UNIVERSITY OF NAPLES FEDERICO II

SCHOOL OF MEDICINE

PhD Thesis

in

Neuroscience and Pathology of Brain Aging

Action processing: neural basis and clinical implications

Coordinator

Prof. Lucio Annunziato

PhD student

Ludovica Labruna

Tutor

Prof. Elio Marciano

ACCADEMIC YEAR 2005-06

Acknowledgements

This work would not have been possible without the support and encouragement of Prof. Luigi Trojano, under whose supervision I chose this topic and began the work for this thesis. It is difficult to overstate my gratitude to Prof. Dario Grossi who has introduced me to the world of neuroscience and has motivated and supported me. Both have the special gift of understanding the appropriate time to put me under pressure, or to give me confidence.

I would like to deeply thank my tutor, prof. Elio Marciano, who has been helpful and comprehensive in his guidance over these four years.

I am also grateful to prof. Maurizio Taglialatela, new mentor of my new academic life.

Thanks are due also to prof. Rich Ivry who has shown to me a different way to do “research”, and to Julie and Ayelet who have rendered this experience more special.

Last but by no means least, special thanks go to Alberto without who it would have been more difficult, and much less amusing, to begin and to end this journey.

Table of contents

The neural bases of meaningless and meaningful gesture processing. A review.

Gilles de la Tourette syndrome and voluntary movement: a functional MRI study

List of abbreviations

APB: abductor pollicis brevis
AVD: automatic-voluntary dissociation
BA: Brodmann’s areas
DLPFC: dorsolateral prefrontal cortex
dPM: dorsal premotor cortex
EEG: electroencephalography
FDI: first dorsal interosseous
fMRI: functional Magnetic Resonance Imaging
IFG: inferior frontal gyrus
IG: intransitive gestures
IPL: inferior parietal lobe
IPS: intraparietal sulcus
MEPs: motor evoked potentials
MFG: meaningful gestures
MI: primary motor area
MLG: meaningless gestures
PET: Positron Emission Tomography
SG: symbolic gestures
SMA: supplementary motor area
STS: superior temporal sulcus
TG: transitive gestures
TMS: Transcranial Magnetic Stimulation
TS: Tourette syndrome
VLPFC: ventrolateral prefrontal cortex
vPM: ventral premotor cortex

Introduction

I.1 Theoretical Background[1]

I.1.1 Action and gesture

The human brain can plan, represent and execute a wide range of specific actions in response to environmental stimuli. Action production and comprehension have been the topic of many neuropsychological, clinical, neurophysiological and neuroimaging studies devoted to clarifying this complex motor behaviour.

On a behavioural basis, such "natural", skilled meaningful gestures (MFG) may be operationally distinguished into two main classes, depending on whether they involve the actual or pantomimed use of tools or objects (transitive gestures, TG) or not (intransitive gestures, IG). In the natural environment, among IG can be considered those action patterns that, although arbitrary (and most often culture-specific), are commonly intended to convey messages or meanings (symbolic gestures, SG). Moreover, gestures could be classified as tool-actions when utensils were used according to their function, and as non-tool actions, when gestures were finalised to move an object (Foundas et al., 1995a).

In clinical settings, other kinds of gestures, that do not usually imply the use of objects, are employed to explore the ability to produce motor patterns independently of previously acquired knowledge: such novel, "artificial" gestures may be identified as meaningless gestures (MLG).

McNeill (1992) has identified a number of different types of gestures that speakers routinely use when they talk. Iconic gestures transparently capture aspects of the semantic content of speech. Metaphoric gestures are like iconics in that they are pictorial; however, the pictorial content is abstract rather than concrete. Just as we speak metaphorically about 'presenting' an

---

[1] This section is a modified version of an chapter with the title “I disturbi del gesto di origine frontale” by L. Labruna and L. Trojano which has been published in the book: Neuropsicologia dei lobi frontali. Sindromi disesecutive e disturbi del comportamento. Edizione il Mulino, 2005, pp. 107-127.

idea or argument, gesture makes an abstract entity concrete by treating it as a bounded object supported by the hands and presented to the listener.

Beat or baton gestures are so named because the hand moves up and down with the rhythm of speech and looks like it is beating time. Unlike iconics and metaphorics, beats tend to have the same form regardless of the content (a simple flick of the hand or fingers up and down, or back and forth). Deictic or pointing gestures indicate entities in the conversational space, but they can also be used even when there is nothing to point at.

During talk, gestures were also classified as content, emphasys and filler, after Foundas et al. (1995b): content gestures can be interpreted without further contextual information, while the remaining conversational gestures are movements used to tie together temporally separated but thematically related portions of discourse, and do not convey meaning by themselves.

The execution of different actions, imply various and different cognitive processes and anatomical substrates. As an example, the execution of a TG demands, respect to a IG, the acknowledgment of an object, the correct grasp and at last its utilization. A MLG doesn't have the semantic components that characterize a SG or a TG, and it is executed only on imitation. Still, the distal gestures, regarding the proximal, demand different amplitude of the movements and a greater precision in the execution Moreover, the execution of a sequence of movements imposes a greater memory load regarding the reproduction of one posture.

I.1.2 Cognitive model of gestures processing

Studies on brain damage patients with disturb of the elaboration of the gestures have evidenced the existence of dissociations in the performances for the various classes of gestures. Therefore, the theoretical models on the gesture elaboration have foreseen, from the early studies, various components, whose selective deficit could explain such dissociations. The first theoretical model of gesture elaboration has been proposed from Liepmann [1908], which assumed the existence of three distinct stages for the production of the voluntary movements. At the origin of purposeful action there is a spatio-temporal image of the intended action, a “movement formula”. The movement formula does not consist of kinetic memories and hence does not specify motor innervations. In the majority of instances it is constituted by a visual image of the action, but it may also be an acoustic image as, for example, when the action consists of playing a musical instrument. One pregnant characteristic of the movement formula is its plasticity, in the sense that during the development of the action is susceptible of modification according to the contextual information. The movement formula belongs to the intrapsychic sphere. Liepmann (ibidem) proposed that these representations were the product emerging from the whole cerebral cortex, though posterior regions may play a prominent role when the movement formula is provided by a visual image. Only subsequently Liepmann (1925) assumed the dominance of the left hemispheric also for this first stage of the gesture elaboration.

The second step from intention to action is the “ability to direct the extremities according to directional images. This is a transfer of a scheme of movement to the (motor) innervation, a cooperation of innervatory and extra-innervatory areas” (Liepmann, 1908). This transfer requires intact connections between the whole cortex and the central region. The third stage, consists in the activation of the corrected sequence of cinematic memories, in order to put into effect codified how much in the action plan. Such memories, the so-called the innervatory pattern, could be activated only totally and they would not be modifiable during the execution. For “certain short, stereotypically recurring purposeful movements like waving, knocking on a door, handshaking” the central region itself possesses a “kinetic memory” which can direct movements of the opposite extremities “without intervention of directional or optical images (by shortcut)” (Goldenberg, 2003).

The anatomical substrate of the cinematic memories, according to Liepmann, is localized in the sensorimotor cortex, namely the primary sensorial and motor areas of the left hemisphere (Geschwind [1965] will replace the concept of sensorimotor with that one of premotor cortex). The elaborated gesture can therefore be executed with the right hand, while in order to execute the same gesture with the left hand it is necessary that the information are transferred, through the corpus callosum, to the sensorimotor of right hemisphere. The concept of the left hemispheric dominance in the programming of the movements was founded on the observation of patients with specific disturbs of gesture elaboration: already at that time it had been noticed that, of rule, a lesion of the left hemisphere provokes a bilateral disturbance, while patients with lesion to the corpus callosum show only disturb to left limb. In particular, the unilateral disturbance of the movements of the not-dominant hand from callosal lesion demonstrated that the right hemisphere when disconnected from the left was not able to carrying out a correct program of the movements (Liepmann 1908).

The theoretical model of Liepmann (1908; 1925), modified and integrated from Geschwind (1965) and Heilman et al. (1982), is still thought valid in its general lines. The latter defined the neural network responsible for mediating learned, skilled movement. Specifically, gesture to command, the classic test of limb apraxia, requires that auditory input via primary auditory cortex (Heschel's gyrus) project to auditory association cortex (Wernicke's area), which in turn flows to motor associationcortex (Brodmann's area 6). Motor association cortex subsequently activates the primary motor areas (Brodmann's area 4), resulting in the production of the target right hand gesture. When gestures are performed by the left hand, motor programs from the left motor association cortex cross the corpus callosum to the contralateral premotor cortex, thus activating the primary motor cortex for gesture production (Figure I1). It has been suggested that the "visuokinesthetic engrams," or neural representations of learned, skilled movements, are localized primarily to the left inferior parietal lobule (Heilman et al. 1982, Rothi et al, 1982].

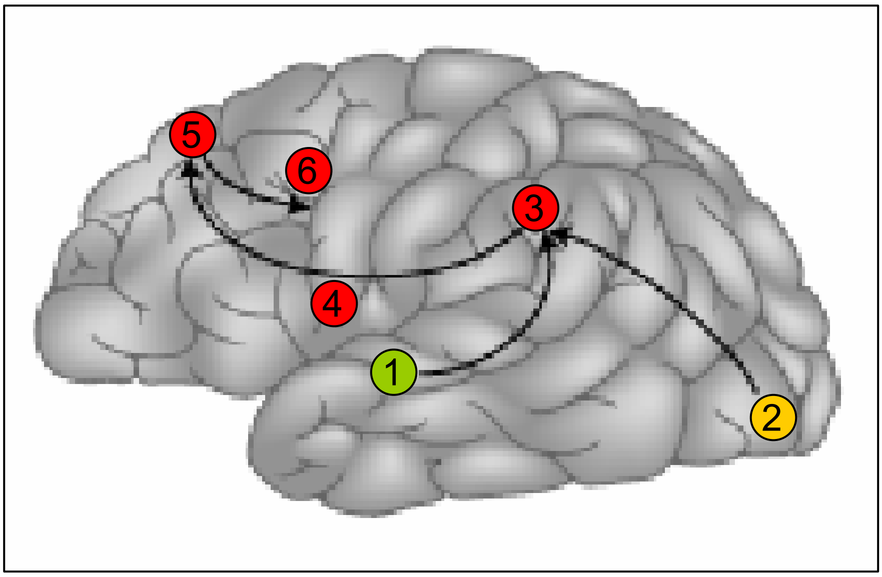

Figure I1. Neural networks for skilled movement. To produce movements with the left hand, the flow of information passes from the left hemisphere via the corpus callosum to right hemisphere motor regions (BA6, 4; SMA). Frontal regions (BA 9, 46) are also implicated. (1: auditory representation, BA 41, 42, 22; 2: visual representation, BA 17, 18, 19, 37; 3: cross-modal associations, BA 39, 40; 4: white matter connections; 5: motor-frontal representation, BA 6; 6: primary motor cortex, BA 4). From McClain and Foundas (2004).

In a classic review of the argument, De Renzi and Faglioni (1996) suggest that the left inferior parietal lobe carries out a crucial role in the elaboration of the action plan, and that this "parietal locus" can be activated through independent sensory channels (sight, hearing, touch). Moreover, De Renzi and Faglioni (ibidem) emphasize that the communication between the two hemispheres, necessary for the transmission of the motor programs elaborates in the left frontal and parietal cortex, can occur also through subcortical circuits or by a callosal connection between the parietal lobes. In such a way it would be possible to explain the frequent observation of patients with left frontal lesions, with right hemiparesis or hemiplegia, than do not shows deficit in the motor programming of the left hand.

During the last few years of the nine hundred the enormous development of the cognitive neuropsychology has carried to the elaboration of theoretical models specifically dedicates to gesture elaboration. All these models provided distinct processes responsible of gesture recognition, comprehension and production. It is placed, therefore, greater emphasis on the specific phases required in the elaboration of motor programs, rather than on the correspondence between theoretical model and anatomical structures. Recently, however, the great spread of the neuroimaging techniques has allowed obtaining new data given on the possible anatomo-functional correlates of the cognitive processes been involved in various tasks.

One of the first cognitive models of gesture elaboration has been formulated from Rothi et al. (1991, 1997). This model has three main features. First it distinguishes between a semantic and a nonsemantic route for MFG and MLG respectively: the gesture may be retrieved via the semantic path or programmed through the nonsemantic route. Second, within the semantic route, besides the praxis conceptual system, the semantics proper, which was postulated also by earlier authors, a lexical level is assumed, which encompasses a repertoire of learned gestures. The semantic system (see Roy & Square, 1985) stores the knowledge about objects and tools, their function and the way in which they are used. The semantic system also stores the meaning of intransitive gestures, either iconic, which represent the shape of an object, or symbolic. Third, the lexicon is further subdivided into input and output, with the input level responsible for the recognition of familiar gestures, the output level for their production.

Rothi et al model (1991, 1997) was refined by Cubelli et al. (2000) that encompass three processing components: a “lexical route”, a visuo-motor conversion mechanism and a short-term memory workspace. The lexical route supports recognition (action “input lexicon”), identification (action semantic system) and production (action “output lexicon”) of familiar gestures, while the visuo-motor conversion mechanism turns visual information into motor programmes, upholding the reproduction of all seen gestures. Finally, the short-term memory workspace, on which both the lexical and the non-lexical route converge, storing the motor programmes to be executed.

Currently, the exact neuroanatomic substrate of the praxis system has not been fully elucidated. The advent of more sophisticated neuroimaging techniques has facilitated such work, and many of the more recent studies in apraxia have used methods such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) to provide evidence to substantiate, refute, or rework the traditional cognitive models of limb apraxia. Peigneux et al. (2004) used PET to establish the anatomic components of Rothi et al.'s (1997) neuropsychological model of limb apraxia. Subjects were scanned during completion of complex combinations of tasks, which were hypothesized to activate specific brain regions associated with discrete elements of the praxis system. Critical to this model is the concept that discrete storage modules, or "praxicons," are central to the praxis system and contain information pertaining, respectively, to the visual analysis and recognition of movements and objects, and for the execution of the motor patterns associated with specific movements. Functionally, the model holds that the input praxicon is activated by the visual analysis of gestures or objects, thus activating the action semantic system, which serves as the repository for knowledge of familiar gestures. Activation of the semantic information pertaining to a specific gesture, in turn, results in the activation of the visuokinesthetic programs for skilled movement, which are stored in the output praxicon and which, once activated, stimulate the motor performance of target movements.

On this line another cognitive models have been propose, elaborate on the base of neuroimaging studies (Labruna et al., under revision) that will be discuss in the fist chapter of the present thesis.

I.1.3 Neural basis of action: the human mirror system

There is a large body of evidence that several brain regions are activated both during action generation and during the observation of others' actions

(Decety, et al., 1997; Grafton et al, 1996; Hari et al., 1998; Rizzolatti et al., 1996a). Premotor and parietal cortices are activated both by the perception of action and by the execution of action. Furthermore, premotor and parietal cortices are activated to a greater extent when subjects observe movements with the intention to imitate them later compared with the intention simply to recognize them later (Grezes et al, 1999). We can recognize a large variety of actions performed by other individuals, including those belonging to other species (Buccino et al., 2004a), simply by matching the observed actions onto our own motor system. The neural substrate of this direct-matching is the mirror neuron system.

Iacoboni and Dapretto (2006) in a recent paper have drawn an overview of the areas meanly involved in the fronto-parietal mirror neuron system (see figure I2). An anterior area with mirror neuron properties is located in the inferior frontal cortex, encompassing the posterior inferior frontal gyrus (IFG) and adjacent ventral premotor cortex (vPM). A posterior area with mirror neuron properties is located in the rostral part of the inferior parietal lobule (IPL). The main visual input to the mirror neuron system originates from the posterior sector of the superior temporal sulcus (STS). Together, these three areas form a ‘core circuit’ for imitation. The information flow from the parietal mirror neuron system, which is mostly concerned with the motoric description of the action, to the frontal mirror neuron system, which is more concerned with the goal of the action. Moreover efference copies of motor imitative commands are sent back to the STS to allow matching between the sensory predictions of imitative motor plans and the visual description of the observed action.

In some brain regions, the overlap between action observation and action execution is highly specific. Action observation activates premotor cortex in a somatotopic manner (Buccino et al., 2001). In this fMRI experiment, subjects observed actions performed by the mouth, hand and foot that were

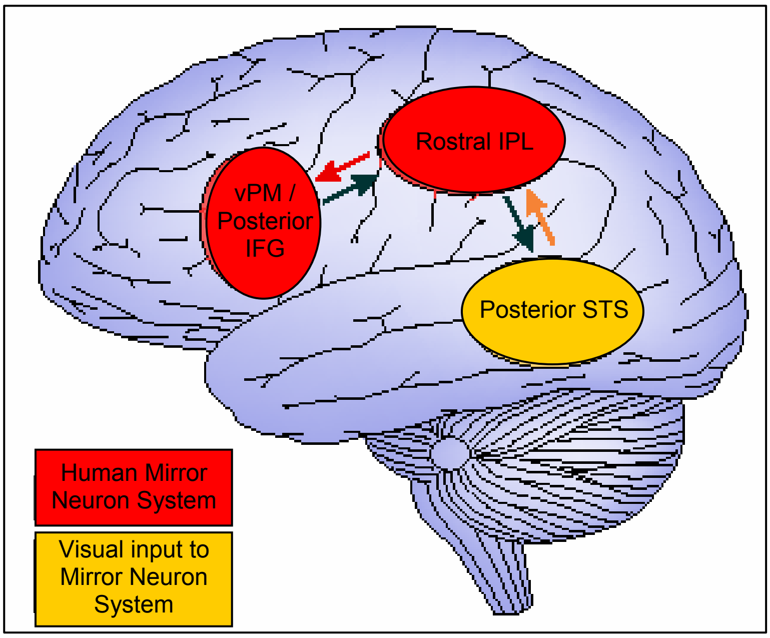

Figure I2. Schematic overview of the fronto-parietal mirror neuron system (red) and its main visual input (yellow) in the human brain. The visual input from the STS to the mirror neuron system is represented by an orange arrow. The red arrow represents the information flow from the parietal to the frontal mirror neuron system. The black arrows represent efference copies of motor imitative commands that are sent back to the STS.
IFG: inferior frontal gyrus; vPM: ventral premotor cortex; IPL: inferior parietal lobule; STS: superior temporal sulcus. Modify from Iacoboni and Dapretto, 2006.

performed in isolation (mimicking chewing, grasping and kicking) or with an object (chewing food, grasping a cup and kicking a ball). The results demonstrated that watching mouth, hand, and foot intransitive movements activates the same functionally specific regions of premotor cortex as making those respective movements. When actions involved objects the parietal cortex became activated. Again, different regions of the parietal cortex were activated according to the specific object-directed action being performed. Thus, it seems that the premotor activation is not dependent on the movement having a goal (an object), whereas the parietal cortex was activated only when the action was directed towards a goal. Jeannerod (2001) has argued that the mirror system facilitates action understanding, suggesting that neural simulation allows us to plan our own actions and also to interpret the actions of others. Rizzolatti et al. (2001) have argued that imitating every observed action is unnecessary and that the purpose of the mirror system is not to reproduce observed actions. However, there is evidence that the motor system is geared up for making actions it observes (cf. Jeannerod, 1994). For example, people change their breathing when observing other people making effortful actions (Paccalin and Jeannerod, 2000) as if preparing to make such actions themselves.

Observing a movement has measurable consequences on the peripheral motor system (Fadiga et al, 1995). Fadiga et al. stimulated left primary motor cortex of human subjects using Transcranial Magnetic Stimulation (TMS) while the subjects observed meaningless actions and grasping movements (and other visual control stimuli). It was found that during action observation there was a decrease in the threshold needed to evoke motor evoked potentials (MEPs) in the hand muscles that would be used to make the observed movements. This was not the case for MEP thresholds from other muscles that would not be used to make the observed movement. Thus, the peripheral motor system seems to prepare to execute observed movements. Moreover, the degree to which action observation activates motor areas is dependent on the level of the skill of the observer (Calvo-Merino et al., 2005). "Mirror" areas, namely the premotor cortex, intraparietal sulcus, superior temporal sulcus, and superior parietal lobule, were activated more strongly when these experts viewed movements they were extensively trained to perform: the human mirror system is sensitive to higher levels of action organization and influenced by training in a particular motor skill.

The mirror network has also been shown to be modulated by contextual/intentional differences between stimuli (Iacoboni et al., 2005). Participants either watched a hand grasp a cup as part of a larger context (e.g., to drink, to clean) or watched the same action without a background context. Greater activation of the ventral premotor cortex was observed when actions occurred within the appropriate context. Thus, context, which provides the goal of the action (e.g. to eat or clean) and from which the intentions of the actor may be deciphered, can modulate the degree of engagement of the mirror network.

I.1.4 Brain mechanisms linking language and action.

The cortical systems for language and action develop specific links between each other whenever actions correlate with specific language processes (figure I2). The theory of embodied semantics states that conceptual representations accessed during linguistic processing include sensory and/or motor representations related to the concept in question (Glenberg and Kaschak, 2002, Feldman and Narayanan, 2004). By this view the perception-action representations developed during action production and comprehension are essential for developing the conceptual representations required to understand language. Thus, to understand action related sentence would require activation of mirror-neuron based representations that would be engaged when perform the action or observing another individual perform this act. Moreover, such conceptual representations would reflect the same form of goal-based specificity observed during action production and comprehension. That is, the concept "grasping" would be represented by motor areas that control grasping actions whereas the concept "kicking" would be represented by motor areas that are involved in actions involving the lower limbs.

Moreover, like action observation, it seems that processing action related sentences has also measurable consequences on the peripheral motor system (Buccino et. al, 2005; Pulvermuller et al., 2005). However, while for action observation there is a general agreement that it determines an increase of the excitability of the primary motor cortex, studies on linguistic processing showed contradictory results. Although there are methodological differences between the papers, during action language processing Buccino (2005) found that TMS led to effector-specific inhibition of the motor area whereas Pulvermuller (2005) proposed that the TMS led to effector-specific facilitation. However, as we will discuss in the chapter four, an alternative interpretation of the Pulvermuller et al. (2005) results can be develop.

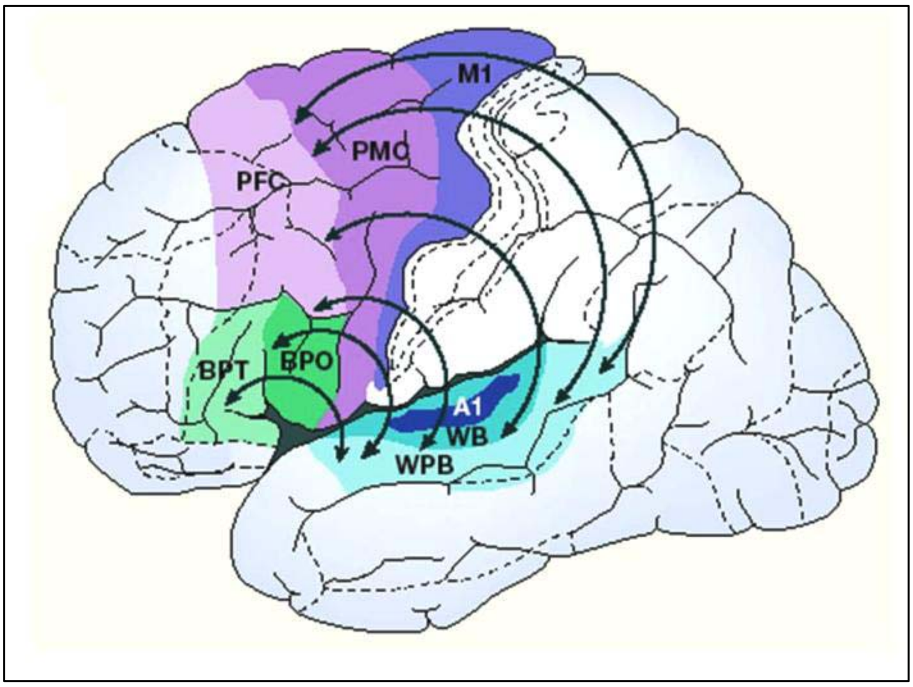

Figure I3 Connections between the language and action systems. Inferences about cortico-cortical links in humans are based on neuroanatomical studies in monkeys. The arrows indicate long-distance cortico-cortical links (from Pulvermuller, 2005).
A1, core region of the primary auditory cortex; BPO, Broca's area, pars opercularis; BPT, Broca's area, pars triangularis; M1, primary motor cortex; PFC, prefrontal cortex, posterior part adjacent to motor system; PMC, premotor cortex; WB, auditory belt region in Wernicke's area; WPB, auditory parabelt region in Wernicke's area.

I.1.5 Gestures elaboration deficit

A specific disturbance of gestures elaboration, in absence of elementary perceptive deficits, and deficit of the force or the motor coordination, has been identified and described from Liepmann (1908), which proposed the use of the term "apraxia". The model of Liepmann (Liepmann, 1908; 1920; 1925), described previously, is born from the clinical observation of patients who showed three different types of deficit in upper limb gestures elaboration: selective disturbances of one of the steps yielded three variants of apraxia. Errors typically resulted from faulty integration of the elements of the action according to their superordinate purpose. These errors were "ideational". As the function of single objects is defined by their relationship to other objects, faulty use of single objects was included in this definition. Liepmann postulated that Ideational apraxia is mainly caused by diffuse brain lesions but also considered the possibility that lesions located at the transition from the occipital to the parietal lobe might cause it.

Failure of the transition from the movement formula to motor innervation characterized the variety of apraxia which Liepmann initially called "motor apraxia" and later proposed the name "ideo-kinetic apraxia" (now know as Ideomotor Apraxia). In this form the kinematics of the extremities are preserved but separated, dissociated from the ideational general scheme of the movement. Ideo-kinetic apraxia was caused by interruption of fibres from the whole cerebral cortex to the motor cortex of the affected limb. Lesions in the white matter below the supramarginal gyrus were thought to have particular strategic importance, because they cut through fibres leading from the optical cortex in the parietal and occipital lobes to the central region (Liepmann, 1920).

Finally, loss of purely innervatory inherent memories of an extremity led to "limb-kinetic apraxia", resulting from lesions to the central region. In contrast to the other variants of apraxia, limb-kinetic was not confined to movements directed by a conscious plan, but affects as well the routine use of objects.

Still today, in clinical setting, the diagnostic criteria of Liepmann are used, but the new cognitive studies have allowed tocharacterize patients with more selective deficit. The alterations to the single components provided from the model formulated from Rothi, et al (1991-1997) determine pictures clinical form not completely assimilable to those provided from the traditional classification. A deficit of the semantic knowledge of gestures, defined as "conceptual" apraxia (Ochipa et al., 1992), could correspond to the ideational apraxia, but such parallelism is not applicable to other cases. A lesion to the input lexicon would determine a selective agnosia for pantomime: the patients cannot comprehend or to discriminate the observed gestures, but they are able to imitating and producing gestures on command (Rothi et al., 1986). Such deficit does not correspond to nobody of the classic diagnostic categories. Conductional apraxia, characterized from the selective damage of the directed way, it would determine a selective disturbance in the imitation of the MLG (Ochipa et al., 1994), and could correspond to the Ideomotor apraxia of Liepmann. However, other cognitive deficits characterized from specific errors in the production of complex movements could be consider you like a variant of the ideomotor apraxia (Ochipa and Rothi 2000).

I.2 Purpose of the thesis

This thesis aims to investigate the cognitive process and the neural basis of action processing and, in particular, of gesture elaboration. The topic has been dealt with in clinical and neuroimaging studies, and the functional role of the fronto-temporo-parietal regions, with a particular focus on the motor and premotor areas.

The first chapter presents a critical revision of neuroimaging findings on the neural basis of gesture processing, with the aim of verifying whether different neural structures are involved in processing various kinds of gestures and with specific reference to the distinction between meaningless (MLG) and meaningful gestures (MFG). The review also proposes an attempt at reconciling cognitive models with available neuroimaging data, and serves as the starting point for further clinical investigation. In the second chapter, the role of the supplementary motor area (SMA) - the major target of basal ganglia output - in the control of voluntary movement was investigated in a functional MRI study on a patient with Tourette syndrome.

The topic of the voluntary control of action has been discussed from a different clinical perspective in the third chapter, by means of a study on the automatic-voluntary dissociation (AVD) in patients affected by disorders of gesture processing (limb apraxia); apraxic patients usually perform the same gestures better in a naturalistic context than upon an examiner's request. The comprehension of the cognitive mechanisms underlying this phenomenon in single patients can provide further information about how the fronto-temporo-parietal network interacts with environment in gesture planning.

Finally, in the fourth chapter, the activity of the primary motor area (MI) has been addressed in relation of the embodiment theory by means of a Transcranial Magnetic Stimulation (TMS) study, in which the effects of action observation and action sentence comprehension on the activity of the motor system in different ways have been compared.

Chapter 1

The neural bases of meaningless and meaningful gestures processing: a review. [2]

Abstract

The distinction between Meaningful (MFG) and Meaningless (MLG) gestures is relevant both to clinical classification frameworks and for comprehension of gesture processing within cognitive models. The specific aim of this review is to verify whether recent functional imaging studies support the view that different neural structures are involved in processing different kinds of gestures, with specific reference to the distinction between MLG and MFG. We selected 16 papers relevant to this issue, from which 27 contrasts and 157 activation peaks were examined.

The main conclusion of our review is that the processing of MFG shares most neural bases with MLG but also involves the activation of additional neural structures. No brain region was demonstrated to be consistently activated by MLG processing; however, several regions that are activated bilaterally in MFG processing appear to be activated predominantly on the right side during MLG processing. We propose an attempt at reconciling cognitive models with recent neuroimaging data, that might best illustrate the role of cerebral regions, and in particular of the fronto-parietal mirror circuit, in gesture processing.

1.1 Introduction

Since the pioneering studies by Liepmann (1905), the operational distinction between well-known, "skilled" or "meaningful" gestures (MFG), and “novel” or “meaningless” gestures (MLG) has had a relevant role in the description and interpretation of gesture production disorders caused by brain lesions. In recent years, the distinction between MFG and meaningless MLG gestures has informed cognitively-oriented models of gesture

---

[2] This section is a modified version of an article with identical title by L. Labruna, C. Colonnese, and L. Trojano which has been submitted in Journal Cognitive Neuroscience

processing (Rothi et al., 1991; Rothi et al., 1997; Cubelli et al., 2000; Peigneux et al., 2004). Although differing in several respects, all models foresee that different cognitive processes are put in motion to observe, recognise or execute MFG or MLG. Therefore, the distinction between MFG and MLG is relevant both to clinical classification frameworks and for comprehension of gesture disturbances within cognitive models, and serves as a starting point to devise neuroimaging studies devoted to understanding the neural basis of gesture production. In fact, several papers have been published focusing on MFG or MLG but results so far are somewhat divergent.

Available reviews on neuroimaging studies of gesture processing have not tried to elucidate the possible divergence in the neural basis of different kinds of gestures, with specific reference to the distinction between MFG and MLG. Koski et al., (2002) and Grezes and Decety (2001) reviewed neuroimaging studies with reference to the kind of task employed in the experimental paradigms, rather than to the kind of gestures elicited. Either study did not address the possible MFG/MLG dichotomy. Other reviews focused only on one specific kind of gesture, mainly TG or tool actions, without contrasting the neural bases of the two kinds of gestures (Johnson-Frey, 2004; Johnson-Frey and Grafton, 2003). This specific issue is the focus of the present paper: a comparison of functional neuroimaging studies involving MFG or MLG could provide relevant information for clinical and cognitive studies of gesture processing.

1.2 Methods

We reviewed neuroimaging papers (both PET and fMRI based) abstracted on MEDLINE and concerned with experimental studies involving observation, production or imagery of MFG or MLG in normal subjects. For the present purposes we have selected studies in which specific, novel or skilled, motor patterns had to be represented or elicited in response to different target stimuli. Therefore, we have excluded from the present review the studies concerned with repetitive motor actions (e.g., finger tapping, finger opposition), unless such tasks were chosen as reference tasks for more complex motor activities. Moreover, we have excluded studies in which subjects had to grasp (e.g., Grezes et al., 2003; Buccino et al., 2001), reach (Connolly et al., 2003) or manipulate objects or geometrical shapes devoid of specific use (e.g. Grezes et al., 2003; Decety et al., 2002; Inoue et al., 2001), or non-tool objects (Binkofski et al., 1999). These last motor activities can be referred to as "action on" objects (Johnson-Frey and Grafton, 2003), and are not used in the traditional clinical assessment of gesture processing (but see Leiguarda and Marsden, 2000, for a discussion of this issue).

Following other reviews of neurofunctional imaging studies (e.g., Cabeza and Nyberg, 2000), we considered the contrasts between different experimental conditions as the most appropriate source of information. In this sense, the word "contrast" is used in a very broad sense to include almost any statistical procedure that yields a set of activations. We did not consider all contrasts discussed in the individual papers, but selected the results we thought best tackled the issue of gesture processing; in several cases, we included multiple entries from individual studies. Regardless of the type of study, we summarised the activations identified by each contrast in terms of Brodmann's areas (BA). Where BA were not provided in the paper, we determined them by locating coordinates in Talairach and Tournoux's (1988) atlas.

For the aim of the present review, we selected 16 papers, from which we considered 27 relevant contrasts. All contrasts are listed in Tables 1.1 and 1.2, according to the kind of gesture and task (imitation, execution on verbal command or observation). We report details about the paper (first author and year of publication), about the experimental and control conditions, and whether the experimental paradigm mainly involved proximal or distal movements. Functional results are displayed in Tables 1.3 and 1.4.

Contrast	Experimental condition	Control condition	Body part
Iacoboni (1999, 2001), Koski (2003)	observation of static left and right hand ML action	observation of static left and right hand with a symbolic cue	finger
Hermsdofer (2001)	discrimination of sequentially presented finger actions	discrimination of pairs of persons	finger
Hermsdofer (2001)	discrimination of sequentially presented hand actions	discrimination of pairs of persons	hand
Peigneux (2000)	judging spatial orientation of ML gestures	judging spatial orientation of meaningless objects	hand
Decety (1997)	observation of ML action (in order to recognize + in order to imitate)	observation of pantomime (in order to recognize + in order to imitate)	hand
Iacoboni (1999)	right hand ML action production by observation of static left hand with a symbolic cue	observation of static left and right hand with a symbolic cue	finger
Krams (1998)	right hand MLG production by observation of static right hand with a cue, after a "go" signal	observation of static right hand with a symbolic cue, after a "go" signal	finger
Iacoboni (1999, 2001), Koski (2003)	right hand imitation of static left hand MLG (Speceular I.)/ right hand imitation of static left and right MLG (Specular and Anatomic I)	right hand ML action production by observation of static left hand with a symbolic cue	finger
Koski (2003)	right hand imitation of static right hand MLG (Anatomic I.)	right hand ML action by observation of static right hand with a symbolic cue	finger
Peigneux (2004)	imitation of dinamic MLG	imitation of dinamic familiar gestures (SG and pantomime of TG)	hand
Tanaka (2001)	imitation of static MLG	imitation of SG	finger
Tanaka (2001)	imitation of static MLG	observation of fixation point	finger
Tanaka (2002)	imitation of static finger MLG	observation of open hand	finger
Tanaka (2002)	imitation of static hand MLG	observation of open hand	hand

Table 1.1 MLG contrasts selected for the review.

The first column provides details about the paper in which each contrast has been reported (first author and year of publication). The remaining columns report details about the experimental and control conditions, and whether the experimental paradigm mainly involved proximal or distal movements. The papers are listed in the Table according to the kind of task and not in chronological order.

Contrast	Experimental condition	Control condition	Body part
Hamzei (2003)	observation of a picture of actual use of object (TG)	observation of a picture of person sitting still	hand
Decety (1997)	observation of pantomime (in order to recognize after scan + in order to imitate)	observation of MLG (in order to recognise after scan + in order to imitate)	hand
Hamzei (2003)	Production of actual use of object (TG) by observing the tool	Observation of three stars in the middle of the screen	hand
Rumiati (2004)	imitating the pantomime observed + pantomiming the use of the object shown	naming the pantomime observed + naming the object shown	hand
Rumiati (2004)	pantomiming the use of the object shown - imitating the pantomime observed	naming the object shown - naming the observed pantomime	hand
Choi (2001)	production of pantomime by reading tool names	production of finger tapping reading function words	hand
Moll (2000)	pantomiming the use of the object by auditory presentation	production of ML action by auditory command (non-tool object)	hand
Peigneux (2004)	imitation of familiar gestures (SG and TG pantomimes)	imitation of MLG	hand
Moll (2000)	Simulation of pantomiming the use of the object by auditory presentation	simulation of ML action production by auditory command (non-tool object)	hand
Ruby (2001)	imagining self-performed TG by observation of tools + imagining self-performed TG by listening to sentences describing familiar actions	passive observation of objects + passive listening to sentences describing landscape	hand
Ruby (2001)	imagining the experimenter performing TG by observation of tools + imagine the experimenter performing TG by listening to sentences describing familiar actions	passive observation of objects + passive listening to sentences describing landscape	hand
Peigneux (2000)	Name aloud SG, visually presented	naming aloud MF intransitive objects, visually presented	hand
Tanaka (2001)	Imitation of SG	observation of fixation point	finger

Table 1.2 MFG contrasts selected for the review.
The first column provides details about the paper in which each contrast has been reported (first author and year of publication). The remaining columns report details about the experimental and control conditions, and whether the experimental paradigm mainly involved proximal or distal movements. The papers are listed in the Table according to the kind of task and not in chronological order.

1.3 Results and discussion

Data reviewed here demonstrate that both hemispheres are involved in MFG and MLG, and that, in each hemisphere, some areas are activated for both kinds of gestures while others are specific for only one kind of gesture. So, we will first discuss areas that are shared by MFG and MLG, and then we will discuss areas that show gesture-specific activation.

1.3.1 Shared Areas

Most areas involved in processing both kinds of gestures were activated during both observation and production tasks, while others were specifically recruited in production tasks.

Production-specific activation (for both MFG and MLG) has been reported in the primary sensory-motor cortex, BA 2 and BA 4, exclusively in the left hemisphere. BA 2 and 4 activation was detected in all experimental conditions requiring subjects to perform actual or imagined movements with the right hand, when the reference task did not include motor activity. Only one study assessed also the left hand, but in this case the activation of the sensory-motor cortex was subtracted by the control condition (Choi et al., 2001).

Also activation of the dorsal portion of the left premotor area (dPM, BA 6) has been repeatedly observed in different experimental conditions, all of which required execution of MFG or MLG. These findings, together with extensive neurofunctional and neurophysiological literature on reaching and planning of simple movements (Caminiti et al., 1996; Johnson-Frey, 2004), suggest that the left dPM could be involved in sensory-motor integration during movement execution (Choi et al., 2001), irrespectively of the scope.

Activation of the left anterior cingulate cortex was detected in two studies on gesture production. Krams et al., (1998) suggested that this region could be involved in the suppression of immediate responses when a delay is interposed between stimulus and response. This interpretation would be consistent with studies in which subjects have to shift between responses or inhibit responses (Taylor et al., 1994). However, activation of BA 24 was recorded also in an experimental paradigm requiring an immediate response (Rumiati et al., 2004). Therefore, the definition of the role of the left anterior cingulate cortex would require further experimental evidence, taking into account also the possible differences in the functional specialization within this region (e.g., Kollias et al, 2001).

The dorsolateral prefrontal cortex (BA 9) is activated exclusively in the left hemisphere, during production of MLG and of real and simulated TG. The DLPFC has been extensively studied in relation to short-term memory tasks and it is now generally acknowledged that this area has a role in working memory (for a review, see Fletcher et al, 2001). The present findings suggest the left DLPFC could serve as the anatomo-functional substrate of a working memory system for keeping motor sequences in mind (Decety et al., 1997; Moll et al., 2000). The working memory system could be involved also in storing and manipulating motor sequences when subjects have to produce movements after a delay (Krams et al., 1998).

Activation within the SMA (BA 6) was found for MFG and MLG, mainly in production but also once in observation tasks. As regards lateralisation, the activation was mainly left unilateral, but also right unilateral or bilateral, without consistent patterns in relation to the kind of gesture or the kind of task. However, taking into account the distinction between SMA proper (posterior to the coronal plane through the anterior commissure) and pre-SMA (Rizzolatti et al, 1996b), it appears that left SMA proper activation was specific for production tasks, while pre-SMA was activated in both observation and production tasks. Therefore, present findings are consistent with the hypothesis of a different role of SMA proper and pre-SMA in gesture processing. Pre-SMA appears to be involved in earlier stages of motor processing, such as selection and/or preparation of a motor program (Lee et al, 1999) or in the representation of intention to do the action (Lau et al, 2004). SMA proper, instead, was activated only when subjects had to produce actual or imagined gestures. Therefore, it is possible to argue that

SMA proper is involved in later stages, such as initiation of complex motor programs (Lee et al., 1999). However, the specialisation of pre-SMA and SMA proper in gesture processing has to be verified by studies in which the possible overlap of activation clusters in the two areas is specifically controlled.

Among areas activated during both production and observation tasks, special attention in literature has been devoted to the frontal operculum (BA 44). From the present review it appears that BA 44 was activated in a few contrasts, involving observation and production of both MLG and MFG, in most cases only in the left hemisphere, but in three studies bilaterally. Krams et al. (1998) suggested that Broca's area has a specific role in the selection of actions on the basis of imitation, but, since it is involved in many gesture observation and production tasks, most authors argue that Broca's area show the same properties as mirror neurons in non-human primates (Iacoboniet al., 1999; Iacoboni et al., 2001; Koski et al, 2003; Hamzei et al., 2003). Other studies not reviewed here suggest that Broca's area represents the putative homologue of area F5, specifically involved in grasping (Binkofski et al., 1999; Buccino et al., 2001). More recently, an fMRI study in which subjects looked at pictures of the same objects being grasped or touched, demonstrated that BA44 is selectively activated when subjects passively observe the realised goals of hand-object interactions (Johnson-Frey et al., 2003). This study was consistent with the view that BA 44 activation was specifically correlated to actions that, like grasping, require a specific configuration of fingers (Johnson-Frey and Grafton, 2003). Combining such observation and data reviewed here, showing BA 44 activation only in studies on MLG and on MFG that specifically involved fingers, we can suggest that the role of Broca's area is specific to processing internal motor representations of finger movements.

Only a few studies showed activation of the ventral premotor cortex (vPM, BA 6). In one study on object-related actions the activation was bilateral (Rumiati et al., 2004), while it was unilateral in two constrasts assessing production (left; Tanaka and Inui, 2002) or observation of MLG (right; Decety et al., 1997). These findings would suggest that vPM could have a role in the elaboration of internal motor representations, regardless of the type of gesture, in analogy with the adjacent BA 44. The vPM activation in tool naming (Chao et al., 1999), in generating action words related to visually-perceived tools (Grafton et al., 1997), and in judging tool functions or tool-associated actions (Kellenbach et al., 2003), could be explained by the implicit access to related motor representations.

As for parietal regions, activation of the supramarginal gyrus, BA 40, has been reported in 16 contrasts, during observation and production of both MLG and MFG. Although the supramarginal gyrus is the area most frequently activated across different studies, it is worth underlining that the lateralisation of the activation is not consistent. Bilateral activation has been reported in three studies on MLG, while selective left or right activation has been reported either in MLG or in MFG studies. The issue of the lateralization of BA 40 activation cannot be simplified to any straightforward interpretative schema, as for instance in consideration of the control conditions of different experiments or of distinctions between finger vs. hand movements, or observation vs. production tasks.

Peigneux et al. (2004) and Tanaka et al., (2001) argued that the activity in the left BA 40 in imitation of MLG could be related to computational processes that code features of novel gestures as a combination of simple familiar movements, with reference to previous knowledge of the human body structure (Goldenberg, 1995). A substantially similar position was held by Ruby and Decety (2001), who claimed that left BA 40 has a role in programming movements that can be potentially transformed into execution, also in TG imagery tasks. Our review seems to support such interpretations, while Rumiati et al.'s (2004) suggestion that left BA 40 is involved in object-related actions is not consistent with the finding that BA 40 activation has been reported also in MLG experiments.

As for the right BA 40, Decety et al. (1997) and Krams et al. (1998) suggested that it is involved in processing spatial properties of visually presented gestures. Findings by Hermsdorfer et al., (2001) and Tanaka et al. (2001) could support this interpretation, since both studies reported right BA 40 activation only for finger movements, which probably require careful spatial analysis of finger position. However, it must be noted that unilateral activation of the right BA 40 has also been reported by Peigneux et al. (2004) in the contrast between imitation of familiar versus novel hand movements, thus rendering less straightforward this interpretative hypothesis. Finally, the activation of the right inferior parietal lobe (operculum, BA 40) has been interpreted as due to reafferent sensory signals associated with action performance (Iacoboni et al., 1999; Iacoboni et al., 2001; Koski et al., 2003).

While it is not possible to support strong claims about the different roles of left and right BA 40 activation, reviewed data suggest that the supramarginal girus, involved independently of the kind of gesture in both production and observation tasks, has a specific role in the context of a mirror system devoted to representing elementary motor acts (Buccino et al., 2004b ; Iacoboni et al., 1999, 2001; Koski et al., 2003).

The superior lateral parietal lobule (BA 7) has been described in both MLG and MFG observation and production tasks, mainly in the left hemisphere, but three times bilaterally and once exclusively in the right hemisphere. Hermsdorfer et al. (2001) reported BA 7 activation in the right hemisphere during discrimination of finger gestures and in the left hemisphere for hand gesture discrimination. From these findings, the authors argue that the right superior parietal lobule (as well as Intraparietal Sulcus, IPS) could be activated in relation to higher demands on precise visuospatial analysis in finger gestures. A similar position was held by Decety et al. (1997), who claim that right BA 7 and BA 40 share a role in visuospatial analysis of the stimulus, within a right occipitoparietal network involved in MLG processing. Tanaka & Inui (2002), too, suggest that right BA 7 activation is specific for finger gestures, although this conclusion does not closely follow BA 7 activation patterns observed in their study on imitation of hand (bilateral activation) and finger (left activation) MLG.

As for the left BA 7, Choi et al. (2001) maintained that it could play a key role in pantomiming tool actions, regardless of the hand used. However, this position is not supported by our review, because the left superior parietal lobe was also activated in MLG studies. The inspection of precise location of activation peaks reported within BA 7 (Fig. 1) would suggest that most of them are in fact located in close proximity to the anterior part of IPS, as if this region represented an integrated area crucially involved in the processing of MFG and MLG.

Indeed, 13 contrasts reported activation of the IPS, nine of which were in the anterior part (BA 7/40) and the other two were in the posterior part of the sulcus (BA 7/39). Lateralisation of activation seems to be consistent: anterior IPS activation has been reported in the right hemisphere for both MLG and TG, and in the left hemisphere only for TG. Moreover, also the posterior part of the IPS (BA 7/39), bilaterally, seems to be specific for TG production. Therefore, findings converge in suggesting that the right anterior IPS might serve as a common neural substrate for gesture processing, irrespectively of the content, in both observation and imitation of gestures, and more specifically for coding the precise kinaesthetic aspects of movements (Iacoboni et al., 1999). On the basis of our review, it is possible to exclude alternative explanations of IPS activation in terms of visuospatial attention (Nobre et al., 1997), since IPS was activated also in tasks with auditory presentation of stimuli (Moll et al., 2000). Therefore, the right anterior IPS, as well as BA 40 and BA 7 bilaterally, could be part of a mirror system involved in the coding of elementary motor actions and of their motor-kinestesic aspects. This hypothesis would be entirely consistent with the idea that the anterior parietal lobule is a region involved in multiple parallel parieto-frontal circuits devoted to the transformation of sensory information into action (Rizzolatti and Arbib, 1998), not specific for tool use. However, present findings suggest that several regions along the IPS would be recruited only in processing TG, as will be discussed below (see section on MFG specific activation).

Only a few studies reported activation within the temporal lobes and the location of activation peaks appears to be quite variable. MLG observation and production tasks activated the right superior or inferior gyrus and the right superior sulcus, but also the left superior temporal gyrus. MFG observation and production tasks showed activation of left temporal gyri, mainly in the posterior regions. Although activation peaks related to both MFG and MLG processing have been attributed to different anatomical structures, most of them were centred in the posterior temporal regions, as confirmed by the comparison of their Talairach coordinates in Fig. 1. Moreover, these peaks referred to quite large activated clusters, so it is plausible to argue that the posterior temporal region, including and surrounding the superior temporal sulcus (STS), plays a specific role in gesture analysis (Decety et al., 1997; Peigneux et al., 2000). Iacoboni et al. (2001) suggested that, in terms of information processing, regions around the right STS might provide an early description of the observed action to parietal and frontal mirror neurons, and also monitor the action to be imitated. This interpretation is consistent with findings of a bilateral activation of the posterior part of the STS during observation of biological motion (e.g., Saxe et al., 2004).

Activation of the occipito-temporal junction (BA 19/37) has been reported in 9 contrasts, mainly in the left hemisphere but also bilaterally. The occipito-temporal junction activation was present in discrimination of both hand and finger MLG, judgement of spatial orientation of MLG, recognition of SG, and observation, production and simulation of TG in both first and third person perspectives. Since this area encroaches upon visual area MT/V5, responsible for actual or imagined visual motion processing (Watson et al., 1993; O’Craven et al., 1997), it would be involved in processing movement-related information (Hermsdorfer et al., 2001;

Peigneux et al., 2000; Hamzei et al. 2003; Rumiati et al. 2004; Ruby and Decety, 2001). Peigneux et al. (2004), moreover, underlined that bilateral activation of area MT/V5 during actual imitation was due to the gesture observation component, but it might be additionally activated during gesture production, especially when the performed gesture involves positioning the arm in extrapersonal space.

Bilateral activation of occipital areas (BA 18, BA 19) has been reported mainly in MLG observation (in particular, with finger gestures) but also in one study on SG observation, in the left hemisphere. Such an activation could be related to the visual analysis component. Actually, it is possible to speculate that MLG and SG observation requires additional analysis of form and shape information with respect to MFG (Hermsdorfer et al., 2001). In both studies reporting occipital activation related to MLG observation, the experimental paradigm enclosed control conditions with at least comparable visual analysis requirement, so findings cannot be ascribed to methodological flaws.

Finally, evidence about involvement of subcortical structures in gesture processing is quite scarce. The left putamen has been reported to be activated in both MLG and TG production with the right hand. Cerebellar activation has been reported in 8 contrasts, mainly for MFG but also in an MLG study, in either hemisphere. All tasks involved gesture production (actual, imagined or planned); the only observation task that activated the cerebellum required subjects to observe gestures in order to reproduce them after scanning time. It has been argued that the cerebellum is involved in controlling complex (versus simple) and multi-joint (versus single-joint) movements (Thach et al., 1992). However, present findings demonstrate that the cerebellar activation was found also in simple finger gesture production, and are consistent with the view that the cerebellum is involved in monitoring and optimising movements on the basis of sensory (proprioceptive) feedback (Jueptner and Weiller, 1998).

1.3.2 TG specific areas

Among the MFG specific areas, all regions, but one, were specifically activated in TG processing and not in SG, and this would suggest that they are related to tool representation and tool-related actions.

Prefrontal areas (BA 45, 47, 11) are activated in both hemispheres exclusively for TG, in observation and production of pantomimes. Decety et al. (1997) reported left BA 45 activation in observation of TG, irrespectively of the subsequent scope, and suggested that it could be involved in action recognition, as already suggested by Rizzolatti et al. (1996). Moreover, in the same contrasts, two foci of activation were observed in the orbital frontal region (left in BA 47, right in BA 11), that could be related to inhibition of actions to be reproduced later. However, the inferior prefrontal cortex could also be associated with visuomotor transformation for grasping and manipulating objects, in the left hemisphere (Binkofski et al., 1999) or bilaterally (Johnson-Frey et al., 2003). Since similar activation was reported in tool naming and object observation (Chao and Martin, 2000), it is possible to suggest that the left anterior and the left inferior prefrontal regions (BA 47 and the inferior part of BA 45) are involved in semantic processing, and in particular in retrieving, maintaining, monitoring and manipulating semantic representations stored elsewhere (Wagner, 1999).

More consistent evidence has been gathered about TG-specific activation in the left anterior IPS (BA 7/40) and in the posterior part of the IPS (BA 7/39), bilaterally. These findings could be related to activation of the left posterior inferior parietal cortex (BA 39) reported in one study on imitation of familiar gestures. The anterior IPS could represent the homologue of the AIP in monkeys (Binkofsky et al., 1999), and was activated in the left hemisphere in both observation and production of actual or imagined TG. Therefore, it is plausible that this region is part of the parietal mirror circuit (Hamzei et al., 2003), but, in the left hemisphere it appears to be specialised in storing engrams of tool-related actions. However, according to a recent review on grasping and reaching movements (Johnson-Frey and Grafton, 2003), the anterior IPS could be involved in the transformation of object-intrinsic spatial properties into hand configurations in humans, while the left posterior IPS could be involved in on-line correction of the unfolding reaching schema. While these conclusions are based on a large body of experimental results, it is worth underlining that most contrasts showing TG-related activation in these areas implied pantomiming of tool use in the absence of the actual objects, therefore not implying reaching or grasping movements. These apparently contrasting hypotheses, one suggesting that IPS is involved in reaching and grasping tools and objects, and the other postulating a specific role of the left anterior IPS and of bilateral posterior IPS in the representation of skilled tool-related actions could be reconciled. Actually, reaching and grasping movements are indeed based on the activation of skilled motor programs, or, alternatively, even pantomiming object use could implicitly activate grasping and manipulating motor representations. Specific experimental studies are necessary to disentangle the two alternatives.

At the moment, on the basis of the present findings, we could suggest that, while the right anterior IPS could have a role in coding the precise kinaesthetic aspects of movements as discussed above, the left anterior IPS (BA 7/40) and the bilateral posterior IPS (BA 7/39) could be involved in processing the kinesthetic gestural representations related to tools. Moreover, the anterior part of the parietal lobe (BA 40, BA 7/40) in both hemispheres (but with different specific functions) seems to participate in a fronto-parietal mirror circuit, whereas the posterior parietal areas (BA 39, BA 7/39) seem to be specifically involved in gesture production.

The precuneus (BA 7) was activated bilaterally only in an experimental condition requiring mental simulation of TG in the third-person perspective. Ruby & Decety (2001) suggested that this region of the parietal lobe could have a prominent role in distinguishing self movements from those generated by others. This hypothesis has not been tested in other studies.

Activation of the temporal lobe specific for TG were found in the middle and in the inferior temporal gyrus, and in the hippocampus bilaterally. A left posterior inferior temporal activation (BA 37) was observed only by Choi et al. (2001) in pantomiming TG with the right (but not with the left) hand. The authors suggested that this area could have a prominent role in storing conceptual knowledge of tools and related actions, since BA 37 is known to be associated with lexical retrieval of words designating tools (Buchel et al., 1998) and with semantic processing of objects (Boucart et al., 2000).

The anterior part of the left middle temporal gyrus (BA 21), activated during observation of TG pantomimes, could have a role in semantic object processing (Decety et al., 1997), consistent with studies on recognition of visually presented tools (Chao et al., 1999; Kellenbach et al., 2003).

Finally, only the study by Decety et al. (1997) showed a bilateral activation of the hippocampal gyrus (BA 28), when subjects had to memorise TG pantomime. The authors interpreted this activation related to memory stored of semantic aspect of action, but this hypothesis is not supported by other experimental evidence.

1.3.3 SG specific areas

Among the MFG specific areas, no areas were found to be specifically activated in SG processing and not in TG. The MFG specific areas involved in both TG and SG could be related to the activation of semantic information not specific for the kind of the evoked motor program. The left middle temporal gyrus conformed to this pattern since it was reported to be activated by both kinds of gestures, but in different locations (Fig. 1). The temporal activation found during SG naming was indeed located in the posterior part of the gyrus, and therefore can be related to visual analysis of biological movements, as discussed above.

1.3.4 MLG specific areas

Apart from the left paracentral lobule (medial parietal lobe, BA 3), activated in only one MLG imitation task, no areas have been found to be activated specifically for MLG. This finding does not support Peigneux el al.'s (2004) claim about the existence of different routes for MFG and MLG gesture processing. In particular, the authors suggested that, in MLG imitation, the transformation from vision to action is mediated by the left inferior parietal lobe (BA 40), but our review would demonstrate that this area is involved in coding features of both familiar and novel gestures. Thereofore, we suggest that MLG processing recruits the same cortical areas as MFG, but requires more extensive activation of several temporo-occipital areas, mainly in the right hemisphere, involved in visual analysis of form and shape features and related to biological motion perception (see above).

MLG	**F**											**P**								**T**					**T,O**	**O**	**subcortical**	
Contrast	**11**	**47**	**45**	**9 VL**	**9 DL**	**44**	**6 vPM**	**6 dPM**	**6 SMA**	**24 cing**	**4 MI**	**3 par ac**	**2 SI**	**40 SMG**	**39 ANG**	**7/40 aIPS**	**7/39 pIPS**	**7 lat**	**7 med**	**22 sup**	**21/22 STS**	**39, 21 mid**	**37 inf**	**28 Hip**	**19/37**	**18 & 19**	**cereb**	**basal ganglia**
Iacoboni (99, 01), Koski (2003)						x										o					o							
Hermsdofer (01)														*		o		o							x	*		
Hermsdofer (01)									*					X				x							x			
Peigneux (2000)																				o		o			*			
Decety (1997)							o							O				*					o			*		
Iacoboni (1999)						x										o												
Krams (1998)					x	*		x		x	X		x	*						x							*	x
Iacoboni (99,01), Koski (2003)						*			O					O		o					o							
Koski (2003)												x		O							o							
Peigneux (2004)														X														
Tanaka (2001)											X		x	O														
Tanaka (2001)								x	X		X		x	*													o	
Tanaka (2002)						x	x							X				x										
Tanaka (2002)																		*										

Table 1.3 Summary of functional results for MLG. The locations of the 157 activation peaks are reported in reference to Brodmann's areas (BA). The first columns identify the contrast as in Table 1.1, while the remaining columns report locations of the cerebral activations in each contrast with reference to Brodmann's areas. X: left hemisphere; O: right hemisphere; *: bilateral.

MFG	**F**											**P**								**T**					**T,O**	**O**	**subcortical**	
Contrast	**11**	**47**	**45**	**9 VL**	**9 DL**	**44**	**6 vPM**	**6 dPM**	**6 SMA**	**24 cing**	**4 MI**	**3 par ac**	**2 SI**	**40 SMG**	**39 ANG**	**7/40 aIPS**	**7/39 pIPS**	**7 lat**	**7 med**	**22 sup**	**21/22 STS**	**39, 21 mid**	**37 inf**	**28 Hip**	**19/37**	**18 & 19**	**cereb**	**basal ganglia**
Hamzei (2003)						x								X		x		x							x			
Decety (1997)	o	x	x																			x		*			x	
Hamzei (2003)						*		*	*		X		x			*		*							*		o	
Rumiati (2004)			*		x		*		x		X			O											*		o	x
Rumiati (2004)				x	x					x				X		x												
Choi (2001)								x	x									x					x				x	x
Moll (2000)					x			x					x			*	*											
Peigneux (2004)					x									O	x													
Moll (2000)					x			x					x			*	*											
Ruby (2001)									x		X			X											x		x	
Ruby (2001)									x		X								*						x			
Peigneux (2000)																				*		*			*	x		
Tanaka (2001)								x	x		X		x	X													o	

Table 1.4 Summary of functional results for MFG. The locations of the 157 activation peaks are reported in reference to Brodmann's areas (BA). The first columns identify the contrast as in Table 1.2, while the remaining columns report locations of the cerebral activations in each contrast with reference to Brodmann's areas. X: left hemisphere; O: right hemisphere; *: bilateral.

1.4 Concluding Remarks

The present paper aimed to verify whether recent functional imaging studies support the view that different neural structures are specialised in processing different kinds of gestures. The reviewed papers, specifically concerned with MLG or MFG, converged on several points. However, several brain regions were found to be activated in only one contrast (for instance: in the right hemisphere: BA 11, 45, 6 dPM, 19; in the left hemisphere: BA 47, 9 VLPFC, 39, paracentral lobule BA 3; bilaterally: BA 7 precuneus, 37, 28), and others were reported only in a very limited number of contrasts. No brain region was reported to be activated in all contrasts, even among those considered most likely to be involved in gesture processing. Of course, these findings must be interpreted taking into account that the studies reviewed here employed study paradigms that differed not only for the specific experimental condition, but most of all, for the reference tasks. With these caveats in mind, and taking into account only the areas that showed more than one activation, some conclusions can be drawn.

The main finding was that processing of MFG shares most neural bases with MLG but also involves the activation of additional neural structures. Moreover, among MFG specific areas, most cerebral regions were activated only in TG processing, while no brain region was specifically activated by SG processing. No brain region has been consistently demonstrated to be MLG specific; however, several regions that are activated bilaterally in MFG processing appear to be activated predominantly on the right side during MLG processing.

The discussion of the possible role of different brain regions involved in both MLG and MFG processing has highlighted that the “shared areas” may be responsible for observation, coding, planning and execution of all kinds of gestures. Among these, some brain regions are task-specific, and others are not.

Task-independent cerebral areas were activated during both gesture observation and production. This finding suggests that the observed action evokes a discharge in the same neurons that fire when the action is performed. Such an activation pattern conforms to the hypothesis of an execution-observation matching system, namely the mirror neuron system (Iacoboni et al., 1999; Iacoboni et al., 2001; Buccino et al., 2004b). Evidence from the studies reviewed here strongly supports the specific role of Broca's area in processing finger movements in both MLG and TG. The anterior parietal lobe, instead, seems to be involved in a system implied in processing elementary components of perceived or performed movements, likely in relation to topographical organisation of body parts (Goldenberg, 2001; Hermsdorfer et al., 2001). The right anterior IPS might serve as a common neural substrate for gesture processing, irrespectively of the content, coding the precise kinaesthetic aspects of movements.

All the "shared" areas discussed so far can be considered as a complex, interconnected, pathway that enables humans to imitate novel and familiar gestures. By practice, it is possible to acquire complex motor schemata, as those used in skilled utilisation behaviour, implemented in dedicated cerebral regions. These regions have been operatively identified as those specifically reported in contrasts tapping MFG. However, only a few of these showed consistent activation across several studies. The left anterior IPS (BA 7/40) seems to have a role in representing complex skilled motor schemata related to tool use, and is organised respecting the mirror principle, because it is active during observation and production tasks. Moreover, during TG production tasks, there was also additional recruitment of the bilateral posterior IPS (BA 7/39). This area was not activated by observation tasks, so, it could be considered as the neural basis of kinesthetic gestural representation related to tools. However, the few available data do not allow precise localisation of activation within posterior IPS and parietal regions (Moll et al., 2000).

Finally, the activation of the posterior temporal areas around STS and of the occipito-temporal junction (BA19/37, area MT/V5), independently of tasks and stimuli, suggests that these areas are activated during processing of visual movement-related gesture information, even in tasks involving only static postures, that likely imply the idea of biological motion (Peigneux et al. 2000, Hermsdorfer et al., 2001). In this case, the activation is related to visual analysis of biological movements and of moving stimuli, and the involvement during gesture production tasks could have the purpose of monitoring gesture production.

Production specific areas include primary and secondary sensitive-motor areas, BA 2 and BA 4, that have been found to be activated in the left hemisphere only in experimental conditions requiring actual or imagined movements. The same tasks activated the left dPM and SMA proper (BA 6), and we suggest that these areas are involved in the implementation of motor schemata in reference to their component single acts, but not specifically for reaching and grasping (as suggested by related papers not included in the present review). Also the left DLPFC (BA 9) was specifically involved in gesture production, mainly in TG but also in one MLG contrast. DLPFC could be considered as the anatomo-functional substrate of a working memory system for keeping motor sequences in mind (Decety et al. 1997; Krams et al., 1998; Moll et al., 2000). Regarding subcortical structures, task-dependent activation specific for production was seen in the left putamen, activated in pantomiming gestures with the right hand, and in the cerebellum, activated in several studies involving actual, imagined or planned production of gestures. In this respect, our review would support the idea that basal ganglia and the cerebellum do play a role in the execution of complex movements, but the limited amount of studies showing basal ganglia activation, and the lack of consistency in the lateralisation of cerebellar activation, would require further experimental evidence to define the respective role of these structures.

The present findings have several implications for cognitive models of upper limb apraxia (Rothi et al., 1991, 1997; Cubelli et al. 2000, Buxbaum et al., 2000; Peigneux et al., 2004). Actually, functional neuroimaging studies provide constraints for such models, and impose the refinement of hypothesis about the cerebral organisation of gesture processing. An in-depth discussion of relationships between present functional data and findings from clinical and experimental studies on brain-damaged patients is beyond the scope of the present paper. However, we believe that an attempt at comprehending the neural and cognitive basis of gesture processing has to take into account the functional data from different experimental paradigms. As a conclusion of the present paper, we want to tackle some controversial aspects of current theoretical cognitive models and sketch an outline of a possible reconciliation between cognitive models and functional data.

First, all cognitive models agree in identifying a visual gesture analysis component in gesture imitation. The present data would demonstrate that visuo-gestural analysis is based on activity in the posterior temporal region and in temporo-occipital junction, regions that participate in real and implied motion processing, and in biological motion perception, respectively. These areas have been reported to be activated also during gesture production tasks, likely with a monitoring function.

Second, the present review demonstrates that imitation of novel or familiar gestures may proceed through the activation of the same pathway, and that additional cortical regions are specifically involved in MFG processing. Most cortical areas have been shown to be activated during MFG and MLG processing, and we infer that they could ensure imitation of gestures, irrespectively of their kind. The core of this system is represented by a distributed fronto-parietal mirror circuit (including the Broca’s area and vPM, the anterior and the superior parietal regions), which contains an inner vocabulary of simple motor acts and has the role of coding elementary motor acts and in parsing complex (novel or familiar) movements in their basic component acts. Therefore, data reviewed here confirm that a unifying system deputed to representation of actions may be used for various purposes, namely action generation and imitation (Rizzolatti and Luppino, 2001).

This system, therefore, would represent the equivalent of the so-called direct route for gesture imitation foreseen by most cognitive models (Rothi et al., 1991, 1997; see also Peigneux et al., 2004). The damage to this system by a focal cerebral lesion could generate an impairment in imitating MLG and MFG. However, MLG processing more extensively relies on several areas specialised in analysing visual information, in particular in the right hemisphere, while MFG production can proceed via the activation of cortical areas (the left anterior IPS) that appear to be specialised in representing and processing skilled movements. From this point of view, it is possible that selective focal cerebral lesions generate relative dissociations between MLG and MFG imitation (e.g., Goldenberg and Hagmann, 1997).

Third, the controversial distinction between two cognitive components specifically responsible for skilled action recognition and production (the so-called input and output praxicons; Rothi et al., 1991, 1997) is not supported by present findings. In fact, no areas have been found to be activated specifically for MFG observation and recognition. In agreement with Peigneux et al. (2004), our data support the idea that one single system (the so-called "praxicon") is actually responsible for representing, and holding in long-term memory, sequences of skilled movements. In other words, areas involved in storing long-term representation of skilled movements appear to be involved also in processing (and recognising) visually perceived gestures. This cognitive component, therefore, appears to be organised according to the general "mirror" principle: more specifically, the left anterior IPS, one region of the fronto-parietal mirror circuit, could be the neural basis of the praxicon since it is specialised in representing

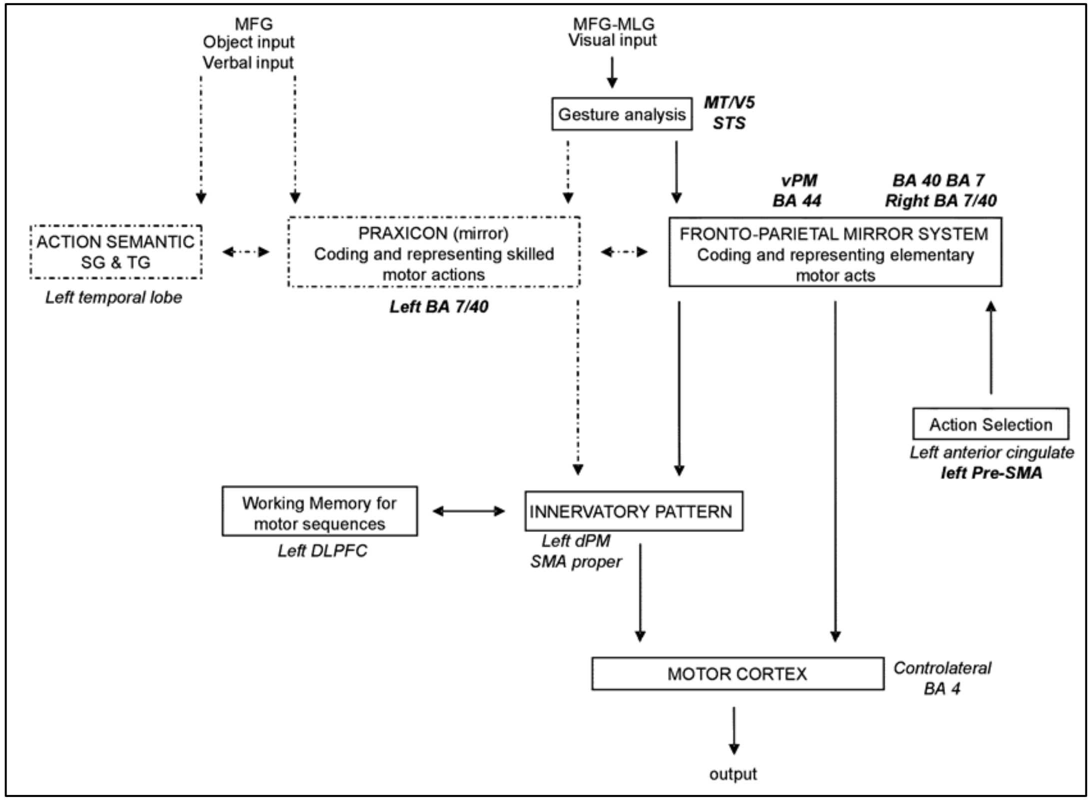

Figure 1.1 A provisional integrated model of gesture processing. A provisional model reconciling cognitive and functional data on gesture processing. Solid arrows and squares indicate the common flow of information of both MFG and MLG, broken line arrows and squares indicate the MFG specific components. Cursive refers to the anatomical substrate of the cognitive components; cortical areas involved in gesture observation and production, including the mirror system, are printed in bold. Where the hemispheric lateralization is not specified, cortical activation is intended to be bilateral.

skilled actions, including actual or pantomimed tool use and, possibly, purported tool use (on the basis of data showing the activation of the fronto-parietal mirror circuit when the action is performed behind a screen; Umiltà et al., 2001). The posterior IPS (BA 7/39) and the posterior parietal regions (BA 39) could be also involved in processing MFG, but evidence available so far does not allow strong claims about their role. The existence of the so-called "representational" route (Rothi et al., 1991, 1997; Peigneux et al., 2004) for imitation, one specific for imitation of skilled movements, would rely on the possible direct access to the praxicon from cortical areas devoted to visual analysis. This remains an open question.

Fourth, all modern cognitive models (e.g., Rothi et al., 1991, 1997; Cubelli et al. 2000; Peigneux et al., 2004) support the hypothesis of the existence of a long-term memory system specifically devoted to storing conceptual information on gestural behaviour. This cognitive component would be involved in performing MFG upon verbal command or on visual presentation. Although such a component is logically plausible and its existence would explain some findings in brain-lesioned patients (Heilman et al., 1997; Dumont et al., 2000), present functional findings still do not provide conclusive information. Therefore, also the segregation of the so-called action-semantic system has not received strong support by available functional data.

Finally, we suggest that several areas, activated only in production tasks and shared by MFG and MLG, can represent the neural basis for implementation of complex motor schemata with reference to their component single acts. Gesture representations computed by the fronto-parietal mirror circuit would feed, for the actual production of selected movements, frontal areas specifically involved in motor integration and execution (dPM, SMA, MI). Several subcortical structures (basal ganglia, cerebellum) would be devoted to movement implementation and control. Among frontal areas, dPM and SMA proper are strongly interconnected with primary motor cortex and could participate in performing integrated motor schemata. In Liepmann's terminology (1905), these areas would represent the cortical substrate of innervatory patterns, that are implemented via other cortical structures. In this respect, cognitive models usually do not take into account several additional components that yet are involved in gesture processing. The present review, instead, highlights that production of motor sequences often implies a working memory load possibly expressed in functional studies by activation of the left DLPFC, and that other areas likely participate in action selection and in inhibition of non relevant motor acts (the anterior cingulate gyrus, pre-SMA). However, these issues have to be specifically addressed by future functional studies.

The present provisional model is consistent with most studies on motor organisation in primates and human beings, but its heuristic value remains to be specifically verified. We suggest that such an integrated approach to cognitive and functional studies on gesture processing could serve as a starting point for devising new functional studies on the issues still open to discussion. Moreover, we hope that it will provide an interpretative framework for improving the comprehension of clinical findings in brain-damaged patients.

Chapter 2

2. Gilles de la Tourette syndrome and voluntary movement: A functional MRI study[3]

Abstract

Tourette syndrome (TS) is hypothesised to be caused by an abnormal organization of movement control. The aim of this study was to use functional magnetic resonance imaging to study motor cortex activation in a TS patient. Usual and unusual self-paced voluntary movements were performed. The TS patient displayed supplementary motor area (SMA) activation during both tasks. This activation reflects a continuous use of the SMA to perform the voluntary motor movements required in both tasks. Moreover, the absence of tics during the execution of these voluntary motor tasks suggests that tic activity may be suppressed by additional mental effort.

2.1 Introduction

Tourette syndrome (TS) is a disorder characterised by irregular motor and vocal tics (whose onset usually occurs in childhood), attention deficit hyperactivity disorder, obsessive–compulsive disorder and learning difficulties (Leckman, 2002). TS has been ascribed to various factors including inherited genetic vulnerability, prenatal and perinatal insults, or bacterial and viral infections (Robertson, 2000). The neuropathology underlying TS is unknown (Moriarty et al., 1997). The pathophysiology of TS has been associated with dysfunction of both the basal ganglia and related thalamo–cortical circuits (Singer, 1997; Bradshaw and Sheppard, 2000). Neuroimaging data have shown reduced volumes and abnormal asymmetries in the caudate, putamen and globus pallidus in TS patients (Peterson et al., 1998; Singer et al., 1993; Hyde et al., 1995). Moreover,

---

[3] This section is a modified version of an article with an identical title by Fattapposta F, Restuccia R, Colonnese C, Labruna L, Garreffa G, Bianco F. which has been published in Psychiatry Res. 2005 Apr 30;138(3):269-72

studies conducted with PET and electroencephalography (EEG) suggest that motor function is abnormally organized in TS (Stern et al., 2000).

Numerous studies (Shibasaki et al., 1993; Gerloff et al., 1997; Erdler et al., 2001) have pointed to a dysfunction in TS patients of the supplementary motor area (SMA), which controls above all the initiation of complex motor programs (Lee et al., 1999). The aim of this study was to use functional magnetic resonance imaging (fMRI) to evaluate the cortical motor circuit in a TS patient using both a usual and an unusual self-paced voluntary movement.

2.2 Methods

2.2.1 Subject

We describe a 24-year-old man with childhood onset of involuntary movements and stuttering that became increasingly marked. There is no family history of any neuropsychiatric or autoimmune disorder. No prenatal or infectious risk factors or drug abuse problems have been reported. He is right-handed. The patient is a professional kickboxer who represents a remarkable case because he becomes tic-free when he fights.

The neurological examination showed multiple motor and vocal tics, coprolalia, echolalia and rituals. No other neurological signs were present. The patient was evaluated with neurophysiological tests, EEG and MRI, all of which were normal. Routine laboratory studies, including thyroid function tests and serum immunologic analysis, were also normal.

The TS patient was compared with an age-matched control subject. Both subjects gave their informed consent before they were enrolled in the study, as specified in the Declaration of Helsinki.

2.2.2 Imaging data acquisition and motor task

Functional MR images were acquired by means of a GE LX SIGNA NV/I 1.5 T equipped with a SUN Ultra 60 workstation for Real Time Imaging (GE Medical System, Milwaukee, WI). A gradient echo EPI single shot pulse sequence was used with the following parameters: echo time=60; matrix =64 64; field of view =24 cm; number of slices =10; thickness=5 mm; spacing=3 mm; 100 image volumes with a repetition delay of 3 s. Each study consisted of 10 on and 10 off phases and a total acquisition time of 5 min.

Task performance was visually monitored during the fMRI study. The motor task used is a repetitive, bilateral tapping of the index finger compared with the little finger, such as those used in other movement disorders (Biswall et al., 1998; Erdler et al., 2001; Serrien et al., 2002).

During fMRI, the patient performed a repetitive, bilateral index finger (usual) and little finger (unusual) tapping task in two separate block designs of 30 s, alternated with a 30-s rest period, a total of 5 times for each paired block. The patient was instructed to perform the movement as quickly as he could. The tapping speed for both conditions was assessed by an independent examiner.

2.2.3. Data analysis

Statistical data analysis was performed on a SUN Ultra 60 with Functool 2000 (GE proprietary software) by means of a t-Student routine; activated pixels in the sensorimotor cortex and SMA are shown using colour scale coefficient correlation maps with a range of 0.6–0.8 and a confidence level of 0.001.

2.3 Results

Activated pixels in the premotor cortex region and the SMA were detected in both subjects. In the control subject, significantly increased premotor cortex and SMA activation was seen during the unusual task alone; premotor cortex activity was more evident than SMA activity during the usual task. By contrast, no significant fMRI differences were observed in the TS patient, in whom the premotor cortex and SMA were activated during both the usual and unusual tasks (Figure 2.1). It is remarkable that the patient displayed no tics while performing either of these tasks.

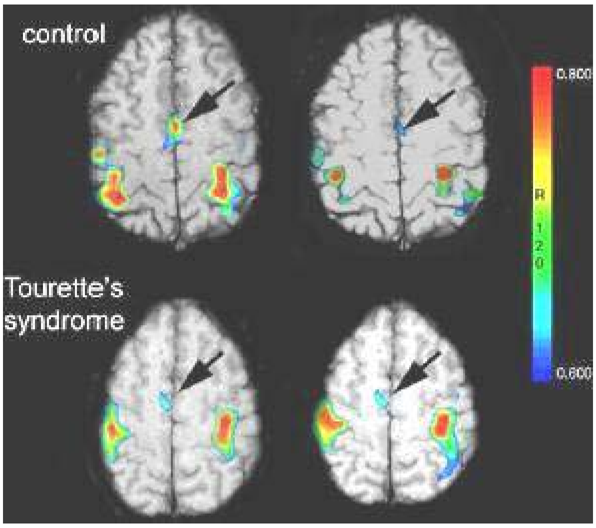

Figure 2.1 Functional MR images show premotor cortex and SMA (arrows) voxels activated by little finger, unusual (on left side) and index, usual (on right side) tapping motor tasks in a control subject (top) and in a Tourette's syndrome (TS) patient (bottom). In the control patient, the SMA is markedly activated in the unusual task; in the TS patient, similar SMA activation is observed in both the usual and unusual tasks.

2.4 Discussion

It has been suggested that the basal ganglia and cortico–striato–thalamo–cortical circuits are involved in the pathogenesis of TS. These circuits play a fundamental role in the control of motor and cognitive functioning. A number of studies have suggested that the SMA is closely involved in the control of voluntary movements in normal subjects; the SMA is believed to be activated when the subject is thinking of the movement, as opposed to when the movement is actually being executed (Morris et al., 1996).

The data observed in our control subject confirm that the SMA and primary sensorimotor area are hierarchically complementary to each other in the programming and execution of voluntary movements (Ikeda et al., 1995), with SMA activation reflecting greater difficulty in the execution of the unusual task.

The increased SMA activity during both movements in the TS patient invites some comment. The SMA is involved in the preparation of voluntary movements (Deecke and Lang, 1996) and thus reflects specific cortical activation in the pre-programming of new motor planning. The fact that similar SMA activation is observed during both tasks suggests that the TS patient is unable to switch from a usual to an unusual mode. Therefore, continuous SMA activation in the patient suggests that he perceives each task as unusual. The absence of tics during either movement, which rendered the fMRI examination possible, may be related to constrained pre-programming activity modulated by the SMA. In this respect, the excellent performance of the tic-free patient while kickboxing may be due to consistently high attentional motor strategies that induce persistent self-paced pre-programming activity modulated by the SMA.

In conclusion, in TS, the SMA may be considered a major target of basal ganglia input. The increased SMA activation in TS patients may reflect the use of more cerebral cortex to perform a voluntary motor task as a result of the additional effort required to suppress tic activity.

Chapter 3

3. An experimental investigation of the automatic/voluntary dissociation in limb apraxia.[4]

Abstract

The ability of apraxic patients to perform gestures in everyday life is a controversial issue. In this paper we aimed to evaluate the presence of the automatic/voluntary dissociation (AVD) in four patients affected by clinically-relevant limb apraxia. For this purpose, we sampled different kinds of gestures belonging to patients' motor repertoire and then assessed their production in a testing session. Our experimental procedure consisted of two steps: in the first phase we recorded gestures produced by patients in two natural conditions; in the second phase, we assessed production of correctly produced tool-actions, and of spontaneous non tool-actions and meaningless conversational (cohesive and beats) gestures under different modalities. AVD was observed for all types of gestures, albeit to a different degree in single patients. Impairments to specific cognitive mechanisms may be responsible for the observed pattern of AVD in different patients. The present findings demonstrate that the context provides strong bottom-up cues for the retrieval of motor patterns, while artificial testing conditions impose an additional cognitive load.

3.1 Introduction

Traditional clinical descriptions of patients affected by limb apraxia (Liepmann, 1900, 1905) suggest that patients may produce gestures correctly in ecological conditions, when they act spontaneously, but not in testing sessions, when they have to execute gestures upon request. Since then, the so-called automatic/voluntary dissociation (AVD) has often been reported in apraxic patients (e.g., Basso and Capitani, 1985), but studies demonstrating that limb apraxia is related to impaired performance in

---

[4] This section is a modified version of an article with an identical title by L. Trojano, L. Labruna and D. Grossi, which has been submitted in Cortex.

ecological tasks (e.g. Ochipa et al.,1989; Foundas et al., 1995a) may undermine the concept of AVD.

The problems in the assessment of AVD may arise from several methodological issues (Cubelli and Della Sala, 1996). The automatic/voluntary dissociation might be more frequently detected when lenient diagnostic criteria for apraxia are adopted: patients with subtle, "sub-clinical" disorders on apraxia testing ("false positives"; Cubelli and Della Sala, 1996), or those who exclusively make not highly indicative errors (e.g., use of body parts in producing pantomimes, Goodglass and Kaplan, 1963), are not expected to show difficulties in ecological settings. Such conditions cannot be considered as true AVD, while it seems reasonable to use the term AVD when patients with relevant apraxic disorders do not show equivalent difficulties in testing conditions and in everyday life. Another possible cause of misdetection of AVD could be ascribed to the fact that altered gestures produced by apraxic patients may nonetheless be recognised and comprehended in an ecological context. In other words, errors observed in gesture production tests sufficient to diagnose limb apraxia might not be so dramatic as to hamper the accomplishment of a certain activity or to affect communicative efficacy.

On the other hand, studies supporting the presence of significant correlation between limb apraxia and loss of autonomy in daily activities often rely on interviews to patients (Sundet et al., 1988) or caregivers (Hanna-Pladdy et al., 2003). Other studies on apraxic patients have demonstrated impairments in everyday activities (having a meal) performed in ecological contexts (Foundas et al., 1995a), or in naturalistic multiple-object actions performed in artificial contexts (Schwartz et al., 1999; Rumiati et al., 2001). Although these findings converge in demonstrating that limb apraxia is an enduring disorder with negative impact on an individual's functional independence (Ochipa and Rothi, 2000), they do not directly address the AVD issue. At the moment, to the best of our knowledge, no study has attempted to systematically verify the presence of AVD by comparing actual gestures produced in ecological conditions with performance on testing sessions, and to try to relate AVD to specific cognitive mechanisms.

In the present paper, we aimed to verify whether the ability of patients affected by limb apraxia to produce a certain gesture may depend on the context in which gestures are elicited. As for transitive actions, it has already been reported that apraxic movement errors can be circumvented (Wada et al., 1999; Westwood et al., 2001) or heightened (Heath et al., 2003) by the actual use of a tool. However, in this paper we were interested in verifying whether the very same tool may be used correctly or incorrectly depending on the context. For this purpose we set up an experimental paradigm in which we first recorded patients' gestural performances in ecological conditions, and then asked patients to reproduce on imitation or upon command the same gestures spontaneously produced in daily-life situations. Moreover, to comprehend the possible mechanisms underlying the context-related expression of apraxic disorders, we planned to extend AVD assessment to a wide range of gestures, both meaningful and meaningless, produced in manipulating tools and in conversational contexts, and also assessed patients on several additional tasks tapping visual processing of gestures.

In our study we tried to avoid the biases on both sides highlighted above. The systematic study of the same gestures in ecological and "artificial" conditions was aimed to withdraw reliance on subjective reports. The possibility of including "false positive" apraxic patients was circumvented by selecting only patients who showed clinically relevant apraxic disorders, failing on several clinical tasks of gesture production. In doing so, however, we did not select patients affected by specific kinds of limb apraxia, since diagnostic criteria are not strongly consistent among authors. For instance, some authors identify ideomotor apraxia on the basis of defects in production of transitive and symbolic gestures upon verbal command, and ideational apraxia on the basis of disorders in the use of multiple objects (Ochipa et al., 1989); other authors instead identify ideomotor apraxia as the impairment in imitation of meaningless and symbolic gestures, and ideational apraxia also on the basis of defective use of single tools (De Renzi et al.,1980; De Renzi and Lucchelli, 1988).

3.2 Methods

3.2.1 Subjects

Among a consecutive series of 40 focal brain-damaged patients recruited in a center for neurological rehabilitation, we selected those affected by relevant apraxic disorders conforming to the inclusion criteria specified below. Four patients met inclusion criteria and gave their informed consent prior to participating in the study. One patient (pt. 1) had right-sided hemispheric damage, and the remaining three (pts. 2-4) had a left-hemisphere lesion; all patients were right-handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971), and had suffered an ischemic stroke. Patients 1-3 were affected by hemiplegia, while patient 4 had only mild right hemiparesis. Patients 2 and 3 were affected by aphasia, while patient 4 had reading, writing and calculation disturbances, and was disoriented in time.

Twenty right-handed normal subjects, 8 women and 12 men (age range: 44-74 years), without any known history of neurological or psychiatric disorders, were examined as controls for apraxia testing. Control subjects were selected in order to match as closely as possible the age and years of formal education of the stroke patients.

3.2.2 Diagnosis of limb apraxia

All screened brain-damaged patients completed an assessment battery for apraxia, including several tests for gesture production. In setting up the battery, we adapted tests already in clinical use but with uniformed administration and scoring procedures, and modified number of stimuli; basically, we selected 12 tool-use actions and 12 symbolic gestures (see

Appendix), and 12 meaningless gestures, to be reproduced in several tasks. Moreover, we asked subjects to perform two multiple-object actions.

Patients were considered to be affected by limb apraxia, and enrolled for subsequent testing, if they achieved a score below the normal range (i.e., lower than the worst score observed in our 20-subject control sample) in at least one task for each type of gesture (meaningless gestures, symbolic gestures, actual tool use and pantomimes). These conservative diagnostic criteria allowed us to identify patients affected by relevant apraxic disorders, who represent the most suitable subjects for the study of AVD.

3.2.3 Gesture production tests

We assessed production of the different kinds of gestures in the following seven tasks:

- Meaningless gestures: imitation of 12 meaningless gestures (De Renzi et al., 1980).
- Symbolic gestures: production of 12 symbolic gestures on verbal command (Chainay and Humphreys, 2002), and upon imitation (De Renzi et al., 1980);
- Tool-use: pretended use of 12 tools on verbal command (Rothi et al., 1992), on visual presentation of tools (De Renzi and Lucchelli, 1988) and upon imitation (Roy et al., 2000); actual use of the same 12 single tools (De Renzi and Lucchelli, 1988).

In all tasks, a gesture was considered not adequately performed if the patient reproduced it with inappropriate posture or with wrong spatio-temporal features; for tool-actions and pantomimes object misuse, object or action mislocation, and body-part-as-a-tool were also considered as errors. In case of failure, a maximum of three attempts were allowed for each stimulus. A score of 3, 2 or 1 points was assigned for each trial if patients produced a correct response respectively at the first, second or third attempt; in case of repeated failures a score of 0 was assigned. Maximum score for all tasks was 36.

The gesture production battery also included a test assessing two multiple-object actions: to light a candle with a match and to prepare an expresso pot (De Renzi and Lucchelli, 1988). For this test, the maximum score was 10, corresponding to the number of steps required for doing the two actions correctly (each step performed correctly by patients scored 1 point; no repeated attempts were allowed).

The gesture production tests were given in a fixed order, arranged for modality of presentation, independently from the kind of gesture: gesture production upon verbal command was assessed first, followed by gesture production upon visual presentation, imitation, and actual use of single and multiple objects. Patients 1-3 were assessed on their ipsilesional arm; patient 4 had residual movements in her right arm, so she was assessed on both upper limbs, but for the present study we considered only movements performed with the ipsilesional arm.

3.2.4 Recognition and identification of gestures

All brain damaged patients also underwent four tests to verify their ability to process visually presented gestures. These tests were not considered for the diagnosis of apraxia, but were intended to provide cues about the possible defects in gesture processing. Basically two kinds of tasks were given:

- recognition tasks: subjects had to discriminate familiar gestures from meaningless gestures (“Is the gesture performed by the examiner familiar or novel to you?”); two tasks were given in which 12 pantomimes or 12 symbolic gestures (Ochipa et al., 1992; Bartolo et al., 2001) were intermixed with meaningless gestures. Gestures were executed one at a time in a random order, and the subjects were required to judge whether they knew each of them or not;
- identification tasks: subjects were asked to associate gestures performed by the examiner to a visually presented picture. The same 12 pantomimes and 12 symbolic gestures as above were presented, one at a time, together with a display containing three pictures (Ochipa et al., 1992; Bartolo et al.,

2001): subjects were required to point to the picture of the tool matching the pantomime (“Which tool did the examiner pretend to use?”), or, for symbolic gestures, to the photograph depicting the contextual situation semantically related to the stimulus (“With which drawing does the gesture performed by the examiner match?”, e.g. a priest corresponded to the cross making; Bartolo et al., 2001).

In these tasks, each correct answer scored 1 point; maximum score for recognition tasks was 24, and for identification tasks the maximum was 12.

3.2.5 Experimental tests: automatic/voluntary dissociation

Assessment of AVD has been performed by means of a two-step procedure.

In the first phase, patients were videorecorded during two semi-structured ecological situations (having a meal and talking with a psychologist). In both settings, a small videorecorder was used, hidden from the patients’ view, but patients (or their close relatives, in case of language defects) had accepted to undergo the procedure three days before recording. The video camera was placed in front of the subject on a high vantage point.

The meal was served, as usual, in the patients’ room, with patients sitting at their table; a relative or a caregiver was present, as always, but was instructed to intervene only upon explicit requests. The food tray was placed on patients’ table, and eating utensils were placed on the tray always in the same position. Meal routinely included a pasta plate, a meat-vegetable combination, and a fruit salad; water was served in a (loosely) closed bottle.

The talk with the psychologist was performed in the psychologist’s room, as on other occasions, with patients sitting at the table in front of the examiner. This time, however, the talk was specifically directed to the following issues, always in the same order: history of the disease, composition of family, and menu of the last meal.

For each patient, and for each situation, video recording lasted for ten minutes, starting when patients sat at their table. Two trained judges independently viewed each videotape and determined the number and the type of gestures made by patients. The gestures' analysis was limited to movements of the arm and hand. A single gesture was defined as a discrete movement by the arm and/or hand that resulted in one continuos motion followed by a visible pause in the action. If patients performed the same gestures more than once (e.g., drinking with the glass), the judges were instructed to consider only the first production.

Actions spontaneously performed by patients were coded as follows. During the meal, gestures were classified as tool-actions when patients used eating utensils according to their function, and as non-tool actions, when gestures were finalised to move an object (Foundas et al., 1995a). During talk, gestures were classified as content, emphasys and filler, after Foundas et al. (1995b): content gestures can be interpreted without further contextual information, while the remaining conversational gestures are movements used to tie together temporally separated but thematically related portions of discourse, and do not convey meaning by themselves. These latter gestures are particularly relevant for our purposes, since we wanted to verify if patients can produce meaningless gestures that do belong to their motor repertoire in testing conditions.

The testing session (second phase) was held within two or three days from the first phase. In this session we assessed production of all tool-actions identified as correctly produced by patients, while recognisable tool-actions performed with altered kinematics were discarded. Among non-tool actions and conversational gestures only those consistently classified by the two judges were used for testing. Reproduction of tool actions was required as actual tool-use, and as pantomime upon imitation; reproduction of non-tool actions and of meaningless conversational gestures was assessed upon imitation.

Administration and scoring procedures were the same as in the gesture production tasks described above. Maximum score varied for each task and for each patient, and was equal to the number of gestures selected for testing multiplied by three. For the sake of simplicity, we also presented scores as percentages of the maximum score. Although patient 4 gestured with both upper limbs in ecological settings, only ipsilesional movements were considered for the present study.

In a pilot study, five normal subjects (2 females and 3 males, age range: 45-72) underwent the same two-step procedure: no subject failed in reproducing any tool-action or non-tool action, while no subject needed more than two attempts to correctly reproduce her or his own conversational gestures upon imitation. Therefore, no normal subject achieved a percent correct score below 90 at any task.

3.3 Results

Patients' performances on the battery for gesture production are reported in Table 3.1. Patients 2 and 3 showed a similar pattern and failed all gesture production tasks. Patient 1 was impaired in most tasks, but she was unimpaired in imitating symbolic gestures and using single tools. Patient 4 showed a normal performance in producing symbolic gestures on verbal command, but failed all remaining tasks.

Results on the gesture recognition and identification tasks are reported in Table 3.2. Patient 3 could not recognise and identify gestures, while pt. 4 performed all tasks within normal range. Performance by the remaining two patients varied in the different tasks: pt. 1 performed as normal controls on recognition tasks, but failed in associating gestures to the corresponding figures (identification tasks), while pt. 2 succeeded only in identifying symbolic gestures.

Scores on the AVD assessment are reported in Table 3.3. During mealtime behaviour, all patients showed evidence of some praxis errors consisting in awkward object use or object misuse; however, upon repeated attempts, patients could complete their meal without help. As specified above, inadequate tool-actions were not considered for the subsequent testing phase, but we could select several tool-actions correctly performed by each patient. A larger number of non-tool actions and meaningless conversational gestures could be selected for testing. Cumulating observations from both ecological situations, we could assess 5 tool-actions, 8 non-tool actions and 11 meaningless conversational gestures on average. No content gesture could be selected for testing.

Results of the testing session showed a dissociation between production of gestures in ecological and "artificial" testing conditions: all scores were clearly below the normal range, with only one exception. Actually, patient 1 could correctly produce in the testing session all the actual tool-actions he had performed during meal. The remaining patients correctly produced most but not all actual tool-use actions; in particular, all of them needed repeated attempts to perform most tool-actions, and even so pt. 2 and 3 did not succeed in using some tools correctly (e.g., pt. 2 could not use the spoon properly, and pt. 3 used a fork as a spoon repeatedly).

When use of the same tools was assessed in the pantomime to imitation condition, all patients achieved lower scores with respect to the previous task: in particular, patient 1 often needed three attempts to reproduce gestures, while 4 was unable to perform any pantomime.

In imitation of non-tool actions and of meaningless conversational gestures all patients showed a systematic tendency to make posture and kinematic errors, so that repeated attempts were often necessary to achieve the correct movements.

Subject	Pt. 1	Pt. 2	Pt. 3	Pt. 4	Controls' mean		Cut-off	
Hand	Right	Left	Left	Left	Right	Left	Right	Left
Meaningless gestures on imitation	**18**	**19**	**9**	**15**	33	33	29	29
Symbolic gestures on verbal command	**14**	**3**	**3**	36	35	35	33	33
Symbolic gestures on imitation	30	**26**	**8**	**25**	34	33	30	33
Pantomime on verbal command	**28**	**3**	**2**	**19**	36	35	34	33
Pantomime on visual command	**24**	**0**	**0**	**17**	36	35	34	33
Pantomime on imitation	**15**	**19**	**12**	**26**	34	32	29	32
Actual use of single tools	36	**28**	**21**	**32**	36	36	36	36
Actual use of multiple objects	**8**	**9**	**2**	**3**	10		10	

Table 3.1. Scores on gesture production tasks. Scores under controls' cut-off are printed in bold

Subject	Pt. 1	Pt. 2	Pt. 3	Pt. 4	Controls' mean	Cut-off
Recognition of pantomimes	22	**16**	**12**	22	22	20
Recognition of symbolic gestures	22	**16**	**12**	22	21	20
Identification of pantomimes	**9**	**9**	**7**	11	12	11
Identification of symbolic gestures	**5**	9	**5**	8	10	8

Table 3.2. Scores on gesture recognition and identification tasks. Scores under controls' cut-off are printed in bold

Subject Hand	Pt. 1 Right	Pt. 2 Left	Pt. 3 Left	Pt. 4 Left
Tool-actions and pantomimes				
Ecological (lunch): number of correct spontaneous tool actions	6	6	4	3
Testing (actual tool use) Score	18/18	12/18	6/12	6/9
Testing (actual tool use) percent correct	100	67	50	67
Testing (pantomime to imitation): Score	10/18	5/18	2/12	0/9
Testing (pantomime to imitation): percent correct	56	28	17	0
Non-tool actions				
Ecological (lunch): number of spontaneous gestures	11	12	8	2
Testing (gesture on imitation): Score	12/33	5/36	0/24	2/6
Testing (gesture on imitation): percent correct	36	14	0	33
Meaningless conversational gestures				
Ecological (talk): number of spontaneous gestures	13	15	12	4
Testing (gesture on imitation): Score	20/39	9/45	11/36	5/12
Testing (gesture on imitation): percent correct	52	20	31	42

Table 3.3. Results of the test for automatic/voluntary dissociation

3.4 Discussion

The present results demonstrate the presence of AVD in four patients affected by limb apraxia. In an "artificial" setting, our patients could not produce the same gestures they had produced correctly in ecological conditions.

In attempting an interpretation of ADV, we will not commit ourselves to one particular cognitive model (e.g. Rothi et al., 1997; Chainay and Humphreys, 2002), but we will adopt basic ideas shared by most authors. We could start from the hypothesis that if patients can execute some gestures in natural conditions, it implies their motor systems can store and spontaneously retrieve specific motor schemata of different kinds. If they fail to reproduce the same gestures in artificial conditions, the impairment may vary depending on the kind of gesture and of assessment modality.

All patients showed AVD for meaningless conversational gestures and non-tool actions that are part of their motor repertoire but are not related to specific semantic content. To imitate such gestures during the testing session, patients have to analyse the respective configurational pattern, represent it in their mind, and select the appropriate motor schemata to reproduce the desired movement. We collected evidence that patients 2 and 3 had defective performances in discriminating transitive and symbolic gestures from meaningless gestures (gesture recognition tasks), and this could suggest a defect in visual analysis of gestures, for the subsequent reproduction; this could explain the reason why patients 2 and 3 showed AVD on this class of stimuli. The same explanation cannot be applied to patients 1 and 4, who achieved normal results on the gesture recognition tasks. In this latter pair of subjects, a specific impairment in converting correctly analysed gestures into patterns of specific motor acts could be hypothesised, following the terminology suggested by Rothi et al. (1997). Alternatively, the finding that the same gesture produced during conversation could not be reproduced on imitation, in presence of spared visual analysis abilities, could suggest an impairment in the elaboration of a mental representation to guide motor execution (Goldenberg and Hagmann, 1997). It is not possible to exclude such a defect in patients 2 and 3, but their impairment in visual analysis prevents any speculation about the "intermediate" processing step between visual analysis and motor execution.

This cognitively-oriented account for AVD in meaningless gesture production does not explain AVD for tool actions. In the testing session, transitive gesture production has been assessed by means of both pantomime on imitation and actual use of tools. Since we selected only gestures that had been performed correctly during lunch, we can infer that patients could retrieve those tool-related motor schemata appropriately. The defect in reproducing pantomimes on imitation for the same tools could be interpreted in analogy to what has been proposed for meaningless gestures, but this would imply that seeing a well-known gesture for reproduction would not necessarily activate gesture-related semantic knowledge (Rumiati et al., 2005). No inference is possible for patients 2 and 3, whose defects in visual analysis render speculative any other consideration on input gesture processing. Patients 1 and 4, instead, did not fail in gesture analysis (i.e., gesture discrimination tasks), but presented contrasting patterns in the gesture identification test. Patient 1 failed in associating gestures to the corresponding figures so that it is possible to hypothesise that he could not access gesture-related semantic knowledge and was forced to rely on the same cognitive processes as for meaningless gesture to try to imitate pantomimes. Patient 4 could comprehend the meaning of gestures but this access to semantic knowledge was not sufficient to ensure activation (on imitation) of the motor schemata he could access in natural conditions.

Bartolo et al. (2003) suggested that a temporary workspace is involved in production of both meaningless gestures and pantomimes (figure 3.1). The role of such a workspace could be that of integrating information simultaneously activated from different long-term memory sources with new environmental inputs. The defect showed by patient 4 could be ascribed to this level of gesture processing. According to Rumiati and Tessari (2002) a specific working memory component could be involved in imitation of meaningless gestures and pantomimes (figure 3.1)..

An AVD has been observed also in the actual use of tools in natural and artificial conditions for patients 2, 3, and 4. This observation could suggest that in patient 1 the AVD was specific for pantomimes, while tool intrinsic affordances made possible the execution of correct actions (Goldenberg et al., 2004), independently from the context. This explanation is not viable for the other patients, who, despite the correct use of tools in natural contexts, showed several errors in using them in the testing session. These findings would suggest that for some patients the context can provide strong facilitatory cues for the retrieval of adequate motor patterns. This is consistent with De Renzi et al.'s (1980) claim that the praxic defect may reside more on the circumstances under which a gesture is evoked than in the nature of the gesture itself.

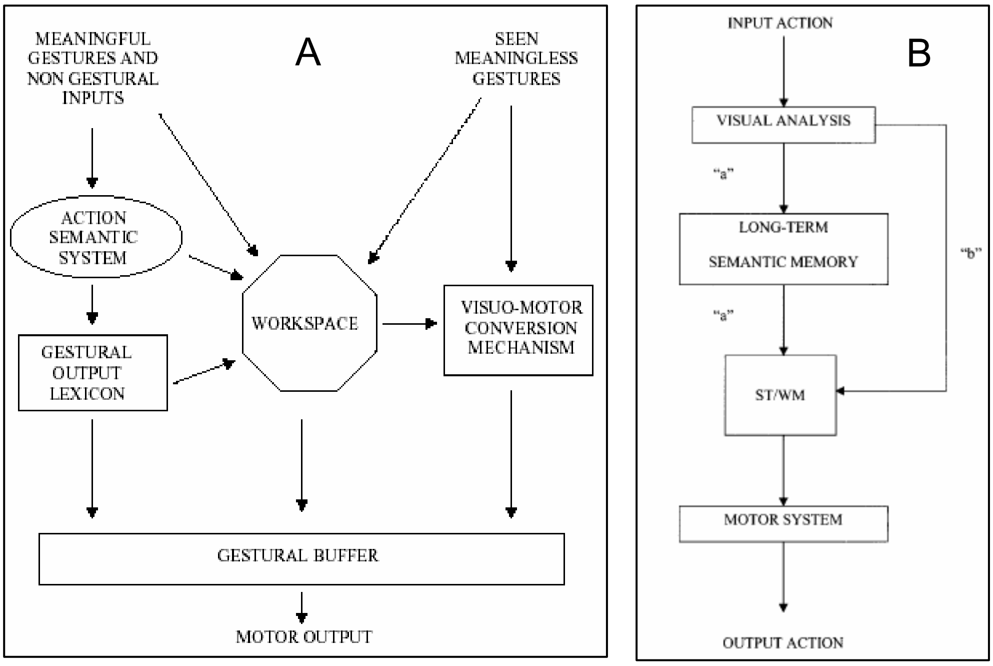

Figure 3.1 A) Model of gesture production by Batolo et al., (2003), that includes the workspace whose dysfunction would account for a selective deficit in pantomiming. The dotted lines represent the alternative route that may be used to imitate meaningless gestures in the absence of stimulus support. B) The Rumiati and Tessari model (2002) represents the two processes involved in the imitation of meaningful (MF) and meaningless (ML) actions. After the visual analysis, if the action to be imitated is ML, the process a is selected, whereas if imitation involves a MF action, both the semantic and nonsemantic processes may be selected (route b and route a, respectively). (ST/WM short-term/working memory)

The context appears to be far stronger in activating motor schemata than the single tools. In this sense the whole seems to be more than the sum of its parts. Bottom-up influences in determining motor behaviour can drive tool-actions even in patients with profound loss of conceptual knowledge (Buxbaum et al., 1997), but this effect has often been restricted to the facilitatory effect of tool affordances (Goldenberg et al., 2004; Laimgruber et al., 2005). Since we could demonstrate that even the same gesture, evoked by the very same tool, can be produced correctly or not depending on the kind of context, we suggest that facilitatory "natural" conditions may have a crucial influence. It has already been demonstrated that artificial conditions requiring tool actions, on verbal command or upon imitation, impose a specific cognitive load (Goldenberg and Hagmann, 1997; Rumiati and Tessari, 2002; Bartolo et al., 2003); we suggest that performing actions in a natural environment can proceed without such a cognitive load. It has been maintained that, although examiner's requirements came from the external world and are mediated via the senses, i.e. seem to be bottom-up, yet they provide a model the subjects have to comply with, i.e. are top-down. In other terms the experimenter may be considered a factor in control of action (Roepstorff and Frith, 2004). Whereas bottom-up control can often be achieved without awareness, we suggest that the top-down control implied even in using common tools upon examiner's request may determine the faulty activation of motor schemata, typical of apraxic patients.

Unfortunately, our patients did not spontaneously produce symbolic gestures or tool-use pantomimes during the natural conditions in which we recorded their gestures. This finding is partially consistent with results by Foundas et al. (1995b), who found that left brain-damaged patients tend to produce many meaningless gestures (beats and filler gestures) and only a few meaningful gestures (i.e. content gestures conveying meaning independent of the discourse) with their left ipsilesional hand. Therefore, we could not verify whether our considerations about the role of context may be extended to all kinds of well-known gestures, or have to be restricted to tool actions.

Another point of interest of our research is related to the usefulness of AVD assessment in apraxia patients. All patients enrolled for the present study completed a complex activity (consuming a meal) without making "fatal errors", i.e. without making errors because of which the patient was unable to proceed without help, or the task could not be fulfilled (Goldenberg and Hagmann, 1998). However, in the testing session they could not complete activities implying the use of multiple objects. This finding raises some caveats on assessing daily activities in semi-artificial contexts (e.g. Hartmann, Goldenberg et al., 2005; Buxbaum et al., 1998) to evaluate patients' independence in everyday life.

In conclusion, our paper has systematically evaluated the presence of AVD for different kinds of gestures in apraxic patients. Although the limited number of gestures we could assess limits possible generalisation of our results, the present findings would suggest that AVD can be observed in patients affected by clinically relevant limb apraxia. By assessing gestures sampled from patients' motor repertoire, we could document that gesture reproduction in artificial context may substantially differ from spontaneously-evoked motor activity. The existence of AVD does not imply that limb apraxia has no detrimental effect on patients' personal and social independence in their daily activities. Actually, our patients made tool-action errors while eating their lunch, as in other studies on mealtime behaviour (Foundas et al., 1995a). However, in the present study we used ecological conditions as a means to select testing "material" and not as an outcome. Although all four apraxic patients we assessed had a variable degree of AVD, further research is needed to verify whether, and to which extent, other apraxic patients show AVD.

Commenting on the contrasting findings on AVD, Cubelli and Della Sala (1996) suggested that automatic and voluntary gesture production may be considered at the opposite extremes along a continuum (Smith et al., 1994), without clear-cut distinction between the two. The present study would suggest that such a distinction exists, although the definition of cognitive mechanisms through which the context-dependent facilitation may arise remains to be clarified. In particular, the interesting dissociation observed for tool-use actions would call for implementation of theoretical models of gesture production to explain the nature of context-related triggering of motor schemata.

Chapter 4

4. Interaction between motor and language systems: action observation and action related sentence comprehension[5]

Abstract

Action observation is associated with increased excitability in the cortical representation of the observed effector in the primary motor cortex (M1). Here, we measured motor evoked potentials in intrinsic hand muscles following transcranial magnetic stimulation (TMS) of the left M1 to compare how motor cortex excitability is modulated during action observation and linguistic comprehension of action-related sentences. Preliminary results on 5 subjects showed a higher modulation of the activity of the hand MI during processing both picture and sentences for the hand actions compared other stimulus types. Moreover while pictures observation showed a motor cortex excitability more similar to that one induced during the baseline, action-related sentence comprehension has produced a progressive decrease in motor cortex excitability activity along the TMS timings.

4.1 Introduction

Neuroimaging studies have shown that, when people observe actions performed by other individuals, activation is observed in motor regions of the brain (Iacoboni et al., 1999; Iacoboni et al., 2001; Buccino et al., 2004). Such an activation pattern conforms to the hypothesis of an execution-observation matching system, or what is referred to as the mirror neuron system. Because of this system we can recognize a large variety of actions performed by other individuals, including those belonging to other species, simply by matching the observed actions onto our own motor system. In some brain regions, the overlap between action observation and action execution is highly specific. Action observation activates fronto-parietal

---

[5] This section is a preliminary version of a study with the same title by Labruna L, Duque J., Landau A and Ivry R, which is in process at the Action and cognition Lab, Berkeley.

circuits in a somatotopic manner (Buccino et al., 2001). Consistently, TMS studies have also shown that action observation is associated with an increased excitability in the primary motor cortex (M1) in an effector specific manner (Fadiga et al., 1995; Strafella et al, 2000). Thus, the process of action comprehension appears to recruit motor regions of the brain, similar to what would be required if preparing to execute the observed movements.

Action intention can also be conveyed linguistically. Processing action-related sentences also induces measurable changes in M1 activity, suggesting that understanding action-related words involves the recruitment of representations of the actions to which the words refer. This idea is central to the theory of embodied semantics, the idea that conceptual representations accessed during linguistic processing include sensory and/or motor representations related to the concept in question (Glenberg, 1997, Barsalou, 1999, Lakoff and Johnson, 1999, Glenberg and Kaschak, 2002, Feldman and Narayanan, 2004). For action-related sentences or words, the neural structures involved in action execution and observation may also play a role in understanding the semantic content of the actions described.

Supporting this hypothesis, fMRI studies have shown that perception of spoken (Tettamanti et al., 2005) and written (Hauk et al., 2004) action words activates cortical areas involved in action observation and execution in an effector-specific somatotopic fashion related to the semantics of the action words. A recent fMRI paper of Aziz-Zadeh et al. (2006) directly compared the activity related to linguistic stimuli with the activity related to action observation. Results showed similar patterns of activation in cortical sectors activated by observing actions and by their verbal descriptions. However, in these imaging studies, the activation during linguistic comprehension was limited to premotor regions and did not extend into primary motor cortex. Thus, the results provide evidence of an involvement of premotor areas with mirror neuron properties in re-enactment of sensory-motor representations during conceptual processing of linguistic phrases describing actions.

While the imaging studies fail to show language-based activation of primary motor cortex, TMS studies indicate that, like action observation, processing action related sentences has measurable consequences on the excitability of primary motor cortex (Buccino et. al, 2005; Pulvermuller et al., 2005). However, whereas TMS studies of action observation has been shown to increase primary motor cortex excitability in an effector (or goal-based) manner, contrasting effects are found during action-based linguistic processing. Buccino et al., (2005) applied single-pulse TMS over the motor cortex to target either the hand or foot area while participants listened to short phrases describing actions related to the hand or foot. The results showed that the magnitude of the MEPs for each effector was lower when the participants heard a sentence involving that effector. Consistent with these direct measures of cortical excitability, a behavioural study showed that reaction times were slower when the effector used to make a response corresponded to the one referred to in the sentences. For example, judgments of sentences about hand action were responded to more slowly with the hand compared to the foot. Buccino et al. (2005) concluded that during linguistic comprehension the motor cortex may be inhibited in an effector-specific manner.

A related study by Pulvermuller et al. (2005) suggests the opposite results. In this study, the hand or foot areas were stimulated in the left hemisphere while participants made lexical decisions on visually presented words related to either leg actions and or arm actions. During stimulation of the hand area, reaction times to lexical decision of hand words were faster than to foot words. Similarly, during stimulation of the foot area, reaction times to lexical decision of foot words were faster than hand words. The authors proposed that stimulation of the motor cortex primes effector-specific regions, and as such, facilitates processing action related words in an effector-specific manner, a conclusion at odds with the inhibition hypothesis of Buccino et al. (2005).

However, an alternative interpretation of the Pulvermuller et al. (2005) results can be developed. Supposing that the TMS pulses added noise in an effector-specific manner within motor cortex, effectively taking the targeted subregion off-line while the participants performed the language task, the effector-specific reduction in RTs on the lexical decision task would occur because the motor cortex region associated with that effector is functionally silenced. This interpretation would be consistent with the results of Buccino et al. (2005), suggesting again that linguistic processing of action concepts may lead to transient inhibition of motor cortex regions representing the effector(s) used to perform those actions.

The aim of the present study is to directly test the hypothesis of a different modulation in MI for action observation and action-related sentence comprehension by using single-pulse TMS over the left primary motor cortex. We recorded MEPs from hands muscles while participants observed hand action and read hand action-related sentences. In order to verify not only a possible modulation of MEPs, but also its specificity related to the effector involved in the action, we also presented foot actions. Landscape stimuli served as a control. Moreover, we used four different TMS timings in order to evaluate possible differences, in terms of timing of processing, between picture observation and sentence reading.

4.2 Methods

4.2.1 Subjects

Five healthy subjects (mean ± SD, 23 ± 7 years; 3 female, 2 male) participated in the study. All were native English speakers and were right handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). Informed consent was obtained from all subjects. The protocol was approved by the Committee for the Protection of Human Subjects at UC, Berkeley. Subjects were financially compensated for their participation and were naive to the purpose of the study.

4.2.2 Transcranial magnetic stimulation (TMS)

Subjects wore a tightly fitting EEG cap. TMS was applied using a figure-of-eight magnetic coil (diameter of wings 90 mm) connected to a rapid Magstim 200 magnetic stimulator (Magstim, Whitland, Dyfed, UK). The magnetic coil was placed tangentially on the scalp, over the left primary motor cortex (M1), with the handle pointing backward and laterally at a 45° angle away from the midline, approximately perpendicular to the central sulcus. The hot spot was defined as the optimal position to elicit motor evoked potentials (MEPs) in the left FDI. The resting motor threshold (rMT) was defined, at the hot spot, as the minimal TMS intensity needed to evoke MEPS in the left FDI larger than 50 μV peak-to-peak in the relaxed FDI in 5 out of 10 consecutive trials. The intensity of TMS was then set at 15% above the resting motor threshold during the whole experiment. MEPs were recorded from both the FDI and the abductor pollici brevis (APB) muscles in the right hand.

4.2.4 EMG Recording

EMG activity was recorded from surface electrodes placed over the right and left FDI and APB muscles for 3000 ms. The EMG signal was amplified and bandpass filtered (50-2000 Hz; Delsys Inc., Boston, USA); then it was digitized at 5 kHz and stored on a personal computer for off-line analysis. Trials associated with background EMG activity in the left or right hand muscles were excluded from analysis.

4.2.4 Experimental Procedure

Subjects were seated on a comfortable chair in front of a computer screen with their elbows flexed at 90° and hands pronated in a totally relaxed position. During the experiment, subjects were required to pay attention to the visual stimuli presented on the screen. Three kinds of stimuli were presented: hand actions, foot actions and landscapes. These stimuli were either displayed as pictures or as written sentences describing actions or landscapes. Subjects were instructed to observe the pictures or read the sentences silently. The experiment was divided into six blocks (two for each stimulus type; hand, foot or landscape). Within each block (92 trials), sentences and pictures were presented in a randomized order (see figure 1).

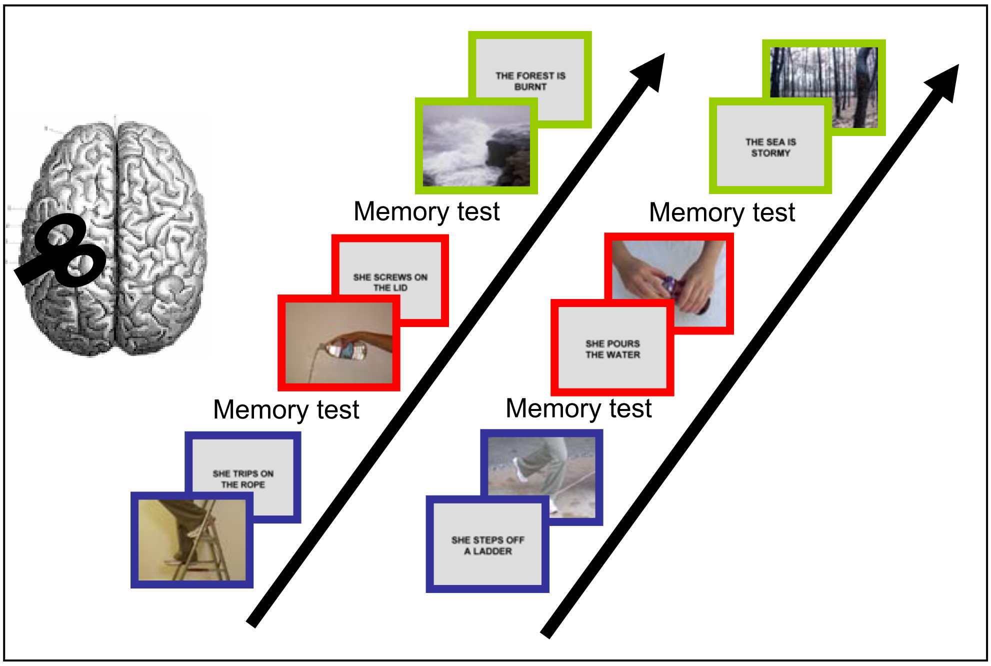

Figure 4.1: schematic representation of the block design TMS study. Each block is represented with different frame colours: blue for foot actions, red for hand actions and green for landscapes. In each block the same action (or landscape) was presented in the form of either a picture or a sentence, but never in both ways. At the end of each block a memory test was administered.

Each stimulus was displayed for 1.500 ms and preceded, 500ms before, by a fixation cross presented for 250 ms. TMS was applied at four different timings during the stimulus presentation (i.e. 400, 550, 700, 850 ms after the stimulus onset; see Fig.2). TMS applied during the “fixation” were used as baseline. A minimum of 24 MEPS were recorded in each condition. Each block was followed by a memory test to make sure that subject paid attention to pictures and sentences. During this test, the experimenter read

10 sentences related to the actions (or to the landscapes) that appeared in the block and asked the subjects whether they were displayed as sentences or pictures.

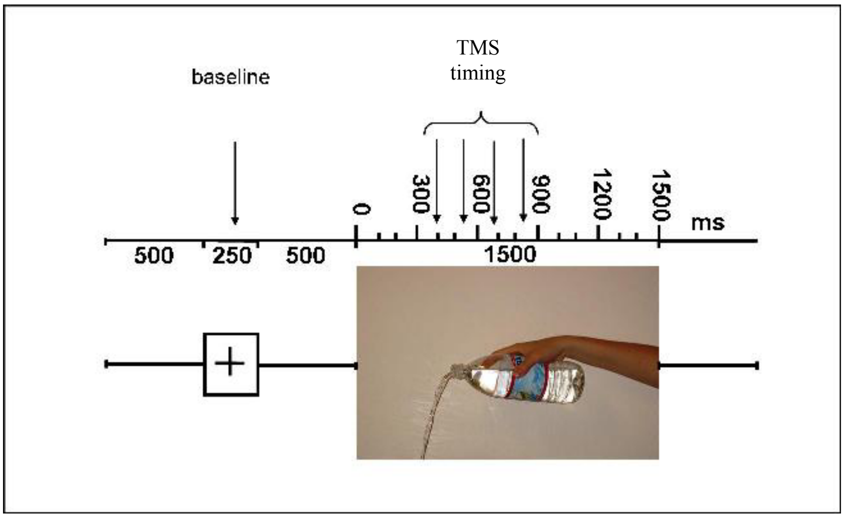

Figure 4.2: TMS timings. TMS pulses occurred at one of different delivery intervals from the onset of the stimuli (400, 450, 700, 800 ms). TMS pulse occurring during the fixation cross was used as baseline.

4.3 Results and discussion

4.3.1 Memory Test

Memory test results indicated that subjects indeed attended to the displays of pictures and sentences. Levels of accuracy is source recollection (was the item presented in sentence or picture) was 86% accurate (SD 5.6%) which is beyond chance level.

4.3.2 TMS study

Due to the small amount of subjects only preliminary results can be drawn. We first looked to a general effects related to the effector involved it the action. Figure 4.1 show the mean value of MEPs recorded during the fixation (baseline). For each kind of stimulus (foot, hand and landscape) we present the data collapsed over display type (picture/sentence). Results show a clear modulation of the activity of the hand MI by the TMS stimulation.

This modulation was higher for the hand actions compared with foot actions and landscapes.

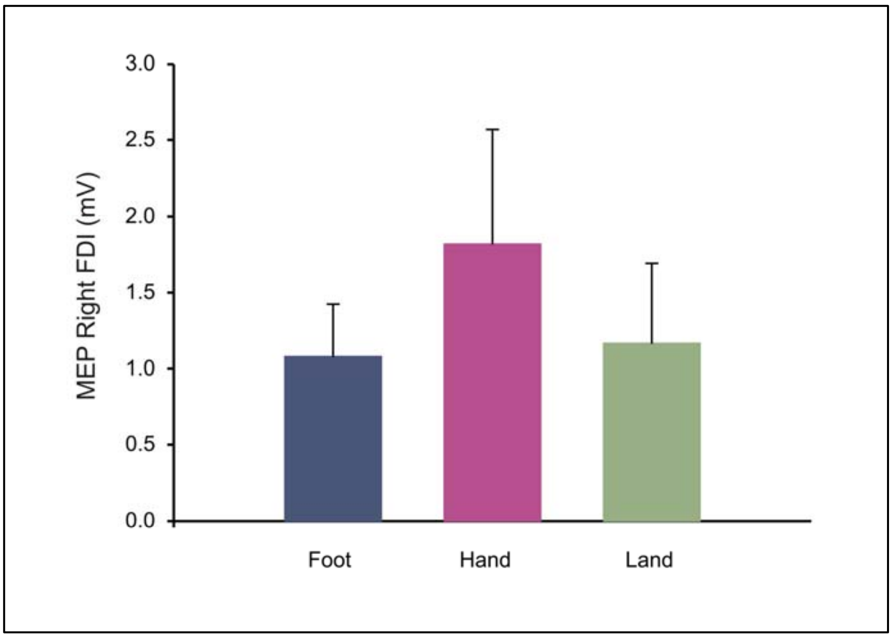

Figure 4.3 Mean values (plus SE) of MEPs amplitude in the right FDI during the fixation (baseline, TMS timing 1500 ms), for the three kinds of stimuli (foot, hand and landscape) included both sentences and pictures.

A second analysis was designed to directly test the hypothesis of a difference in modulation of MI for action observations and action-related sentence comprehension. Figure 4.4 shows the mean values of MEPs amplitude of right FDI, expressed as percentage of the baseline, for pictures and sentences for each kind of stimulus (foot, hand and landscape). For both pictures and sentences the four TMS timings are displayed. Results don't show significant differences of excitability between the two conditions for none of the stimulus types. This is probably due to the limited number of subjects involved in the analysis. However a couple of observation can be made: First, it seams that picture observation leads a motor cortex excitability more similar to that one induced during the baseline. This would

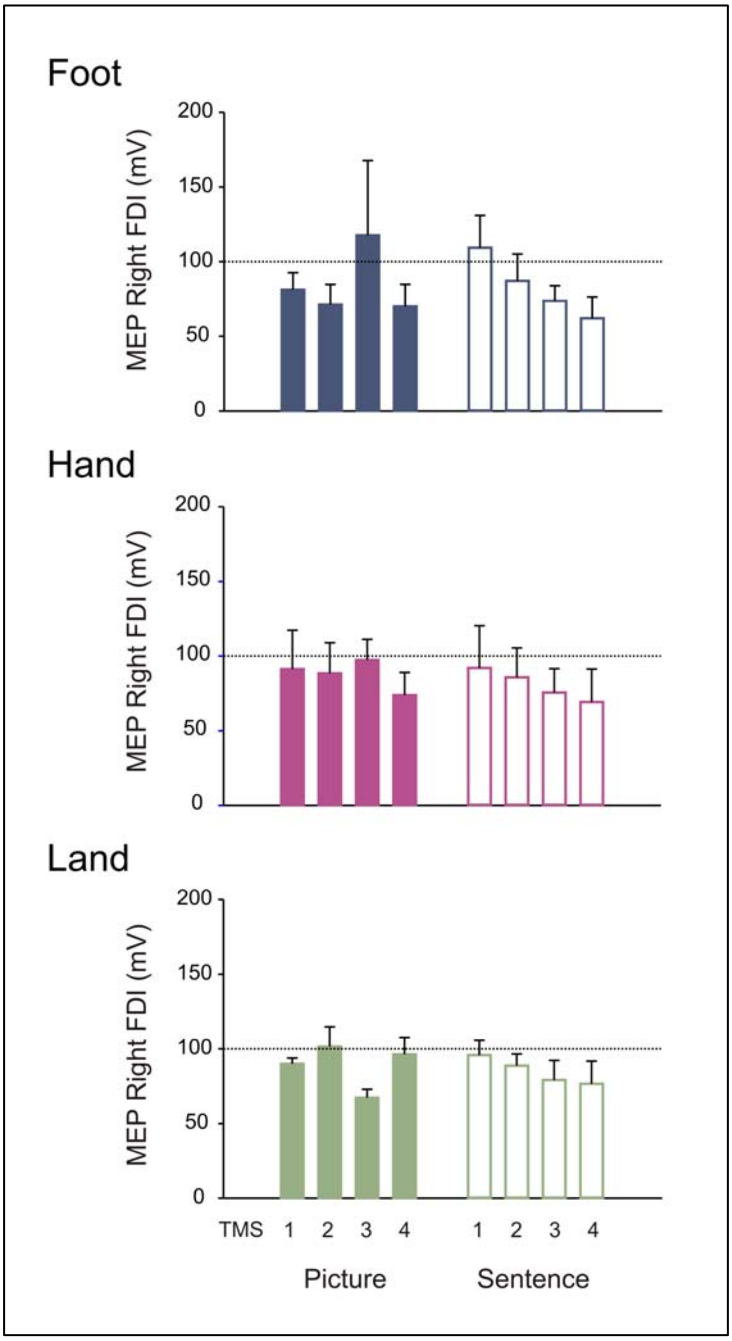

Figure 4.4 Mean values (plus SE) of MEPs amplitude of right FDI, expressed as percentage of the baseline, for the three kinds of stimuli (foot, hand and landscape). In each graph the comparison of pictures (left side) and sentences (right side) of the same kind of stimulus has showed for the 4 TMS timings (corresponding to 400, 450, 700, 800 ms).

mean that our data doesn't show an increase of excitability during this task. Second, is possible to observe a more consistent effect for sentences reading corresponding to a progressive decrease in motor cortex excitability activity as TMS timings progress. Moreover, this decrease is not specific for the effector because is consistent in all the stimuli. The results showed that the magnitude of the MEPs for each effector was lower when the participants heard a sentence involving that effector. This suggests that sentences may have a more gradual course of processing which is consistent across the different stimulus types.

In conclusion, our preliminary results might deal with the hypothesis of a different modulation in MI for action observation and action-related sentence comprehension. While pictures observation showed a motor cortex excitability more similar to that one induced during the baseline, action-related sentence comprehension has produced a progressive decrease in motor cortex excitability activity along the TMS timings. Moreover, with respect to a possible effector specific modulation of MEPs, our data show a higher modulation of the activity of the hand MI during processing both picture and sentences for the hand actions compared other stimulus types. Previous papers have showed that action observation is associated with modulation of primary motor cortex in an effector specific manner (Fadiga et al., 1995; Strafella et al, 2000). Our results might address that this modulation is independent of the way to present the stimuli, because the effect has been observe during processing of both pictures and sentences. For this purpose an ulterior analysis will be done, in witch the mean values of MEPs amplitude during the fixation will take in account separately pictures observations and action related sentences reading.

Summary and conclusion

The present work aimed at investigating the cognitive process related to action processing and his neural basis. This topic has been dealt in different ways, devoted to clarifying this complex motor behaviour.

In the *first chapter* we verify whether recent functional imaging studies support the view that different neural structures are specialised in processing different kinds of gestures. The reviewed papers, have shown that MFG shares most neural bases with MLG but also involves the activation of additional neural structures. Moreover, among MFG specific areas, most cerebral regions were activated only in TG processing, while no brain region was specifically activated by SG processing. No brain region has been consistently demonstrated to be MLG specific; however, several regions that are activated bilaterally in MFG processing appear to be activated predominantly on the right side during MLG processing.

Moreover we have tried to interpret our results in relation of cognitive models of apraxia with the aim of contribute to resolve some controversial aspects. In particular, the controversial distinction between two cognitive components specifically responsible for skilled action recognition and production (the so-called input and output praxicons) is not supported by present findings. In fact, no areas have been found to be activated specifically for MFG observation and recognition. In agreement with Peigneux et al. (2004), our data support the idea that one single system (the so-called "praxicon") is actually responsible for representing, and holding in long-term memory, sequences of skilled movements. This cognitive component, therefore, appears to be organised according to the general "mirror" principle: more specifically, the left anterior IPS, could be the neural basis of the praxicon since it is specialised in representing skilled actions, including actual or pantomimed tool use and, possibly, purported tool use.

Moreover, our review has demonstrated that imitation of novel or familiar gestures may proceed through the activation of the same pathway, and that additional cortical regions are specifically involved in MFG processing.

The core of this system is represented by a distributed fronto-parietal mirror circuit (including the Broca's area and vPM, the anterior and the superior parietal regions). Gesture representations computed by the fronto-parietal mirror circuit would feed, for the actual production of selected movements, frontal areas, namely dPM, SMA and MI, specifically involved in motor integration and execution.

The role of the SMA in the control of voluntary movement was investigated in a functional MRI study on a patient with Tourette syndrome (*second chapter).* This study confirms that the SMA and primary sensorimotor area are hierarchically complementary to each other in the programming and execution of voluntary movements. The increased SMA activation in TS patients may reflect the use of more cerebral cortex to perform a voluntary motor task as a result of the additional effort required to suppress tic activity. The absence of tics during either movement, which rendered the fMRI examination possible, may be related to constrained pre-programming activity modulated by the SMA.

In the *third chapter*, the topic of the voluntary control of action has been discussed in relation with the automatic-voluntary dissociation. Our study showed that AVD can be observed in patients affected by clinically relevant limb apraxia, documenting that gesture reproduction in artificial context may substantially different from spontaneously-evoked motor activity. Therefore the context can provide strong facilitatory cues for the retrieval of adequate motor patterns, more than the single tools. In this sense the whole seems to be more than the sum of its parts. Since we have demonstrate that even the same gesture, evoked by the very same tool, can be produced correctly or not depending on the kind of context, we have suggested that facilitatory "natural" conditions may have a crucial influence in determining motor behaviour. It has been maintained that, although examiner's requirements came from the external world and are mediated via the senses, i.e. seem to be bottom-up, yet they provide a model the subjects have to comply with, i.e. are top-down.

Finally, in the *fourth chapter*, the activity of the primary motor area (MI) has been addressed in relation of the embodiment theory. Whereas studies of action observation has been shown to increase primary motor cortex excitability in an effector (or goal-based) manner, contrasting effects are found during action-based linguistic processing. Our preliminary results showed a higher modulation of the activity of the hand MI during processing both picture and sentences for the hand actions compared other stimulus types. Moreover while pictures observation showed a motor cortex excitability more similar to that one induced during the baseline, action-related sentence comprehension has produced a progressive decrease in motor cortex excitability activity along the TMS timings.

References

Aziz-Zadeh L., Wilson S.M., Rizzolatti G., Iacoboni M. (2006). Congruent embodied representations for visually presented actions and linguistic phrases describing actions. Current Biology 18, 1818-23.

Bartolo A, Cubelli R, Della Sala S and Drei S (2003). Pantomimes are special gestures which rely on working memory. Brain and Cognition, 53 483-494,.

Bartolo A, Cubelli R, Della Sala S, Drei S and Marchetti C (2001). Double dissociation between meaningful and meaningless gesture reproduction in apraxia. Cortex 37, 696-699.

Basso A and Capitani E (1985). Spared musical abilities in a conductor with global aphasia and ideomotor apraxia. Journal of Neurology, Neurosurgery and Psychiatry 48, 407-12.

Binkofski F., Buccino G., Posse S., Seitz R.J., Rizzolatti G. and Freund H. (1999). A fronto-parietal circuit for object manipulation in man: evidence from an fMRI-study. European Journal of Neuroscience 11, 3276–3286.

Biswall B., Ulmer J.L., Krippendorf R.L., Harsch H.H., Hyde D.J. and Haughton V.M. (1998). Abnormal cerebral activation with a motor task in Tourette syndrome. American Journal of Neuroradiology 19, 1509–1512.

Boucart M., Meyer M.E., Pins D., Humphreys G.W., Scheiber C., Gounod D. and Foucher, J. (2000). Automatic object identification: an fMRI study. Neuroreport 11, 2379-83.

Bradshaw J.L. and Sheppard D.M. (2000). The neurodevelopment frontostriatal disorders: evolutionary adaptiveness and anomalous lateralization. Brain and Language 73, 297–320.

Buccino G., Riggio L., Melli G., Binkofski F., Gallese V., Rizzolatti G. (2005). Listening to action-related sentences modulates the activity of the motor system: a combined TMS and behavioral study. Cognitive Brain Research. 3, 355-63.

Buccino G., Lui F., Canessa N., Patteri I., Lagravinese G., Benuzzi F., Porro C.A., Rizzolatti G. (2004a). Neural circuits involved in the recognition of actions performed by nonconspecifics: an FMRI study. Journal of Cognitive Neuroscience 1, 114-26.

Buccino G., Binkofski F. and Riggio L. (2004b). The mirror neuron system and action recognition. Brain and Language 89, 370-6.

Buccino G., Binkofski F., Fink G.R., Fadiga L., Fogassi L., Gallese V., Seitz R.J., Zilles K., Rizzolatti G. and Freund H.J. (2001). Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study. European Journal of Neuroscience 13, 400-404.

Buchel C., Price C. and Friston K. (1998). A multimodal language region in the ventral visual pathway. Nature 394, 274–277.

Buxbaum L., Schwartz M.F. and Carew T.G. (1997). The role of semantic memory in object use. Cognitive Neuropsychology 14, 219-254.

Buxbaum L., Schwartz M.F. and Montgomery M.W. (1988). Ideational apraxia and naturalistic action. Cognitive Neuropsychology 15, 617-643.

Buxbaum L.J., Giovannetti T. and Libon D. (2000). The role of the dynamic body schema in praxis: evidence from primary progressive apraxia. Brain and Cognition 44, 166-91.

Cabeza R. and Nyberg L. (2000). Imaging cognition II: An empirical review of 275 PET and fMRI studies. Journal of Cognitive Neuroscience 12, 1-47.

Calvo-Merino B., Glaser D.E., Grezes J., Passingham R.E. and Haggard P. (2005). Action observation and acquired motor skills: an FMRI study with expert dancers. Cereb Cortex. 15, 1243-1249.

Caminiti R., Ferraina S. and Johnson P.B. (1996). The sources of visual information to the primate frontal lobe: a novel role for the superior parietal lobule. Cerebral Cortex 6, 319–328.

Chainay H. and Humphreys G.W. (2002). Neuropsychological evidence for a convergent route model for action. Cognitive Neuropsychology 1, 67-93.

Chao L.L. and Martin A. (2000). Representation of manipulable man-made objects in the dorsal stream. Neuroimage 12, 478–484.

Chao L.L., Haxby J.V. and Martin A. (1999). Attribute-based neural substrates in temporal cortex for perceiving and knowing about objects. Nature Neuroscience 2, 913-919.

Choi S.H., Na D.L., Kang E., Lee K.M., Lee S.W. and Na D.G. (2001). Functional magnetic resonance imaging during pantomiming tool use gestures. Experimental Brain Research 139, 311–317.

Connolly J.D., Andersen R.A. and Goodale M.A. (2003). FMRI evidence for a 'parietal reach region' in the human brain. Experimental Brain Research 153, 140-5.

Cubelli R and Della Sala S (1996). The legacy of automatic/voluntary dissociation in apraxia. Neurocase 2, 449-454.

Cubelli R., Marchetti C., Boscolo G. and Della Sala S. (2000). Cognition in action: testing a model of limb apraxia. Brain and Cognition 44, 144-65.

De Renzi E. and Lucchelli F. (1988). Ideational apraxia. Brain 111, 1173-1185.

De Renzi E., Motti F. and Nichelli P. (1980). Imitating gestures: a quantitative approach to ideomotor apraxia. Archives of Neurology 37, 6-10.

De Renzi E. and Faglioni C. (1996). L'aprassia, in Manuale di neuropsicologia, a cura di G. Denes e G. Pizzamiglio, Bologna, Zanichelli, pp. 557-593.

Decety J., Chaminade T., Grezes J. and Meltzoff A.N. (2002). A PET exploration of the neural mechanisms involved in reciprocal imitation. Neuroimage 15, 265-72.

Decety J., Grezes J., Costes N., Perani D., Jeannerod M., Procyk E. Grassi F. and Fazio F. (1997). Brain activity during observation of actions: influence of action content and subject's strategy. Brain 120, 1763–1777.

Deecke L. and Lang W. (1996). Generation of movement-related potentials and fields in the supplementary motor area and in the primary motor area. Advances in Neurology 70, 127–146.

Dumont C., Ska B. and Joanette Y. (2000). Conceptual apraxia and semantic memory deficit in Alzheimer's disease: two sides of the same coin? Journal of International Neuropsychological Society 6, 693-703.

Erdler M., Windischberger C., Lanzenberger R., Edward V., Gartus A., Deecke L., Beisteiner R. (2001). Dissociation of supplementary motor area and primary motor cortex in human subjects when comparing index and little finger movements with functional magnetic resonance imaging. Neuroscience Letters, 313, 5–8.

Fadiga L., Fogassi L., Pavesi G. and Rizzolatti G. (1995). Motor facilitation during action observation: A magnetic stimulation study. Journal of Neurophysiology 73, 2608–2611.

Feldman J. and Narayanan S. (2004). Embodied meaning in a neural theory of language. Brain and Language 2, 385-92

Fletcher P.C., Anderson J.M., Shanks D.R., Honey R., Carpenter T.A., Donovan T., Papadakis N. and Bullmore E.T. (2001). Responses of human frontal cortex to surprising events are predicted by formal associative learning theory. Nature Neuroscience 4, 1043-8.

Foundas A.L., Macauley B.L., Raymer A.M., Maher L.M., Heilman K.M. and Rothi L.J (1995a). Ecological implications of limb apraxia: evidence from mealtime behavior. Journal of the International Neuropsychological Society 1, 62-66.

Foundas A.L., Macauley B.L., Raymer A.M., Maher L.M., Heilman K.M. and Rothi L.J (1995b). Gesture laterality in aphasic and apraxic stroke patients. Brain and Cognition 2, 204-213.

Gerloff C., Corwell B., Chen R., Hallett M., Cohen L.G. (1997).Stimulation over the supplementary motor area interferes with the organization of future elements in complex motor sequences. Brain 120, 1587–1602.

Geschwind N. (1965). Disconnection syndromes in animals and man. Brain, 88, 237-294; 585-644.

Glenberg A.M. and Kaschak M.P. (2002). Grounding language in action.

Psychonomic Bulletin and Review 3, 558-65.

Goldenberg G. (1995). Imitating gestures and manipulating a manikin. The representation of the human body in ideomotor apraxia. Neuropsychologia 33, 63–72.

Goldenberg G. (2001). Imitation and matching of hand and finger postures. Neuroimage 14, S132–136.

Goldenberg G. (2003). Apraxia and beyond: Life and work of Hugo Liepmann. Cortex, 39, 509-524.

Goldenberg G. and Hagmann S. (1997). The meaning of meaningless gestures: A study of visuo-imitative apraxia. Neuropsychologia 35, 333-341.

Goldenberg G. and Hagmann S. (1988). Therapy of activities of daily living in patients with apraxia. Neuropsychological Rehabilitation 8, 123-141.

Goldenberg G., Hentze S. and Hermsdorfer J. (2004). The effect of tactile feedback on pantomime of tool use in apraxia. Neurology 63, 1863-1867.

Goodglass H. and Kaplan E. (1963). Disturbance of gesture and pantomime in aphasia. Brain 86, 703-720.

Grafton S.T., Arbib M.A., Fadiga L. and Rizzolatti G. (1996). Localization of grasp representations in humans by positron emission tomography. 2. Observation compared with imagination. Experimental Brain Research 112, 103–111.

Grafton S.T., Fadiga L., Arbib M.A. and Rizzolatti G. (1997). Premotor cortex activation during observation and naming of familiar tools. Neuroimage 6, 231-236.

Grezes J. and Decety J. (2001). Functional anatomy of execution, mental simulation, observation, and verb generation of actions: a meta-analysis. Human Brain Mapping 12, 1–19.

Grezes J., Costes N. and Decety J. (1999). The effects of learning and intention on the neural network involved in the perception of meaningless actions. Brain 122, 1875–1887.

Grezes J., Tucker M., Armony J., Ellis R. and Passingham R.E. (2003). Objects automatically potentiate action: an fMRI study of implicit processing. European Journal of Neuroscience 17, 2735-40.

Hamzei F., Rijntjes M., Dettmers C., Glauche V., Weiller C. and Buchel C. (2003). The human action recognition system and its relationship to Broca's area: an fMRI study. Neuroimage 19, 637-44.

Hanna-Pladdy B., Heilman K.M. and Foundas A.L. (2003). Ecological implications of ideomotor apraxia: evidence from physical activities of daily living. Neurology 60, 487-490.

Hari R., Fross N., Avikainen E., Kirveskari E., Salenius S. and Rizzolatti G. (1998). Activation of human primary motor cortex during action observation: A neuromagnetic study. Proceedings of the National Academy of Sciences of the United States of America 95, 15061–15065.

Hartmann K., Goldenberg G., Daumuller M. and Hermsdorfer J. (2005). It takes the whole brain to make a cup of coffee: the neuropsychology of naturalistic actions involving technical devices. Neuropsychologia 43, 625-637.

Hauk O., Johnsrude I., Pulvermuller F. (2004). Somatotopic representation of action words in human motor and premotor cortex. Neuron 41, 301-7.

Heath M., Almeida Q.J., Roy E.A., Black S.E. and Westwood D. (2003). Selective dysfunction of tool-use: a failure to integrate somatosensation and action. Neurocase 9, 156-163.

Heilman K.M., Rothi L.J., Valenstein E. (1982). Two forms of ideomotor apraxia. Neurology 32, 342–346.

Heilman K.M., Maher L.M., Greenwald M.L. and Rothi L.J. (1997). Conceptual apraxia from lateralized lesions. Neurology 49, 457-64.

Hermsdorfer J., Goldenberg G., Wachsmuth E., Conrad B., Ceballos-Baumann A., Bartenstein P., Schwaiger M. and Boecker H. (2001). Cortical correlates of gesture processing: clues to the cerebral mechanisms underlying apraxia during the imitation of meaningless gestures. Neuroimage 14, 149-161.

Hyde T.M., Stacey M.E., Coppola R., Handel S.F., Rickler K.C., Weinberger D.R. (1995). Cerebral morphometric abnormalities in Tourette’s syndrome: a quantitative MRI study of mono-zygotic twins. Neurology 45, 1176–1182.

Iacoboni M. and Dapretto M. (2006). The mirror neuron system and the consequences of its dysfunction. Nature Review Neuroscience 12, 942-951.

Iacoboni M., Woods R.P., Brass M., Bekkering H., Mazziotta J.C. and Rizzolatti, G. (1999). Cortical mechanisms of human imitation. Science 286, 2526 –2528.

Iacoboni M., Koski L.M., Brass M., Bekkering H., Woods R.P., Dubeau M.C., Mazziotta J.C. and Rizzolatti G. (2001). Reafferent copies of imitated actions in the right superior temporal cortex. Proceedings of the National Academy of Sciences USA 98, 13995–13999.

Iacoboni M., Molnar-Szakacs I., Gallese V., Buccino G., Mazziotta J. C. and Rizzolatti G., (2005). Grasping the Intentions of Others with One's Own Mirror Neuron System. PLoS Biology 3, 1-7.

Ikeda A., Lqders H.O., Shibasaki H., Collura T.F., Burgess R.C., Morris H.H. and Hamano T. (1995). Movement-related potentials associated with single and repetitive simultaneous and unilateral movements recorded from human supplementary motor area. Electroencephalography and Clinical Neurophysiology 95, 323–334.

Inoue K., Kawashima R., Sugiura M., Ogawa A., Schormann T., Zilles K. and Fukuda H. (2001). Activation in the ipsilateral posterior parietal cortex during tool use: a PET study. Neuroimage 14, 1469-75

Jeannerod M. (1994). The representing brain – neural correlates of motor intention and imagery. Behavioural Brain Sciences 17, 187–202.

Jeannerod M. (2001). Neural simulation of action: A unifying mechanism for motor cognition. Neuroimage 14, S103–S109.

Johnson-Frey S.H. (2004). The neural bases of complex tool use in humans. Trends in Cognitive Sciences 8, 71-78.

Johnson-Frey S.H. and Grafton S.T. (2003). From 'acting on' to 'acting with': the functional anatomy of object-oriented action schemata. Progresses in Brain Research 142, 127-39.

Johnson-Frey S.H., Maloof F.R., Newman-Norlund R., Farrer C., Inati S. and Grafton S. (2003). Actions or Hand-Object Interactions? Human Inferior Frontal Cortex and Action Observation. Neuron 39, 1053–1058.

Jueptner M. and Weiller, C. (1998). A review of differences between basal ganglia and cerebellar control of movements as revealed by functional imaging studies. Brain 121, 1437-49.

Kellenbach M.L., Brett M. and Patterson K. (2003). Actions speak louder than functions: the importance of manipulability and action in tool representation. Journal of Cognitive Neuroscience 15, 30–46.

Kollias S.S., Alkadhi H., Jaermann T., Crelier G.and Hepp-Reymond, M.C. (2001). Identification of multiple nonprimary motor cortical areas with simple movements. Brain Research Review 36,185-95.

Koski L., Iacoboni M. and Mazziotta J.C. (2002). Deconstructing apraxia: understanding disorders of intentional movement after stroke. Current Opinion in Neurology 15, 71-7.

Koski L., Iacoboni M., Dubeau M.C., Woods R.P., and Mazziotta J.C. (2003). Modulation of cortical activity during different imitative behaviors. Journal of Neurophysiology 89, 460-71.

Krams M.., Rushworth M.F., Deiber M.P., Frackowiak R.S., and Passingham R.E. (1998). The preparation, execution and suppression of copied movements in the human brain. Experimental Brain Research 120, 386-98.

Labruna L., Colonnese C., Trojano, L. (under revision). The Neural bases of Meaningless and Meaningful Gesture Processing: a review.

Laimgruber K., Goldenberg G. and Hermsdorfer J. (2005). Manual and hemispheric asymmetries in the execution of actual and pantomimed prehension. Neuropsychologia 43, 682-692.

Lakoff G. and Johnson M. (1999). Philosophy in the Flesh: the Embodied Mind and its Challenge to Western Thought. Basic Books, New York, USA.

Lau H.C., Rogers R.D., Haggard P. and Passingham R.E. (2004). Attention to intention. Science 303, 1208-10.

Leckman J.F. (2002). Tourette’s syndrome. Lancet 360, 1577–1586.

Lee K.M., Chang K.H. and Roh J.K. (1999). Subregions within the supplementary motor area activated at different stages of movement preparation and execution. Neuroimage 9, 117–123.

Leiguarda R.C. and Marsden C.D. (2000). Limb apraxias: higher-order disorders of sensorimotor integration. Brain 123, 860-79

Liepmann H. (1900). Das Krankheitsbild der Apraxie (motorische Asymbolie) auf Grund eines Falles von einseitiger Apraxie. Monatschrift fur Psychiatrie und Neurologie 8, 15-44, 102-132, 182-197.

Liepmann, H. (1905). Die linke Hemisphere und das Handeln. Münchner medizinische Wochenschrift. 49, 2322- 2326, 2375-2378.

Liepmann H. (1908). Drei Aufsätze aus dem Apraxiegebiet, Berlin, Karger.

Liepmann H. (1925). Apraktische Storungen, in Lehrbuch der Nervenkrankheiten, a cura di H. Curschmann e F. Kramer, Berlin, Springer, pp. 408-416.

McNeill D. (1992). Hand and Mind, University of Chicago Press.

Moll J., de Oliveira S.R., Passman L.J., Cunha F.C., Souza L.F. and Andreiuolo P.A. (2000). Functional MRI correlates of real and imagined tool-use pantomimes. Neurology 54, 1331–1336.

Moriarty J., Varma A.R., Stevens J., Fish M., Trimble M.R. and Robertson M.M. (1997). A volumetric MRI study of Gilles de la Tourette's syndrome. Neurology 49, 410–415.

Morris M.E, Iansek R., Matyas T.A., Summers J.J. (1996). Stride length regulation in Parkinson's disease. Normalization strategies and underlying mechanisms. Brain 119, 551–568.

Nobre A.C., Sebestyen G.N., Gitelman D.R., Mesulam M.M., Frackowiak R.S.J. and Frith C.D. (1997). Functional localization of the system for visuospatial attention using positron emission tomography. Brain 120, 515–533.

O'Craven K.M., Rosen B.R., Kwong K.K., Treisman A. and Savoy R.L. (1997). Voluntary attention modulates fMRI activity in human MT-MST. Neuron 18, 591–598.

Ochipa C. and Rothi L.J.G. (2000). Limb Apraxia. Seminars in Neurology 20, 471-478.

Ochipa C., Rothi L.J.G and Heilman K.M. (1989). Ideational apraxia: A deficit in tool selection and use. Annals of Neurology 25, 190-193.

Ochipa C., Rothi L.J.G and Heilman K.M. (1992). Conceptual apraxia in Alzheimer's Disease. Brain 115, 1061-1071.

Ochipa C., Rothi L.J.G. and Heilman K.M. (1994). Conduction apraxia. Journal of Neurology, Neurosurgery and Psychiatry 57, 1241-1244.

Oldfield Rc. (1971). The assessment and analysis of handedness: the Edinburgh Inventory, Neuropsychologia 9, 97-113.

Paccalin C. and Jeannerod M. (2000). Changes in breathing during observation of effortful actions. Brain Research 862, 194–200.

Peigneux P., Salmon E., van der Linden M., Garraux G., Aerts J., Delfiore G., Degueldre C., Luxen A., Orban G. and Franck G. (2000). The role of lateral occipitotemporal junction and area MT/V5 in the visual analysis of upper-limb postures. Neuroimage 11, 644-55.

Peigneux P., van der Linden M., Garraux G., Laureys S., Degueldre C., Aerts J. Del Fiore G., Moonen G., Luxen A. and Salmon E. (2004). Imaging a cognitive model of apraxia: the neural substrate of gesture-specific cognitive processes. Human Brain Mapping 21, 119-42.

Peterson B.S., Skudlarski P., Anderson A.W., Zhang H., Gatenby J.C., Lacadie C.M., Leckman J.F., Gore J.C. (1998). A functional magnetic resonance imaging study of tics suppression in Tourette syndrome. Archives of General Psychiatry 55, 326–333.

Pulvermüller F., Hauk O., Nikulin V.V. and Ilmoniemi R.J. (2005). Functional links between motor and language systems. European Journal of Neuroscience 21, 793–797.

Rizzolatti G., and Arbib M.A. (1998). Language within our grasp. Trends in Neurosciences 21, 188-94.

Rizzolatti, G. and Luppino G. (2001). The cortical motor system. Neuron 31, 889-901.

Rizzolatti G., Fadiga L., Matelli M., Bettinardi V., Paulesu E., Perani D., et al. (1996a). Localization of grasp representations in humans by PET. I. Observation versus execution. Experimental Brain Research, 111, 246–252.

Rizzolatti, G., Luppino, G. & Matelli, M. (1996b). The classic supplementary motor area is formed by two independent areas. Advances in Neurology 70, 45-56.

Rizzolatti G., Fogassi L. and Gallese V. (2001). Neurophysiological mechanisms underlying the understanding and imitation of action. Nature Reviews Neuroscience 2, 661–670.

Robertson M.M. (2000). Tourette syndrome, associated conditions and the complexities of treatment. Brain 123, 425–462.

Roepstorff A. and Frith C. (2004). What's at the top in the top-down control of action? Script-sharing and 'top-top' control of action in cognitive experiments. Psychological Research 68, 189-198.

Rothi L.J.G., Heilman K.M. and Watson R.T. (1982) Pantomime comprehension and ideomotor apraxia. J Neurol Neurosurg Psychiatry, 4, 207–210

Rothi L.J.G., Mack L. and Heilman K.M. (1986). Pantomime agnosia. Journal of Neurology, Neurosurgery and Psychiatry 49, 451-454.

Rothi L.J.G., Ochipa C. and Heilman, K.M. (1991). A cognitive neuropsychological model of limb praxis. Cognitive Neuropsychology 8, 443-458.

Rothi L.J.G. Raymer A.M., Ochipa C., Maher L.M., Greenwald M. and Heilman K.M. (1992). Florida Apraxia Battery, Experimental Edition.

Rothi L.J.G. Raymer A.M. and Heilman KM (1997). Limb praxis assessment. In: LJG Rothi and KM Heilman (Eds.), Apraxia: The Neuropsychology of Action. East Sussex, UK: Psychology Press, pp. 61-73.

Roy E.A., Heath M., Westwood D., Schweizer T.A., Dixon M.J., Black S.E., Kalbfleisch L., Barbour K. and Square P.A. (2000). Task demands and limb apraxia in stroke. Brain and Cognition 44, 253-279.

Roy E.A. and Square P.A. (1985). Common considerations in the study of limb, verbal, and oral apraxia. In E. A. Roy (Ed.), Neuropsychological studies of apraxia and related disorder. Amsterdam: North-Holland, pp. 111–116.

Ruby P. and Decety J. (2001). Effect of subjective perspective taking during simulation of action: a PET investigation of agency. Nature Neuroscience 4, 546-50.

Rumiati R.I. and Tessari A (2002). Imitation of novel and well-known actions: the role of short-term memory. Experimental Brain Research 142, 425-433.

Rumiati R.I., Zanini S., Vorano L. and Shallice T (2001). A form of ideational apraxia as a deficit of contention scheduling. Cognitive Neuropsychology 18, 617-642.

Rumiati, R.I., Weiss, P.H., Shallice, T., Ottoboni, G., Noth, J., Zilles, K., & Fink, G.R., (2004). Neural basis of pantomiming the use of visually presented objects. Neuroimage 21, 1224-31.

Rumiati R.I., Weiss P.H., Tessari A., Assmus A., Zilles K., Herzog H. and Fink G.R. (2005). Common and differential neural mechanisms supporting imitation of meaningful and meaningless actions. Journal of Cognitive Neuroscience 9, 1420-1431.

Saxe R., Xiao D.K., Kovacs G., Perrett D.I. Kanwisher N. (2004). A region of right posterior superior temporal sulcus responds to observed intentional actions. Neuropsychologia 42, 1435-46.

Schwartz M.F., Buxbaum L.J., Montgomery M.W., Fitzpatrick-Desalme E., Hart T., Ferraro M., Lee S.S. and Coslett H.B. (1999). Naturalistic action production following right hemisphere stroke. Neuropsychologia 37, 51-66.

Serrien D.J., Nirkko A.C., Loher T.J., Lfvblad K.O., Burgunder J.M. and Wiesendanger M. (2002). Movement control of manipulative tasks in with Gilles de la Tourette syndrome. Brain 125, 290–300.

Shibasaki H., Sadato N., Lyshkow H., Yonekura Y., Honda M., Nagamine T., Suwazono S., Magata Y., Ikeda A., Miyazaki M., Fukuyama H., Asato R. and Konishi J. (1993). Both primary motor cortex and supplementary motor area play an important role in complex finger movement. Brain 116, 1387–1398.

Singer H. Patients S. (1997). Neurobiology of Tourette syndrome. Neurologic Clinics 15, 357–379.

Singer H.S., Reiss A.L., Brown J.E., Aylward E.H., Shih B., Chee E., Harris E.L., Reader M.J., Chase G.A., Bryan R.N. and Denckla M.B. (1993). Volumetric MRI changes in basal ganglia of children with Tourette's syndrome. Neurology 43, 950–956.

Smith M.M., Collins A.F., Morris P.E. and Levy P. (1994). Cognition in action, 2nd ed. Hove: Lawrence Erlbaum.

Stern E., Silbersweig D.A., Chee K.Y., Holmes A., Robertson M.M., Trimble M., Frith C.D., Frackowiak R.S. and Dolan R.J. (2000). A functional neuroanatomy of tics in Tourette syndrome. Archives of General Psychiatry 57, 741–748.

Strafella A.P., Paus T. (2000). Modulation of cortical excitability during action observation: a transcranial magnetic stimulation study. Neuroreport. 10, 2289-92.

Sundet K., Finset A. and Reinvang I. (1988). Neuropsychological predictors in stroke rehabilitation. Journal of Clinical and Experimental Neuropsychology 10, 363-379.

Talairach P. and Tournoux J.A. (1988). Co-Planar Stereotaxic Atlas of the Human Brain. Thieme, Stuttgart.

Tanaka S. and Inui T. (2002). Cortical involvement for action imitation of hand/arm postures versus finger configurations: an fMRI study. Neuroreport 16, 1599-602.

Tanaka S., Inui T., Iwaki S., Konishi J. and Nakai T. (2001). Neural substrates involved in imitating finger configurations: an fMRI study. Neuroreport 8, 1171-4.

Taylor S.F., Kornblum S., Minoshima S., Oliver L.M. and Koeppe R.A. (1994). Changes in medial cortical blood flow with a stimulus-response compatibility task. Neuropsychologia 32, 249-55.

Thach W.T., Goodkin H.P. and Keating J.G. (1992). The cerebellum and the adaptive coordination of movement. Annual Reviews in Neurosciences 15, 403-42.

Tettamanti M., Buccino G., Saccuman M.C., Gallese V., Danna M., Scifo P., Fazio F., Rizzolatti G., Cappa S.F., Perani D. (2005). Listening to action-related sentences activates fronto-parietal motor circuits. Journal of Cognitive Neuroscience 17, 273-81.

Umiltà M.A., Kohler E., Gallese V., Fogassi L., Fadiga L., Keysers C. and Rizzolatti G. (2001). "I know what you are doing": a neurophysiological study. Neuron 31, 155–165.

Wada Y., Nakagawa Y., Nishikawa T., Aso N., Inokawa M., Kashiwagi A., Tanabe H. and Takeda M. (1999). Role of somatosensory feedback from tools in realizing movements by patients with ideomotor apraxia. European Neurology 41, 73-78.

Wagner A.D. (1999). Working memory contributions to human learning and remembering. Neuron 22, 19-22.

Watson J.D., Myers R., Frackowiak R.S., Hajnal J.V., Woods R.P., Mazziotta J.C., Shipp S. and Zeki S. (1993). Area V5 of the human brain: Evidence from a combined study using positron emission tomography and magnetic resonance imaging. Cerebral Cortex 3, 79–94.

Westwood D.A., Schweizer T.A., Heath M.D., Roy E.A., Dixon M.J. and Black S.E. (2001). Transitive gesture production in apraxia: visual and nonvisual sensory contributions. Brain and Cognition 46, 300-304.

Appendix

Publications related to the thesis

Scientific publications

Fattapposta F, Restuccia R, Colonnese C, Labruna L, Garreffa G, Bianco F. Gilles de la Tourette syndrome and voluntary movement: a functional MRI study. Psychiatry Res. Neuroimaging 2005 Apr 30;138(3):269-72.

Publications on revision

Labruna L, Colonnese C and Trojano L. The neural bases of meaningless and meaningful gesture processing. Submitted in Journal Cognitive Neuroscience.

Trojano L., Labruna L., Grossi D. An experimental investigation of the automatic/voluntary dissociation in limb apraxia. Submitted in Cortex.

Publications in preparation

Labruna L., Duque J., Landau A. and Ivry R. Interaction between motor and language systems in MI: action observation and action related sentence comprehension.

Books Chapters

Labruna L., Trojano L. I disturbi del gesto di origine frontale. In: Neuropsicologia dei lobi frontali. Sindromi disesecutive e disturbi del comportamento. Edizione il Mulino, 2005, pp. 107-127