confirms such paradigm shift, equally perceptible for numerous mental processes traditionally investigated as explicit logico-deductive reasoning. For instance, a specific activation of the motor system during learning improves the consolidation and/or the retrieval of memories (Cherdieu, et al., 2017, Trevisan et al., 2017), and motor affordances play a role during object retention (Lagacé and Guérard, 2015). Superimposition of cognitive onto motor processes is also supported by studies showing that social cognition ability is strongly embodied. Particularly, action understanding and mind reading processes ("Theory of Mind" -ToM) would not result exclusively from explicit mental inference but would be based on a mapping of visual input onto correspondent internal motor representations (Rizzolatti et al., 2001; see also Ponari et al.2012, Baumeister et al. 2015, and Ferrari, 2014 for reviews onto the role of motor resonance during encoding and retrieval of emotional information). In this frame, the brain continuously anticipates what should be done next, all the way down to unfolding actions themselves, in contrast to the classical perception-cognition-action loop, a pure serial account of cognition that cannot work in real time. *Embodied cognition* stresses the coupled nature of thinking and acting: perception and action are directly relevant for our thinking, and it is a mistake to regard them as separate. (O'Regan, 1992; Van Gelder, 1995; Clark, 1997; Barsalou, 1999; Wilson, 2002; Noe, 2004; Gallagher, 2005; Wheeler, 2005). Il also considers cognition processes as resulting from brain and body co-evolution and from successive body-environment interactions ("enactive perspective"; Ziemke, 2016).

At last, recent investigations on supposed high-level cognitive processes (e.g., language) reveal the basic role of the motor system. In particular, according to the "embodied semantics", the meaning of a concept is represented in the brain by the same neuronal networks implicated in the motor and sensory experiences associated to it (Perlovsky and Ilin, 2013). According to this theory, for example, a prediction is that understanding sensori-motor concepts leads to activation of sensori-motor cortices. So, when people read about hand and foot actions, parts of the motor cortex involved in moving the hands and the feet are activated (e.g., Hauk et al., 2004; Tettamanti et al., 2005; see Figure 21). In a most general way, *Embodied Cognition* views cortical neurons (and particularly the MN system) linking together knowledge about actions and perceptions not only to integrate perception in action planning and execution but, furthermore, as a brain basis for a wide range of higher cortical functions, including attention, meaning and concepts, goals and intentions, and even communicative social interaction (Pulvermüller et al., 2014). In fact, the evolution of the brain, and its volume increase, is associated to more complex behavior, which results in more sensorimotor sophisticated response to environmental constraints, an idea highly consensual in evolutionists (Northcutt 2002; Krubitzer 2007).

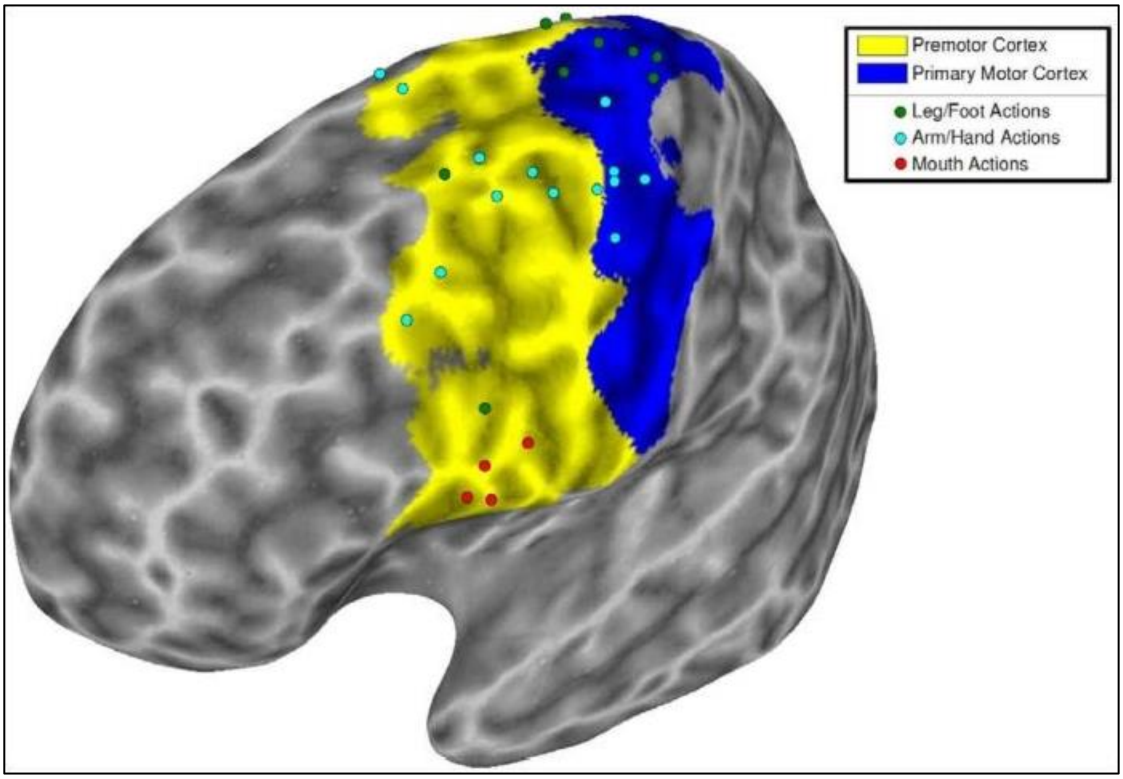

***Figure 21**: Activation peaks in left primary motor and premotor cortices reported by some of the fMRI studies that have probed the neural substrates of the motor features of verbs and sentences encoding leg/foot actions, arm/hand actions, and mouth actions (From Kemmerer et al., 2012; in the original article, the figure was created and kindly provided by Javier Gonzalez Castillo)*

We will now briefly list the experimental evidences which link MN, considered as the neural substrates allowing action to perception coupling, to human cognitive functions, mainly inter-subjectivity, language and memory in normal subject.

<u>1.2.3.1 Inter-subjectivity and social cognition</u>

A large body of experimental evidences suggest that the MN system contributes to understanding not only other people’s actions but also their emotions (Gallese et al., 2003, 2004; Wicker, 2003; Agnew et al., 2007; Pineda and Hecht, 2009). In this sense, a crucial role of MN would be to foster empathy, which is defined as a sense of similarity between the feelings one experiences and those expressed by others. Empathy means not only to understand other people’s emotional state, but to incorporate in his/her own body the experience of that state ("embodiement": Singer, 2006; Singer et al., 2006): it is thus considered as an affective resonance (Decety and Jackson, 2004; Lamm et al., 2007) providing the way to shift from the third to the first-person perspective and consecutively to predict others' behavior. Studies on emotional states demonstrate that a large-scale neural network—

including the ventral premotor cortex and the inferior frontal gyrus (two putative mirror neuron areas), in addition to classical cerebral regions involved in feeling emotions, such as the anterior insula and the amygdala—is active for instance during facial expression observation and imitation (Carr et al., 2003; Rizzolatti & Craghiero, 2004; Iacoboni, 2009; Budell et al., 2010; Grosbras and Paus, 2006). In children, activity in the frontal component of the MN system, elicited by observation and imitation of emotional expressions, correlates with measures of empathic behavior and interpersonal skills (Pfeifer et al., 2008). Likewise, it is now proposed that the core deficits of autism, which are motor, language and social impairments, are indicative of dysfunction of the MN system (Williams et al., 2001; Nishitani et al., 2004; Iacoboni & Dapretto, 2006; Dapretto et al., 2006; Bernier & Dawson, 2008; Fishman et al., 2014), and more and more works suggest a role of MN in schizophrenia (Kato et al., 2011; Schilbach et al., 2016; Saito et al., 2018). However, lack of empathy is a characteristic of other neurological diseases, such as in FTD (Laforce, 2013; Baez et al., 2014) but also in AD (Fernandez-Duque et al., 2010).

1.2.3.2 Language

According to Lieberman (2016), no brain mechanisms appear to be specific to speech or language. Rather, circuits linking the basal ganglia (a classical motor structure) with various areas of the prefrontal cortex, posterior cortical regions and other subcortical structures confer the ability to master and execute complex speech motor commands, and are active in linguistic tasks such as lexical retrieving and syntax comprehension. Moreover, a large body of data shows that the brain systems for language and action are heavily interwoven within each other. Hearing a word may automatically activate the motor system (Fadiga et al, 2002), and performing actions may help us to understand words (Cartmill, et al.,2012). In the same vein, Tettamanti et al. (2005) demonstrated that listening to sentences describing actions performed with the mouth, the hand, or the leg activated a left fronto-parieto-temporal network that included the pars opercularis of the inferior frontal gyrus (Broca's area), the intraparietal sulcus, and the posterior middle temporal gyrus, in a somatotopic manner. Based on these studies, as previously cited, it has been suggested that cerebral areas establishing a correspondence among performed and observed actions in monkeys (F5Area) match to those that are appointed to language production in humans (Broca’s Area; Kohler et al., 2002; Molnar-Szakacs et al., 2005, Tettamanti et al., 2005; Cooper, 2006;), even if a recent study raised doubts about this presumed matching (Cerri et al., 2015). Other neuroimaging studies revealed areas in the human premotor cortex that activate both when participants observe actions being performed and when they read phrases relating to those actions (Aziz-Zadeh et al., 2006). Further, Hauk et al. (2004) found a somatotopically-organized activation in the motor and premotor cortex when participants passively read action related words (i.e. leg-related action words lead to activations more medially than arm- or face-related action words, see Figure 22). Motor representations also play a role in language production: verb naming is facilitated by the degree of embodiment (characterized on the base of the bodily sense described by Borghi and Cimatti -2010-), but not by subjective imageability (Sidhu et al., 2014).

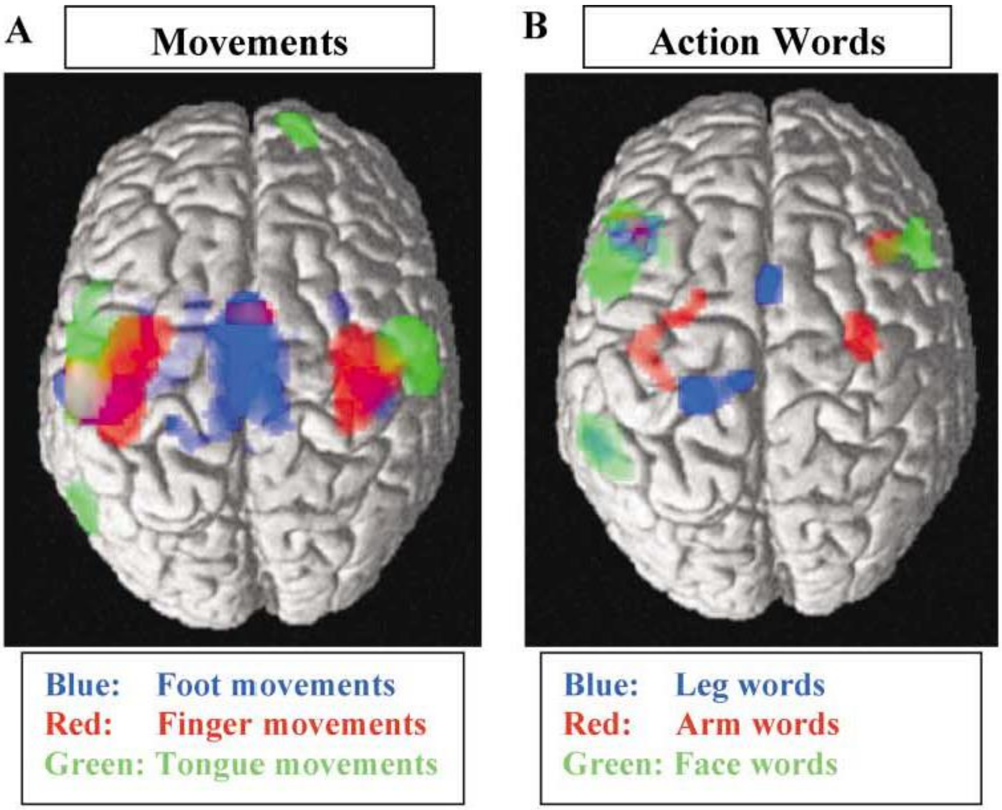

***Figure 22**: (From Hauk et al., 2004) Brain areas activated by subcategories of action words are adjacent to and partly overlap with activations produced by the corresponding movement types*
(A) Hemodynamic activation during tongue, finger, and foot movements
(B) Hemodynamic activation during reading action words related to face (green), arm (red), and leg (blue) movements
Results are rendered on a standard brain surface

All these studies have given support to the already cited theory of the "embodied semantics", according to which the meaning of a concept is represented in the brain by the same neuronal networks implicated in the motor and sensory experiences associated to it (Perlovsky & Ilin, 2013). Rizzolatti and others (2001) had already proposed a very tightly linked idea, the "direct matching hypothesis", according to which primates understand actions when they map their visual representations onto their correspondent internal motor representations. In other words, action, perception and understanding are not only the result of abstract processes relying only on visual representations. On the contrary, the observer's motor system is actively involved in this process, and the specific role of MN is to represent and possibly reenact actions in terms of their motor goal, in a bi-directional causal relationship allowing language comprehension (Zarr et al. (2013).

If this theory is true, changing the motor system will causally affect language comprehension, and changing language comprehension will causally affect the motor system. Glenberg et al. (2008) demonstrated half of the bi-directional link, namely that adapting the motor system through repeated literal action affects language comprehension. In their experiment, participants moved beans from a box to another for about 15min. For half of the participants, the direction of movement was from a location close to the participant to one further away, and for the other half the direction of movement was toward the body. This repeated action affected language comprehension: after repeated action in the Away direction, participants were slower to comprehend sentences describing action Away (e.g., “You give Alice the pizza”), and after repeated action Toward, participants were slower to comprehend sentences describing action Toward (e.g., “Alice gives you the pizza”). One possibility to explain this slowing is that the relevant action control system is fatigued. A second possibility is that the action control becomes specialized for the repeated movement. Then, when the action control system is asked to simulate a different movement, fewer neural resources are available. Zarr et al. (2013) demonstrated the other half of the bi-directional link: participants read blocks of multiple sentences where each sentence in the block described transfer of objects in a direction away or toward the reader. Following each block, adaptation was measured by having participants predict the end-point of videotaped actions. The adapting sentences affected prediction of actions in the same direction, but only for videos of biological motion, and only when the effector implied by the language (e.g., the hand) matched the videos.

More generally, the role of MN system in evolutionary language development is recurrently proposed (Rizzolatti and Arbib, 1998; Fischer and Zwaan, 2008; Meteyard et al., 2008; Chwilla et al., 2011, Fogassi and Ferrari, 2012, see also Figure 23), even if it is still under discussion (Caramazza et al., 2014). As an example, for Bonini and Ferrari (2011) the MN system would be first exploited as a monitoring system for tracking one's own behavior, then by functioning as an extended recognition system matching one’s own and other motor representations, and finally for contributing to speech perception and production in humans.

A critical review of the predictions of the action-perception circuits model and alternative theories in language, also providing discussion of some seemingly contradictory findings and of recent disputes about the role of MN and Embodied Cognition in language and communication can be found in Pulvermüller, 2018; see also Figure 24)

Figure 23: *Hand-arm gesture and vocalization, the language prototype (from Pollick and de Waal, 2007, and Eisen et al., 2014). A juvenile chimpanzee is reclaiming food taken away, by combining the reach out up begging gesture with a scream vocalization.*

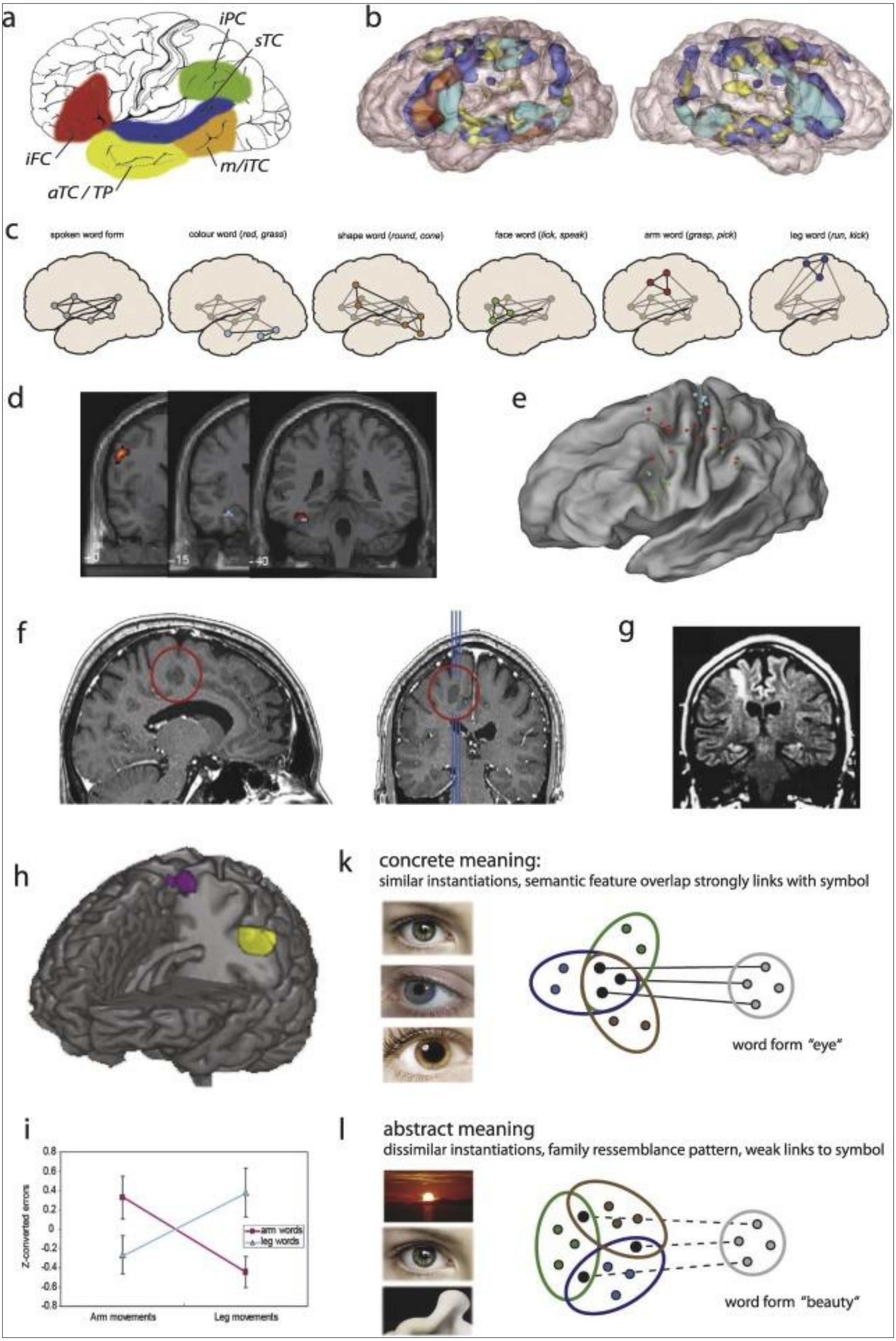
a
iPC
sTC
iFC
m/iTC
aTC / TP
b
c
spoken word form
colour word (red, grass)
shape word (round, cone)
face word (lick, speak)
arm word (grasp, pick)
leg word (run, kick)
d
e
f
g
h
k
concrete meaning:
similar instantiations, semantic feature overlap strongly links with symbol
word form "eye"
i
Z-converted errors
arm words
leg words
Arm movements
Leg movements
l
abstract meaning
dissimilar instantiations, family ressemblance pattern, weak links to symbol
word form "beauty"

Figure 24**: From Pulvermüller, 2018:* ***Semantic grounding in action and perception systems: *a. Areas proposed in the literature to process semantic meaning across categories. b. Cluster analysis reveals left-perisylvian activation for all word types (in brown and orange) and, in addition, widespread topographically specific brain activation for different semantic word types (face related action words in light blue, arm word in purple, leg words in yellow, abstract shape words in dark blue). c. Cell assembly model of cortical circuits for different semantic word types. d. Foci of significantly different brain activity elicited by color (in red) and shape words (in blue, Pulvermüller and Hauk, 2006) and e. by action words related to the face (green), hand (red) and leg (blue) as shown by a range of studies (Carota et al., 2012). f. Lesion in the white matter underlying the hand motor cortex in a patient with specific deficit in tool word recognition (from Dreyer et al., 2015) and g. in the motor and premotor cortex of a patient with specific action verb processing deficit (from Neininger and Pulvermüller, 2001). h. Semantic priming in the motor system, as revealed by EEG source localization. Face and leg motor regions, respectively, showed relatively reduced activity when action words were preceded by a body-part congruent action sound (from Grisoni et al., 2016). i. Complex movements of the arms and feet impair the processing of arm- and leg-related words in healthy subjects (from Shebani and Pulvermüller, 2013). k-l. Semantic grounding of concrete and abstract symbols. Whereas a common set of sensorimotor features may be shared by the instantiations of concrete words such as "eye", and the corresponding neuronal elements may therefore strongly bind with the word form circuit (h), a pattern of family resemblance without feature overlap applies to the instantiations of an abstract term, thus leading to weaker correlation-based sensorimotor links but, interestingly, to a new combination of 'anchor' features, which may not be present in the environment (Pulvermüller, 2018).*

1.2.3.3 Memory

Several behavioral investigations support the idea of the embodied nature of memory processes. For instance, when normal subjects are asked to retain lists of objects in memory while performing a congruent or incongruent action with these objects, performing an incongruent action impaired memory performance, in comparison to congruent action. Interestingly, the manual experience with the object determines the amount of interference (Yee et al., 2013). Further, accompanying words or phrases of a foreign language with gestures leads to better learning (Macedonia, 2014); retrieving autobiographical memories in body-congruent and body-incongruent positions relative to that of the original experience influences performance (Dijkstra et al., 2007).

Neurophysiological approach similarly showed MN network involvement in imitational learning of familiar elementary movements (Iacoboni et al., 1999), and in the acquisition of new motor skills (Buccino et al., 2004; Mattar and Gribble, 2005; Gatti et al., 2013). Stefan et al (2005) demonstrated that a specific motor memory similar to that induced by practicing movements is formed by observation. Gelbard-Sagiv et al., (2008) showed, in patients with pharmacologically intractable epilepsy implanted with depth electrodes, that neurons in the medial temporal lobe are reactivated during spontaneous recall of previously seen audiovisual sequences (episodic memory). According to the Authors, these neurons could match the sight of actions of others with the memory of those same actions performed by the observer, in agreement with the idea that during action execution, a memory of the executed action is formed, and during action observation this memory trace is reactivated. The same group (Mukamel et al., 2010), by recording extracellular activity, described neurons with mirror-like properties in the hippocampus, an important observation suggesting that in humans multiple neuronal systems might be endowed with mechanisms of mirroring: the functional significance of the mirror mechanism might vary according to the location of the MN, thus supporting different functions, memory included. Even if these data need to be confirmed by further studies, they open exciting perspectives for a novel interpretation of memory mechanisms.

1.3.1 AGING

In the current demographic context, aging and neurodegenerative diseases are well very known and discussed in the media as they become a very important societal issue. Interest has been rapidly growing in interventions which slow down the autonomy loss in elderly people. These interventions may also possibly prevent the onset of neurodegenerative diseases.

Aging is usually related to decline and losses of various kinds. Particularly, aging reduces the brain weight between 10 and 20%, and the cerebral blood flow between 30 and 40%. Shrinkage of prefrontal cortex, hippocampus, and basal ganglia (Raz et al., 2005) is typically associated with a deterioration not only of cognitive functioning, which is seen in multiple domains, including memory, attention, decision- making, and cognitive control (Brown & Ridderinkhof, 2009; Fisk & Sharp, 2004; Luo & Craik, 2008).

Decline is associated with a decrease in synthesis and binding of dopamine, serotonin and acetylcholine (Wang et al., 1995; Volkow et al., 1998; Schliebs and Arendt, 2011) and alterations in connectivity (O'Sullivan et al., 2001; Madden et al., 2009). Both functional (which reflects the organization of the brain in distinct performance-relevant networks) and structural (which represents the integrity of anatomical connections in white matter), connectivities have been demonstrated to change with aging. Structural degeneration has been found in the entire cerebral white matter with greatest deterioration in frontal areas, affecting whole brain structural network efficiency. With regard to functional connectivity, both higher and lower functional coupling has been observed in the aging compared to the young brain (Antonenko & Floel, 2013).

However, aging is not only related to some deterioration of cognitive functioning. Age-related motor decline is common and associated with a wide range of adverse health consequences. Motor impairment can include reduced gait speed, loss of muscle strength and bulk, and reduced balance, as well as dexterity. (Buchman & Bennett, 2011; Serbruyns et al., 2015).

Several constructs based on assessments of different motor abilities have been used to document mild motor symptoms in old age, including sarcopenia, based on muscle bulk or mass and strength; physical frailty, based on grip strength, body composition, gait speed, fatigue and physical activity; parkinsonian signs, based on signs of bradykinesia, tremor, rigidity and parkinsonian gait; and various summary measures, based on testing for a wide range of common motor performances. (Baumgartner et al.,1998; Fried et al., 2001; Stump et al., 2006). Regardless of the motor measures that have been employed, most studies have demonstrated that mild motor symptoms are all associated with adverse health consequences, including all-cause mortality, as well as incident disability, and other outcomes, including the development of AD. Assessments that employ several motor measures may more accurately identify individuals at risk for adverse health consequences in old age (Buchman et al., 2011). These concepts will be further developed later in this chapter.

1.3 Aging and Neurodegenerative diseases

1.3.2 Alzheimer disease and Mild Cognitive Impairment

2.2.2.1 Alzheimer Disease

Aging is strictly linked to neurodegeneration. Alzheimer Disease (AD), the most common form of dementia, is a neurodegenerative disease whose incidence grows exponentially in aging. Worldwide, it is currently estimated that 35 million people have AD or a related dementia, and with increasing life expectancy, global prevalence is projected to increase to around 66 million by 2030 and to more than 115 million by 2050 (Alzheimer's Disease International [ADI], 2012).

In the early stages, the most common symptom is difficulty in remembering recent events. As the disease advances, symptoms include temporal and spatial disorientation, confusion, irritability, aggression, mood swings, trouble with language, visuospatial and executive functions. Gradually, motor and bodily functions are lost, ultimately leading to death (Corey-Bloom, 2002; Grossberg, 2002).

Memory impairment is the most classic and pervasive feature of AD. Early in the disease course, recent episodic memories are most affected, while memories from the distant past are usually spared. As the disease progresses, all aspects of episodic memory become affected. In contrast to episodic memory, working memory and semantic memory are compromised later in the disease course (Apostolova, 2016). Implicit forms of memory, such as priming, conditioning and procedural memory are conserved until later stages (Thomas-Anterion and Laurent, 2006).

In everyday practice, AD diagnosis is still based in most cases on clinical criteria (National Institute on Aging and Alzheimer's Association-NIA-AA- criteria: McKhann et al. 2011). However, biological markers of the disease are now available, and an influent scientific group has proposed to obligatory include these biomarkers in the diagnostic workup and definition (International Working Group-IWG criteria: Dubois et al., 2007, 2010; Cummings et al., 2013): patients must show either pathophysiologic or topographic abnormalities characteristic of AD. Pathophysiologic markers include typical abnormalities in the cerebrospinal fluid (low amyloid ß peptide plus increased levels of tau or hyperphosphorylated tau) or abnormal amyloid imaging at positron emission tomography with one of the available ligands specific for fibrillar amyloid. Topographic markers include medial temporal/hippocampal atrophy at magnetic resonance imaging or bilateral parietal hypometabolism on positron emission tomography (Cummings et al., 2013).

When considering cognitive functions thought to be most tightly linked to mirror neurons -language and empathy- literature reports that worsening of language abilities, or aphasia, has been suggested to have more clinical relevance in AD than other domains, such as memory, orientation, and reasoning, in progression from the moderate to severe stages of AD: this given that decline in language has been shown to correlate with noncognitive items, such as personal care, hobbies, occupations, and behavior. Language impairment is a significant issue in most patients as they pass through moderate into severe disease stages. Yet even early in the disease state, aphasia is an important characteristic; recently published criteria for the clinical diagnosis of AD include language impairment at onset in one of the subtypes (McKhann et al., 2011; Ferris and Farlow, 2013; Hyman et. al, 2012).

Research about empathy in AD and other dementias has not been extensive till now. Lack of empathy is a well-recognized clinical characteristic of behavioral variant of Frontotemporal Degeneration (bvFTD- see after), but one study found impaired empathy also in AD patients (Fernandez-Duque et al., 2010).

2.2.2.1 Mild Cognitive Impairment

As there is no cure for AD now, several studies are focusing on preventing or at least slowing its onset. A category which now represent a preferential target of intervention is represented by persons with Mild Cognitive Impairment (MCI).

MCI is characterized by cognitive decline that is greater than expected for an individual’s age and education level, but it does not significantly interfere with everyday function (i.e., instrumental activities of daily living). As originally proposed, MCI was characterized primarily as an amnestic disorder that represented an intermediate stage between normal aging and Alzheimer’s dementia (AD) (Petersen et al., 1999). More recently, broader conceptualizations of MCI have emerged that too encompass cognitive domains other than memory. The term amnestic MCI (aMCI) was recommended for individuals in the predementia phase prior to AD as a separate group from those with MCI preceding other forms of dementia. Amnestic MCI can be single (only memory affected) or multi domains (other functions are affected along with memory; Petersen et al., 2001; Petersen and Morris, 2005).

In general, in the last years, MCI is considered as a “symptomatic pre-dementia stage” on the continuum of cognitive decline, characterized by objective impairment in cognition that is not severe enough to require help with usual activities of daily living (Langa and Levine, 2014). In 2011, the diagnostic criteria for dementia due to AD were revised (NIA-AA guidelines, McKhann et al., 2011). In this context, “MCI due to Alzheimer's disease,” was also defined as “those symptomatic but non-demented individuals whose primary underlying pathophysiology is AD.” These guidelines also proposed research criteria for the use of biomarkers— measures of amyloid-beta (Aβ) deposition and of neuronal injury—to increase the likelihood that a patient's MCI is due to AD, but these tests were not yet recommended for routine clinical use (McKhann et al., 2011).

Even if MCI definition has been criticized (the degree of functional preservation is sometimes difficult to define), MCI is a clinical useful concept because it represents a well-recognized risk factor for dementia: longitudinal studies report that seniors with MCI develop Alzheimer’s disease at a rate of 10–30% annually, compared to 1-2% of seniors without MCI (Busse et al., 2003;Ward et al., 2013) Variation was observed in conversion rates due to the population sampled, diagnostic criteria, and duration, and because many studies did not account for loss to follow-up. In any case, MCI represents a critical window of opportunity to intervene and alter the trajectory of both cognitive and functional decline in seniors.

Several reports indicate that MCI subjects can exhibit language impairment. In a recent study multidomain amnesic and not amnesic MCI people showed performance decrements in total words and switching production compared with healthy controls in fluency tasks, whereas the single-domain amnesic MCI group show unimpaired performance (Weakley et al., 2013). Another study reported a significant impairment in word generation (semantic fluency) in the amnestic MCI group relative to normal elderly group (Price at al., 2012). Furthermore, the amnesic MCI group produced significantly smaller cluster sizes and accessed fewer subcategories. MCI people also show difficulties in retrieving proper names in comparison with normal controls (Juncos-Rabadàn et al., 2012) and are consistently less accurate and slower than healthy comparison subjects in semantic decisions in which words are used as stimuli (Kirchberg et al., 2012).

As far as empathy is concerned, a recent study found heightened emotional contagion in both MCI and AD, in association with temporal lobe degeneration (Sturm et al., 2013).

2.2.2.1 The continuum AD-MCI and motor functions

AD and MCI have always been viewed as "pure" cognitive disorders (Rossor, 1992). However, over the last decade there has been increasing recognition of a link between deficiencies in motor function and these two clinical entities. Some studies have reported alterations of kinematic profile of simple arm movements in AD (Ghilardi et al., 1999; Bisio et al., 2012, see Figure 25) and even in MCI (Yan et al., 2008). Movement inaccuracy increases without visual feedback, and correlates significantly with scores of disease severity (Ghilardi et al., 1999; 2000; Tippet and Sergio, 2006; Bisio et al., 2012).

***Figure 25**: Alzheimer's patient (AD, red lines) and healthy ageing participant' (CG, blue lines) velocity profiles in the work of Bisio et al., 2012. The velocity values (y-axis) are represented as function of time (x-axis).*

Several community-based studies report that mild parkinsonian signs, including motor slowing, gait and posture disturbances, rigidity and resting tremor, may be present in up to 50% of community-dwelling older persons without clinical PD. They are associated with an increased risk of developing both MCI and AD (Louis et al., 2005). In general, motor performances, including gait and balance or finger tapping, are commonly impaired in older persons (Buchman and Bennet, 2011). Both a lower level and more rapid rate of motor decline in cognitively intact individuals predict the subsequent development of MCI and AD, and loss of motor function can precede cognitive impairment by several years (Camicioli et al., 1998; Aggarwal et al., 2006; Wang et al., 2006).

Recent studies also suggest that changes in body mass index (BMI) may be an early noncognitive sign of AD. Several studies report that baseline lower BMI, as well as a more rapid rate of declining BMI, are associated with an increased risk of AD. Declining BMI may occur several years before the clinical diagnosis of dementia and raises the question of whether mild motor symptoms may represent an early sign of AD. BMI is also associated with incident MCI (Buchman et al., 2005, 2007, 2011). Further, impaired motor function is a prominent characteristic of physical frailty: this is a heterogeneous syndrome which includes loss of muscle strength, reduced physiologic functions, impaired gait and fatigue (Ringer et al., 2017). Longitudinal studies suggest that a higher level of physical frailty is associated with the subsequent development of both MCI and AD (Buchman et al., 2007; Boyle et al., 2010), and that low grip strength is associated with an increased risk of incident AD and MCI (Boyle et al., 2009).

On the other hand, physical activity (above all aerobic exercise) is recurrently associated to lower incidence of dementia and to better cognition in affected patients (Groot et al., 2016; Ginis et al., 2017). The Brain Derived Neurotrophic Factor (BDNF), a member of the neurotrophin family (Poo, 2001), has been identified as a crucial mediator of the benefits of exercise for brain health (Cotman and Berchtold, 2002). Voluntary exercise increases levels of BDNF mRNA and protein in the hippocampus and other brain regions (Neeper et al., 1995; Cotman and Berchtold, 2002), whereas the beneficial effect of exercise on cognitive function is inhibited when blocking BDNF action in the hippocampus (Vaynman et al., 2004). Aerobic exercise training in adults increased the size of the anterior hippocampus and BDNF levels, leading to improvements in spatial memory and reversing age-related loss in volume by 1 to 2 years (Erickson et al., 2011). A recent investigation has compared the effects of a dancing intervention and traditional health fitness training on hippocampal subfields volumes and balance abilities in seniors. Before and after intervention, both groups revealed hippocampal volume increases, mainly in the left hippocampus. The dancers showed additional increases in the left dentate gyrus and the right subiculum, and achieved a significant increase in the balance composite score (Rehfeld et al., 2017)

1.3.3 Frontotemporal Dementia and Amyotrophic Lateral Sclerosis

Frontotemporal dementia (FTD) is a common cause of pre-senile dementia, accounting for 5–17% of autopsy-proven cases presenting under the age of 70 (even if it can be diagnosed at any age after twenties). It can manifest as a spectrum of clinical syndromes, ranging from behavioral impairment (behavioral variant of the frontotemporal dementia: bvFTD) to language (Primary progressive aphasia: PPA) or motor dysfunction. Recently published consensus criteria outline the diagnostic criteria for bvFTD and PPA (Gorno-Tempini et al., 2011; Rascovsky et al., 2011).

The bvFTD is a clinical syndrome characterized by progressive changes in personality, social attitude (either apathy or dis-inhibition), and mental functions. These symptoms are combined with a scarce awareness and, frequently, non-fluent language impairment. bvFTD is usually associated with frontal, insular and temporal atrophy (Neary et al., 1998; Rascovsky, et al., 2011).

PPA is an aphasic dementia characterized by progressive decline in language function, but relative sparing of other cognitive domains associated with damage to the left hemisphere perisylvian language network (Mesulam, 2003). Experts generally recognize three main variants of the syndrome: Three main variants of PPA are now recognized: non fluent or agrammatic, fluent (or semantic dementia) and logopenic (Gorno-Tempini, et al., 2011; Mesulam et al., 2012; Rascovsky & Grossman, 2013; Lashley et al. 2015).

Typical age of onset for bvFTD and PPA is under age 65 and collectively they are thought to represent the most common form of young-onset dementia (Knopman et al., 2004; Ratnavalli et al., 2002). While true epidemiologic data are scarce, recent consensus estimates suggest prevalence rates of FTD range between 15 and 22 per 100,000 and incidence rates are between 2.7 and 4.0 per 100,000 person-years (Knopman et al., 2011).

The majority of FTD cases have no known cause ('sporadic' FTD), but approximately a third is due to autosomal dominant mutations in one of several FTD associated genes (Onyike and Diehl-Schmid, 2013). FTD is heterogeneous from a neuropathological and genetic point of view showing mostly tau or ubiquitin/TDP-43 positive inclusions at autopsy (Mackenzie and Neumann, 2016), and mutations in MAPT, GRN and C9ORF72 genes as the most commonly identified causes of familial FTD (Woollacott and Rohrer, 2016).

FTD is also the most striking example of cognitive and motor symptoms combination in a neurodegenerative disease In fact, FTD is strictly linked to motoneuron disease (MotND)/ALS (the form of MotND in which both central and spinal motor neurons degenerate). Around 10–15% of patients with FTD develop MotND (Lomen-Hoerth et al. 2002; Burrell et al. 2011), with an even higher prevalence of 'subclinical' evidence of motoneuron signs (Lomen-Hoerth et al. 2002). Conversely, 10–20% of MotND patients meet diagnostic criteria for FTD, but at least 50% of patients presenting with MotND develop cognitive-behavioral impairment (Strong et al., 2009). The hexanucleotide repeat expansion in the C9ORF72 gene is the most frequent genetic cause of both ALS and FTD (Cipolat Mis et al., 2016) indicating that the same molecular mechanisms can be at the base of either a primarily motor or social-cognitive dysfunction, a biological finding which supports the idea of a strict relationship between motricity and social behavior.

There is also a strictly relationship between FTD and parkinsonism: along the course of the disease, extrapyramidal symptoms (mostly cogwheeling-rigidity, or bradykinesia or dystonia) can be present. It can even worsen till a frank atypical parkinsonian syndrome, with features of Corticobasal Degeneration (CBD; Graham et al. 2003; Josephs et al. 2006; Josephs and Duffy 2008) or Progressive Supranuclear Palsy (Josephs et al. 2005, 2006).

1.3.4 Parkinson Disease and Dementia with Lewy Bodies

Parkinson Disease (PD), the most common extrapyramidal disorder, is characterized by three cardinals motor symptoms (bradykinesia, rigidity and resting tremor), then associated to postural instability. The diagnosis of PD in mainly a clinical one and based on the identification of characteristic signs and symptoms, along with exclusion with atypical symptoms (Linee Guida Italiane per la Diagnosi e la Terapia della Malattia di Parkinson, 2013). In the last years, however, the DAT scan – a nuclear medecine technique which demonstrate the loss of dopaminergic innervation in the striatum - has been more and more utilized as a support to the clinical diagnosis (Tolosa et al. 2007; Seifert & Wiener, 2013).

Due to the prevalent motor symptoms PD is usually classified in movement disorders. However, it is now recognized that non-motor symptoms, such as cognitive impairment, autonomic, affective (and behavioral) disturbances (e.g. depression, anxiety, anhedonia, psychotic symptoms, compulsive disorders) are of relevance in the disease course and change along the disease progression in each patient (Moustafa and Poletti, 2013; Rodríguez-Violant et al., 2017). Cognitive symptoms in PD include first deficits in functions classically described as "executive" ones, such as working memory, explicit motor planning, and visuospatial attention. But they can also include an impairment of long-term memory, even if different from hyppocampal amnesia typical of AD (Muslimovic et al., 2005; Pillon et al., 1993); at the end, they can turn out to a clear dementia picture (PD dementia – PDD; Emre, 2007).

PD is mainly due to loss of dopaminergic projections in the striatum, due to the severe degeneration of neurons located in the substantia nigra (pars compacta). From the neuropathological point of view, PD is also characterized by the deposition of filamentous eosinophilic intracytoplasmatic inclusions, called "Lewy bodies", above all in the substantia nigra. These aggregates are present not only in the brainstem but also in the cortex and in the peripheral enteric nervous system (Kövari et al., 2009). Lewy bodies link PD to the second most common cause of dementia, DLB. DLB is characterized by dementia, associated with visual hallucinations, prominent fluctuations and REM behavior disorder (McKeith et al., 2017). Extrapyramidal motor symptoms develop simultaneously or soon thereafter. The first affected cognitive domains are usually the same than in PDD, although anterograde memory can also be involved (Salmon et al., 1996; Gomperts, 2016). Indeed, some Authors consider now that PD and DLB represent the extremes of a continuum, in which the presence of Lewy Body neurodegeneration can cause both motor and/or cognitive pictures in various combinations (see Goldman et al., 2014 for a discussion about this point).

1.4 Mirror Neurons and neurorehabilitation

In the last decade, AOT, which stimulates the MN network, was developed as a supplementary therapeutic tool for patients with stroke, in order to stimulate brain plasticity and obtain positive functional results (Garrison et al. 2010; Small et al., 2010; Sale & Franceschini, 2012; see Carvalho et al, 2013 for a review on this topic). This has also been extended to motor deficits of children with Cerebral Palsy (Sgandurra et al., 2011; Buccino et al., 2012; Masahup et al., 2012; Bassolino et al., 2015) and, as we are seeing later, of patients with PD (Buccino 2011, 2014). Studies in monkeys and humans both suggest the possibility to activate the motor cortex not only by performing movements, but also by simply observing actions without any motor activity. The motor facilitation, revealed by the amplitude modulation of motor responses which are evoked by TMS applied to premotor cortex, maintains the temporal structure and the muscular organization of the observed actions (Rizzolatti & Craighero, 2004; Fadiga et al., 2005). Importantly, the motor cortex atrophy due to normal subject arm immobilization can be totally prevented by AOT performed during the immobilization period (Bassolino et al., 2013, Figure 26).

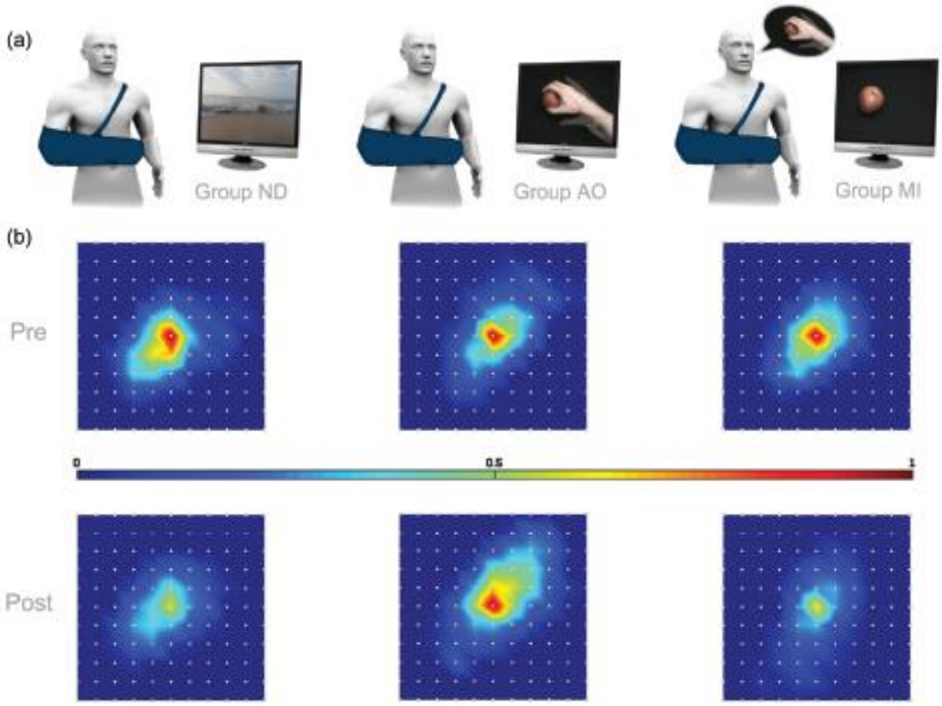

Figure 26*: Mean first dorsal interosseous corticomotor maps recorded before (Pre) and after (Post) immobilization in the 3 groups. (a) In control (on the left), AOT (in the middle), and MI (on the right) groups, participants performed the requested task for 10 hourly sessions during the immobilization period. (b) Each map was centered on the maximal response obtained for each participant in every condition. Colors indicate the amplitude of MEP, normalized with respect to the maximal response obtained in the Pre-condition in every subject, from "blue" (the lowest values) to "red" (the highest responses; modified by Bassolino et al., 2014).*

1.4.1 Previous clinical applications

The first proposal to use AOT in rehabilitation has been formulated for stroke patients. A significant functional limitation to the use of one superior arm due to a neurological lesion (e.g. a stroke) drives the person to perform most of the activities of daily living with the unaffected arm (Gordon et al. 2005). Moreover, in these patients, the regular participation to an intensive rehabilitation treatment can be associated to a great prevalence of pain (Brattberg, 2004). In this context, the activation of the motor system in an alternative way could represent a further opportunity to improve classical rehabilitation programs.

Franceschini et al. (2010) evaluated the efficacy of the mirror therapy for chronic upper limb motor impairment in 28 post-stroke patients. They underwent a treatment consisting of watching videos of hand movements for 5 days a week for 4 weeks, and the subjects performed imitation of the movement. The Authors found improvement in all functional scales after treatment. This improvement was still present at the two-month follow-up. Due to the significant findings, they concluded that the observed action can be used as an effective strategy in post-stroke rehabilitations. Other groups have proposed the use of virtual reality motor rehabilitation systems for stroke patients with upper limb paresis (Eng et al., 2007).

Michielsen et al. (2010) divided 40 chronic post-stroke patients into two groups: control and mirror therapy groups. The control group had a direct view of both hands, whereas the mirror group practiced with the affected hand positioned behind a mirror while they looked at the reflection of the unaffected hand in the mirror. To ensure that patients focused at the mirror reflection of their unaffected hand instead of their moving unaffected hand itself, a cover was placed over their unaffected hand (see Figure 27). Both mirror and control groups performed bimanual exercises, with the difficulty of the exercises depending on the patients' individual levels of functioning. The Fugl-Meyer Scale (FMS, a scale which evaluates motor function) results showed that the group with mirror therapy significantly improved its scores, but these changes were not sustained in the follow-up trials. On the other hand, the Authors demonstrated that mirror therapy caused a shift in the activation balance of the primary motor cortex toward the lesioned hemisphere at fMRI. The same group used the mirror therapy in 22 post-stroke patients who performed unimanual and bimanual tasks under two conditions: hand observation (no mirror condition), and observation of the hand reflex in the mirror (mirror condition). They found a significant increase in precuneus and the posterior cingulate cortex, areas associated with awareness of the self and spatial attention, during the movement with the mirror in the bimanual task. However, the fact that the Authors did not observe mirror-related activity in areas of the motor or MN system questions the theory that attribute the clinical effects of mirror therapy to these systems (Michielsen et al., 2011)

Figure 27*: The setup for mirror therapy (Michielsen et al., 2010)*

Recently, a Korean group evaluated the effects of AOT to improve on balance and gait function of stroke patients, finding that the activation of MN through AOT, combined with a conventional stroke physiotherapy program, enhances lower-extremity motor recovery and motor functioning in stroke patients (Lee et al., 2017).

Even if most studies in stroke proposed MN stimulation as a method to improve arm recovery, this method has been also proposed to ameliorate aphasia. Lee et al.(2010) have developed IMITATE, a computer-assisted system for aphasia therapy based on action observation and imitation. As we have already reported, it has also been demonstrated that changing the motor system affects language comprehension, and changing language comprehension affects the motor system, in a bi-directional causal relation. Glenberg et al. (2008) demonstrated half of this bi-directional link, namely that adapting the motor system through repeated actions (moving beans from a box to another farther away or towards the body) affects language comprehension. Zarr et al. (2013) demonstrated the other half of the bi-directional link, that is adaptation due to repeated sentence reading affected prediction of actions in the same direction, but only for videos of biological motion. Altogether, these data clearly support promising clinical implications for aphasia rehabilitation.

In children affected by cerebral palsy, Buccino et al. (2012) showed functional gains after observation of video clips showing daily-appropriate actions, while Masahup et al. (2012) demonstrated that a MN stimulation program can improve motor function at least as much as the conventional physical therapy. Other trials on children with cerebral palsy with the use of AO as an innovative rehabilitation approach are in progress (Sgandurra et al., 2011).

1.4.2 Enhancing the potential of Mirror Neurons stimulation in rehabilitation

The motor system activity can be also modulated as a response to an acoustic stimulus associated to action (e.g, breaking a peanut) (Kohler et al., 2002; Aziz-Zadeh et al., 2004; Fadiga et al., 1995; Gazzola et al., 2006). Moreover, the cortical facilitation due to action observation is at its maximum when we furnish both acoustic and visual stimuli linked to the action (Alaerts et al., 2009). In fact, our experience with the world is typically mediated by multiple sensorial experiences and the sight of an action is usually influenced by the sound (Alaerts et al. 2009). The increase in MEPs recorded from the same muscles that would be active during actual execution of the same movement -Fadiga-effect, for short- (Fadiga et al. 1995) is expanded by listening to action-related sounds (Aziz-Zadeh et al. 2004). Interestingly, this effect has been observed when stimulating the left, language-dominant hemisphere only: this finding supports the existence of a close link between action and language (Aglioti & Pazzaglia, 2010). It seems that some MN are triple cells which can be activated not only by action observation and execution but also by the acoustic perception of action-related sounds (Kohler et al., 2002). Others of these complex perceptuo-motor neurons respond strongly to action sounds but not to the observation of actions performed by another human or monkey agents thus indicating their audio-motor specificity (Keysers et al., 2003).

These data suggest the fascinating possibility to potentiate AOT. The success of a rehabilitation therapy based on a single sensory channel could improve if the related sound is furnished to recreate the action context. This method could influence the integration and coordination of different cerebral networks and functional strategies, which is considered one of the main limitations not only in patients with stroke but also in patients with neurodegenerative diseases. This kind of stimulation could push brain reorganization and functional results, in addition to cognitive development. That is, stimulation of MN through multimodal action observation could improve not only motor functions but also cognitive status, due the status of this neurons population which are involved in both motor learning and imitation, language functions ad empathy.

CHAPTER 2 – ISSUE OF THE THESIS: COGNITIVE DECLINE AT THE LIGHT OF THE EMBODIED COGNITION THEORY AND OF THE DISCOVERY OF THE MIRROR NEURONS SYSTEM

2.1 MIRROR NEURONS, EMBODIED COGNITION AND NEURODEGENERATIVE DISEASES

When taking into consideration neurodegenerative diseases, it appears evident that in each of them both cognitive and motor symptoms are represented in a sort of continuum. We have also viewed that the theory of embodied cognition stresses the coupled nature of thinking and acting, reforming the traditional model of cognitive processing, with its strict perception-cognition-action scheme (e.g., Hurley, 2001). The traditional model, according to which almost all studies on neurodegenerative diseases have been conducted, considers cognitive functions as higher-level supervisor functions which utilize perception and action as separated slave systems, providing input to cognitive processors (perception) and executing its commands (action). Instead, embodied cognition considers that it is a mistake regarding cognitive processors, perception and action as separate (e.g., O'Regan, 1992; Van Gelder, 1995; Clark, 1997; Barsalou, 1999; Wilson, 2002; Noe, 2004; Gallagher, 2005; Wheeler, 2005). Reinterpreting neurodegenerative diseases, and particularly AD and MCI (thought as a pre-dementia phase of AD) at the light of this hypotheses could help a better comprehension of clinical manifestations and opening new pathways to rehabilitate patients affected by these diseases.

MN represent in fact the neuronal population which link perception and action, cognition and motility. Characterizing the functioning of MN system in neurodegenerative diseases could allow to better understand functional mechanisms underlining clinical manifestations. It would also allow to exploit this kind of neurons in rehabilitation of motor and cognitive symptoms. In this sense, there have been some theoretical proposals about interpreting some neurodegenerative diseases, in particular ALS and FTD, as linked to dysfunction of perception-motor circuits including MN. These proposals have been based on neuropsychological data which show preferential impairment of action verbs on tools and an impairment of ToM –strictly related to one of the putative MN functions, that is empathy- in these diseases (Eisen et al., 2014; Bak, 2013).

However, direct studies on MN functioning through neuroimaging or neurophysiological techniques in neurodegenerative diseases are scarce. Most data are available for PD, but they are controversial. Even data about MN and aging are scarce, as most MN studies in normal humans were performed in young or adult subjects, with a few exceptions (see Vallet. 2013 for a discussion about embodied cognition and aging).

Given these premises we first performed a bibliographic research aimed to clarify the state of the Art on neurodegenerative disorders, embodied cognition and MN. Then, considering literature data, we conceived a study focused on MN in aging and cognitive impairment in neurodegeneration linked to aging.

2.2 State of the Art on neurodegenerative disorders and embodied cognition

2.2.1 Methods: Literature searching of studies linking Action, Cognition (Mirror Neurons) and neurodegenerative diseases

To understand the actual "state of the art" in this field I screened first all fields of the PubMed database at December, 31 2017 with the term "mirror neurons" and "embodied cognition" and any of the following terms: neurodegenerative diseases; Frontotemporal degeneration or dementia; Amyotrophic Lateral Sclerosis; Motoneuron Disease; Primary Progressive Aphasia; Alzheimer; Mild Cognitive Impairment; Parkinson. I also screened the Pubmed Database with the corresponding Mesh terms and with the Mesh term "cognitive dysfunction". That gave a result of 100 articles, but 78 articles were excluded after reading the title and the abstract because they did not fill with the scope of the review; 3 additional articles were excluded for the same reason after a full lecture. This procedure left 19 articles for the review. I then repeated a search with the same free terms in Web of Science, obtaining a list of 315 articles/proceedings. 265 articles were excluded after reading the title and the abstract because they did not fill with the scope of the review or because they doubled the findings of the previous search, and 11 articles after full lecture. This procedure left 39 additional articles for the present review. The reference list of the identified studies and reviews was then hand searched for additional articles, thus giving a total sum of (19+39+50=108) findings to report. Articles/proceedings were included if 1) they were published in a peer-review journal, 2) they investigated the MN or the embodied cognition theory and any of the neurodegenerative diseases, or 3) they proposed a theory/interpretation linking the MN or the embodied cognition theory and any of the neurodegenerative diseases, 4) previous reviews were included as a source of additional references or because they proposed theories linking embodied cognition and neurodegenerative diseases. Articles which not fitted in these criteria were excluded.

However, even I performed a systematic search of sources, the aim was appraising the existing studies considering the embodied cognition theory, MN system and neurodegenerative diseases (to stimulate research in this field) rather than to perform an exhaustive and comprehensive review. Few studies aimed to directly explore MN functioning through neurophysiological or neuroimaging techniques in neurodegenerative diseases were found, while more studies were available linking embodied cognition and any of the neurodegenerative diseases.

2.2.2 Results

2.2.2.1 The Mirror Neurons network, embodied cognition and Parkinson Disease

Most available studies considering both cognition and action systems are focused on PD, and results are controversial. The functioning of the MN network in PD has been studied, as in normal subjects, through neurophysiological techniques (EEG, and TMS), neuroimaging (fMRI), and kinematic studies. Some neuropsychological and behavioral studies investigated task performance at the light of the embodied cognition theory. Several other studies suggested rehabilitative training based on stimulating the MN network and the embodied cognition framework in PD. We will also make a hint to studies on motor imagery (MI) in PD.

- *Neurophysiological studies*

Alegre et al. (2010) have proposed basal ganglia involvement in AOT, as the subthalamic nucleus shows changes in activity during movement observation like those observed during movement execution. The Authors recorded EEG and local field potentials in 18 parkinsonian patients through surgically implanted electrodes for deep brain stimulation (DBS). Oscillatory changes in electrical activities were recorded during movement execution, AOT and two control conditions. AOT (as movement execution) was associated to a bilateral reduction of subthalamic power in the beta range. The effect was present in both *on* and *off* state, even if higher in the first one. This result suggests a substantial conservation of MN network in PD, with a possible influence of the medication state. Another recording study in DBS implanted patients again found a change in subthalamic nucleus oscillatory activity (Marceglia et al., 2009) during action observation: this response could be driven by the modulation of cortical regions belonging to the MN system, thanks to connections between the basal ganglia and the frontal and prefrontal cortex.

Other groups however found different results: in a small study μ-rhythm desynchronization, classically recorded during movement observation, was impaired in patients with early PD (Heida et al., 2014; see Figure 28 a and b). Tremblay et al. (2007) tested 11 PD patients in the *on* condition and the same number of healthy elderly controls, by recording MEPs amplitudes in four conditions: rest, AOT (a video depicting a hand cutting a piece of paper with scissors), MI and active action imitation (see Figure 29). The MEP amplitude (recorded at the first dorsal interosseous and abductor digiti minimi) increased in PD patients during active imitation (compared to resting state) but neither during AOT nor during action imagery. This indicated a failure to engage the motor system more at the covert than at the overt stage of action execution. According to the Authors, this failure is due to a deficit in motor activation affecting critical nodes in the motor cortical network normally involved in action preparation. Tremblay et al. (2007) hypothesize that these nodes could be the supplementary motor area and the inferior parietal cortex. However, these observations may also be explained by the involvement of the frontal-subcortical circuits that connect the basal ganglia to the premotor cortex (Alexander et al., 1990; see also Alegre et al., 2011 and Figure 30). A more recent study (Gündüz et al., 2015) showed a normal facilitation of MEP amplitude by mental imagery and active movements in normal controls and non-apraxic PD patients. The same was true for F-wave amplitudes over the dominant upper extremity during mental imagery, AOT and active movements. This facilitation was lost in apraxic PD patients, raising the possibility that apraxia in these patients could be due to an impairment of MN network (McGeoch et al., 2007).

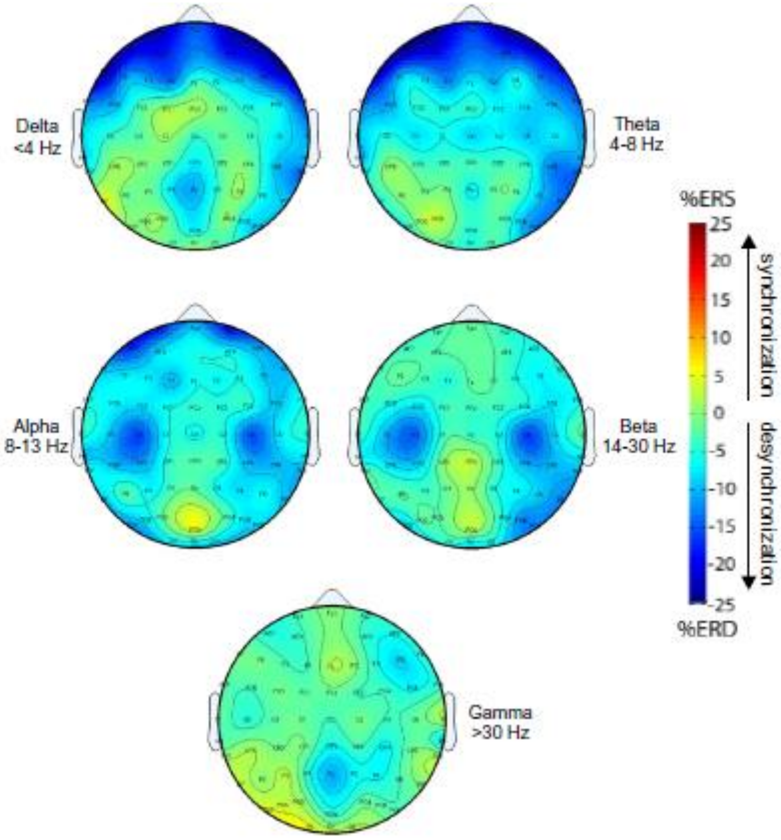

Figure 28a*: Grand average Event-Related-Desynchronization maps of the control group resulting from the observation of the ball grasping movement performed by the right hand. Bilateral alpha and beta band desynchronization (around C3 and C4) indicate mu-rhythm desynchronization (Heida et al., 2014).*

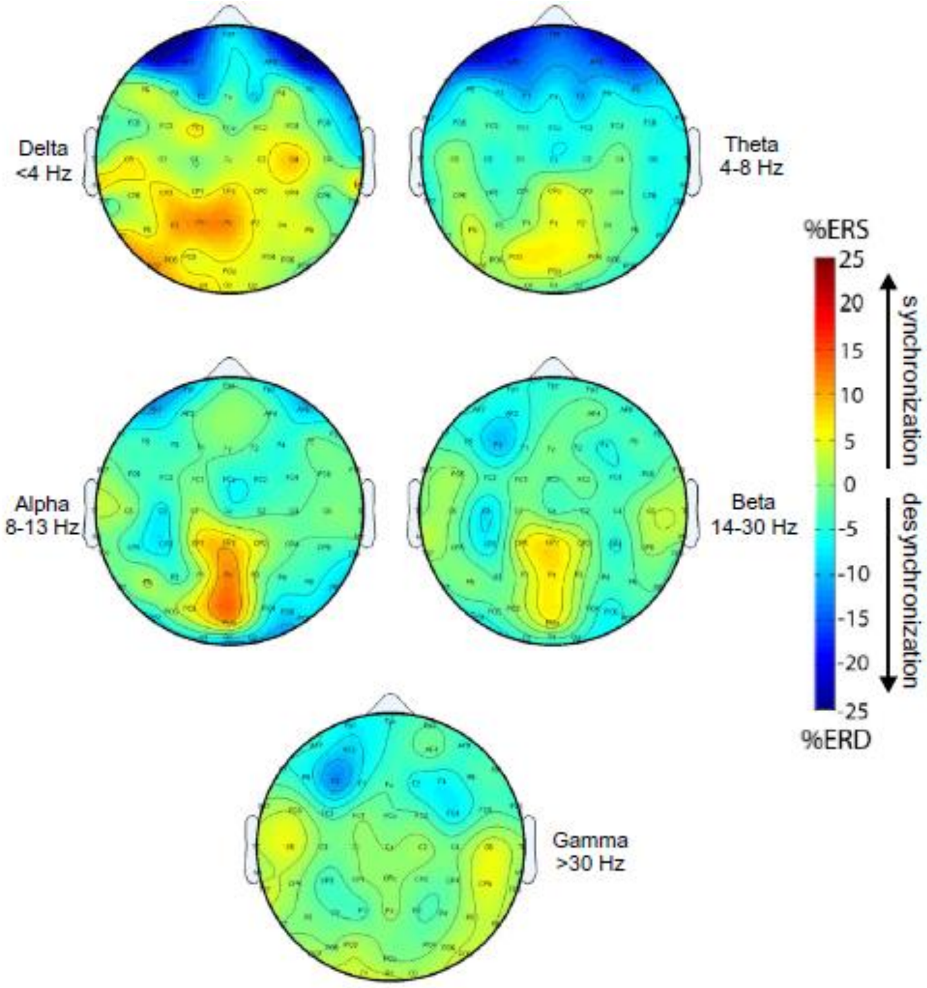

***Figure 28b**: Grand average Event-Related-Desynchronization maps of the Parkinson group. The alpha and beta band ERD levels around C3/C4 are much lower compared to the control group (Heida et al., 2014).*

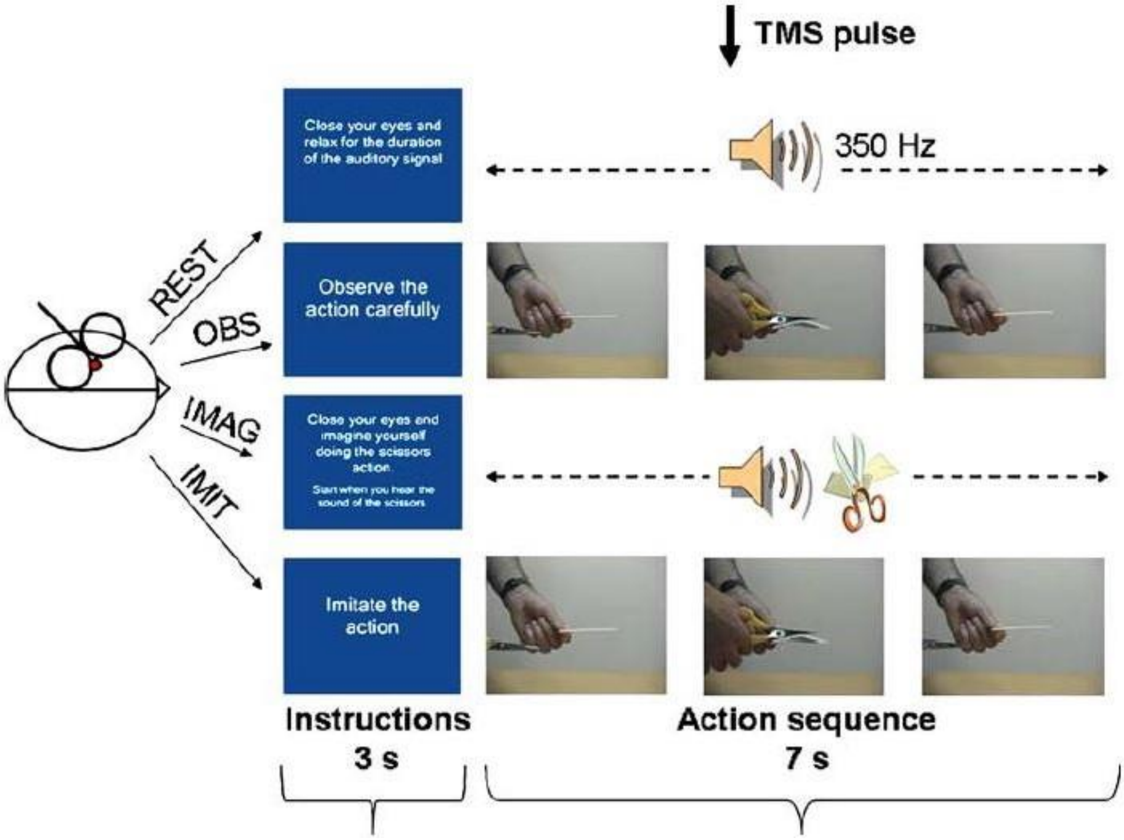

Figure 29*: paradigm used to assess corticomotor facilitation associated with observation, imagery and imitation of actions in the study of Léonard and Tremblay, 2007.*

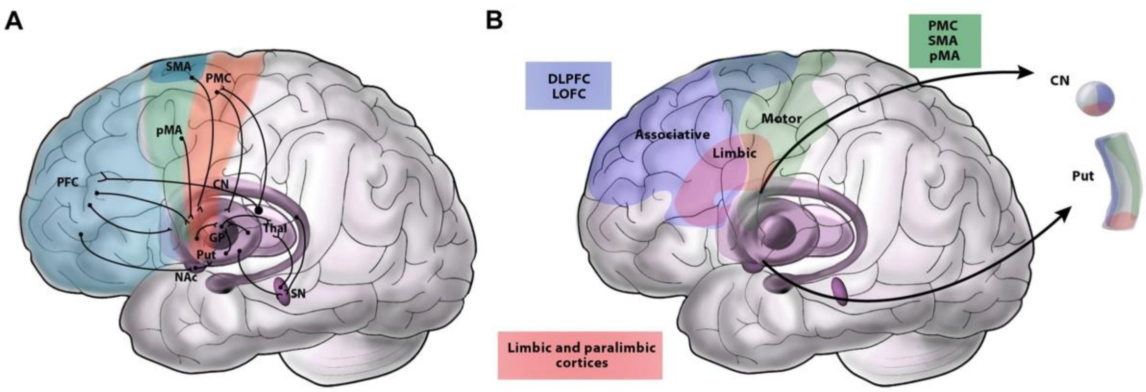

Figure 30*: Schematic representation of frontostriatal circuits according to Birba et al., 2017. The striatum (caudate nucleus, putamen, and nucleus accumbens) receives inputs from a range of cortical areas, including various motor and frontal regions. Connections between such regions and striatal structures comprise three distinct circuits: motor, associative and limbic, which overlaps each other. SMA: supplementary motor area; pMA: premotor area; PMC: primary motor cortex; CN: caudate nucleus; NAc: nucleus accumbens; SN: substantia nigra; Thal: thalamus; Put: putamen; GP: globus pallidus; DLPFC: dorsolateral prefrontal cortex; LOFC: lateral orbitofrontal cortex; PFC: prefrontal cortex.*

- *fMRI studies*

In an interesting neuroimaging study Anders et al. (2012) recruited 8 pre-symptomatic carriers of a single mutant Parkin gene, who presented a slight but significant reduction of dopamine metabolism in the basal ganglia. Indeed, it is well known that PD has a long pre-symptomatic stage, during which the brain compensates for dopaminergic nerve degeneration by increasing motor-related cortical activity thus preventing clinical manifestation of the disease (Morrish et al., 1996). This work aimed to study whether similar compensatory mechanisms were effective in non-motor basal ganglia–cortical gating loops. Execution and perception of facial gestures are thought to be linked to MN in the ventrolateral premotor cortex (Leslie et al., 2004; Hennenlotter et al., 2005). Parkin mutation carriers first performed fMRI while observing neutral and affective dynamic facial expressions and then performed a facial emotion recognition task. As expected, recruited participants showed significant stronger activity in the right ventrolateral premotor cortex during execution and perception of affective facial gestures than healthy controls. Furthermore, Parkin mutation carriers showed a slightly reduced ability to recognize facial emotions that was inversely proportional to the increase of ventrolateral premotor activity. According to the Authors, these findings are consistent with the hypothesis that compensatory activity in a MN area during processing of affective facial gestures can reduce impairment in facial emotion recognition in subclinical Parkin mutation carriers. A breakdown of this compensatory mechanism might lead to the impairment of facial expressivity and facial emotion recognition observed in clinically manifest PD. On the other hand, it is possible that the stimulation of MN could favor these compensation mechanisms at least in the first stages of the disease, thus allowing PD patients to have better social interaction.

An additional support to the putative link between MN area impairment and the well-known emotional deficit of PD patients (Péron et al., 2012) comes from a similar recent study by the same group (Pohl et al., 2017). In this investigation 13 PD patients and controls underwent an emotion recognition task: they observed video clips depicting emotional, non-emotional, and neutral facial expressions or were asked to produce these facial expressions, during fMRI measurement. Patients performed slightly worse in the emotion recognition task, but only for the most difficult expressions to be interpreted. Inferior frontal and anterior inferior parietal "mirror neuron" areas activated during observation and execution of the emotional expressions in both groups, but in PD patients they activated at a lesser extent; further, activation of the right anterior IPL positively correlated to patients' emotion recognition ability.

Péran et al., (2009) explored fMRI cortical activities during the generation of action-verbs, compared to object naming, in 14 non-demented PD patients. Data revealed the involvement of an extended cortical network during action-verb generation: differences in comparison with the object name generation were located above all in the premotor and prefrontal cortices (Figure 31). These results suggest an essential role of the frontal cortex in action verb generation, and that a motor striatal-frontal loops impairment leads to the recruitment of a cortical network aimed at compensating the deficits in these circuits. A following study demonstrated that the patient dopaminergic status conditions the cerebral activation (Péran et al. 2013). Abrevaya et al. (2016, Figure 32) found similar results when subjects listened action verbs and nouns, by considering cortical regions differentially engaged by action and non-action words. The verb lexical category elicited connectivity between primary motor areas and anterior areas (implied in action observation and imitation), in normal controls, while activated posterior areas in PD patients: this suggests that patients might afford alternative pathways to process words when motor substrates are altered.

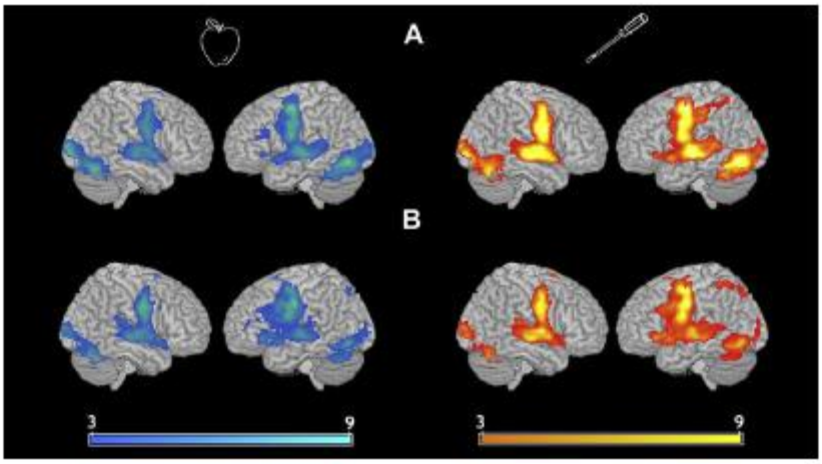

Figure 31 *From Péran et al., 2009: Activation maps in each condition: blue: manipulable biological objects; orange: man-made objects. A: object naming, B: generation of action-verbs*

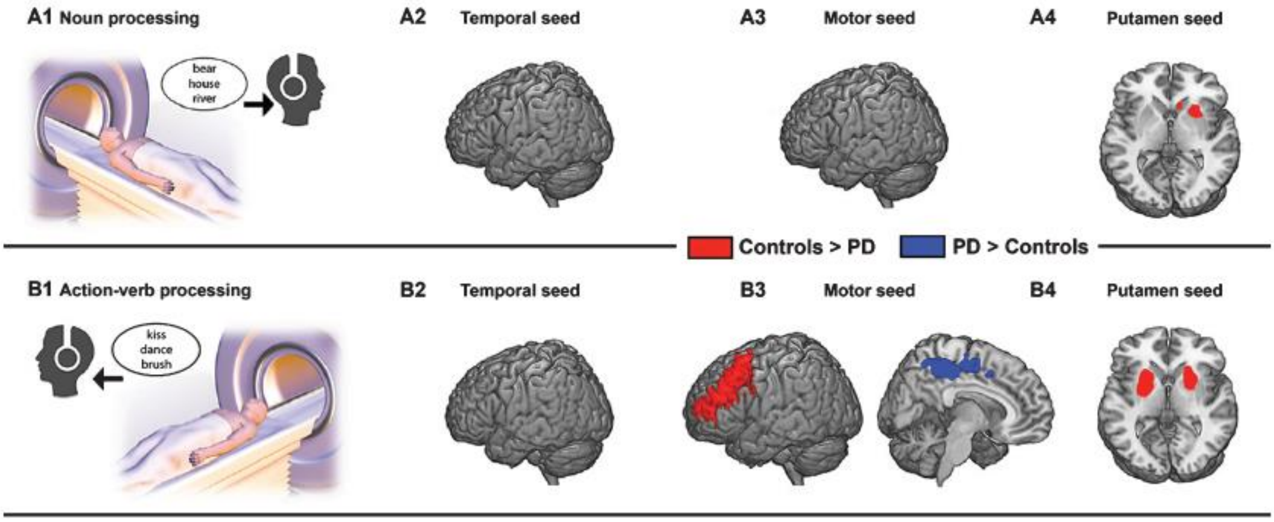

Figure 32*: results from the study of Abrevaya et al. (2016)*

- *Behavioral studies*

Poliakoff et al. (2006, see also Figure 33) measured the effect of movement-relevant visual stimuli (graspable door handles and finger movements) on reaction times in mild to moderate PD patients. Bars and object movements represented the control condition. In a first experiment, participants had to classify visual stimuli (bar and door handles) according to shape and orientation. There was no difference in the overall reaction times for patients and controls but while the spatial compatibility effect (that is faster reaction times when the response hand and the stimulus direction were compatible) was larger in the handle than in the bar condition for controls, this was not true for PD patients. In a second experiment, the two groups observed video clips of finger or object movements and had to respond as quickly as possible if an X appeared at the end. Both patients and normal participants reduced significantly their reaction times after observing finger compared to objects movements, indicating a partial preservation of MN network in PD. However, parkinsonians showed a spatial compatibility effect only for non-living object movements: this result led the Authors to propose that in PD the MN system is not completely preserved, and that external cues would exert their influence through lower-level visual processes.

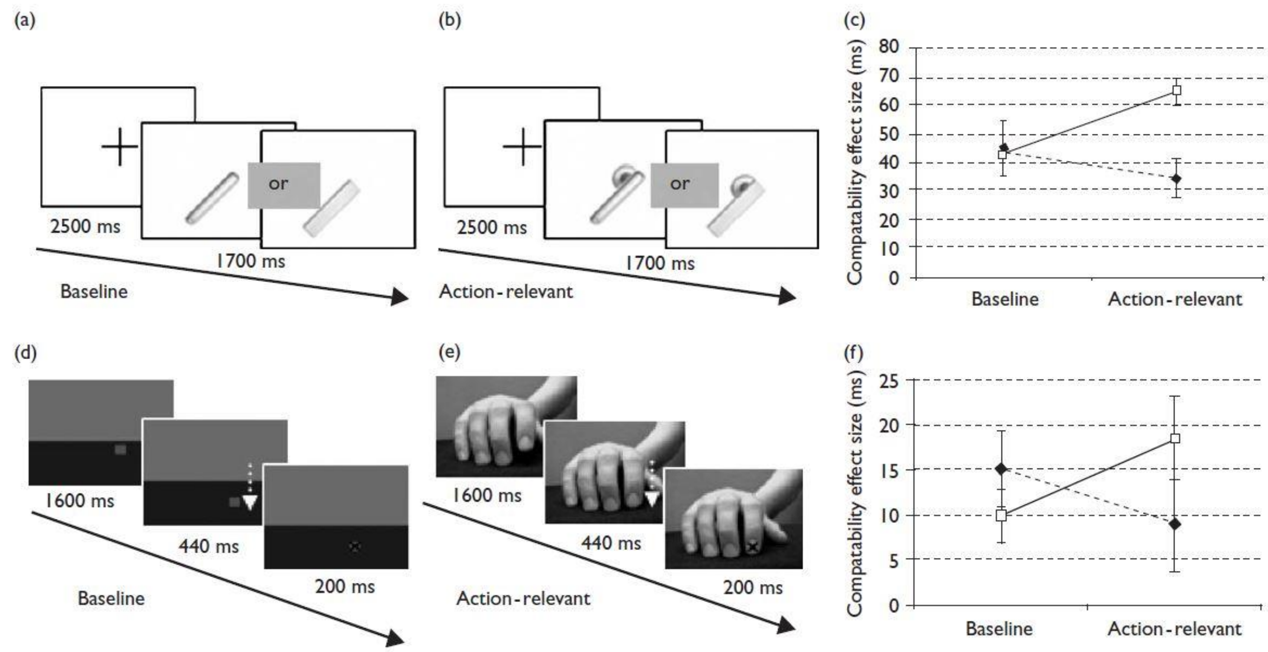

Fig. 1 In Experiment 1, participants classified shapes as being squared or rounded by pressing a left or right key. The shapes were either a simple bar (baseline, a) or a door handle (action-relevant, b). In Experiment 2, participants viewed a video clip of an object (baseline, d) or a finger (action-relevant, e) moving up or down. At the end of the clip, if an X appeared, they were required to respond, by pressing or releasing a button. The results are shown as the mean (±SEM) compatibility effect (ms) for baseline and action-relevant stimuli for shapes (Experiment 1, c) and movement (Experiment 2, f) for Parkinson's patients (broken line) and healthy controls (solid line). In both experiments the controls showed a greater compatibility effect for the action-relevant stimuli (finger and handle) than for the baseline stimuli (object and bar), but the patients did not.

Figure 33*: Experimental set-up and study results from Poliakoff et al., 2006*

In contrast, the lack of any difference between healthy controls and PD patients, tested in off period, during an interference task, suggests a normal coupling between perception and action systems in PD. In this task subjects performed horizontal and vertical arm movements, while watching a person, or a moving dot, performing similar movements in the same-congruent- or orthogonal-incongruent-plane (Albert et al., 2010, see also Alegre et al. 2011).

Castiello et al. (2009) examining PD patients' imitation ability showed kinematic facilitation effects only when the model was a Parkinsonian patient (who performed slower and less fluid movements in contrast to a healthy model. Figure 34). Therefore, differently than normal controls, patients could re-enact their motor representations only when the visual model belonged to patient's motor repertoire. In line with this, the authors proposed that basal ganglia play a role in setting frontal and parietal cortices not only for the execution of actions, but also for the internal simulation of observed behaviors, providing that the internal state of the simulated action is available.

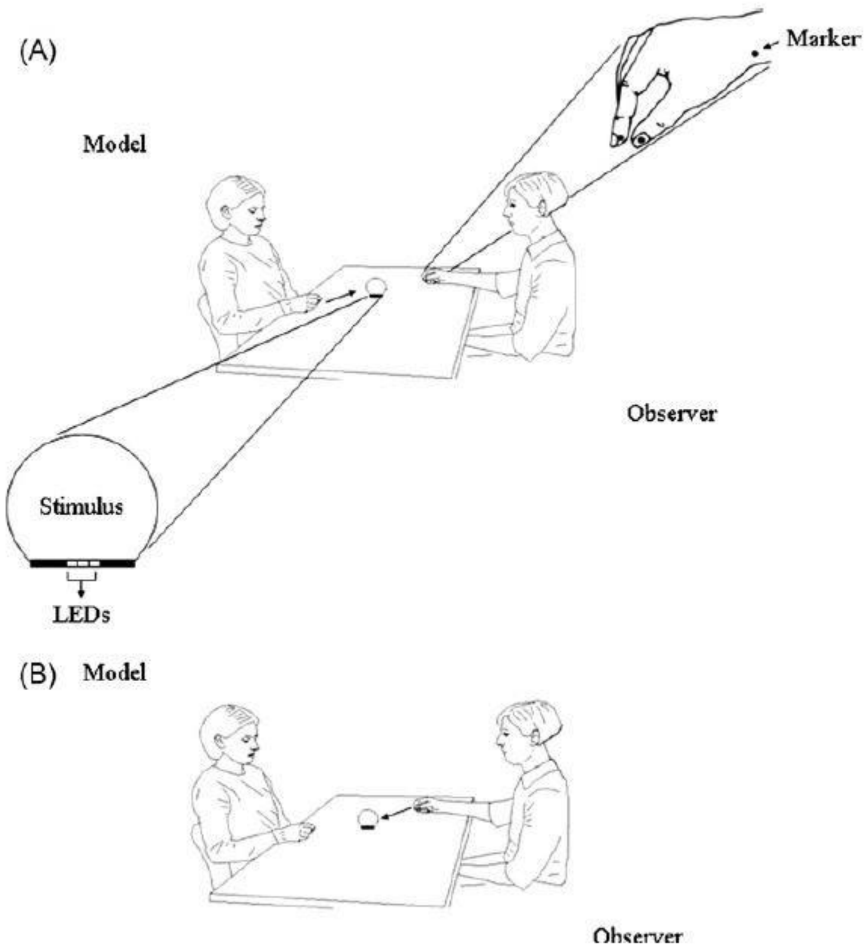

Figure 34*: From Castiello et al., 2009: Graphical representation of the experimental set-up. A schematic representation of the model reaching towards and grasping the object while being watched by the observer. The two call-outs represent the position of the markers on the participant's hand and the apparatus for the illumination of the stimulus (A). A schematic representation of the observer performing a reach-to-grasp movement after having observed the model acting upon the stimulus (B). Filled arrows indicate either the model or the observer reaching towards the stimulus (A and B, respectively).*

Besides investigations testing the influence of action observation on movement production, ability of PD patients to perceive and recognize human action has been studied. Precisely, when displayed with limited visual attributes (a point-light walker) persons with PD showed a reduced visual sensitivity to biological motion (Jaywant et al., 2016b). Likewise, when observing point-light human figures that conveyed communicative and PD non-communicative gestures, patients were impaired, relatively to normal controls, in describing the meaning of non-communicative gestures, while they normally perceived communicative gestures. However, men were more compromised than women and their ability to recognize both types of gestures was reduced. (Jaywant et al., 2016c).

- *Neuropsychological studies*

Action naming is an ability that depends on the inferior frontal gyrus, a "classical" MN area (see Kemmerer, 2012). Action-verb deficits (with relative preservation of noun processing) have been repeatedly documented in PD. In the same vein, it has been reported that motor-language coupling (i.e., the influence between verbal processes and voluntary body movements, see García and Ibáñez, 2014, Figure 35) is altered in PD. For a detailed list of publications on these topics one can refer to the reviews by Cardona et. al. (2013), Silva et al. (2014) and Birba et al. (2017). We report here some of the most significant results.

Boulenger et al. (2008) investigated how non-demented PD patients performed on a lexical decision task in a masked repetition priming experiment, both in the *on* and *off* condition. Participants had to judge whether a letter string was either a real word or a non-word. The real words were either action verbs or object nouns and were preceded by masked stimuli that were either consonant strings or the same real words that were used for lexical decision. In the *off* condition, that is, when motor disability was strongest, masked priming effects for action words were nearly absent in PD patients, while robust priming effects were observed for concrete nouns. In the *on* condition, following Levodopa intake, priming effects for action verbs restored and appeared as strong as for concrete nouns, and comparable to those of healthy controls. According to the Authors their results support the motor theory of language, and provide "compelling evidence that processing lexico-semantic information about action words depends on the integrity of the motor system" (Boulenger et al., 2008, p. 743). Recently, Silva et al. (2017) found PD patients' impairment not only in a lexical task (naming actions), but also in two semantic-association tasks (action/object), thus supporting a similar interpretation.

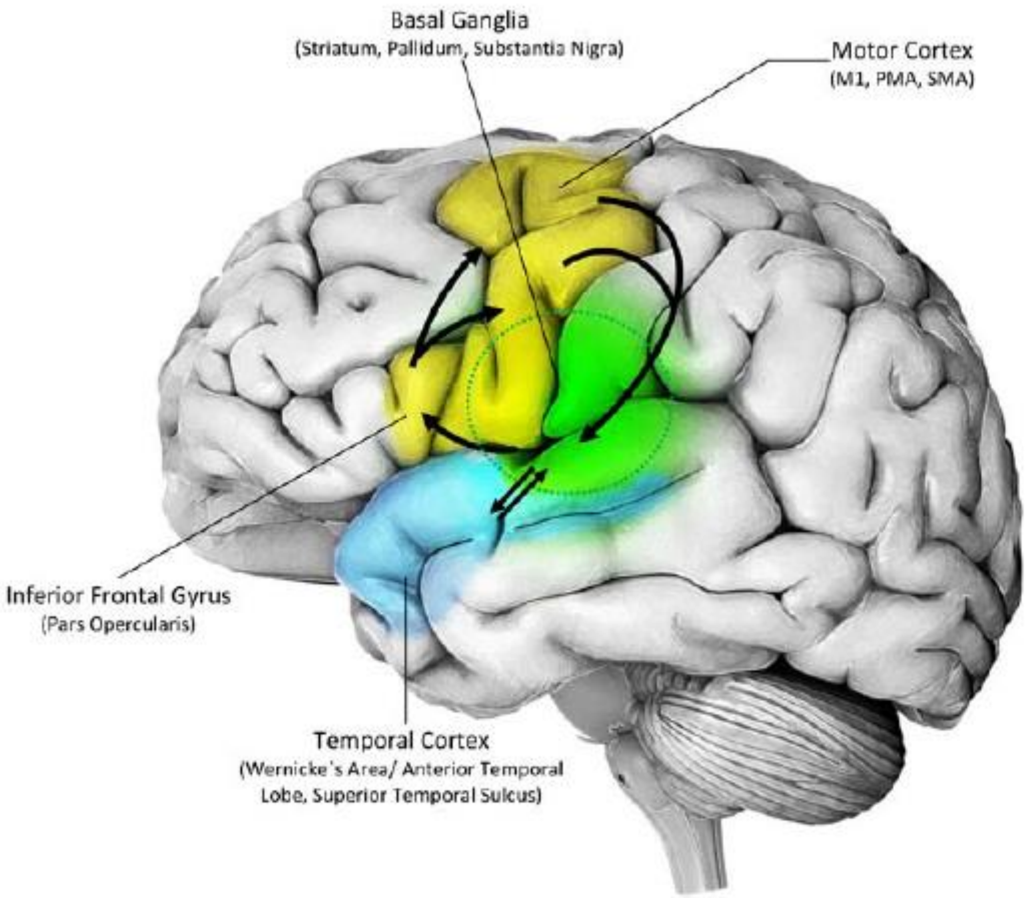

***Figure** 35: Neuroanatomical model of motor-language coupling according to García and Ibàñez, 2014 and Cardona et al., 2013). Neuroanatomical model of motor-language coupling. Coronal and lateral view of the left hemisphere showing the proposed frontotemporal basal ganglia-thalamocortical network (light yellow, blue, and green regions of interest, respectively). The arrows indicate the suggested principal flow of information involved in action-verb processing through two main overlap subcircuits. The frontal lobe, the basal ganglia, and the thalamus (frontal-basal ganglia-thalamocortical component) comprise loops which integrate motor simulation and action programming. These cortical regions play a complementary role in action-verb processing. The temporal lobe, the basal ganglia, and the thalamus (temporal-basal ganglia-thalamocortical component) comprise loops that would play a central role in the grounding of abstract conceptual knowledge involved in words referring to motor concepts.*

Fernandino et al. (2013) administered a semantic similarity judgment task about action (literal action, non-idiomatic metaphoric action, idiomatic action), and abstract verbs to non-demented PD patients and age-matched controls. Most PD patients were in the *on* phase at the time of testing. Compared to healthy controls, PD patients showed longer reaction times for literal and idiomatic action sentences. Parkinsonians also showed a tendency to be less accurate at judging metaphoric action verbs. At first glance, these findings appear to support the Embodied Cognition Framework. However, both studies have been highly criticized, in term either of interpretation (Mahon and Caramazza, 2008) or of statistical method (Kemmerer et al., 2013). Kemmerer et al. (2013) attempted to clarify results from the previous studies by investigating the capacity of PD patients to make subtle semantic similarity judgments about action and non-action verbs. Such judgments were (except for "cutting" verbs), accurate but slow for both types of verbs, both in the on and off condition. According to the Authors, a definite conclusion is difficult to draw about two options, a strong one considering that motor simulations plays an essential role in action verb comprehension; and a weak one where the motor system would only play an augmentative role.

More recently, Silva et al. (2015) again showed that semantic deficits in PD were more pronounced in verbs than nouns, using semantic memory tests that did not involve verbal response. Further, a deficit in the appraisal of action meanings evoked by naturalistic tests was able to distinguish between normal controls and PD patients with normal cognition from PD with initial cognitive decline (García et al., 2018). García at al. also found deficits in a syntactic test of actions involving the verb "to touch" even in presymptomatic genetic carriers of PD mutations (García et al., 2017). According to the Authors, "the crucial role of the basal ganglia for handling syntax (i.e., sequencing hierarchically organized patterns of linguistic information) stems from its more basic specialization for handling movement (i.e., sequencing hierarchically organized patterns of sensorimotor information, see García et al., 2017, p 155)". It has also been proposed that the impairment of motor to language coupling could be an early neurocognitive marker of PD (García and Ibáñez, 2014): this hypothesis is based on results showing an altered action-sentence compatibility (ACE) effect (Ibáñez et al., 2013; Cardona et al., 2014). Of interest is the study by Kargieman et al. (2014), reporting motor-language coupling deficits as earlier as 10 years before the appearance of clinical symptoms in Huntington disease carriers. Results pointing at action-language and syntactic deficits as a window into motor network integrity in PD have however been criticized because they mainly investigated Indo-European languages while data from other languages without a clear distinction between verbs and nouns (Calvo et al., 2018) are still lacking.

Tomasino et al. (2014) studied the effect of DBS on lexical decisions of PD patients about hand action-related verbs, abstract verbs and pseudo-words presented either in a positive or negative sentence context. Presenting negative sentences is a way to explore implicit motor representations, as the negative context can suppress motor simulation processes: indeed, in normal subjects, reaction times to negative commands are slower than to positive ones (Tomasino et al., 2010). When the DBS was at 100% *on*, both normal controls and PD patients showed the normal pattern of reaction times; however, when the stimulation was reduced at 50%, PD patients exhibited identical reaction times to both positive and negative sentences. Here, DBS was able to improve the clinical signs and to restore the normal pattern shown by controls during an action lexical decision task.

An interesting finding to interpret deficits in PD at the light of the embodied cognition framework is the existence of a significant relationship between voluntary control of facial muscles and emotion recognition deficits in these patients (Marneweck et al., 2014; Jacobs et al., 1995, Ricciardi et al., 2017, Livingstone et al., 2016). If the MN system is involved in both production and perception of facial emotional expression, one can expect an alteration of MN in PD. However, the MN network is not the only neuronal system involved in emotion perception (Wang et al., 2014). In any case, similar data to those ones reported in PD have been obtained in Huntington disease (Trinkler et al., 2017).

These data are important for caregivers of persons with PD and Huntington, who must take into account that this emotional impairment can affect both sides, that is the sender and the receiver of the emotional communication. Other studies reporting impaired emotion recognition in both PD and Huntington disease (e.g. Clark et al., 2008; Sprengelmeyer et al., 1996), will not be detailed here. However, one must mention Nobis et al. study (2017) showing a relationship between the performance at the Reading the Mind in the Eyes test (RME) and the severity of motor symptoms, along with disease duration, in PD patients. In the RME (a test measuring empathic abilities) subjects must attribute mental states to persons (represented in pictures) by focusing on their eye-gaze (Baron-Cohen et al., 2001): a bad performance in this test correlates with autistic traits measured with a specific scale.

- *Action Observation Training for PD Rehabilitation*

Several works found that AOT has a positive effect in PD rehabilitation. Most studies focused on walking disturbances. One of first studies came from Buccino and al. (2011), who, in a randomized controlled trial investigated the efficacy of AOT as a complementary therapy to standard pharmacological and rehabilitative treatment. After treatment, the experimental group reported better scores in the Unified Parkinson Disease Rating Scale and the Functional Independence Measure, while there was no objective difference in gait performance. Jaywant et al. (2016a) found similar results: no difference in gait performance was observed; however, the AOT group obtained a better score in a subscale of self-perceived mobility. Santamato et al. (2015) also performed a study on efficacy of AOT in balance and walking of parkinsonians. They obtained negative results, but there was no control group in the study.

An additional effect on recovery of walking ability in PD patients with freezing of gait was observed by Pelosin et al., (2010). The patients were randomly attributed to an “action group”, who watched video clips showing specific movements and strategies to circumvent freezing episodes, or to a “landscape group” who saw video clips of static landscape pictures. Both groups underwent identical physical therapy training. The same working group has subsequently shown that watching video clips showing repetitive finger movements paced at 3 Hz increased the spontaneous rate of finger movements. AOT significantly influenced movement rate in both the *on* and *off* conditions, but 45 minutes after training, the effect was still present only in the *on* condition. The Authors conclude that AOT could be a promising approach in the rehabilitation of bradykinesia, even if the dopaminergic state contributes to the effects of AOT (Pelosin et al., 2013). In another work focusing on arm bradikynesia, Bienkiewicz et al. (2013) demonstrated that it was possible to improve motor performances in PD patients, by using a LED display simulating biological motion.

Finally, the use a “mirror box”, through which a motor training is performed with the non-affected limb, but the patient receives a visual feedback from the affected limb, has been proposed to reduce hand bradykinesia in PD (Bonassi et al, 2016). This procedure has been used above all for stroke patients (Ramachandran and Altschuler, 2009) The involvement of the MN system or at least some areas strictly linked to the MN network (such as the superior temporal gyrus-STG) has been proposed among the possible neural substrates (Deconinck et al., 2014).

The mechanism through which AOT improves motor performances in PD needs however to be further elucidated. AOT does not directly stimulate basal ganglia, but might activate MN prefrontal areas that rely to the basal ganglia through frontal-subcortical circuits. Such a kind of connections has been proposed by several Authors (Alegre, 2011; Bonini, 2016). Recent anatomical data (Gerbella et al., 2015) have in fact shown that most of the areas forming the cortical MN network for hand actions (inferior parietal areas, ventral premotor cortex, and the ventrolateral prefrontal cortex (which, according to some Authors -Borra et al., 2011; Gerbella et al., 2012, Nelissen et al., 2011- could also have MN like properties), send convergent projections to specific sectors of the putamen. In birds, imitation learning would develop, assuming a Hebbian model, using pathways between basal ganglia and MN areas (Giret et al., 2013).

A recent study (Agosta et al., 2016), showed a positive effect of AOT on gait freezing and associated brain functional changes. In a protocol like that one of Pelosin et al. (2010), PD patients with freezing of gait were randomized into two groups: AOT (action observation combined with practicing the observed actions) and ‘‘Landscape’’ (same physical training combined with landscape-videos observation). After 4 weeks, both groups showed reduced freezing of gait severity, improved walking speed and quality of life, but in the AOT group motor disability was additionally reduced and balance improved. After 8 weeks, only the AOT group showed a sustained positive effect on motor disability, walking speed, balance and quality of life. Patients were then scanned while executing foot movements, a MI task related to freezing of gait, and during AOT. The AOT group showed increased recruitment of fronto-parietal mirror areas during fMRI tasks, and in the same group, functional brain changes were associated with clinical improvements. It was concluded that AOT may enhance motor learning and facilitate the building of a motor memory in PD with gait freezing through MN network activation.

A recent review about the efficacy of AOT and MI in PD (Caligiore et al., 2017) concluded that AOT facilitates motor behavior at least in the earlier stages while there is less agreement about MI efficiency. Another recent review (Patel, 2017) has taken into account studies on PD rehabilitation thought AOT as a mean to modify postural way and gait. As in the case of Caligiore et al., the general conclusion of the Author is that AOT could be an effective adjunctive therapy to conventional treatment in rehabilitation, by exploiting the MN network and its ability to understand the motor planning of other people, which could favor anticipatory postural responses and reactive reflexes.

However, we now know that the motor system activity can be also modulated not only by AOT but also by an acoustic stimulus associated to action (e.g, breaking a peanut) (Kohler et al., 2002; Aziz-Zadeh et al., 2004; Fadiga et al., 1995; Gazzola et al., 2006). Moreover, the cortical facilitation due to action observation is at its maximum for both acoustic and visual stimuli linked to the action (Alaerts et al., 2009). This result agrees with the idea that daily life activities are typically mediated by multiple sensorial experiences and that action production is always multimodal.

MN are multimodal cells, which can be activated not only by action observation and execution but also by the acoustic perception of action-related sounds (Kohler et al. 2002). Others of these complex sensory-motor neurons respond strongly to action sounds but not to the observation of actions, thus indicating their audio-motor specificity (Keysers et al. 2003). These data suggest the fascinating possibility to combine the visual information with the action sound to maximize the positive effect of AOT in subjects with PD. Schiavio and Altenmüller (2015) have proposed the use of music in the rehabilitation of PD. It is well known that periodicity, such as the fact to match their walking to the musical beat, or to a metronome, improve velocity, cadence, and stride length of parkinsonian gait (del Olmo and Cudeiro, 2005). Indeed, as Schiavio and Altenmüller underline, “timing and periodicity are fundamental aspects of human gait and because basal ganglia-cortical circuitry is typically involved in time-related processes”, therefore musical stimulation could offer a way to for a better sensorimotor coupling (Schiavio and Altenmüller, 2015). Bacigalupe and Pujol (2014) propose that the external auditory and visual cues (often used in PD rehabilitation) represent the main stimulus for the paradoxical kinesia, the phenomenon according to which PD patients improve their motor performance thanks to external stimuli relevant for movement (e.g. bradykinetic PD patients begin, suddenly and for a while, to run). Provoking this phenomenon would be possible by exploiting the two main streams of the perceptual-action coupling (but above all the dorsal stream, more linked to action) and the MN system. Exploiting paradoxical kinesia could be useful in rehabilitation, and it could be done by using motor affordances in recreational and artistic activities.

Therefore, multimodal stimulation could boost AOT effect and it could also be used in the frame of art therapy (Mirabella, 2015), by promoting creativity with artistic activities (Miller, 2008).

For a summary of the literature searching about Action, Cognition (Mirror Neurons) and PD, see Appendix, Table 1a-e.

- *Explicit Motor Imagery*

Motor Imagery (MI) is a cognitive process in which subjects imagine performing a movement without actually doing it. According the simulation theory, actions involve both an overt and a covert stage (Jeannerod & Frak, 1999; Jeannerod, 2001). MI would represent the result of conscious access to the intention to move (Jeannerod and Decety, 1995). Many studies, since the last decade of the twentieth century (e.g. Abbruzzese et al., 1996; Decety, 1996) have shown that this process involve many areas also recruited during action execution. Among these areas, there are regions thought to be part of MN network in humans, such as the premotor cortex and the inferior parietal lobule. Differently than AOT, which is an implicit on-line process, MI can only be performed off-line that is when one is disconnected from other potential interactions with other subjects or objects. Moreover, while AOT is automatic, MI in rehabilitation requires attention sometimes difficult to obtain. Several studies investigated MI in PD with different approaches (electrophysiological, neuroimaging and neuropsychological ones): results are once again controversial. Studies performed in patients implanted with DBS suggest an engagement of basal ganglia during MI (Leiguarda et al., 2009; Kühn et al., 2006; Thobois et al., 2002). A TMS research (Tremblay et al., 2007) and a neurophysiological study (Cunnington et al., 1997) recording movement-related potentials (usually associated with voluntary movements preparation and execution) reported an impaired facilitation by MI in PD. Conson et al. (2014) tested whether the most affected side by PD influenced patients’ ability to mentally manipulate whole-body images (Figure 36). PD patients were specifically impaired in judging laterality of the hand corresponding to their own affected side when presented with back-facing human figures, in comparison with normal subjects. However, no difference was found for front-facing figures. Authors hypothesized that two kinds of whole-body transformation could exist: an "embodied" one, for back-facing figures, and a "perspective one", activated for front-facing bodies. However, their interpretation is questionable, and their results could be also interpreted in another way: a defective "embodied" mechanism could succeed in judging front-facing figures, but not back-facing ones, because this kind of judgment is less frequently requested (and therefore exerted) in everyday life. It must be also kept in mind that aging affects MI abilities, particularly for the non-dominant side of the body (Saimpont et al., 2009, 2010): this could exert a confounding effect in studies focusing on MI, PD and laterality.

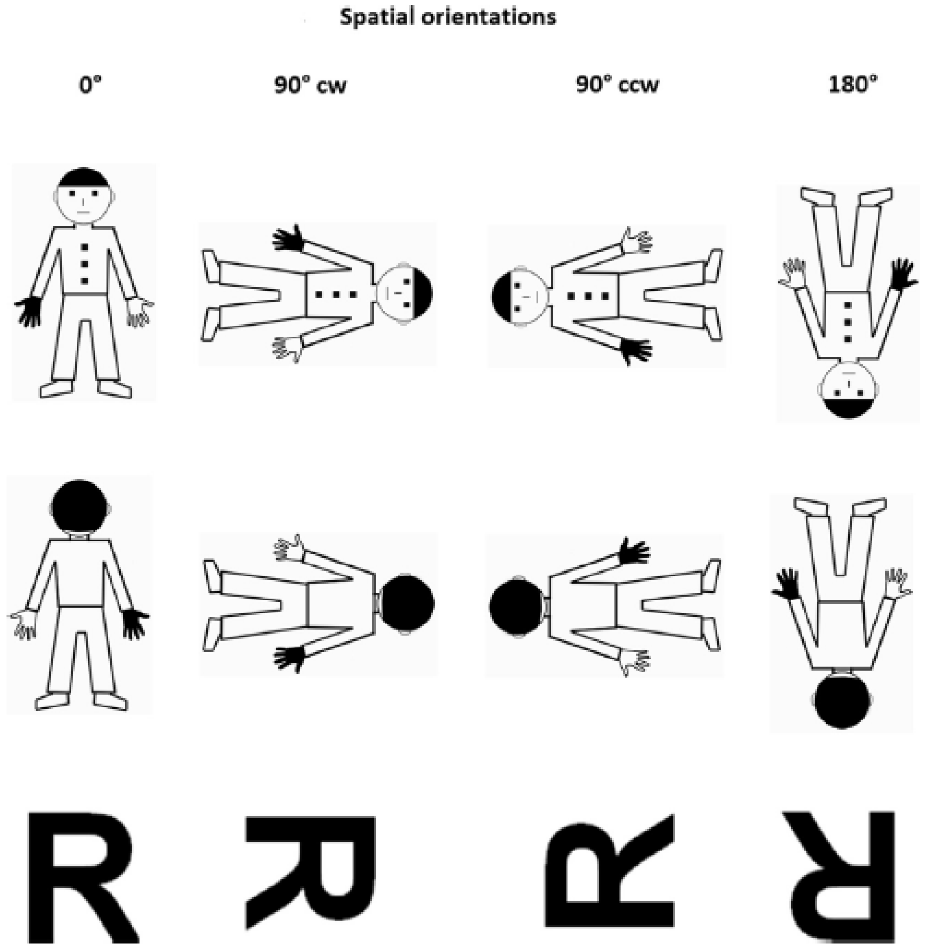

Figure 36: *Instances of stimuli used in the three mental transformation tasks used by Conson et al., 2014: front-facing figures (first row), back-facing-figures (second row), and letter rotation task (third row), in the four spatial orientations: 0°, 90° clockwise, 90° counterclockwise and 180° (schematic human figures with their left hand marked in black.*

Recent investigations testing MI through ad hoc assessment batteries did not find differences between parkinsonians and normal controls (Heremans et al., 2011; Maillet et al., 2015) both during the *on* and *off* phases (Peterson et al., 2012, see Abbruzzese et al.-2015- for a complete review). A position emission tomography (PET) investigation showed that MI in PD was associated with a normal activation when imagining movements in the supplementary motor area, and a significant activation of the ipsilateral inferior parietal cortex (both in the "*off*" and the "*on*" state) and the ipsilateral premotor cortex (when "*off*" only). Inferior parietal cortex hyperactivation could compensate the reduced activation of other areas in comparison with controls, including the right dorsolateral prefrontal area, which deals with the working memory component of the imagery task (Cunnington et al., 2001). Another PET study found hypoactivation of motor regions, basal ganglia and cerebellum along with the dorsolateral prefrontal areas, with a compensatory hyperactivation of the left lateral premotor-parietal cortices and of ponto-mesencephalic areas in *off*, while in *on* the activation was similar to that one of normal controls (Maillet et al. 2015). A possible cortical (and subcortical) compensation was also shown in a paper reporting fMRI results (Helmich et al., 2007). Therefore, a possible hypothesis is that neural compensation mechanisms can maintain a good performance in MI tasks.

2.2.2.2 The Mirror Neurons network, embodied cognition and the Amyotrophic Lateral Sclerosis/Frontotemporal Dementia continuum

- *MRI studies*

In the study of Li et al. (2015) 30 patients with ALS and 30 matched healthy controls underwent fMRI while observing a video of repetitive flexion-extension of the fingers at three frequency or complexity levels, alternated with periods of a static hand. AOT activated brain regions related to the MN system in both ALS and healthy subjects. In ALS patients, however, the dorsal lateral premotor cortex, inferior parietal gyrus, and supplementary motor area, were more activated compared with the activation in the controls. Increased activation within the primary motor cortex, the dorsal lateral premotor cortex, the inferior frontal gyrus, and superior parietal gyrus correlated with hand movement frequency/complexity in patients. This finding indicates an ongoing compensatory process occurring within the motor-processing system of ALS patients that would overcome the loss of function. However, this study was restricted to action observation.

Using fMRI, while subjects observed an actor's hand rhythmically squeezing a ball or squeezed themselves a ball, Jelsone-Swain et al. (2015) showed greater activity in ALS patients than in controls in MN regions within the right frontal inferior operculum, and the right frontal and the left parietal lobes. These results suggest a compensatory response of the MN system during action observation processing in ALS. The second experiment aimed to test ability in understanding actions. Participants watched a short video of an actor pantomiming an action with his hands; they had either to passively observe it or to "actively recognize" the action by choosing the correct action from two phrases displayed on the screen. The contrast analysis of the cerebral activity during active recognition versus passive observation displayed greater activity in various anterior and posterior regions in the normal group; on the contrary, in the ALS group only the right occipital activity increased. Patients were then divided into two groups according to their performance at the recognition task: only the best performers showed activation in bilateral frontal superior gyri. Their performance was also proportional to that one at the RME test. Thus, social cognition would be affected in some ALS patients, an impairment which may be related to a MN system dysfunction (Jelsone-Swain et al., 2015).

Emotions are physiologic responses embodied by nature. Emotional response and feelings represent the engagement of individuals with their surroundings (Johnson, 2015). Jastorff et al. (2016) investigated brain regions involved in the processing of emotional stimuli in patients diagnosed with bvFTD. They combined behavioral testing with structural and resting state imaging. bvFTD patients were impaired in emotion detection as well as emotion categorization tasks in comparison with controls. Their performance in emotion categorization inversely correlated with atrophy of the left IFG, a region belonging to the MN network. Functional connectivity analysis also showed a reduced connectivity of this area. An explanatory hypothesis is the fact that, due to the IFG atrophy, an absence of motor mirroring could prevent emotion recognition. Similarly, Brioschi-Guevara et al. (2015), found that the atrophy of prefrontal and premotor regions at structural MRI inversely correlated with the ability of bvFTD patients to infer intention and emotional beliefs of others. Data from bvFTD patients support the role of the MN system in emotion recognition, as summarized in a previous section. Marshall et al. (2016) found different grey matter correlates between impaired emotion recognition and automatic imitation according to the different clinical forms of FTD. The brain regions involved delineated a distributed neural network previously linked to embodied cognition.

Finally, another study in ALS deserves to be reported. Verstraete et al. (2013) investigated the longitudinal effects of the disease on brain networks using diffusion tensor imaging. Their analyses revealed an expanding sub-network of affected brain connections over time, with a central role for the primary motor cortex and loss of structural connectivity mainly propagating to frontal and parietal brain areas (regions also belonging to the MN network).

Some papers suggested a possible role of the MN network alteration in the pathogenesis of ALS and FTD. According to Eisen et al. (2014), in the ALS/FTD complex the disruption of MN network might be associated to an impairment of different evolutionarily-interlinked functions, leading to the different clinical forms of the disease, and in particular: 1) hand function specialization, and the associated development of bipedalism (associated to the "classical" form beginning from the upper limbs or to the pseudo-polyneuritic form, beginning from the lower limbs); 2) sound production, swallowing, and breathing (which the Authors designate as "the brainstem functional complex"; this impairment would be associated to the "bulbar" ALS variant); 3) cognitive functions linked to social behavior and communication ability, through gestures and language (associated to FTD).

Previously, Bak and Chandran (2012) had already proposed that dementia associated with MotND could be interpreted as the fifth major clinical presentation of the disease, alongside with bulbar thoracic, upper and lower limb presentation. Accordingly, in ALS the most impaired aspects of cognitive functions are those with the tightest functional links to the motor system, such as verb and action processing (see the following paragraph).

- *Neuropsychological and behavioral studies*

A series of neuropsychological researches showed an impairment of action rather than object naming in ALS (Bak and Hodges, 1997; Bak et al., 2001; Grossman et al., 2008; York et al., 2014), and FTD (Cappa et al., 1998; Hillis et al., 2004). When combining neuropsychological assessment and morphological MRI, York et al., (2014) showed that performance in action verb judgment was related to gray matter atrophy in bilateral frontal regions, including motor association cortex and pre-frontal regions. Similarly, Grossman et al. (2008); had shown that cortical atrophy in premotor areas associated with the representation of the face, arm, and leg correlated with performance on measures requiring action knowledge. This supports the hypothesis that the difficulty shown by ALS patients in naming actions is partly related to the degradation of action-related conceptual knowledge represented in motor-associated cortex. Bak and Chandran (2012), focusing on cognitive impairment in some ALS patients, underlined that the most impaired aspects of cognitive function are those with the closest functional links to the motor system, a pattern explaining the disproportionate impairment of verb and action processing in this disease (see also Bak, 2013). It would be of interest testing whether AOT is able to improve this kind of cognitive impairment.

Fiori et al. (2013) investigated controls and ALS patients' responses during a task testing the effects of biomechanical constraints on MI. Effects present in normal subjects were compromised in ALS, at least for the proximal muscles (comfortable/awkward postures: see Figure 37).

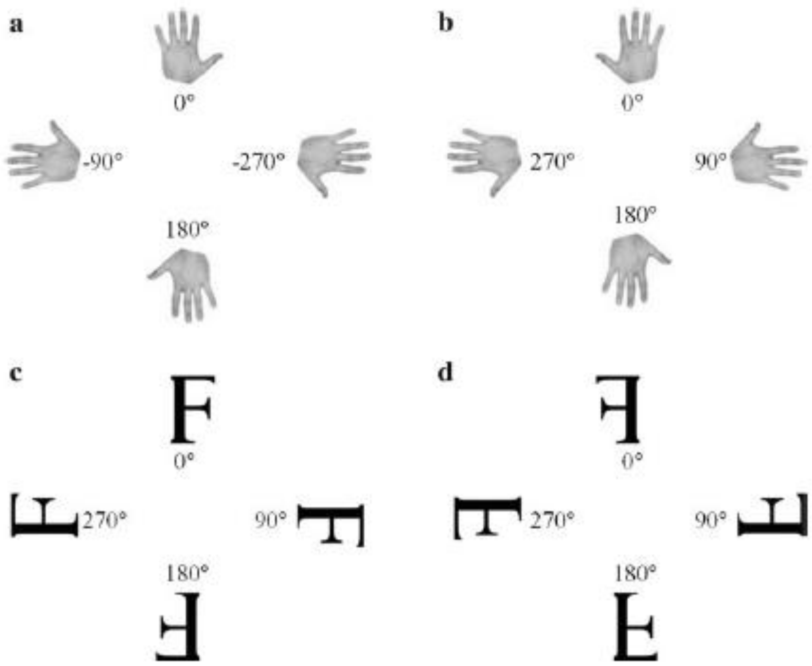

Figure 37*: stimuli used in the work of Fiori et al., 2013. For the letter task, canonical (****c****) and mirror form (****d****) letters were shown at each orientation (0°, 90°, 180°, 270°). For the hand laterality task stimuli, left hands (****a****) and right hands (****b****) were shown to highlight that left hand images are considered mirror-images of right hands. Fiori et al. labeled the right hand stimuli from 0°, +90°, 180° and +270° in clockwise direction, whereas the left hand stimuli were labeled from 0°, −90°, 180° and −270° in counter clockwise direction. Adopting this data set allowed to distinguish between stimuli across and away from the body's midsaggital plane: the +270° right hand and −270° left hand were considered across body plane stimuli, whereas the +90° right hand and −90° left hand were considered away body's plane stimuli. Furthermore, this methodology allowed also to distinguish easily between comfortable postures (−270° left hand and 270° right hands) and awkward postures (−90° left hand and 90° right hands).* ***a*** *Left hand;* ***b*** *right hand;* ***c*** *F in the canonical form;* ***d*** *F in the mirror form.*

Otherwise, it must be cited a well-conducted case study by Vannuscorps et al. (2016, Figure 38), who longitudinally examined a patient with CBD, a clinical picture related to FTD, for 4 years. During the period of investigation, the patient presented with increasing action production disorders with associated increasing bilateral atrophy in cortical and subcortical regions involved in sensorimotor control (the superior parietal cortex, mostly on the right side, the primary motor and premotor cortex, the inferior frontal gyrus, and the basal ganglia). In contrast, the patient's performance in processing action-related concepts (e.g action naming and action comprehension) was spared during the same period. These data, suggesting that action concept processing is based on distinct cognitive and neural resources from those underlying the sensorimotor control of actions, defies the “strong” embodied view, while being compatible with a “weak embodiment” view (Meteyard et al. 2012). In the “weak option” of the embodied theory, sensorimotor information (activated within the action production system while conceptual processing takes place) is constitutive, but not central, of actions meaning. However, in our opinion, it cannot be excluded that the relative sparing of some brain areas (both the inferior parietal lobes, the right superior parietal lobe, the right precentral gyrus and both the caudal middle frontal gyri) could have support the preservation of action naming of Vannuscorps’ patient.

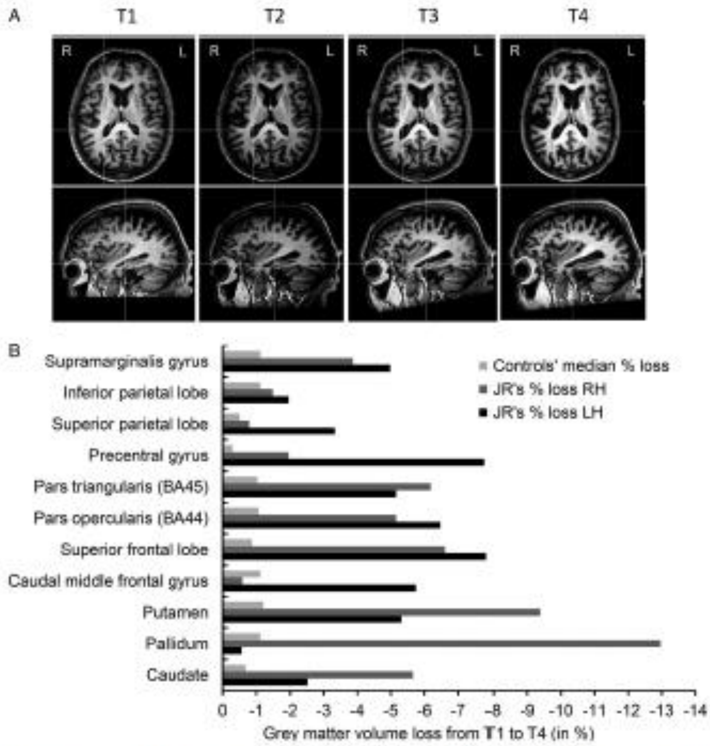

Figure 1. (A) Transversal (top) and sagittal (bottom) sections of J.R.'s brain at the four periods of testing (T1, T2, T3, and T4). (B) Percentage of volume loss between T1 and T4 in regions of interest (ROIs) within the left (LH) and right (RH) hemispheres. BA = Brodmann area. Bars in light grey represent the volume loss in the same ROIs in healthy elderly control participants (mean age = 75.6 years) calculated from the annual rate reported by Fjell et al. (2009).

Figure 38: *results from the study of Vannuscorps et al., 2016*

For a summary of the literature searching about Action, Cognition (Mirror Neurons) and FTD/ALS, see Appendix, Table 2a-b.

2.2.2.3 *The Mirror Neurons network, embodied cognition and the Mild Cognitive Impairment/Alzheimer disease continuum*

- *Correlation between morphological MRI data and EEG spectral analysis*

Recently, 74 adult subjects with MCI have undergone EEG recording and high resolution MRI by Moretti (2016). Alpha3/alpha2 frequency power ratio – whose increase has been detected in MCI subjects who will convert in AD (Moretti et al., 2011) – as well as cortical thickness were computed for each subject. High EEG alpha3/alpha2 frequency power ratio was correlated with atrophy of cortical regions belonging to the posterior MN network (IPL) areas in MCI subjects. Thus, a possible pathological uncoupling of the MN system would explain the cognitive deficits in prodromal AD. The location of the IPL at the junction of the parietal, temporal and occipital lobes makes it ideally situated to perform cross-modal integration (hearing/vision/proprioceptive): its impairment would induce both praxis, language, calculation and topographical deficits characterizing AD, a hypothesis agreeing with traditional neurological views (Greene et al., 2010).

- *fMRI studies*

A fMRI study by Lee et al. (2013) aimed at evaluating neural activities during processing of facial expressions of others in AD patients. The patients showed weaker activations in left cerebral regions associated with MN or empathic simulation (ventral premotor cortex and the anterior insula and adjacent frontal operculum, respectively) compared to matched controls. Importantly, levels of brain activation in those regions also predicted the level of affect in the AD group. Thus, neural changes in regions associated with motor and emotional simulation (comprised MN regions) could play a role in the development of AD symptoms, and explain affective impairment associated with this disease.

Peelle et al. (2014) tested a semantic judgment task, involving shape and color of natural kinds or manufactured items. AD patients were impaired in this task, and exhibited significantly less activation the in left temporal-occipital cortex than did healthy seniors, and a reduced activity in the left inferior frontal cortex. According to the Authors, these results are consistent with a sensory-motor approach of semantic memory: knowledge associated with object concepts would be stored in brain regions that are responsible for perceptual and motor functions of a certain material (Barsalou et al. 2003).

- *Behavioral studies*

In a first study Bisio et al., (2012) tested AD patients in mild and moderate stages of the pathology, if the implicit imitation is preserved. AD patients and healthy elderly participants were required to observe a dot moving on a screen and to point to its final position when it stopped. The dot speed similarly influenced AD patients' and healthy elderly participants' actions, suggesting that perception-action matching is not prevented by pathology. In contrast, only patients had anticipatory motor response: i.e. they started moving before the end of the stimulus motion, unlike what was requested by the experimenter. While the imitation of the stimulus velocity suggests an intact ability to match the internal motor representations with that of the visual model, the uncontrolled motion initiation would indicate AD patients' deficiency to voluntarily inhibit response production. The

Authors hypothesize that the first part to their results would point to a relative preservation of the MN network (responsible of perception-action matching). However, MN parietal areas would be less spared than frontal ones, leading to the impaired movement inhibition.

In a second experiment (Bisio et al., 2016) the authors tested voluntary imitation in AD and how this ability was modulated by the nature of the observed stimulus by comparing the ability to reproduce the kinematic features of a human demonstrator with that of a dot moving on a screen (Figure 39). Results showed that when asked to imitate the velocity of the stimulus AD patients showed an intact ability to reproduce it. This ability improved when the stimulus was a human agent. This result suggests that high-level cognitive processes involved in voluntary imitation might be preserved in mild and moderate stages of AD and that voluntary imitation abilities might benefit from the implicit interpersonal communication established between the patient and the human demonstrator. These findings open new clinical perspectives and innovative techniques in training programs for people with dementia. In particular, the preservation of the motor resonance mechanisms, not dependent on conscious awareness, constitutes an intact basis upon which clinicians could model both physical and cognitive interventions for healthy elderly and AD patients. Furthermore, by stimulating the voluntary imitation of everyday activities the caregivers might help the patients to maintain intact, as long as possible, the ability to easily move in their familiar environment and to feel they are still part of their family community.

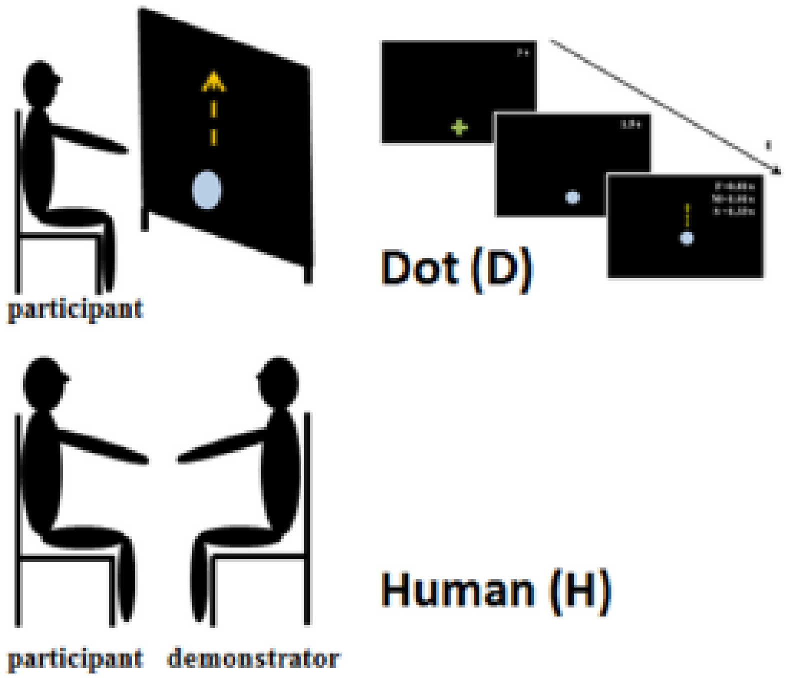

Figure 39: *Experimental set-up in Bisio et al., 2016.*

The upper part of the figure represents the set-up when the participants observed the Dot stimulus. They were seated in front of a large screen and they observed the upward displacement of the Dot at three different speeds and durations. The bottom part of the figure shows the experimental set-up for the human observation condition, with the participants and human demonstrator seated face to face. In both conditions participants were requested to observe the stimulus movements and when the stimulus stopped to reach its/his final position, imitating its/his velocity.

- *Neuropsychological studies*

Some studies pointed out a more severe impairment in action than in object naming in AD patients (Robinson et al., 1996, Kim and Thompson, 2004; Druks et al., 2006), even if at a lesser extent than in FTD (Cappa et al., 1998). Cotelli et al. (2014) found a correlation between action comprehension, action naming abilities, language impairment and apraxia. These studies not only suggest a tight link between language and execution of complex motor movements, but also support the idea that a stimulation of the motor system could improve language performance, and in general cognitive abilities in people with AD. In contrast, other researchers reported that nouns were more impaired than verbs in AD patients (Williamson et al., 1998) or did not report any difference between nouns and verbs (Masterson et al., 2007, Rodríguez-Ferreiro et al., 2009). According to Vonk (2012, 2015), these contrasting results remain consistent with an embodied cognition framework. In fact, both verb and nouns subcategories with semantic features (e.g. words indicating a "change or state") linked to brain areas particularly altered by AD (temporoparietal areas) seem to be more affected in this disease than other subcategories.

Behavioral studies have also shown deficits among individuals with AD in recognizing facial emotions (Guaita et al., 2009; Bediou et al., 2009; see also McLellan et al., 2008 for a review), mainly in the recognition of happy, sad, and fearful expressions (Kohler et al., 2005). These data appear coherent with a putative impairment of the MN network in AD, since this network is involved in recognizing other people emotions.

On the contrary, De Scalzi et al. (2015) found a conservation of the action compatibility effect in people with AD: when patients are asked to make judgments on sentences that describe a transfer of an object toward or away from their body, they are faster to respond when the response requires a movement in the same direction as the transfer described in the sentence. This raises the possibility to exploit the motor systems to improve language comprehension of AD (e.g., by requiring performing the action while listening to a sentence).

Recently, Vallet et al. (2017) tested young and elderly people, and persons with AD or semantic dementia (the fluent form of PPA) with the SEMEP: SEMantic-Episodic memory test: see Figure 40). This test allows to test both episodic and semantic memory at the same time. In the free recall and recognition tasks of the SEMEP, a confusion error is defined as the recall or recognition of an item presented in the encoding phase that was not to be learned, while an intrusion error consists in the recall or recognition of an item never presented to the participant in the encoding phase. According to "embodied cognition" theory, memory and perception are very tightly bound, and multimodal integration occurs during the retrieval of a memory trace (e.g., Zimmer et al., 2006),. The different groups showed specific patterns of performance: normal elderly committed confusion errors for presented items, but not intrusions (recall or recognition of items never presented). AD patients presented the worst episodic memory performance associated with intrusion errors and did not benefit from a visual isolation (addition of a yellow background), a method known to increase the distinctiveness of the memory traces. The sematic dementia group evidently suffered from the most severe semantic impairment. The increase of memory errors in normal elderly is supposed to reflect the sensory/perceptual decline in healthy aging (see Roberts and Allen, 2016 for a review). On the contrary, the lack of efficacy of visual isolation in AD would be linked to the impaired multisensory integration (Vallet et al., 2013) due to the AD related disconnection syndrome

(Delbeuck et al., 2007). If confirmed, these results would prompt for a training based on motor cognition framework in normal elderly or at least in a very early phase of memory impairment, when methods such as visual isolation still work.

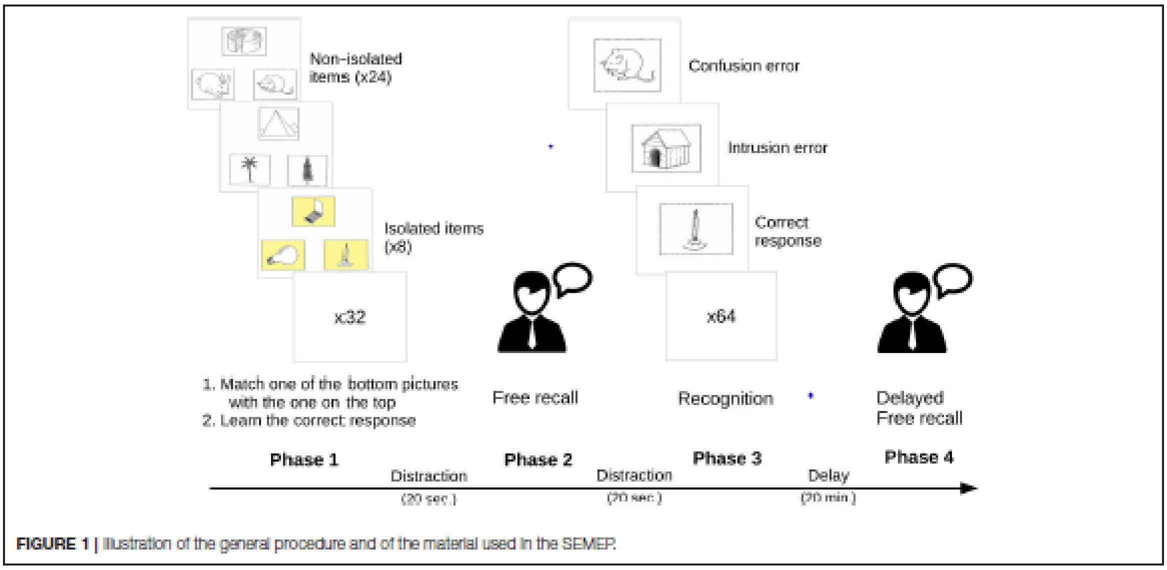

FIGURE 1 | Illustration of the general procedure and of the material used in the SEMEP.

***Figure 40**: The SEMEP: SEMantic-Episodic memory test (Vallet et al., 2017). During the encoding phase, the instructions insist on the fact that two tasks had to be done at the same time: a matching task (judging which one of the two pictures, presented at the bottom, best matches the model) and a learning task (learning the corresponding name of the correct answer of the matching task).*

- *TMS studies*

In a study from Cotelli et al. (2006), TMS of both the left and right dorsolateral prefrontal areas (a region) improved action naming but not object naming in 15 AD patients. Similar results were obtained for a mild AD group (Cotelli et al., 2008), while an improved naming accuracy for both action and objects was found in the moderate to severe group. These results are difficult to interpret. The role of the dorsolateral prefrontal cortex in action naming must be further elucidated. A possibility might be the fact that this cerebral area can intervene by selecting and combining motor representations in the MN system (Vogt et al., 2007) It must be also mentioned a recent study finding neurons with mirror-like properties in the dorsolateral prefrontal cortex, linked to self and other people head rotation (Lanzilotto et al., 2017). In any case, TMS studies raise the interesting possibility to improve language performance in AD via magnetic stimulations of the motor system.

- *Rehabilitative studies*

So far, the only published research about AOT with AD is from Eggermont et al. (2009). Nursing home residents with dementia watched either videos showing hand movements (19 subjects, AOT group) or a documentary (25 subjects) for 30 min, 5 days a week, for 6 weeks. At the end of treatment, patients treated with AOT showed improvements in attention and facial recognition (which depends on the STS, a region tightly linked to the MN system). A preliminary research in progress, performed on small groups (9 each) of patients diagnosed with mild to moderate AD, compared AOT with multidimensional stimulation (Spada, 2012). The data analysis showed a significant improvement between test and retest in a naming action task. However, recently an intervention focused on MN in AD patients showed negative results (Caffarra P, 2016, oral communication at XI Sindem National Congress, Florence, Italy).

For a summary of the literature searching about Action, Cognition (Mirror Neurons) and AD/MCI, see Appendix, Table 3a-f.

2.2.3 Conclusions of the review on studies linking Action, Cognition (Mirror Neurons) and neurodegenerative diseases

Data about the status and role of MN network, and in general studies based on embodied cognition concepts, in neurodegenerative diseases are poor with the partial exception of PD. A hypothetic conclusion of existing studies in PD could be that the MN network is in some way altered in this disease (the rationale in this case could be the degeneration of cortical-subcortical loops linking the basal ganglia to the frontal cortex): an hyperactivation of this system might support motor and cognitive performances, at least in early stages, while in later stages the more severe impairment of the MN network could prevent compensation at least in a part of patients. The dopaminergic state, and DBS, could have a role in compensating the functional deficits of circuits linked to motor cognition, too. The compensation mechanism could explain why studies on AOT as a rehabilitative method for people with PD report positive results. Interestingly, a very recent study on mild to moderate PD patients showed that they can be highly influenced by motor contagion induced by AOT also in a negative sense (Pelosin et al., 2018). Most studies in the field of PD rehabilitation have recruited very small samples. On the other hand, it must not be forgotten that, in rehabilitative studies, studying large samples of people does not allow to individualize the treatment according to the clinical picture that, as we have seen, can be very various along the course of the disease in each patient. Therefore, in the field of rehabilitation, the ideal situation would be often to characterize each patient to follow him/her as a single case experiment.

In the ALS/FTD continuum, preliminary evidences point out to an involvement of the MN network, a possibility, which is not unexpected, as MN are primarily motor neurons. The MN system decay could explain language and inter-subjectivity deficits shown in these patients. In the MCI/AD spectrum, data are very scarce. Recent studies suggest a possible involvement of the MN network. However, more researches are needed to confirm this hypothesis, also because previous behavioral researches pointed in the opposite direction.

2.3 Reasons and aim of the experimental study

As already stated, almost all studies on neurodegenerative diseases have been conducted according to the traditional model, which considers cognitive abilities as higher-level supervisor functions, and perception and action as separated lower-level systems. Reinterpreting neurodegenerative diseases at the light of the embodied cognition hypothesis could help a better comprehension of clinical manifestations and open new pathways to rehabilitation.

According to Vallet (2015), exploring embodiment in normal and abnormal aging would be of interest both from a theoretical point of view, as becoming older is associated with changes in all brain, sensory and bodily functions, and from a practical point of view, because it would possibly allow to develop interventions to help patients. Vallet briefly reviews the few studies that explored cognition in elderly people according to the embodied cognition theory and concludes that it would be possible to influence their memory performance by focusing on multisensory features of the stimulus and/or the motor context of learning. At the same time, it would be possible to improve cognition in aging by focusing on the whole-body functioning of the individual. Interestingly, Tia et al. (2010) demonstrated that training elderly people through AOT could induce a reactivation in mental representation of action, leading to an increase of their walking speed and a decrease of the duration of back-to-sit movements. It is obvious that these data open exciting possibilities to improve motor performance in elderly population after an inactivity period.

On the other hand, several studies have shown positive effects of cognitive (e.g., Davis et al., 2001 Rebok et al., 2014) or physical training (Colcombe et al., 2004; Miller et al., 2012; see also Kramer et al., 2007) on elderly people's cognition and quality of life. Some studies included both physical and cognitive aspects in the training (e.g. Cesari et al., 2014; Gajewski & Falkenstein, 2012). Some Authors showed more benefits from combined training (Oswald et al., 2006; see also the review of Bamidis et al., 2014) while other ones (Theill et al., 2013) did not. Therefore, further systematic investigations are necessary to determine the respective role of these two types of training in cognitive improvement in older people, even if more and more scientists claim for a multimodal stimulation (Bamidis et al. 2014). In the last years, studies combining cognitive and physical training have been also performed with people suffering from MCI or AD (Suzuki et al., 2012; Fiatarone et al., 2014; Baglio et al., 2015; Kim et al., 2016). The results of a recent metanalysis emphasize the clinical relevance of combined cognitive and physical training strategies, on global cognitive function, activities of daily living and mood (Karssemeijer et al., 2017). The positive impact of such combination would reflect the strong link between the two components arbitrarily dissociated and gives support to the idea that that cognition is embodied.

Action could also represent a way to support memory performance in AD. It has been assumed that the superiority of action to support retrieval is explained by the non-explicit nature of encoding during action (as opposed to a verbal encoding) and by richer set of cortical area involvement including visual, spatial, and motor input (Zimmer et al. 2001). Indeed, AD patients improve their memory performance when memory is feed-back by voluntary movement and associated sensory modalities, such as vision, proprioception, tactile and auditory cues (which could involve different preserved brain areas such as cerebellum, and premotor cortex; Ghio et al., 2018): better memory resulting from action production has been observed at the early, moderate and severe stages of AD (Lekeu et al. 2002), after a delay (Masumoto et al. 2004), and in working memory (Charlesworth et al. 2014). Other studies demonstrated that recall of different aspects of episodic memory (recall of what, where, when and binding) has been enhanced after an active exploration in MCI or AD patients (Plancher et al. 2012; 2013). Indeed, in an active exploration strategy, the brain closes the loop by linking intentionality and predictions to sensory feedbacks. In contrast, passive movements (i.e., guided by a robot arm or a physiotherapist) provide feedback unrelated to a specific goal and unverifiable. These results promote the idea that memory can be treated as embodied in nature by proposing that the past is 'situated' in the body of the individual. In consequence, all episodic memories would contain links with actions and could efficiently subserve the need of perception and action coupling (Wilson 2002 for a review).

As explained in a previous paragraph, AOT, which is a mean to stimulate the MN network, has been proposed as a rehabilitative motor tool (see Bassolino et al., 2015 for a review). However, AOT could also play a role in maintaining cognitive functions, if one accepts the indissociable nature of cognition from the motor system. Based on the supposed role of the motor system in memory building-up, it is hypothesized that MN stimulation through AOT maintain and speed the execution of complex motor sequences needed to perform activities of daily living and facilitate the formation of memory traces of actions executed during a normal day in people with AD or at least with MCI. It might be a powerful tool to improve motor, language and/or social cognition deficits in people with PD or FTD, too.

However, studies evaluating the integrity of motor resonance in neurodegenerative diseases would be a prerequisite for rehabilitation. Of interest, too, is to study MN with fMRI or neurophysiological techniques and correlating data with neuropsychological tests exploring functions traditionally linked to MN. As it has emerged from the literature review, data in this domain are still scarce.

The aim of the current study was to investigate integrity of MN network in normal aging, MCI and AD. For this purpose, three matched groups of subjects (normal elderly people, people affected by MCI and AD patients) were evaluated with a fMRI task specifically constructed to test functioning of MN (Cabinio et al., 2010). According to this previous fMRI study in normal subjects and to fMRI MN literature, we expected activation of the frontal cortex (Brodmann area BA6 and precentral gyrus,) the parietal cortex (rostral part of the inferior parietal lobule, BA40) and the temporal cortex (STG, BA22 and BA42) in the case of preservation of MN system functioning.

CHAPTER 3 – EXPERIMENTAL CONTRIBUTION

3.1 MATERIALS AND METHODS

3.1.1 SUBJECTS

Sixteen AD patients and an equal number of aMCI subjects and aged healthy subjects (NE) were enrolled and performed a fMRI study and a neuropsychological assessment.

Table 1 summarizes the demographic data of the three groups. Age, education level and gender was not significantly different (ANOVA). Probable AD was diagnosed according to NIA-AA criteria (McKhann et al., 2011). aMCI subjects were diagnosed according to Petersen's criteria (Petersen et al., 1999, 2001). Only MCI subjects with significant atrophy of at least one hippocampus were included in the study (see later). The following is the exclusion criteria: patients unable to understand and/or follow instructions; severe attentional deficits, untreated psychiatric disorders, joint deformity of arthritic origin, visual or hearing deficits, previous stroke or other neurological disorders, contraindications to MRI. Persons with MCI or dementia were consecutively recruited from the Don Carlo Gnocchi Foundation Service for Cognitive Disorders and Dementia. Patients were diagnosed after taking their clinical history and carrying out medical and neurological examinations, routine blood tests and neuropsychological assessment. All patients also underwent either brain CTs or MRIs to evaluate the vascular lesion load and to exclude rarer causes of dementia (e.g. tumors, hematomas, etc.). The control group consisted of spouses or hospital volunteers.

Table 1: Demographic data of the 3 groups (ANOVA)*

	NE	**MCI**	**AD**	**p**
#	16	16	16	
Age	73.8 ± 6.8	77.0 ± 4.8	77.8 ± 5.4	NS
Level of education (Primary, Secondary, High Scool, University	0\3\8\5	2\3\9\2	5\5\4\1	NS
Gender: F\M (F%)	9\7 (56.3)	6\10 (37.5)	9\6 (60)	NS

** non parametric tests (Kruskal – Wallis) give the same results.*
NE= Normal Elderly people; MCI: Mild Cognitive Impairment; AD: Alzheimer Disease.

This study was carried out in accordance with the recommendations of the Don Gnocchi Foundation ethical hospital committee, with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Don Gnocchi Foundation ethical hospital committee.

3.1.2 fMRI EXPERIMENTAL PARADIGM

During the fMRI scanning, participants were asked to perform 2 block-designed runs (A-B structure): in one run, they were instructed to observe (observational runs) and in the remaining run to execute hand grasping movements (motor run), according to a paradigm described in Cabinio et al., 2010. Briefly, in the observation run, all subjects viewed movies of hand grasping different objects (see fig 1-A). In the motor run, subjects observed visual stimuli consisting of objects oriented in order to be grasped with the right hand; and they were asked to perform a grasping movement appropriate to the shape of the object (see fig 1 -B; subjects were asked to perform movements as if they had the observed object actually in their hand, therefore the execution condition was a mime of the action). The motor act was performed continuously during the observation of the image of each object, with a frequency of about 0,5 Hz and a total number of 27 objects (brush, manual perforator, coffee cup, eraser, box, torch, knife, screwdriver, sun glasses, pen, lighter, bottle, glass, pot, fork, lego brick, keys, meterstick, stapler, phone, scissors, padlock, nail polish, wrench, ball, sponge, cup). The decision to use different types of grasp (both observed and executed) was driven by the need to recruit the highest percentage of MN and thus increment the BOLD signal (Iacoboni et al., 2005; Cabinio et al., 2010; Marino and Ricciardelli, 2017; Ehrsson et al., 2000). Figure 41 shows some visual stimuli presented to the subjects in each experimental condition. Before the fMRI experiment, the participants were verbally instructed to execute the movements as if the object was close to their hand, and to carry out the task only with the hand and the wrist: repeating this action, until the appearance of the next picture.

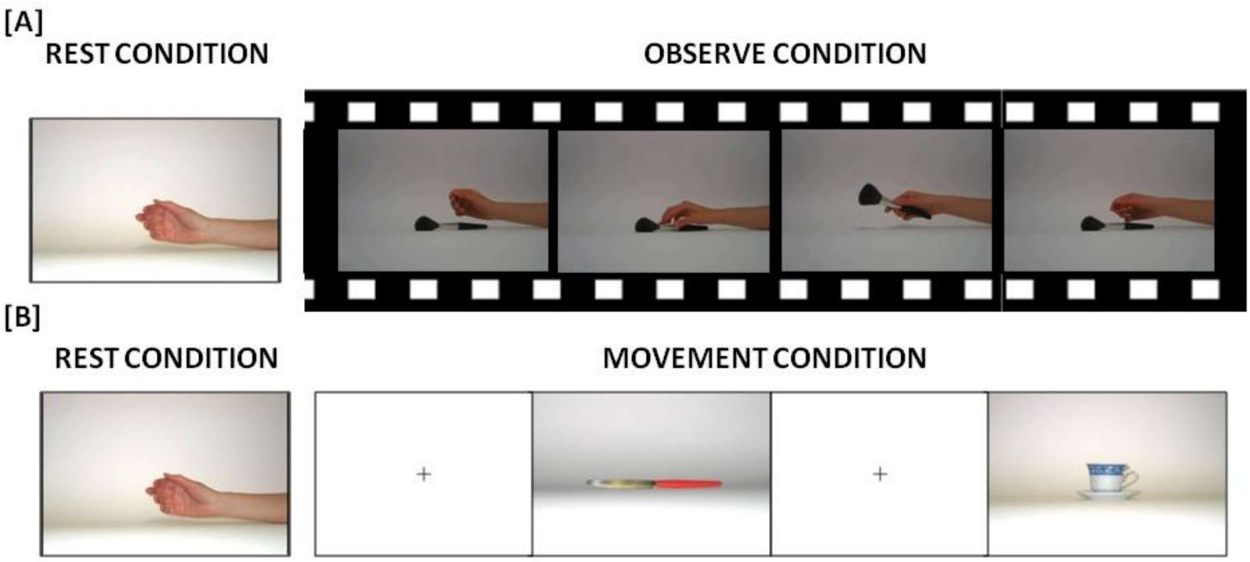

Figure 41: *Visual stimuli presented to the subjects in each experimental condition. (A) Picture used during rest conditions and samples of frames from one of the videos presented to the subjects during the observation condition. (B) Pictures shown to the subjects during the rest and execution condition.*

Participants were trained outside the scanner for 15 min before data acquisition. During the training session, subjects were instructed to keep their gaze on the fixation point for the entire duration of the experiment, and to execute grasping movements about once every 2 seconds. If the training task (that was conducted with different parallel versions), was not properly executed by the subjects, they were not included in the study.

We used an MR-compatible visual system to present the stimuli (VisuaStim Digital system, Resonance Technology Inc.). The use of E-Prime software (E-Prime 2.0 Psychology Software tool, http://www.pstnet.com) ensured exact timing of prompts during MR acquisition. The performance was visually checked by the examiner during the execution of the task. The examiner maintained accuracy by reporting all the tasks correctly performed. The design was fully randomized (both blocks and runs).

3.1.2.1 MRI acquisition

Functional images were collected by a gradient echo-planar (EPI) T2* sequence (TR = 3000 ms; TE = 50 ms; flip angle = 90°; voxel size = 2,8125 × 2,8125 × 4 mm; matrix size = 448 × 448; number of slices = 38; thickness = 4 mm) using BOLD (blood oxygenation level dependent) contrast. Each fMRI session included two runs of 122 dynamics.

MRI data was acquired on a 1.5 Tesla Siemens Magnetom Avanto at Santa Maria Nascente Institute IRCCS, Don Carlo Gnocchi Foundation.

A conventional T2-weighted scan (TR = 2920 ms; TE = 108 ms; voxel size = 0,75 × 0,75 × 5,2 mm; matrix size = 320 × 320; slice thickness = 4 mm; number of slices = 25) was performed in every subject in order to exclude brain abnormalities. A 3D T1-weighted FFE scan (TR = 1900 ms; TE = 3.37 ms; voxel size = 1 × 1 × 1 mm; matrix size = 192 × 256; slice thickness = 1 mm; number of slices = 176) was acquired to be used as an anatomical reference for fMRI analysis and to compute hippocampal volumes on every subject.

3.1.2.2 Hippocampal segmentation

Bilateral hippocampi were segmented using a dedicated software (FSL-FIRST Patenaude et al, 2011). Brain tissue volume, normalized for subject head size, was estimated with SIENAX (Smith 2002), part of FSL (Smith 2004). An ANCOVA analysis was performed to compare hippocampal volumes between groups. The Scaling Factor, obtained using SIENAX, was included as a covariate in the analysis. Results were considered as statistically significant if surviving $p<.05$ with Bonferroni correction for multiple comparisons.

3.1.2.3 fMRI analysis

fMRI data was analyzed in agreement with the General Linear Model running on MATLAB 7.6 (MathWork, Natick, MA) and SPM12 (Wellcome Dept. Cogn. Neurol., London; http://www.fil.ion.ucl.ac. uk/spm). Images were first corrected for motion, then they were realigned and movement parameters were estimated. Anatomical and functional images were then spatially normalized to the MNI template using a 2 × 2 × 2 voxel size with a trilinear algorithm. The normalized functional images were spatially smoothed using a 8-mm full-width at half-maximum isotropic Gaussian kernel.

At the first-level, we modeled the expected hemodynamic response function of the software package with a block design. Six parameters related to head movement during scanning, were included as regressors of no interest. For each subject, we estimated two t-contrasts: observation of a hand grasping (O) and execution of grasping movements (M).

All contrasts defined in the First Level were included in the Second Level analysis of the three groups: NE, MCI and AD.

In order to identify MN areas active during both movement, observation and execution, we performed on each group a conjunction analysis, between O and M contrasts. We exclude from the analysis, voxels not active in both contrasts at a certain threshold. To this aim, we masked the conjunction analysis with voxels active in both contrasts used to perform the conjunction at a threshold of $p<.05$, as done elsewhere (Cabinio et al, 2010; Cerri et al., 2015). We also included in the model, age and MMSE value as nuisance covariates. With this analysis, we determined voxels active during both observation and execution of hand movements. The assumption is that neurons involved in the MN system are among those activated during both conditions. Thus, the conjunction analysis can be considered as a mask through which only those voxels that are significantly active in the two conditions are selected (O, M), even if they have different p values (provided that the p values are above the selected threshold). Moreover, one-way analysis of variance (ANOVA) was used to determine whether there were any significant differences between the three groups (NE, MCI, AD) in the single experimental conditions (O, M) including age and MMSE value as nuisance covariates in the GLM. F-Contrasts tested for the difference between the three groups and for mean activations in the entire sample. All these second-level results have been considered as statistically significant if surviving a threshold of $p<.05$ FWE-corrected with a $k=50$ contiguous voxels.

3.1.3 Neuropsychological assessment

The neuropsychological assessment was centered on functions considered to be linked to the MN system, such as language (particularly action naming; Kemmerer et al. 2012) and empathy; we also tested memory (as memory deficits characterize AD and aMCI) and attention/executive functions (abilities which are associated to frontal lobe functioning) (see Table 2 for test list). Subjects were all right-handed in according to the Edinburgh Handedness Inventory (Oldfield, 1971).

Table 2: List of Neuropsychological tests

Test	Acronym	Description	References
Mini Mental State Examination	MMSE	The most popular instrument to screen dementia and to quantify global cognitive level	Folstein et al., 1975 Measso et al., 1993
Free and Cued Selective Reminding Test Immediate Free Recall Immediate Total Recall Delayed Free Recall Delayed Total Recall Cueing Sensitivity Index	FCSRT FCRST-IFR FCRST-ITR FCRST-DFR FCRST-DTR FCRST-CSI	A test of verbal memory which controls for individual differences in attention and cognitive processing through a "controlled learning" study procedure in which the examinee searches for study items in response to a category cue. The category cues are then used to facilitate the recall of items not retrieved during a free recall test phase of the task. The FCSRT has been used to identify MCI, and distinguish AD from other types of dementia	Grober and Buschke, 1987 Frassoni et al., 2011
Phonemic Fluency	PF	Assessing the timed production of words after phonemic cues.	Novelli et al., 1996
Semantic Fluency	SF	Assessing the timed production of words after semantic cues.	Novelli et al., 1996
Trail Making Test Part A Part B	TMT TMT-A TMT-B	Assessing cognitive abilities such as visual scanning and visual-motor tracking (Part A), executive function, visuo-conceptual function, visuo-motor tracking and sustained attention (Part B)	Giovagnoli et al., 1996
Repeatable Battery for Assessment of Neuropsychological Status naming test	RBANS-N	The naming test taken from the Repeatable Battery for Assessment of Neuropsychological Status, a brief battery which measures immediate and delayed memory, attention, language, and visuospatial skills	Randolph et al., 1998 Ponteri et al., 2007
Revised Reading the Mind in the Eyes	RRME	Testing the ability of inferring others' mental states. Performance on this test correlates with an empathic personality	Baron-Cohen et al., 2001 Vellante et al., 2013
Action naming	AN	An ad-hoc task to test of action naming, a function considered to be linked to MN	Spada, 2012

3.2 RESULTS

3.2.1 HIPPOCAMPAL VOLUME MEASUREMENTS

The ANCOVA analysis showed statistically significant differences in bilateral hippocampal volume between the NE and the MCI groups, as well as between the Control and the AD groups. No volumetric differences were observed between the MCI and the AD groups. Differences were found in both Left and Right Hippocampi (see Tab. 3).

Table 3: Hippocampal (HP) volumetric comparison between the three groups

	2	3	1		
HP Volume	CTR	MCI	AD [MM+SdE		Post HOC (Bonferroni)
Left HP [MM, SdE]	3521.6542 [123,1601]	2872.3732 [126,4296]	2791.97 [125.35]	*p<001	1vs2 2vs3
Right HP	3718.7444 [111,7622]	3086.8005 [108,872]	2763.1426 [110,804]	*p<001	1vs2 2vs 3

MM= marginal mean
SdE= standard Error
NE= Normal Elderly people; MCI: Mild Cognitive Impairment; AD: Alzheimer Disease.

3.2.2. fMRI CONJUNCTION ANALYSIS

All subjects correctly performed the fMRI runs. Given the premise that regions included in the MN network must be activated both in movement execution and in movement observation, to identify cortical areas involved in this network we performed conjunction analysis between activation of the two conditions M and O. This analysis was carried out separately for the three groups of NE, MCI and AD subjects. All regions of significantly increased activation (pFWE<.05 at cluster level with K=50 contiguous voxels) are summarized in Table 4 and illustrated in Figure 42, each group separately.

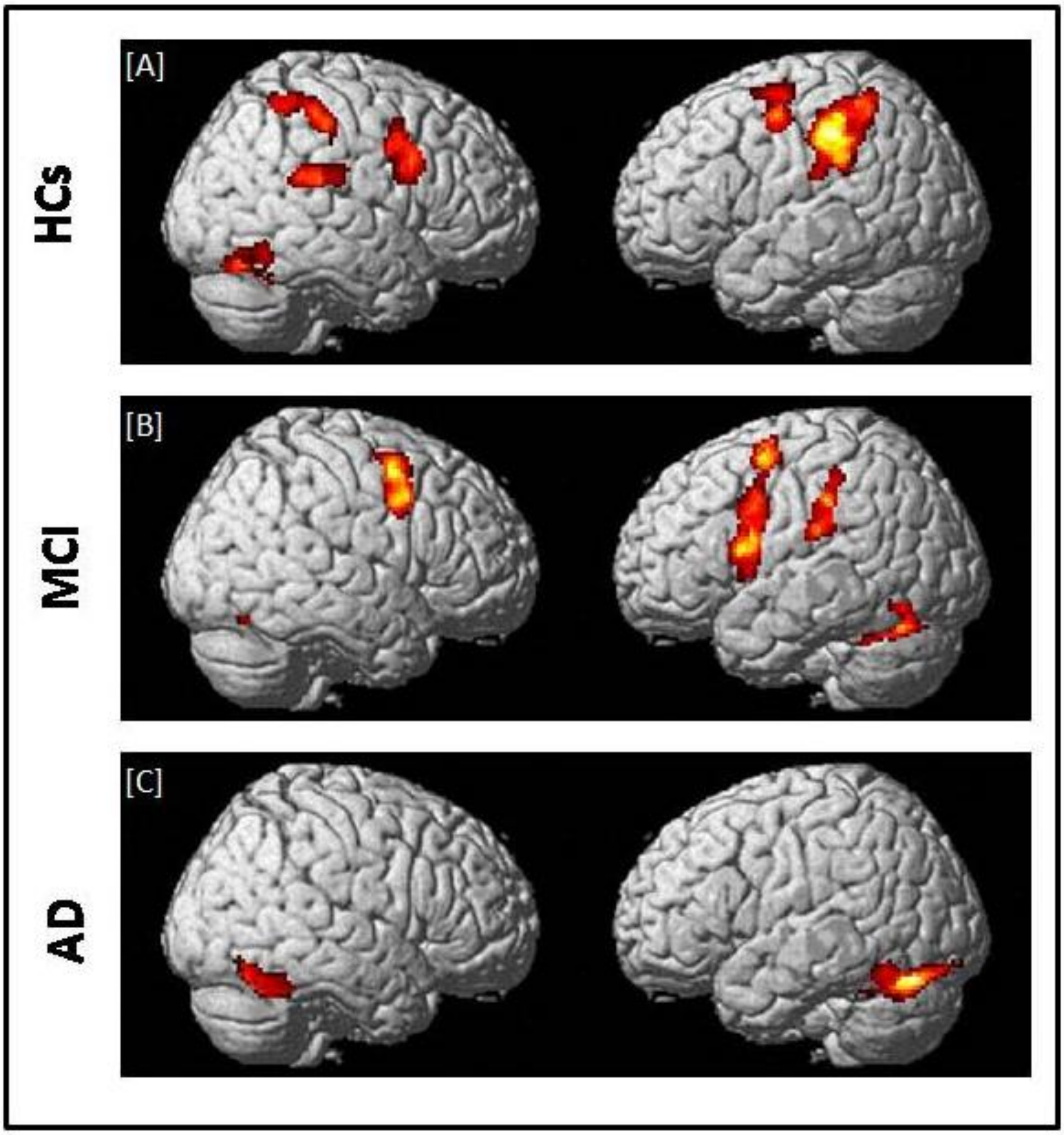

Figure 42: *Conjunction analysis (comparing fMRI activation during observation of transitive hand grasping and execution of grasping movements) results respectively, in NE, MCI and AD.*
[A] Normal elderly (NE) group; [B] Mild Cognitive Impairment (MCI) group [C] Alzheimer's Disease (AD) group [t contrast 3.41; k=50; pcluster(FWE-corr)<.05 only].

In NE subjects the conjunction analysis showed a statistical significant [t contrast 3.41; k=50; pcluster (FWE-corr)<.05] activation of the bilateral fronto-parietal network (left>righ side) formed by the frontal cortex (Precentral Gyrus, PrCG, BA6) and the parietal cortex (Inferior Parietal Lobule, IPL, BA40) along with activation of the right STG (BA22/42) and the right Fusiform Gyrus (FuG), In MCI subjects the same conjunction analysis [t contrast 3.41; k=50; pcluster(FWE-corr)<.05] revealed the activation of the frontal-parietal network (right<left side) including also the left Inferior Frontal Gyrus (IFG, BA44), but activation of BA40 was not as strong as in NE participants. A bilateral cerebellar activation was also detected. See Table 4.

Finally, in AD patients the conjunction analysis [t contrast 3.41; k=50; pcluster (FWE-corr)<.05] showed a statistical significance recruitment in the bilateral FuG and in the left cerebellum. It found no activations in the fronto-parietal network.

An additional analysis to investigate potential differences in brain activation between the three groups for the M or O condition was carried out separately, and did not reveal any significant group differences. The Figure 43 and Table 5 report the statistical results of the main effect in the O condition [ANOVA, F contrast 14.74; K=50; p(FWE-corr)<.05] and in the M condition [ANOVA, F contrast 13.48; k=50; p(FWE-corr)<.05].

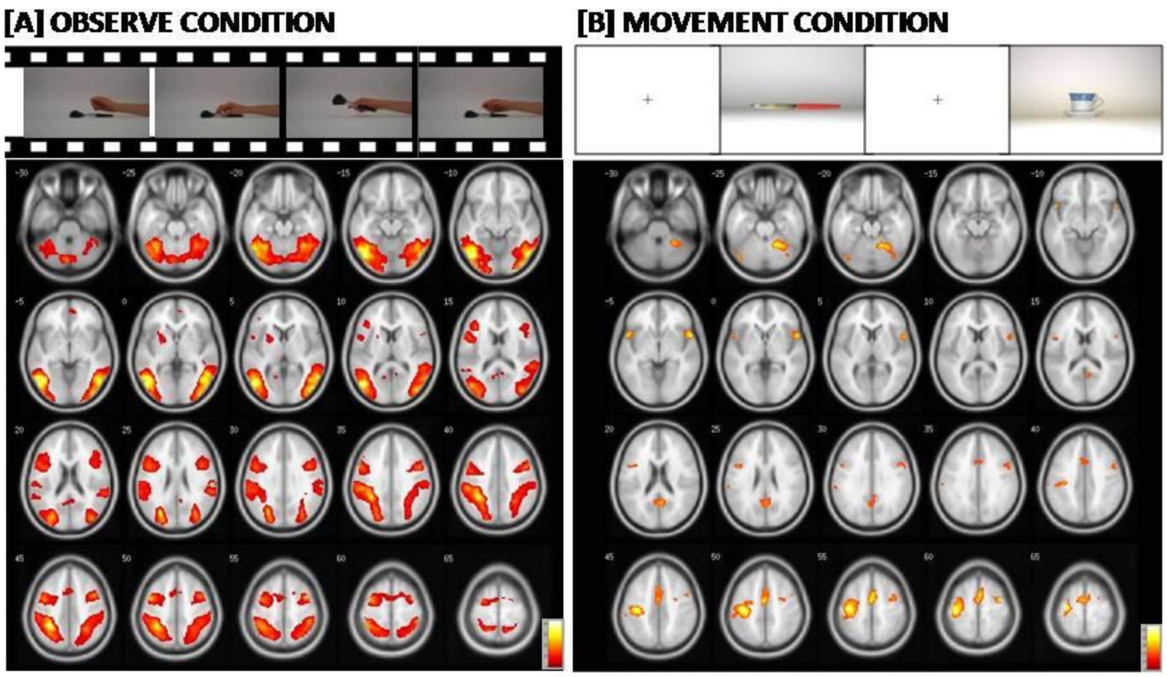

Figure 43: *At the left: Representation of the cerebral areas involved in the Observed condition versus the Rest condition in the three groups (NE, MCI and AD). At the right: Representation of the cerebral areas activated in the Movement condition versus the Rest condition in the three groups (NE, MCI and AD). In the Observed condition, visual areas are also highly activated.*
[Main effect of fMRI task: [left] Observed condition (F contrast 14.74; k=50; p(FWE-corr)<.05); [right] Movement condition (F contrast 13.48; k=50;p(FWE-corr)<.05)].

Table 4: Conjunction analysis results respectively, in NE, MCI and AD

cluster *[k]*	cluster level *p FWE-corr*	*p uncorr*	Z_score	coordinates *x,y,z [mm]*	Brain Region [BA]
[A] **NE**					
1719	0.000	0.000	5.48	-42 -36 42	L Inferior Parietal Lobule [40]
			5.14	-36 -38 48	
			4.75	-50 -30 42	
591	0.002	0.000	4.79	40 4 28	R Precentral Gy [9 /6]
			4.37	46 12 30	
			4.11	46 4 40	
383	0.013	0.002	4.73	50 -34 54	L Inferior Parietal Lobule [40]
			4.14	58 -28 48	
			3.81	40 -46 58	
361	0.017	0.002	4.54	-42 -6 50	L Precentral Gy [6]
			3.75	-32 -6 64	
			3.60	-32 2 62	
292	0.038	0.005	4.14	62 -40 22	R Inferior Parietal Lobule [40]
			4.06	68 -24 22	
			3.57	60 -32 20	
351	0.019	0.003	4.05	32 -54 -22	R Fusiform Gy
			4.04	60 -60 -14	
			4.03	38 -72 -20	
[B] **MCI**					
506	0.004	0.001	5.49	38 2 58	R Precentral Gy [6 / 9]
			5.08	46 4 36	
			4.06	44 2 46	
1060	0.000	0.000	5.03	-36 0 58	L Precentral Gy [6]
			4.47	-50 4 14	L Inferior Frontal Gy [44]
			4.41	-36 6 20	
271	0.047	0.007	4.50	30 -60 -18	R Cerebellum / Fusiform Gy
			4.19	28 -44 -24	
326	0.025	0.004	4.04	-52 -66 -14	L Middle Occipital Gyrus / Fusiform Gy
			4.02	-42 -70 -22	L Cerebellum
			3.99	-34 -52 -26	
332	0.023	0.003	4.00	-62 -28 26	L Inferior Parietal Lobule [40]
			3.78	-56 -24 22	
			3.53	-52 -34 48	
[C] **AD**					
831	0.000	0.000	5.16	36 -62 -18	R Fusiform Gyrus [37]
			4.45	44 -46 -20	
			4.34	44 -54 -24	
1222	0.000	0.000	4.91	-40 -72 -22	L Cerebellum
			4.75	-34 -48 -24	
			4.58	-30 -72 -20	L Fusiform Gyrus [37]

R = right; L = left; BA = Brodmann area; IFG: Inferior Frontal Gyrus; PrCG: Precentral Gyrus; IPL: Inferior Parietal Lobule; STG: Superior Temporal Gyrus; FuG: Fusiform Gyrus; MOG: Middle Occipital Gyrus; cbl: cerebellum; NE= Normal Elderly people; MCI= Mild Cognitive Impairment; AD= Alzheimer Disease. Coordinates are expressed in MNI space; statistical values refer to the conjunction analysis in [A] NE, [B] MCI, [C] AD [t contrast 3.41; k=50; pcluster (FWE-corr)<.05].

Table 5: Main effect of fMRI task in the Observe run and Movement run

cluster *[k]*	Z_score	coordinates *x,y,z [mm]*	Brain Region [BA]
OBSERVE vs REST			
7451	7.68	-42 -70 -12	L MTG / MOG
	7.58	-34 -44 46	L IPL [40]
	7.49	-46 -72 10	
3617	7.34	50 -68 -8	R MTG /MOG
	6.97	44 -64 2	
	6.96	58 -60 6	
549	6.83	38 2 58	R PrCG [9 / 6]
	6.13	40 6 48	
	5.86	46 4 40	
935	6.79	-44 0 50	L PrCG [9 / 6]
	6.33	-34 -2 60	
	5.80	-48 4 34	
736	6.20	44 -38 58	R IPL [40]
	5.96	28 -54 44	
	5.42	38 -50 56	
369	6.11	-4 -78 -34	L cbl
	5.61	8 -80 -36	R cbl
	5.43	-12 -76 -46	
MOVEMENT vs REST			
1670	7.11	-40 -20 54	L PrCG / PoCG [6 / 4]
	6.69	-32 -18 66	
	5.29	-56 -30 50	
350	6.64	54 14 -8	R IFG
600	6.52	18 -52 -22	R cbl
	5.24	38 -72 -22	
151	6.36	-50 16 -8	L IFG
1081	6.33	-2 -6 52	L SMA [6]
	6.12	2 6 58	
	5.75	-4 -6 66	
209	6.10	36 -6 60	R MFG [6]
	5.51	24 -2 64	
	5.03	28 -4 48	
65	5.86	-42 -72 -22	L cbl
396	5.66	4 -58 20	R PC [23]
	4.70	2 -44 30	
207	5.33	48 4 46	R PrCG [9 / 6]
	5.25	54 4 38	
	5.06	46 8 30	
52	5.28	-64 -26 24	L IPL [40]
	4.85	-62 -26 36	

R = right; L = left; BA = Brodmann area; MFG: Middle Frontal Gyrus; IFG: Inferior Frontal Gyrus; PrCG: Precentral Gyrus; PoCG: Post Central Gyrus; SMA: Supplemental Motor Area; PC: Posterior Cingulate; IPL: Inferior Parietal Lobule; MTG: Middle Temporal Gyrus; MOG: Middle Occipital Gyrus; cbl: cerebellum; NE= Normal Elderly people; MCI= Mild Cognitive Impairment; AD= Alzheimer Disease.
Coordinates are expressed in MNI space; statistical values refer to the main effect of Observe condition [ANOVA, F contrast 14.74; k=50] and Movement condition [ANOVA, F contrast 13.48; k=50], at statistical threshold voxel-wise pFWE-corrected<.05.

3.2.3 Neuropsychological tests

The results of AD patients were worse than NE subjects in all neuropsychological tests. These tests comprised tests of action naming and empathy, functions attributed to MN network. The only exception was the object naming test (probably due to a ceiling effect). aMCI subjects were significantly different from NE participants only in the episodic memory test, the FCRST, and in semantic fluency (see Table 6 for results) .

Table 6: Neuropsychological tests – Group comparison (ANOVA)

	NE	**MCI**	**AD**	**P §**	**Post hoc (Bonferroni)**	NE vs. MCI *	NE vs. AD *	MCI vs. AD *
#	16	16	16					
Age	73.8 ± 6.8	77.0 ± 4.8	77.2 ± 5.7	NS	–	*.544 (–.454 : 1.542)*	*.542 (– .456 : 1.54)*	*.038 (– .942 : – 1.018)*
Education	12.5 ± 3.3	11.1 ± 3.8	8.9 ± 4.5	.041	NE < AD	*– .393 (– 1.383 : . 596)*	*– .912 (– 1.942 : .117)*	*– .528 (– 1.525 : .469)*
MMSE	28.8 ± 0.9	27.0 ± 2.0	22.4 ± 3.5	< .001	NE>MCI>AD	**– 1.161 (– 2.22 : – .101)**	**– 2.505 (–3.813 : – 1.196)**	**– 1.614 (– 2.742 : – .485)**
FCSRT – IFR	29.0 ± 3.5	19.2 ± 6.0	10.3 ± 7.3	< .001	NE>MCI>AD	**– 1.195 (– 3.195 : – .796)**	**– 3.267 (– 4.764: – 1.77)**	**– 1.332 (– 2.415 : – .249)**
FCSRT – ITR	36.0 ± .0	34.9 ± 2.0	27.2 ± 7.5	< .001	NE>AD, MCI>AD	*– .778 (–1.794 : .239)*	**– 1.659 (–2.796 : – .523)**	**– 1.403 (–2.497 : – .309)**
FCSRT – DFR	9.8 ± 1.7	5.9 ± 3.3	2.9 ± 3.2	< .001	NE>MCI>AD	**– 1.486 (–2.593 : – .379)**	**– 2.693 (–4.046 : – 1.34)**	*– .923 (– 1.954 : .108)*
FCSRT – DTR	11.9 ± .5	10.7 ± 2.4	7.3 ± 3.6	< .001	NE>AD, MCI>AD	*– .692 (– 1.701 : .317)*	**– 1.79 (– 2.95 : – 0.63)**	**– 1.111 (– 2.164 : – .058)**
FCSRT – CSI	1.0 ± .0	.94 ± .09	.68 ± .25	< .001	NE>AD, MCI>AD	*– .943 (– 1.976 : .09)*	**– 1.81 (– 2.974 : – .647)**	**–1.384 (– 2.475 : – .293)**
PF	37.9 ± 9.6	31.8 ± 9.6	20.4 ± 7.0	< .001	NE>AD, MCI>AD	*– .635 (– 1.64 : .369)*	**– 2.131 (– 3.358 : – .904)**	**– 1.405 (– 2.499 : – .31)**
SF	39.6 ± 10.4	31.7 ± 9.2	17.6 ± 5.7	< .001	NE>MCI>AD	*– .805 (– 1.823 : .214)*	**– 2.623 (– 3.96 : – 1.287)**	**– 1.842 (– 3.012 : – .673)**
TMT-A	45.2 ± 19.3	53.0 ± 14.6	88.4 ± 43.0	< .001	NE<AD, MCI<AD	*.456 (– .537 : 1.448)*	**1.296 (.218 : 2.374)**	**1.102 (.051 : 2.154)**
TMT-B	95.6 ± 48.3	175.9 ± 106.6	391.1 ± 148.1	< .001	NE<AD, MCI<AD	*.97 (– .066 : 2.006)*	**2.683 (1.332 : 4.033)**	**1.668 (.53 : 2.806)**
RBANS-N	10.0 ± .0	9.7 ± .9	8.8 ± 1.8	.019	NE>AD	*– .471 (– 1.465 : .522)*	*– .943 (– 1.976 : .09)*	*– .632 (– 1.637 : .372)*
RRME	21.3 ± 4.0	18.4 ± 4.9	12.2 ± 4.7	< .001	NE>AD, MCI>AD	*– .648 (– 1.654 : .357)*	**– 2.085 (– 3.303 : – .868)**	**– 1.291 (– 2.369 : – .214)**
AN	35.3 ± 3.6	31.6 ± 4.7	22.8 ± 6.4	< .001	NE>AD, MCI>AD	*– .884 (– 1.911 : .143)*	**– 2.407 (–3.694 : – 1.12)**	**– 1.567 (– 2.688 : – .447)**

§ *ANOVA (non parametric tests -Kruskal – Wallis- give the same results.)*
* *Effect size (Cohen's d – 95% CI): < .2: no effect; .2 to .5: small effect; .5 to .8: intermediate effect; .8 and higher: strong effect*
For test acronyms, see Table 2.

CHAPTER 4 – GENERAL DISCUSSION

We investigated the integrity of MN areas through fMRI in three groups: NE subjects, people with aMCI and AD patients. We detected differences among the 3 groups, suggesting a progressive weakening of the MN network with respect to neurodegenerative process. These differences are discussed in the following sections.

4.1 Mirror Neurons network alteration

In the NE group, the conjunction analysis (fMRI activation recorded during observation of hand grasping compared to overt execution of grasping movements) showed the activation of a bilateral, though strongly left-lateralized, fronto-parietal network (PrCG, BA6; IPL, BA40). The fronto-parietal network activated in our study is considered part of the human MN network (Rizzolatti and Craighero, 2004), given the established homology between the BA6 (human) and the ventral premotor cortex (monkey), the BA40 (human) and PF-PFG (monkey) parietal cortex (Cook et al., 2014). We also found activation of the STG (BA22/42) considered an area which is strongly associated with activation of MN in humans (Aziz-Zadeh et al., 2006).

fMRI and neurophysiological investigations aimed to study the MN network in human were mostly performed on young or adult subjects. We found that the MN network is largely preserved in aging. Our results are in accordance with those of Léonard and Tremblay (2007), who analyzed corticomotor facilitation associated with observation, imagery and imitation of hand actions in younger and older adults by monitoring changes of MEPs elicited in hand muscles by TMS. They found that corticomotor facilitation in association with covert action execution was largely preserved with aging, although with a loss in selectivity for activated muscles. Unlike the original study of Cabinio et al. (2010), in this study (where we exactly replicated their procedure), we noted a loss of selectivity, as the activation of mirror areas was more bi-lateralized than in the younger subjects. This could be explained by a specific mode of brain activation in aging. In fact, fMRI recording in younger, middle-aged and older participants performing the same unilateral hand movements (Fang et al., 2005) showed stronger premotor/motor cortex activity in the contralateral hemisphere in the “older” group when compared to the younger and middle-aged groups. Therefore, together with other authors, we concluded that the older brain requires larger areas to achieve the same task (Fang et al., 2005; Chow et al., 2017), a hypothesis that could also explain the results obtained during a task inducing a motor resonance mechanism (Rizzolatti 2005). In order to exclude any bias, due to differences in the scanners, it would be worthwhile recruiting a subject pool from our center to definitively confirm the data.

Concerning the MCI subjects, we found a different pattern at the conjunction analysis in comparison with the NE subjects. The MCI and the NE groups showed similar activation of frontal and parietal areas. However, in the MCI group the left IPL (parietal BA40) was activated at a lesser extent than in the NE group and neither the right IPL nor the STG (BA22/42) were activated. Moreover, only the MCI participants exhibited activation of the left frontal area IFG-BA44. Therefore, even if the MN network is preserved in MCI, it is mainly recorded towards frontal areas. This suggests a greater resilience to the aging process of the MN areas located in the anterior part of the brain versus posterior areas, and maybe consecutively the capacity of these areas to take on a part of the "work" done by the posterior MN regions. Interestingly, we did not observe any activation of the fronto-parietal network in AD participants. Altogether, our results suggest that the MN network is progressively affected in neurodegenerative cognitive decline following a posterior-anterior gradient. The hypothesis of a posterior-anterior decay in Alzheimer-type degeneration agrees with recent data obtained in MCI using EEG and MRI recording (Moretti, 2016). In this investigation, alpha3/alpha2 frequency power ratio, considered as a predictor of conversion into AD (Moretti et al., 2011) as well as cortical thickness at MRI were computed. Three MCI groups were obtained considering increasing tertile values of alpha3/alpha2 ratio. From this morphological MRI and EEG parameter data the author inferred that MN are impaired in prodromal AD. Conversely, we directly measured the activation of human MN with a specific fMRI task, thus giving a functional support to the hypothesis for the MCI and the AD group.

4.2 Cognitive impairment, Mirror Neurons and neurodegenerative processes

The lack of any activation in "classical" mirror areas in AD is a new result. If other studies confirmed these results, it might be speculated that the degeneration of the MN network is somehow involved in the typical language, praxis and visuospatial dysfunction recorded in AD. This possibility is supported by the damage of hand and eye-derived treatment of information (e.g. ideomotor apraxia, visuospatial deficit and agnosia) associated to frontal degeneration (Futamura & Kawamura, 2014; Pisella et al., 2006) and the related "embodied semantics" theory stating that propose that humans use sensorimotor systems in processing language (Pulvermüller, 2013). Otherwise, frontal and parietal regions are also recurrently associated to memory. Maturation of prefrontal cortex would determine the development of episodic memory during middle childhood and beyond, in addition to the ability to monitor and manipulate information (Ghetti & Bunge, 2012). It is also known that prefrontal cortex is tightly linked to hyppocampal formation where novel associations are formed (Ghetti & Bunge, 2012). Further, parietal areas belonging to human MN network (particularly BA40) have a role in memory retrieval (Shannon & Buckner, 2004). Remarkably, Nelson et al (2010) have divided the left lateral posterior parietal cortex into 6 subregions as a function of resting-state functional connectivity profiles, as well as their episodic memory activation profiles. Among these regions, the left intraparietal sulcus area and the left anterior IPL (MN areas) exhibited retrieval success effects. In the same vein, these areas are functionally connected with portions of the lateral prefrontal cortex that are implicated in episodic memory (Nelson et al., 2010; Seghier, 2013). All these experimental evidences agree with the idea that an alteration of MN network can affect memory performance in AD. A possible explanation of this alteration is the 'last-developed-first-atrophied' principle (Di Patre, 1991; Jacobs et al., 2011), since prefrontal and inferior parietal areas are phylogenetically and ontogenetically the last to develop. The "retrogenesis hypothesis"(Reisberg et al., 1999) also postulate that late-myelinated white matter fibers are most vulnerable to age and disease-related degeneration, which in turn mediate cognitive decline (Brickman et al., 2012; Braak & Del Tredici, 2013; Alves et al., 2015).

Neuropsychological tests exploring cognitive functions considered to be tightly linked to MN system (language and empathy) were normal in aMCI subjects. The preservation and may be hyperactivation of the anterior MN network seen in aMCI might supplement the initial decay of the posterior part of the neural circuit thus preserving their cognitive performance. The only "language" test impaired in aMCI was semantic fluency, but this impairment could be due to a semantic memory damage rather than a true language impairment. As an alternative explanation, the preservation/hyperactivation of the anterior MN network could not be sufficient to support performance in this kind of task because it is highly dependent from parietal areas (Seghier, 2013). In contrast, in AD group MN network appears to be deficient and task performance in both language and empathy tests decays.

While unexpected, the present results also raise other questions. How to explain the cerebellar activation recorded in AD patients and to a lesser extent in MCI subjects? Based on models incorporating the MN system in social learning, the STG-IPL-IFG circuit would create the motor representation available for imitation, starting with the visual input (Iacoboni et al., 1999; Oh et al., 2012). During the imitation phase, the overall processes are equivalent to those of the observation phase, the only difference is that, in parallel with the IFG to the IPL pathway, neural drive is sent to the musculoskeletal system through M1 to perform the action (Oh et al., 2012; Bassolino et al., 2013). It has been suggested that the cerebellum provides the prediction error for the IFG and the IPL to adjust internal models (Miall, 2003; Oh et al., 2012). In this context, the AD patient activation of cerebellar neurons involved in the MN network would correspond to an attempt to compensate for damage of prefrontal and parietal areas. This mechanism would already be present in aMCI. The activation of the cerebellum as a substitute of cerebral cortex alteration has also been suggested to enhance motor control and motor learning in functional recovery from a stroke following mirror therapy (Arya, 2016). In conclusion, cerebellar activation in AD might simply reflect the response of this neural structure to visual inputs during guided limb movements (Liu et al., 2003)

4.3 Clinical implications and limitations

The alteration of the MN motor circuitry in AD patients raises an interesting question related to the link between action and cognition and supports an interesting direction of research. Precisely, it allows the interpretation of AD – as other neurodegenerative diseases (Bak, 2013; Eisen et al., 2014) in the light of the action-perception coupling hypothesis, which postulates that a part of cognition results from the coupling between action and perception representations, and corresponds to implicit action simulation (or "motor resonance") instead of explicit recall of abstract symbols (Jeannerod, 1994, 2001, 2006; Jeannerod et al., 1995; Braitenberg & Schüz, 1998; Boulenger et al., 2008; Pulvermüller and Fadiga, 2010). As we have already noted, the preservation and maybe hyperactivation of the anterior MN network in aMCI might supplement the initial decay of the posterior part of the neural circuit, thus preserving cognitive performance. In contrast, in the AD group the MN network appears to be deficient and cognitive performance deteriorates.

The present study is limited by several factors: the number of subjects tested and the spatial and temporal resolution of our measurements (see Oosterhof et al., 2011 and 2013; Möhring et al., 2014; Thibault and Raz, 2016); the fact that in the execution condition the hand movements were only visually controlled by the examiner. In particular, our results should now be replicated in AD/MCI population on the basis of data collected with different methods dedicated to record MN activity, as MEPs induced by TMS (Gangitano et al., 2004; Fadiga et al, 2005), or the reduction of magnitude (desynchronization) of the µ rhythm at EEG (Fox et al., 2016 for a review). Neurophysiological techniques are easier to perform in people affected by neurodegenerative diseases and allow a better time resolution. Researches studying the MN network in PD and FTD/ALS would be also of interest. Furthermore, we have studied task-evoked neural activity during action observation and execution. Schilbach et al. (2016), in a recent study, demonstrated differential patterns of dysconnectivity in MN and mentalizing networks in schizophrenia. Further research, therefore, needs to investigate functional organization of self-related brain networks during a "resting state". This clinically available measure of functional connectivity could provide further knowledge of alterations of neuro-functional systems in AD and support our findings of MN network dysfunction.

The results of our study have possible implications in rehabilitation. As we have seen in a previous paragraph, the use of AOT as a supplementary therapeutic tool for patients who have had strokes, to stimulate brain plasticity and obtain positive functional results, was reported (Carvalho et al, 2013). This has been extended to motor deficits in children with Cerebral Palsy (Sgandurra et al., 2011; Buccino et al., 2012; Bassolino et al., 2015) and patients with PD (Buccino et al., 2011). The concept of motor cognition, if verified, would provide a clinical support to cognitive stimulation based on the motor resonance mechanism. However, the efficiency of such training is only conceivable if the MN system remains partly achievable. So far, the only published research of this kind of cognitive training via the stimulation of the MN in people with AD, showed improvements in attention and facial recognition (Eggermont et al, 2009) whereas another research showed negative results (Caffarra P, 2016, oral communication at XI Sindem National Congress, Florence, Italy). However, this last study did not test MN system integrity that is supposed to be stimulated in the training program. As our data showed a malfunction in the MN network in the case of AD, our study explains why that intervention obtained negative results. A rehabilitative intervention based on the MN system would be better implemented at the predementia phase.

In general, AOT might be a powerful tool to improve motor, language and/or social cognition deficits in people with neurodegenerative diseases. The possibility to exploit the motor resonance to stimulate cognitive function in this frame appears fascinating because it represents a potential therapeutic solution that does not exist yet: specific drugs have not still been approved for the MCI phase and pharmacotherapy effects are extremely limited in AD (Raina et al., 2008; Petersen et al., 2017); cognitive stimulation and serious game trainings have positive but limited effects (Woods et al., 2012; Hill et al., 2017, Manera et al., 2017) probably because of training performed in artificial environment developing specific skills not transferable to daily normal life activities. No substantial pharmacological therapy is available for ALS/FTD. Even in PD, where various drugs are available, they have only symptomatic effects and do not avoid progression of the motor and cognitive impairment. Other advantages of a rehabilitative treatment based on motor cognition are the fact that it promotes an active involvement of the patient in her/his recovery process instead of rendering him/her a passive medicine consumer and the large possibility to easily personalize the training.

Finally, protocols based on motor cognition, easy and cheap to implement, and less risky than pharmacotherapy, might have a strong impact on prevention of neurodegenerative diseases in the growing elderly population, a very interesting perspective from the public health point of view. As usual in neurodegeneration, a preventive intervention could in fact be far more effective than an intervention applied in the overt phase of the disease. This view is supported both from data coming from PD studies (Anders et al., 2012), recent data on the MCI/AD spectrum (Moretti, 2016; Vallet et al., 2017) and our own study.

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APPENDIX

Appendix: Table 1a: Summary of experimental studies investigating embodied cognition and/or mirror neurons in Parkinson Disease - Neurophysiological studies					
(PD: Parkinson Disease; AOT: Action Observation Training; EEG: Electroencephalography; MEP: Motor Evoked Potentials; TMS: Transcranial Magnetic Stimulation; DBS: Deep Brain Stimulation)					
Authors	**Participants**	**Medication**	**Methods**	**Experimental details**	**Principal findings**
Alegre et al., 2010	18 PD patients, with surgically implanted electrodes for DBS	ON and OFF states	EEG and local field potentials recording through surgically implanted electrodes for DBS	Oscillatory changes in electrical activities were recorded during movement execution (right wrist extensions), AOT (left wrist extension movements by an investigator seated in front of the patient) and two control conditions (simple stimulus-yellow squares- and rotating stimulus observation on a screen)	AOT (as movement execution) was associated to a bilateral reduction of subthalamic power in the beta range. The effect was present in both on and off state, even if higher in the first one. In the EEG channels, the pattern observed in the beta band was parallel to that observed in the subthalamic nucleus
Marceglia et al., 2009	8 PD patients, with surgically implanted electrodes for DBS	OFF state	Subthalamic nucleus local field through surgically implanted electrodes for DBS potential recordings	Local field potentials were recorded while movies of action (grasping a green ball with the left of the right hand) or static images were displayed on a personal computer monitor; static images of stimuli related and unrelated to the grasping were also presented	High-beta oscillations (20–30 Hz) synchronized both during the observation of action and action-related objects
Heida et al., 2014	9 patients with PD at a Hoehn and Yahr stage of I or II and 11 age-matched controls	Patients on their usual medication	EEG recordings while performing AOT	During each of 6 trial, subjects watched a video consisting of eight fragments showing hand movements interspersed with seven baseline fragments. Presented hand actions were randomly executed with left or right hand.	μ-rhythm desynchronization classically recorded during movement observation was impaired in patients with early PD
Tremblay et al., 2007	11 PD patients and 11 healthy elderly controls	ON state	Recording MEP amplitudes at the first dorsal interosseous and abductor digiti minimi of the right hand	MEP amplitudes were recorded in four conditions: rest, AOT (a video depicting a hand cutting a piece of paper with scissors), motor imagery and active action imitation. In each presentation,MEPs were recorded by delivering TMS at a pre-determined delay (7 s) in the video sequence.	The MEP amplitude increased in PD patients during active imitation (compared to resting state) but neither during AOT nor during action imagery.
Gündüz et al., 2015	Eight idiopathic PD patients with apraxia, 11 idiopathic PD patients without apraxia, and 8 healthy subjects (control group)	Patients were at their optimal dopaminergic response	Recording F-waves and MEPs bilaterally at abductor policis brevis	F-waves and MEPs were recorded during 4 states (resting, imagination, observation, and active movement: abduction with the abductor policis brevis). For F-waves, the median nerve was stimulated at the wrist. The MEP recordings were performed using the minimum TMS intensity required to evoke a 1 mV amplitude response.	Normal facilitation of MEP amplitudes by mental imagery and active movements in normal controls and non-apraxic PD patients. The same was true for F-wave amplitudes over the dominant upper extremity during mental imagery, observation and active movements.This facilitation was lost in apraxic PD patients.

Appendix: Table 1b: Summary of experimental studies investigating embodied cognition and/or mirror neurons in Parkinson Disease - fMRI studies					
(PD: Parkinson Disease; AOT: Action Observation Training)					
Authors	**Participants**	**Medication**	**Methods**	**Experimental details**	**Principal findings**
Anders et al., 2012	8 pre-symptomatic carriers of a single mutant Parkin gene, with a slight but significant reduction of dopamine metabolism in the basal ganglia and 8 age- and sex-matched healthy controls	None	Participants performed fMRI while observing neutral and affective dynamic facial expressions and performed a facial emotion recognition task	Three types of gestures were selected: 'smile','kiss', and 'neutral' for a total of 72 video clips. In addition, a scrambled version was produced of each clip. Participants were instructed to execute a facial gesture ('do') whenever they saw a scrambled video and to attentively watch the actor('view') whenever they saw an unscrambled video .To measure the participants' ability to decode emotions from facial expressions, a set of facial stimuli taken from the Facial Expression of Emotions: Stimuli and Test was used.	Participants showed significant stronger activity in the right ventrolateral premotor cortex during execution and perception of affective facial gestures than healthy controls. They also showed a slightly reduced ability to recognize facial emotions that was inversely proportional to the increase of ventrolateral premotor activity.
Pohl et al., 2017	14 PD patients and 13 age-matched controls	ON state	Participants performed fMRI while observing neutral and affective dynamic facial expressions and performed a facial emotion recognition task.	See Anders et al., 2012	Patients performed slightly worse in the emotion recognition task, but only for the most difficult expressions to be interpreted. Inferior frontal and anterior inferior parietal "mirror neuron" areas activated during observation and execution of the emotional expressions in both groups, but at a lesser extent in PD patients. Activation of the right anterior inferior parietal lobule positively correlated to patients' emotion recognition ability.
Péran et al., 2009	14 right-handed PD patients	ON state	Exploring fMRI cortical activities during the generation of action-verbs, compared to object naming.	The fMRI experiment consisted of two tasks in which the same set of object drawings was used: in the first task subjects were asked to name aloud objects drawings; in the second task subjects had to orally produce a verb denoting an action that could be performed with the object depicted. Manipulable objects were selected from Snodgrass and Vaderwart normalized data set.	Data showed the involvement of an extended cortical network during action-verb generation, with differences from the object name generation located above all in the premotor and prefrontal cortices.
Péran et al., 2013	10 PD patients	ON and OFF states	Exploring fMRI cortical activities during the generation of action-verbs, compared to object naming and to mental simulation of actions	The fMRI experiment consisted of 3 tasks: subjects were asked 1) to name aloud objects drawings, 2) to orally produce a verb denoting an action that could be performed with the object depicted, and 3) to mentally simulated the action related to the object. The Snodgrass and Vaderwart normalized data set was again used.	Compared to object naming, action naming generated greater activation of the left prefrontal cortex and the left medial precuneus. Mental simulation of actions generated greater activation of prefrontal cortex and occipito-parietal junction bilaterally. Motor, premotor and prefrontal regions were more activated in the ON than in the OFF state.
Abrevaya et al., 2017	17 PD patients and 15 healthy controls	ON State	Exploring fMRI cortical activities during listening of action verbs and nouns	Participants carried out two fMRI single-word processing studies. In the Noun Study, participants listened to concrete, non-graspable entities (n = 147). In the Action verb Study, stimuli consisted of infinitive verbs(n = 150) denoting bodily movements	The verb lexical category elicited connectivity between primary motor areas and anterior areas (implied in action observation and imitation), in normal controls, while activated posterior areas in PD patients.

Appendix: Table 1c: Summary of studies investigating embodied cognition and /or mirror neurons in Parkinson Disease - Behavioral studies					
(PD= Parkinson Disease; SCE: Spatial Compatibility Effect)					
Authors	**Participants**	**Medication**	**Methods**	**Experimental details**	**Principal findings**
Poliakoff et al., 2006	24 mild to moderate PD patients (21 right handed) and 21 age-matched healthy controls (20 right handed) .	Patients on their usual medication	Measuring the effect of movement-relevant visual stimuli (graspable door handles and finger movements) on reaction times. Evaluation of the SCE, that is faster reaction times when the response hand and the stimulus direction are compatible. Bars and object movements represented the control condition.	In a first experiment, participants had to classify visual stimuli (bar and door handles) according to shape and orientation. In a second experiment, the two groups observed video clips of finger or object movements and had to respond as quickly as possible if an X appeared at the end.	First experiment: no difference in the overall reaction times for patients and controls: however, while the SCE was larger in the handle than in the bar condition for controls, this was not true for PD patients. Second experiment: Both patients and normal participants reduced significantly their reaction times after observing finger compared to objects movements. However, parkinsonians showed a SCE only for non living object movements.
Albert et al., 2010	Ten patients with PD and ten neurologically age-matched unimpaired control participants	OFF state	Studying the effect of an interference task on movement accuracy	Subjects performed horizontal and vertical right arm movements, in phase with a stimulus displayed on a video screen. The stimulus was represented by a person, or by a moving dot performing similar movements in the same-congruent- or orthogonal-incongruent- plane	No difference between healthy controls and PD patients
Castiello et al., 2009	16 patients with PD and 16 neurologically age-matched normal control participants	Patients were at their optimal dopaminergic response. No significant motor complications	Kinematic study to test whether PD patients' imitation ability showed kinematic facilitation effects (shorter movement duration and anticipation of the time at which peak velocity occurred) by observing either a PD or a neurologically healthy model grasping an object	Participants observed either a PD or a neurologically healthy model grasping an object. Subsequently, they were requested to perform a grasping action towards the same object. Two control conditions. In the first, the model performed a kicking rather than a grasping action with the right foot. For the second, the model was standing behind the object without performing a grasping action	Differently than normal controls, PD patients' showed kinematic facilitation effects in their imitation ability only when the model was a Parkinsonian patient in contrast to a healthy model
Jaywant et al., 2006b	26 non-demented individuals with PD and 24 normal control participants matched for age, education, and male:female ratio	ON state	Testing the ability of PD patients to perceive and recognize human motion with limited visual attributes (a point-light walker)	Participants viewed videos of point-light walkers and scrambled versions that served as foils, and indicated whether each video depicted a human walking. Point-light walkers varied by gait type (natural, parkinsonian) and speed. Participants also completed control tasks (object motion, coherent motion perception), a contrast sensitivity assessment, and a walking assessment	Persons with PD showed a reduced visual sensitivity to biological motion, regardless of stimulus gait type or speed, with a less substantial deficit in object motion perception.
Jaywant et al., 2006c	23 individuals with PD and 24 normal controls matched for age and education level.	ON state	Testing the ability of PD patients to discriminating between communicative and non-communicative gestures, and in describing communicative gestures with limited visual attributes (point-light figures)	Participants viewed point-light human figures that conveyed gestures made with the arms, hands, and fingers. The stimuli were composed of 23 white point-lights on a black background. The point-lights depicted gestures that were either communicative ones with commonly accepted meanings, or non-communicative – instrumental pantomimes.	Patients were impaired, relatively to normal controls, in describing the meaning of non-communicative gestures, while they normally perceived communicative gestures as a group. Men were compromised in describing both types of gestures.

Appendix: Table 1d: Summary of experimental studies investigating embodied cognition and /or mirror neurons in Parkinson Disease - Neuropsychological studies					
(PD:Parkinson Disease; MMSE: Mini Mental State Examination; MCI: Mild Cognitive Impairment; BDAE: Boston Diagnostic Aphasia Examination; RME: Reading the Mind in the Eyes test; ToM: Theory of Mind; DBS: Deep Brain Stimulation: ACE: Action-sentence Compatibility Effect).					
For a detailed list of publications on this topic refer to the reviews by Cardona et. al. (2013), Silva et al. (2014) and Birba et al. (2017).					
Authors	**Participants**	**Medication**	**Methods**	**Experimental details**	**Principal findings**
Boulenger et al., 2008	10 PD patients and 10 normal controls matched for age, gender, education and socio-economic status	ON and OFF states	A masked repetition priming experiment with a lexical decision task	Participants had to judge whether a letter string was either a real word or a non-word. The real words were either action verbs or object nouns, and were preceded by masked stimuli that were either consonant strings or the same real words that were used for lexical decision	In the off condition masked priming effects for action words were nearly absent in PD patients, while robust priming effects were observed for concrete nouns. In the on condition, priming effects for action verbs restored and appeared as strong as for concrete nouns, and comparable to those of healthy controls
Silva et al., 2017	First Experiment: 19 patients with Parkinson's disease without dementia. Second Experiment: 21 PD patients Thirteen of these patients participated in Experiment 1. For Both: 42 education and age matched controls.	Patients on their usual medication	Evaluation of action and object lexical semantic processing through three different tasks (verbal fluency, naming and semantic association)	In the first Experiment, participants had to perform verbal fluencies for verbs (action fluency) and for nouns, naming tasks for verbs and for nouns. In the second Experiment, participants performed semantic association tasks for verbs and nouns	PD patients presented worse performance in naming actions and in the two semantic association tasks (action/object). Action verbal fluency performance was significantly associated with PD severity whereas object semantic association deficits and noun verbal fluency scores were associated to lower scores in measures of global cognitive functioning
Fernandino et al., 2013	20 PD patients without dementia and 20 age-matched controls	17 PD patients in ON state; 2 in OFF state. One patient still without medication	Administering a semantic similarity judgment task about action and abstract verbs	Judgement of sentences containing action verbs used with literal and figurative meaning (non-idiomatic metaphoric action, idiomatic action); control condition with abstract sentences. Conditions matched for sentence lenght, response times and accuracy in lexical decision for the content words in the sentence.	Compared to healthy controls, PD patients showed longer reaction times for literal and idiomatic action sentences. Parkinsonians showed also a tendency to be less accurate at judging metaphoric action verbs
Kemmerer et al., 2013	10 PD patients without dementia and 10 healthy controls	ON and OFF states	Similarity judgment of four classes of action verbs and two classes of non action verbs	The four classes of action verbs were running, hitting, cutting and speaking; the two classes of non action verbs were change of state and emotional states. Verbs were similar in frequency and letter lenght (with the exception of verbs of emotional states which had more letters than others)	In PD patients judgments were (except for "cutting" verbs) as accurate as controls for both types of verbs. However, they were slower, both in the on and off condition

Appendix: Table 1d: Summary of experimental studies investigating embodied cognition and /or mirror neurons in Parkinson Disease - Neuropsychological studies *Following*

Silva et al., 2015	19 patients with PD without dementia and 64 matched controls with (similar age, education level, economic status and performance at MMSE)	Not specified	Semantic memory tests that do not involve verbal response and assess the understanding of actions and nouns	The Kissing and Dancing Test for actions and the Camels and Cactus Test for nouns were used	Patients performed worse compared to controls in both the semantic association tasks, but semantic deficits were more pronounced in verbs than nouns.
García et al., 2018	40 PD patients with and without mild cognitive impairment (PD-MCI: 16 and PD-nMCI: 24, respectively) and matched controls for each group.	ON state	Evaluating difficulties in processing units which denote bodily movements, for meanings evoked by context-rich narratives	Participants read two naturalistic stories (an action text and a neutral text) and responded to questions tapping the appraisal of verb-related and circumstantial information	In PD-MCI, impairments in the appraisal of action meanings were independent from general cognitive dysfunction. In PD-non MCI, deficits were observed only for action meanings. A deficit in the appraisal of action meanings evoked by naturalistic tests was able to distinguish between normal controls and non -MCI PD patients from PD-MCI
García et al., 2017	33 sporadic PD patients, 8 genetic PD patients with PARK2 (parkin) or LRRK2 (dardarin) mutation, 9 asymptomatic first-degree relatives of the latter, socio-demographically matched controls	ON state	Evaluating semantic representation of objects and actions plus general assessment of cognitive functions	Semantic representation of objects and actions was assessed through the Pyramids and Palm Trees test and the Kissing and Dancing Test, respectively; action-verb processing was also assessed through the Action Naming subtest of the BDAE. Syntactic comprehension was assessed with two BDAE subtests: Embedded Sentences and Touching A with B	The two clinical groups showed impairments in all measures. Asymptomatic mutation carriers showed deficits in a syntactic test of actions involving the verb "to touch"
Ibañez et al., 2013	17 early Parkinson's disease patients and 15 normal matched volunteers. Epileptic patients with direct electrocorticography recordings	ON state	Investiganting the ACE	Participants listened to sentences that implied an action with the hand in a particular shape (open, or closed) as well as neutral sentences that did not imply an action with the hand. Participants indicated as quickly as possible when they understood each sentence by pressing a button using a preassigned hand-shape (open or closed). They also completed the Kissing and Dancing Test	PD participants showed a much diminished ACE relative to normal volunteers. Moreover, a correlation between ACE performance and action-verb processing was observed
Cardona et al., 2014	3 patient groups: early Parkinson's disease (15 patients), neuromyelitis optica (10) and acute transverse myelitis patients (10), healthy controls	ON state	Investiganting the ACE	The subjects were seated facing a computer screen. They listened to 52 sentences conveying open-hand actions, 52 sentences conveying closed-hand actions, and 52 neutral sentences that did not convey manual actions. Participants indicated as quickly as possible when they understood each sentence by pressing a button using a pre-assigned hand-shape (open or closed). All responses were performed with the dominant hand	Early PD patients exhibited impaired ACE and verbal processing relative to healthy participants, and neuromyelitis optica and acute transverse myelitis patients.

Appendix: Table 1d: Summary of experimental studies investigating embodied cognition and /or mirror neurons in Parkinson Disease - Neuropsychological studies *Following*					
Tomasino et al., 2014	10 right handed PD patients with DBS electrodes bilaterally implanted into the subthalamic nucleus	Patients on their usual medication	Studying the effect of DBS on lexical decisions of PD patients about hand action-related verbs, abstract verbs and pseudo-words	The 3 classes of stimuli was presented either in a positive or negative sentence context. Patients performed the experiment twice in the same day in two stimulation conditions: once on stimulation, and the second time, with a 50% reduction in intensity stimulation	In normal subjects, reaction times to negative commands are slower than to positive ones. When the DBS was at 100% on, both normal controls and PD patients showed the normal pattern of reaction times; however, when the stimulation was reduced at 50%, PD patients exhibited identical reaction times to both positive and negative sentences
Marneweck et al., 2014	32 PD patients and 34 normal controls in Experiment 1 and 25 patient and 25 controls in Experiment 2, approximately one year after Experiment 1. 40 subjects participated in both experiments.	Patients were tested 1,5 hours before taking anti-Parkinson medication	Exploring perception of facial expressions of emotion and its link with voluntary facial musculature control	In two experiments, Authors investigated the perceptual ability to discriminate (a) graded intensities of emotional from neutral expressions, (b) graded intensities of the same emotional expressions, (c) full-blown discrepant emotional expressions from 2 similar expressions and the more complex recognition ability to label full-blown emotional expressions. A modification of the Upper and Lower Face Apraxia Test was used to test voluntary facial musculature control	PD patients were, as a group, impaired in all measures of discrimination and recognition of emotional expressions. Discrimination and recognition of emotional expressions correlated positively with voluntary control of facial musculature (after partialing out disease severity and age)
Jacobs et al., 1995	12 PD patients and 30 control subjects	Not specified	Comparing PD patients and control subjects on perceptual and imagery emotional tasks and evaluating their ability to make emotional faces	To test the ability to perceive emotional faces, subjects were given subtests 1, 2, and 5 from the Florida Affect Battery-revised. Subjects also performed a test of facial imagery, and two control tasks: the emotion facial characteristics task and an object imagery test. 11 PD subjects and 17 controls were asked to make emotional faces for a video camera	Patients were significantly impaired on a task of emotional facial imagery and in perceiving emotional faces but not on a control task of object imagery. PD patients were impaired on making emotional faces. Performance on both the perceptual and motor tasks of facial expression significantly correlated with performance on the emotional facial imagery task
Ricciardi et al., 2017	20 PD patients and twenty healthy matched controls	Patients on their usual medication	Assessing emotion recognition and performing a facial emotion expressivity task	The ability of recognizing emotional facial expressions was assessed with the Ekman 60-faces test. Participants were also video-recorded while posing facial expressions of 6 primary emotions. The most expressive pictures for each emotion were derived from the videos. Ten healthy raters were asked to look at the pictures to identify the emotional label (Emotion expressivity task). Reaction time and accuracy of responses were recorded	PD patients showed difficulties in recognizing emotional facial expressions produced by others and in posing facial emotional expressions compared to healthy subjects. There was a significant positive correlation between the emotion facial recognitionand expressivity in both groups
Livingstone et al., 2016	27 PD patients and 28 age matched controls	Not specified	EMG of facial muscles recording while subjects observed presentations of calm, happy, sad, angry, and fearful emotions	Stimuli from the Ryerson Audio-Visual Database of Emotional Speech and Song were used. Participants had to identify emotion of people speaking or singing with different emotions and to rate the intensity of the expressed emotion	PD patients exhibited a deficit in their facial mimicry responses to emotional displays, showing a particular deficit in mimicking response to happy faces
Nobis et al., 2017	44 PD patients	Not specified	Assessing mind-reading abilities	Patients performed RME, which measures empathic abilities, and The Faux Pas detection test, a measure of "cognitive" ToM	Affective ToM was found associated with motor symptom severity and cognitive ToM predominantly with executive function, but no effect of PD lateralization on this was identified

Appendix: Table 1e: Summary of experimental studies investigating embodied cognition and /or mirror neurons in Parkinson Disease - Rehabilitative studies					
(PD: Parkinson Disease; AOT: action observation training; UPDRS: Unified Parkinson Disease Rating Scale; MVF: Mirror Visual Feedback therapy)					
Authors	**Participants**	**Medication**	**Methods**	**Experimental details**	**Principal findings**
Buccino and al., 2011	15 PD patients	Not specified	Randomized controlled trial investigating the efficacy of AOT as a complementary therapy to standard pharmacological and rehabilitative treatment	Patients in the case group (7) were asked to observe, and subsequently execute, different daily actions presented through video clips (AOT). Controls (8) observed video clips with no motor content and subsequently performed the same actions.	After treatment, the experimental group reported better scores in the UPDRS, and the Functional Independence Measure, while there was no objective difference in gait performance.
Jaywant et al., 2016a	23 individuals with PD	Not specified	Randomized controlled home-based AOT intervention (gait observation) for walking in PD	In the Gait Observation (intervention) condition, participants viewed videos of healthy and parkinsonian gait. In the Landscape Observation (control) condition, participants viewed videos of moving water	No difference in gait performance was observed; however, the AOT group obtained a better score in a subscale of self-perceived mobility
Santamato et al., 2015	15 PD patients with age of < 80 years, time from PD diagnosis of ≤ 10 years	Not specified	AOT (video-therapy) for the treatment of postural instability and balance impairment	Participants underwent an 8-week rehabilitation programme for 3 times a week, under the supervision of a physiotherapist. Patients were sitting and a monitor screen was placed in front of them. They were instructed to carefully watch the videos projected concerning motor tasks and motor sequences linked to balance. At the end of each video, patients were requested to perform the observed action for other 5 minutes	No positive effect of AOT on balance
Pelosin et al., 2010	20 PD patients with freezing of gait	Stable medication regimen	Single randomized controlled trial of AOT plus physical therapy versus sham intervention plus physical therapy	The patients were randomly attributed to an “action group”, who watched video clips showing specific movements and strategies to circumvent freezing episodes, or to a “landscape group” who saw video clips of static landscape pictures. Both groups underwent identical physical therapy training	The freezing of gait was significantly reduced in both groups after training. Motor performance and quality-of-life assessments were also significantly improved in both groups. However, at 4 weeks follow-up examination, a significant reduction in the number of freezing episodes was observed only in the AOT group
Pelosin et al., 2013	38 subjects with PD and 14 healthy controls; 8 participants with PD were recruited for a control intervention	ON state; ON and OFF states for a subgroup	Randomized controlled trial of AOT (10 PD, 7 controls) versus acoustic cues (10 PD, 7 controls); a subgroup of 10 patients was tested in both ON and OFF states. Another group (10 PD) underwent sham intervention.	Participants were randomly divided into 2 groups: the VIDEO group watched video clips showing repetitive finger movements paced at 3 Hz; the ACOUSTIC group listened to an acoustic cue paced at 3 Hz. All participants performed a spontaneous finger sequence at different intervals before and after the intervention. 8 PD patients watched a video representing a static hand (sham intervention). Ten patients participated in the same protocol of the VIDEO group but were tested in the ON and OFF medication states.	Both VIDEO and ACOUSTIC training increased the spontaneous rate in all participants. VIDEO intervention showed a greater effect over time. AOT significantly influenced movement rate in ON and OFF conditions, but 45 minutes after training, the effect was still present only in the ON condition. No effect after sham intervention.

Appendix: Table 1e: Summary of experimental studies investigating embodied cognition and /or mirror neurons in Parkinson Disease - Rehabilitative studies *Following*

Bienkiewicz et al., 2013	7 PD patients		Testing patients in an upper limb mediolateral movement task, with and without a visual point light display, travelling at 3 different speeds.	The dynamic information presented in the visual point light LED display depicted three different movement speeds of the same amplitude. The displays were formerly tested and validated on healthy participants. In the validation stage it was found that young healthy adults were able to use the temporal information conveyed by the LED display to prospectively guide their movements.	Patients demonstrated a significant improvement in terms of movement time and peak velocity when executing movement in accordance with the information afforded by the point light display, compared to when the movement was performed without the display.
Bonassi et al, 2016	21 patients with mild to moderate PD and 12 healthy subjects	Stable medication regimen	Controlled trial with MVF performed with the use of a mirror box to reduce bradikinesia	12 PD and 12 control subjects were involved in the MVF training, while 9 additional patients with PD performed a control experiment (training without MVF). Before and after MVF training, participants performed a finger sequence at their spontaneous pace with both hands. M1 excitability was assessed in the trained and untrained hemispheres by means of transcranial magnetic stimulation.	Movement speed increased after MVF training in either hand of both groups. MVF therapy enhanced cortical excitability of M1s in both groups.
Agosta et al., 2016	25 PD patients with freezing of gait	stable dopaminergic medication regimen for at least 4 weeks	Sigle randomized controlled trial of AOT plus physical therapy versus sham intervention plus physical therapy	PD patients were randomized into two groups: AOT (combined with practicing the observed actions) and ‘‘Landscape’’ (same physical training combined with landscape-videos observation). At baseline and 4-week, patients underwent clinical evaluation and fMRI. Clinical assessment was repeated at 8-week.	After 4 weeks, both groups showed reduced freezing of gait severity, improved walking speed and quality of life, but in the AOT group motor disability was additionally reduced and balance improved. After 8 weeks, only the AOT group showed a sustained positive effect. Patients were then scanned while executing foot movements, and during AOT. The AOT group showed increased recruitment of fronto-parietal mirror areas during fMRI tasks. Functional brain changes were associated with clinical improvements.

Appendix: Table 2a: Summary of experimental studies investigating embodied cognition and /or mirror neurons in Frontotemporal Dementia or Amyotrophic Lateral Sclerosis - MRI studies				
(bvFTD: behavioral variant of Frontotemporal Dementia; ALS: Amyotrophic Lateral Sclerosis; AOT: Action Observation Training: Impairment; MRI: Magnetic Resonance Imaging; fMRI: functional MRI; IFG: Inferior Frontal Gyrus; MN: Mirror Neurons)				
Authors	**Participants**	**Methods**	**Experimental details**	**Principal findings**
Li et al., 2015	30 patients with ALS and 30 matched healthy controls	fMRI study during AOT	Participants observed a video of repetitive flexion-extension of the fingers at three frequency or complexity levels, alternated with periods of a static hand	AOT activated brain regions related to the MN system in both ALS and healthy subjects. In ALS patients some areas (dorsal lateral premotor cortex, inferior parietal gyrus, and supplementary motor area) were more activated. Increased activation within the primary motor cortex, the dorsal lateral premotor cortex, the inferior frontal gyrus, and superior parietal gyrus correlated with hand movement frequency/complexity in patients.
Jelsone-Swain et al., 2015	19 patients with ALS and 20 helathy controls	fMRI study during AOT	Subjects observed an actor's hand rhythmically squeezing a ball or squeezed themselves a ball	Authors observed greater activity in ALS patients than in controls in MN regions (right frontal inferior operculum, right frontal and left parietal lobes)
Jastorff et al., 2016	14 patients with bvFTD and 19 age-matched controls	Behavioral testing plus structural and resting state MRI	Behavioral testing consisted of the presentation of a motion morph on a screen for 10 s. The subject had to first answer whether the stimulus was emotional or neutral, and, dependent on this answer, categorize the emotion as happy, angry, fearful, or sad. For the MRI study: 1) Voxel-based morphometry analysis based on a structural, high resolution, T1- weighted image. 2) Resting state study. A fMRI study during behavioral testing was also performed in young controls.	bvFTD patients were impaired in emotion detection as well as emotion categorization tasks. Their performance in emotion categorization inversely correlated with atrophy of the left IFG, a region belonging to the MN network. Functional connectivity analysis also showed a reduced connectivity of this area.
Verstraete et al., 2013	24 patients with ALS and a group of healthy controls	Diffusion tensor imaging study	The brain network was reconstructed based on "whole brain" diffusion tensor imaging data. The network integrity was examined in ALS patients at baseline and at a more advanced stage of the disease (interval 5.5 months) in comparison with controls; progressive brain network impairment was also examined by comparing patients at two time-points in a paired-analysis	Analyses revealed an expanding sub-network of affected brain connections over time, with a central role for the primary motor cortex and loss of structural connectivity mainly propagating to frontal and parietal brain areas (regions belonging to the MN network)

Appendix: Table 2b: Summary of experimental studies investigating embodied cognition and /or mirror neurons in Frontotemporal Dementia or Amyotrophic Lateral Sclerosis - Neuropsychological or Behavioral studies

(bvFTD= behavioral variant of Frontotemporal Dementia; ALS: Amyotrophic Lateral Sclerosis; AD: Alzheimer Disease; PD: Parkinson Disease: PDD: Parkinson Disease Dementia; MRI: Magnetic Resonance Imaging; BORB: Birmingham Object Recognition Battery)

Authors	Participants	Methods	Experimental details	Principal findings
Bak and Hodges, 1997	three ALS patients with aphasia and FTD	word-picture matching task and naming		Performance was poorer with verbs than nouns, in a word-picture matching task. Moreover, the only patient who could complete the task exhibited significantly poorer performance in action naming than object naming
Bak et al., 2001	6 patients with MotND, in whom communication problems were an early and dominant feature	Tests of comprehension, verb and noun processing, visuospatial functions	Sentence comprehension was assessed with the test of the reception of grammar (TROG); verb and noun processing was evaluated with Berndt's test	Comprehension and production of verbs were consistently more affected those that of nouns and this effect remained stable upon subsequent testing, despite overall deterioration
Grossman et al., 2008	34 patients with ALS (26 for the MRI study)	Word-description matching and associativity judgments with actions and objects. Voxel-based MRI	Associativity judgments: patients were given a target verb for an action, or a noun for an object, and were asked to select the one of two choices that goes best with the target. Word-description matching : Patients were given a phrase describing an action or object, and then were asked to select the best matching among 4 stimuli.	Patients with ALS were significantly more impaired on measures requiring knowledge of actions than measures requiring knowledge of objects. Difficulty on measures requiring action knowledge correlated with cortical atrophy in motor cortex
York et al., 2014	36 patients with ALS (5 with MCI and 4 with FTD); 22 patients with PD spectrum disorders (clinically definite PD, n = 8, PD-MCI, n = 3) PD-DLB, n = 3, PDD, n = 8)	Two-alternative forced-choice associativity judgment task plus T1 MRI imaging of gray matter atrophy	120 frequency-matched action verbs, cognition verbs, concrete nouns and abstract nouns were probed. Performance was related to T1 MRI imaging of gray matter atrophy	Patients with ALS were significantly impaired relative to control participants for action verbs. Patients with PD did not differ from controls Regression analyses related action verb performance to motor-associated cortices in ALS, but not in PD.
Cappa et al., 1998	19 mild to moderate AD patients, 10 FTD patients and 15 age- and education-matched normal controls	Action and object naming	Confrontation naming was assessed with realistic pictures of 40 objects and 40 actions. The objects belonged to different semantic categories (both natural and artefactual); the actions involved largely, but not exclusively, tool utilization	AD and FTD patients were impaired in naming compared with control subjects; action naming was more severely impaired. The discrepancy between object and action naming was significantly greater in FTD than in AD.

Appendix: Table 2b: Summary of experimental studies investigating embodied cognition and /or mirror neurons in Frontotemporal Dementia or Amyotrophic Lateral Sclerosis - Neuropsychological or Behavioral studies *Following*				
Hillis et al., 2004	15 patients with nonfluent nonfluent PPA, 7 patients with fluent PPA and 6 patients with ALS-FTD	Oral and written naming of nouns and verbs, matched in difficulty	Patients were administered tasks of oral and written naming of 30 “pure” nouns and 30 “pure” verbs, matched for word frequency, pictured as black and white line drawings that elicited a high degree of name agreement in pilot testing.	Patients with nonfluent PPA and ALS-FTD were more impaired on verb than on noun naming and significantly more impaired on oral naming than written naming. Patients with fluent PPA showed the opposite pattern for both word class and modality.
Fiori et al., 2013	34 ALS patients and 23 normal controls	A hand laterality and a mirror letter discrimination task	The hand laterality task requires participants to decide whether a picture represents a right or a left hand. In this modified version, participants respond by means of eye-gazes. In the mirror letter discrimination task, participants are requested to indicate whether the displayed alphanumeric characters are in their normal or mirror-reversed orientation	The effects of biomechanical constraints on MI (comfortable/awkward posture) were compromised in ALS at the hand laterality task. No difference was present at the mirror letter discrimination task between patients and controls.
Vannuscorps et al., 2016	A patient diagnosed with corticobasal degeneration	Longitudinal study. Voxel-based morphometric MRI, testing of movement production, tasks of conceptual processing of actions and manipulable objects, tasks of gesture and conceptual processing, neuropsychological assessment	For simplex movement production: the Jamar Hydraulic Hand Dynamometer test, which evaluates hand grip strength; the Box and Block Test, which tests gross hand dexterity, and the Purdue Pegboard Test. For complex movements: gesture imitation and interpretation tasks. For conceptual processing of actions and of manipulable objects: two picture naming tasks. For tasks of gesture and conceptual processing: an object/gesture matching task; a task eliciting gesture production from the name of the object; a picture naming task; a picture association task	The patient presented with increasing action production disorders associated with increasing bilateral atrophy in cortical and subcortical regions involved in the sensorimotor control of actions (i.e., the superior parietal cortex, the primary motor and premotor cortex, the inferior frontal gyrus, and the basal ganglia). In contrast, the patient’s performance in processing action-related concepts remained intact during the same period.

Appendix: Table 3a: Summary of experimental studies investigating embodied cognition and /or mirror neurons in AD/MCI - Correlation between morphological MRI data and EEG spectral analysis

(MCI: Mild Cognitive Impairment; EEG: electroencephalogram; IPL: Inferior Parietal Lobule; MN: Mirror Neurons)

Authors	Participants	Methods	Experimental details	Principal findings
Moretti, 2006	74 adult subjects with MCI	EEG recording and high resolution MRI	Alpha3/alpha2 frequency power ratio as well as cortical thickness were computed for each subject	High EEG alpha3/alpha2 frequency power ratio was correlated with atrophy of cortical regions belonging to the posterior MN network (IPL) areas

Appendix: Table 3b: Summary of experimental studies investigating embodied cognition and /or mirror neurons in AD/MCI - fMRI studies

(AD: Alzheimer Disease; fMRI: functional Magnetic Resonance Imaging; BOLD: blood oxygen level- dependent; MN: Mirror Neurons)

Authors	Participants	Methods	Experimental details	Principal findings
Lee et al., 2013	12 AD patients and 12 matched controls	fMRI and voxel-based morphometry together with a passive viewing of emotional faces paradigm	During the fMRI experiment, happy, sad, fearful, and neutral movie blocks were each presented twice within a session. Participants were asked to watch the movies without generating any overt responses (i.e., passive viewing)	AD patients showed weaker activations in left cerebral regions associated with MN or empathic simulation (ventral premotor cortex and the anterior insula and adjacent frontal operculum, respectively) compared to controls. Levels of brain activation in those regions predicted the level of affect in the AD group. The decline in BOLD signals was not related to structural degeneration
Peelle et al., 2014	12 patients with AD spectrum disease and 21 healthy senior subjects	fMRI study with a semantic memory task	Participants were presented with pairs of printed words and asked whether the words matched on a given visual–perceptual feature (e.g., guitar, violin: SHAPE). The stimuli probed natural kinds and manufactured objects, and the judgments involved shape or color	AD patients were impaired in this task, and exhibited significantly less activation the in left temporal-occipital cortex than did healthy seniors, and a reduced activity in the left inferior frontal cortex

Appendix: Table 3c: Summary of experimental studies investigating embodied cognition and /or mirror neurons in AD/MCI - Behavioral studies

(AD: Alzheimer Disease)

Authors	Participants	Methods	Experimental details	Principal findings
Bisio et al., 2012	25 elderly participants with probable mild and moderate AD and 14 healthy participants	Simple arm upwards pointing movement	Participants were required to observe a dot moving on a screen with different velocities and to point to its final position when it stopped	The dot speed similarly influenced AD patients and healthy elderly participants. In contrast, only patients had anticipatory motor response: they started moving before the end of the stimulus motion, unlike what was requested by the experimenter
Bisio et al., 2016	23 AD patients and 14 healthy controls	Testing voluntary imitation and how this ability is modulated by the nature of the observed stimulus	The ability to reproduce the kinematic features of a human demonstrator and those of a dot moving on a screen was tested. Participants were asked to imitate the velocity of the stimulus	When asked to imitate the velocity of the stimulus AD patients showed an intact ability to reproduce it. This ability improved when the stimulus was a human agent

Appendix: Table 3d: Summary of experimental studies investigating embodied cognition and /or mirror neurons in AD/MCI -Neuropsychological studies (Papers already reported in Appendix Table 1 are not reported)

(AD: Alzheimer Disease; aMCI: amnesic Mild Cognitive Impairment; FTD: Frontotemporal Dementia; SD: Semantic Dementia)

Authors	**Participants**	**Methods**	**Experimental details**	**Principal findings**
Robinson et al., 1996	20 AD patients	Picture-naming task	The task consisted of frequency-matched pairs of nouns and verbs that were homophonic and homographic	Intragroup comparisons revealed that verb naming was significantly more difficult for patients with AD than noun naming
Kim and Thompson, 2004	14 patients with AD and nine with agrammatic aphasia	Testing verb and noun production by controlling both semantic and syntactic features of verbs	Noun and verb naming, sentence completion, narrative tasks; noun and verb comprehension, and a grammaticality judgment task	Both AD and agrammatic subjects showed impaired verb naming. The semantic complexity of verbs affected AD, but not agrammatic, patients' performance
Druks et al., 2006	19 patients with mild to moderate AD and 19 healthy age matched participants	Picture-naming task	A larger set of stimuli with carefully matched object and action items. Accuracy data and naming latencies were collected	Both AD patients and normal controls responded faster and made fewer errors on the object pictures than the action pictures
Cotelli et al., 2014	16 AD patients and 16 control subjects	Direct comparison of linguistic abilities and praxic abilities	Verb and noun naming and sentence comprehension; gesture execution for complex movements (De Renzi apraxia test)	A correlation between action comprehension, action naming abilities, language impairment and apraxia was found in AD patients
Williamson et al., 1998	10 patients with AD and 10 normal control subjects	Picture-naming tasks	The Boston Naming Test and the Action Naming Test were used	Object naming was impaired to a significantly greater extent than action naming in AD. This difference remained after controlling for the effects of word frequency
Masterson et al., 2007	23 AD patients and age-matched controls	Picture-naming tasks and a word-picture verification task	The word-picture verification task consisted of 62 verb and 62 noun items, a subset of the stimuli in the Object and Action Naming Battery. Each item in the task consisted of a single picture presented three times with different printed words: once with the target picture name, once with a semantically related distractor, and once with an unrelated distractor	In the picture naming tasks both patients and controls were faster and produced more target responses for objects than actions. In the comprehension task, accuracy levels were comparable for nouns and verbs, but response times were longer for verbs
Guaita et al., 2009	79 patients with dementia and 64 healthy elderly subjects	Assessing the capability of understanding facial emotions	The test consisted in showing 14 photographic representations of 7 emotions both from male and from female faces, representing happiness, sadness, fear, disgust, boredom, anger and surprise. Patients were asked to observe the face and to recognize the emotion either with a denomination or a description. The spontaneous reactivity to the face expressions was videotaped and classified as a congruous or incongruous reaction	AD patients were impaired in recognizing emotions but did not differ from controls in the spontaneous reaction to facial expressions

Appendix: Table 3d: Summary of experimental studies investigating embodied cognition and /or mirror neurons in AD/MCI -Neuropsychological studies *Following*

Bediou et al., 2009	10 mild to moderate AD patients, 10 aMCI subjects and 10 FTD patients	Evaluation of facial expression, gender and gaze direction decoding abilities	For the facial expression recognition and the gender recognition tasks, morphed faces varying in the intensity of the task-relevant face feature were used	AD patients were impaired in expression recognition and FTD patients were impaired in expression recognition and gaze direction determination. MCI subjects were not impaired.
De Scalzi et al., 2005	25 psychology students, 20 healthy older adults, and 19 volunteers with probable mild to moderate AD with late onset	Evaluation of the of the action compatibility effect	Subjects were asked to make judgments on sentences that describe a transfer of an object toward or away from their body	Patients were faster to respond when the response required a movement in the same direction as the transfer described in the sentence
Vallet et al., 2017	40 young adults, 40 healthy elderly, 20 patients with AD and three patients with SD.	SEMantic-Episodic memory test	The SEMantic-Episodic memory test allows to test both episodic and semantic memory at the same time	Normal elderly committed confusion errors for presented items, but not intrusions (recall or recognition of items never presented). AD patients presented the worst episodic memory performance associated with intrusion errors and did not benefit from a visual isolation (addition of a yellow background). The third group suffered from the most severe semantic impairment

Appendix: Table 3e: Summary of experimental studies investigating embodied cognition and /or mirror neurons in AD/MCI - TMS studies

(AD: Alzheimer Disease; rTMS: repetitiveTranscranial Magnetic Stmulation; DLPFC: DorsoLateral PreFrontal Cortex)

Authors	Participants	Methods	Experimental details	Principal findings
Cotelli et al., 2006	15 patients with probable AD	rTMS	High-frequency rTMS was applied to the left and right DLPFC during object and action naming	Stimulation to the left and right DLPFC improved accuracy in action naming
Cotelli et al., 2008	24 probable AD patients with different degrees of cognitive decline	rTMS	High-frequency rTMS was applied to the left and right DLPFC during object and action naming	Stimulation to the left and right DLPFC improved accuracy in action naming in mild to moderate AD patients. An improved naming accuracy for both action and objects was found in the moderate to severe group

Appendix: Table 3f: Summary of experimental studies investigating embodied cognition and /or mirror neurons in AD/MCI - Rehabilitative studies

(AD: Alzheimer Disease: AOT: Action Observation Training)

Authors	Participants	Methods	Experimental details	Principal findings
Eggermont et al., 2009	Nursing home residents with dementia	AOT	Participants watched either videos showing hand movements (19 subjects, AOT group) or a documentary (25 subjects) for 30 min, 5 days a week, for 6 weeks	Patients treated with AOT showed improvements in attention and facial recognition