

ACTION EXECUTION AND RECOGNITION: A NEUROPSYCHOLOGICAL ANALYSIS

By

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A thesis submitted to
The University of Birmingham
For the degree of
DOCTOR OF PHILOSOPHY

School of Psychology
The University of Birmingham
May 2011

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... To my sister.

Acknowledgements

I thank Prof. Glyn Humphreys for the big help he gave me for my PhD to be completed (almost) in time, especially in the final rush.

Thanks to Dr Pia Rotshtein who was precious in teaching me all I needed for doing the VBM analyses and in giving me support in all the phases of the work.

Thanks to Wai Ling Bickerton for her cooperation in the studies about the BCoS tasks.

Thanks to Prof. Raffaella Rumiati who gave me the opportunity to work in her lab where I run the study on the Parkinson's' patient, and thanks to the doctors (Dr Emauele Biasutti, Dr Federica Mondolo, Dr Roberto Capus, Dr Gilberto Pizzolato, Dr Antonietta Zadini, Dr Alberta Lunardelli) who helped in that study.

Special thanks are for Dr Gioia Anna Lura Negri and Dr Anna Svezut who did the scoring of the huge amount of patients and controls I tested.

Also thanks a lot to my boss who was very tolerant in the past months and let me time to complete this work.

I thank my colleagues at Birmingham University, and in particular Dr Alessia Correani. She had been a lovely flatmate and will ever be a good friend.

And, of course, thanks to all the people who kindly put themselves out to do my tasks.

Finally "GRAZIE" to Giulio, Donatella, Caterina, Giorgia, Giuseppina and Max, my family, who always supported me

TABLE OF CONTENTS

1. GENERAL INTRODUCTION	9
IMITATION, AN OVERVIEW	9
ACTION IMITATION AND RECOGNITION: NEURAL CORRELATES AND THE MIRROR NEURON SYSTEM	13
NEURAL CORRELATES OF ACTION IMITATION OF MF AND ML TRANSITIVE AND INTRANSITIVE GESTURES	18
REASONS FOR THE PRESENT WORK	22
2. GENERAL METHODS	24
PATIENTS	25
CONTROL SUBJECTS	30
TASKS	32
NEUROIMAGING ASSESSMENT	41
3. IMITATING TRANSITIVE AND INTRANSITIVE GESTURES: AN ANALYSIS OF LESION SIDE AND ASSOCIATED COGNITIVE IMPAIRMENTS.	44
ABSTRACT	44
INTRODUCTION	44
GENERAL METHODS	47
RESULTS	48
DISCUSSION	59
4. NEURAL CORRELATES OF TRANSITIVE AND INTRANSITIVE ACTION IMITATION: AN INVESTIGATION USING VOXEL-BASED MORPHOMETRY (VBM)	67
ABSTRACT	67
INTRODUCTION	68

METHODS	71
BEHAVIOURAL RESULTS- TRANSITIVE (MF & ML) AND INTRANSITIVE (MF & ML) ACTIONS	72
VOXEL-BASED MORPHOMETRY	73
ANALYSES	73
VBM RESULTS	74
LESION OVERLAP MAPS	83
DISCUSSION	83
<u>5. RECOGNIZING AND EXECUTING MOVEMENTS: AN INVESTIGATION USING VOXEL- BASED MORPHOMETRY (VBM)</u>	<u>88</u>
ABSTRACT	88
INTRODUCTION	88
METHODS	95
RESULTS	96
DISCUSSION	106
<u>6. DISTINCT AND COMMON NEURAL CORRELATES OF APRAXIA FOR TRANSITIVE AND INTRANSITIVE GESTURES: AN INVESTIGATION USING VOXEL-BASED MORPHOMETRY (VBM)</u>	<u>112</u>
ABSTRACT	112
INTRODUCTION	113
METHODS	116
DISCUSSION	129
<u>7. THE ROLE OF THE BASAL GANGLIA IN ACTION IMITATION: NEUROPSYCHOLOGICAL EVIDENCE FROM PARKINSON'S DISEASE PATIENTS</u>	<u>134</u>
ABSTRACT	134
INTRODUCTION	134

METHODS	136
RESULTS	136
DISCUSSION	142
8. GENERAL DISCUSSION	144
9. SUMMARY	155
APPENDIX 1- CHAPTERS 3 AND 4	157
APPENDIX 2- CHAPTERS 5 AND 6	164
APPENDIX 3- CHAPTER 7	165
10. REFERENCES	167

ABSTRACT

Humans appear to show an innate tendency to imitate, and this may provide one of the foundations of social communication. Several studies have been carried out in social and cognitive science in order to understand how imitation works, which parts of the brain are involved, and what the role of imitation might be in social behaviour. Previous brain imaging and neuropsychological studies report data that favour a dual process account of imitation, according to which actions are imitated through different mechanisms on the basis of whether they are meaningful and familiar (MF actions) or meaningless/unfamiliar (ML actions). However many questions remain to be clarified – such as which brain areas mediate these different actions. In addition to the distinction between MF and ML gestures, there is considerable interest in the production of different types of known gestures – particularly between actions involving tools (i.e. transitive actions) and those subserving communicative (intransitive) gestures, and in how the production of these gestures relates to the processes involved in recognizing the gestures as input. This thesis reports a neuropsychological examination of the functional and neural bases of imitation using converging data from behavioural studies with different patient groups (stroke patients, patients with Parkinson's Disease, PD) and structural brain imaging (particularly using voxel-based morphometric [VBM] analyses) to examine lesion-symptom relations.

The first empirical chapter (Chapter 2) describes a neuropsychological study on the recognition and production of MF actions and the imitation of ML gestures, in patients with unilateral left or right-side brain damage (respectively: LBD and RBD patients). At a group level, LBD patients were worse in imitation than RBD patients only when novel transitive actions had to be reproduced, when both LBD and RBD differed from healthy participants, while intransitive gestures were generally easier to be executed. Also both transitive and intransitive action imitation tasks were correlated to action recognition. At a single subject level, however, there was evidence for some

dissociated symptoms, suggesting that at least partially different mechanisms mediate the imitation of transitive and intransitive gestures and gesture production as opposed to recognition.

Chapter 3 presents a first attempt to use VBM to evaluate the relations between brain lesions and the symptoms of apraxia, contrasting the imitation of meaningful (familiar) and meaningless (unfamiliar) transitive and intransitive actions in a consecutive series of brain damaged patients. Chapters 4 and 5 describe two investigations where VBM was again used in a large-scale lesion-symptom analysis of deficits in i) the recognition and generation to command of MF actions and the imitation of ML actions, and ii) the generation to command of different types of learned action (transitive or intransitive gestures). All three investigations using VBM revealed common and differential neural substrates involved in the execution of the tasks considered, and the data are compatible with a model which posits that different processes are involved in MF and ML action execution, as well as in action understanding. The results also suggest that the distinction between transitive and intransitive actions may be included in an action reproduction system. In the final empirical chapter (Chapter 6), I report a study on PD patients tested for imitation of transitive and intransitive MF and ML actions, also relating their performance to the neurological/peripheral symptoms of the disease. This study revealed that PD patients were impaired in imitation, and they also had different pattern of deficit for transitive and intransitive actions. The correlation with peripheral symptoms was not significant, though there were correlations with underlying cognitive processes likely to support action production. Chapter 7 summarizes the different results and links them back to functional and neural accounts of action recognition, production and imitation. The relations between action production and recognition and other cognitive processes are discussed, as are methodological issues concerning lesion-symptom mapping.

1. GENERAL INTRODUCTION

Imitation, an overview

Imitation is an innate tendency in humans, rather than an ability that is gradually learnt in the first years of life. This was suggested first by Meltzoff & Moore (1977, 1983) who demonstrated that newborn infants spontaneously imitate manual and facial gestures as well as head movements and tongue-protrusion gestures, and that they do so even within the first hour of life. The same authors also pointed out that babies not only imitate when gestures are displayed but also from memory after an action has stopped (Meltzoff & Moore 1989). The results are not confined to humans.

Spontaneous imitation has also been observed in newborn chimpanzees (Myowa et al. 1996; Bard & Russell 1999; Myowa & Yamaloshi et al. 2005) and in infant macaques (Ferrari et al. 2006). In chimpanzees and macaques, however, and unlike humans, imitation is observed only in the first months of life. In contrast to this there is evidence for automatic imitation of action occurring in human adults, and this may be critical both for social communication and for learning a wide range of skills (e.g. effective tool use, or even language skills).

In recent years the existence of a class of visuo-motor neurons (the so-called mirror neurons, MNs) has been reported in the ventral premotor cortex (area F5) of the monkey (Gallese et al. 1996; Rizzolatti et al. 1996), along also with a portion of the superior temporal sulcus (the STSa) and the inferior parietal lobule (area PF) (see Rizzolatti et al. 2001, 2004 for a review). These neurons are termed 'mirror neurons' because they responded not only to the monkey acting but also when the monkey saw the same action being performed. The discovery of MNs has prompted a wide series of studies trying to demonstrate the existence and the location of neurons having mirror properties in humans, which are reviewed in the next section. This has been supported by evidence from brain imaging investigations showing areas that are active during action observation and

observation/execution tasks, and extending also to gestures (note that pantomimes do not activate MN cells in monkeys; see Rizzolati et al. 2001 for a review).

The MN system will be discussed more extensively in the next section, but their existence was introduced here because of the implications for interpreting clinical evidence from neuropsychological patients with impairments in action (apraxia). The existence of the MN system implies that people directly match sensory information into their motor systems in order to interpret the world, and that seeing and reproducing a gesture involves the same multimodal representation in the same brain areas. If that was true, then a brain lesion in areas where the MN system is located would lead to deficits in both action execution and recognition, and, depending perhaps on whether there is any differentiation within the MN system itself, the deficit would extend to any types of gesture.

Brain lesions can impair the ability to imitate creating a set of symptoms that characterize the syndrome known as ideomotor apraxia. Neuropsychological studies, as well as clinical experience with brain damaged patients, indicates that ideomotor apraxia is not a unitary syndrome, however, with symptom dissociations reported among patients in relation to the types of actions to be executed and the body part involved in the task (see Rumiati et al. 2009 for a review). The dissociations do not fit entirely with the MN hypothesis. For instance, neuropsychological observations suggest a double dissociation between the production of meaningful and meaningless gestures, with some studies reporting patients who are more impaired when imitating meaningful (MF) compared to meaningless (ML) gestures (Goldenberg & Hagmann 1997; Peigneux et al. 2000; Tessari et al 2007), while others show the opposite pattern (Bartolo et al. 2001; Tessari et al. 2007). Given that all gestures should be enacted through the MN system, it is not clear why (e.g.) MF gestures should be more difficult to perform than ML, given that MF gestures should have stronger (learned) representations within the MN system.

A cognitive neuropsychological 'dual route' model of praxis was first proposed by Rothi et al. (1991) and then modified by other authors (e.g. Goldenberg & Hagmann 1997; Cubelli et al. 2000; Buxbaum et al. 2001; Rumiati & Tessari 2002). This model postulates (i) a semantic route to action, relying on long-term memory representations, which allow the reproduction of MF (known) gestures, and (ii) a direct route, depending on a short-term memory/ innervatory pattern, which supports the reproduction of ML (new) actions (Figure 1). The starting point of both routes is a visual analysis component, through which the visual properties of actions are processed. Also both semantic and direct processes end at the level of the motor system involved in the actual implementation of the action. In the present work I will consider the model proposed by Rumiati and Tessari (2002) that is a simplified version of the original model by Rothi et al. (1991) and that substitutes the 'innervatory pattern' of the original model with a short-term memory component, stressing its role in the imitation of ML gestures.

Differently from the semantic route, which allows the reproduction only of those gestures that have a representation in long-term memory, the direct route allows the execution of both ML and MF gestures if the route is damaged or if the cognitive resources are limited and MF gestures are presented intermingled with ML, thus avoiding the cognitive costs of switching from one route to the other (Tessari et al. 2004). Besides neuropsychological observations, the existence of different mechanisms for MF and ML actions has been suggested by several behavioural investigations in healthy participants as well as in imaging studies (e.g. Rumiati et al. 2009; Tessari & Rumiati 2004; Peigneux et al. 2004), and it holds for both transitive (tool-related) and intransitive (not-tool related) actions.

Within the class of MF actions, however, differences have been reported between transitive and intransitive actions. For example, neuropsychological data show that apraxic patients can have more difficulties in imitating transitive than intransitive gestures (Haaland et al. 2000; Buxbaum et al. 2005, 2007), but the reverse dissociation has rarely been reported. The preponderance of

impairments in producing transitive over intransitive actions may reflect the greater difficulty of transitive actions (see Carmo & Rumiati, 2009, for data from normal participants), and there is not proof that transitive and intransitive actions depend on different processes. However Stamenova et al. (2009) assessed the production (to name) and imitation of transitive and intransitive gestures in patients with unilateral left or right hemisphere damage after stroke (Stamenova et al. 2009). Although no cases were found demonstrating a complete double dissociation (e.g., with either gesturing to name or imitation for one class of action affected while both tasks were preserved for the other class), there were cases of relative dissociation for one type of action (either gesturing to name or imitation) or either transitive or intransitive actions. So it is still possible that at a single patient level the opposite dissociation could emerge.

Figure1. The dual route model for action imitation (Rumiati and Tessari 2002)

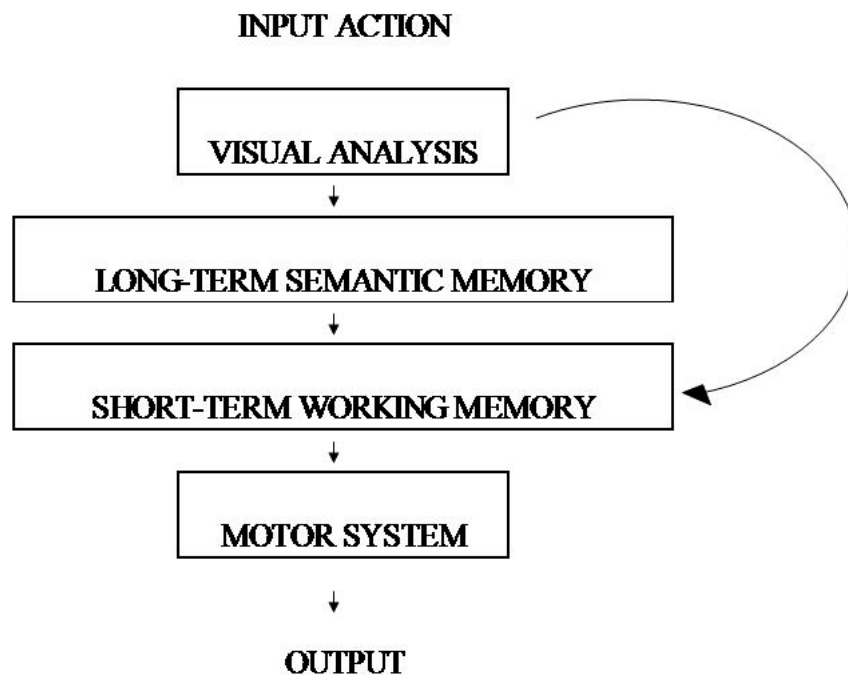


Figure 1- According to the dual route model a semantic route allows the reproduction of MF gestures automatically activating the gestures representation in long-term memory, while a direct route, supports the reproduction of ML actions and relies on short-term memory. The direct route also allows imitation of MF gestures if the semantic route is damaged.

Action imitation and recognition: neural correlates and the mirror neuron system

Mirror neurons are probably the most famous discovery in neuroscience over recent years. The key initial evidence came from physiological studies in monkeys. These studies demonstrated the existence of a class of visuo-motor neurons (the so-called mirror neurons, MNs), that responded when the animals saw actions as well as when they had to produce them - some neurons responding when the executed and perceived actions strictly coincided and others responding when the goals of the enacted and perceived actions coincided (see Rizzolati et al. 2001, 2004 for a review). In monkeys MNs have been documented to respond only for goal-directed actions, but not when those actions were made using a tool. Also MNs appear not to respond to the mere presence of objects, food, or to pantomimes or movements having an emotional meaning (see Hickok 2009, for a review). It has also been pointed out that in monkeys MNs do not support imitation, as adult monkeys do not imitate (Ferrari et al. 2006).

At first MNs were found in area F5 in the monkeys' ventral premotor cortex (Gallese et al. 1996; Rizzolati et al. 1996) but they have also been reported in a portion of the superior temporal sulcus (the STSa) that responds also to biological motion and in the inferior parietal lobule (area PF) that has been shown to respond strongly to the observation of action. The neurons in these three areas also vary in the likelihood that they respond to action execution as well as observation, with almost all neurons that respond to biological movements in F5 discharging also during action execution, two thirds having similar properties in PF and only a minority of the neurons having both characteristics in STMa (Rizzolati et al. 2001). Together these systems comprise the MN system, which has been argued to play a critical role in a range of processes, from action understanding through to intention encoding (Iacoboni et al. 2005; see also Rizzolati et al. 2001, 2010 for a review).

Supportive evidence for a MN system in humans has come from various sources. Early suggestions came in the form of electrophysiological evidence (e.g., EEG) showing activity in motor regions when gestures were observed (Gastaut et al. 1954; Cohen-Seat et al. 1954; Cochin et al. 1998, 1999; Altschuler et al. 1997, 2000; Salmelin et al. 1994; Hari et al. 1997; Salenius et al. 1997; Hari et al. 1998). This has been complemented by evidence from brain imaging investigations showing that ventral premotor/inferior frontal areas (including Broca's region), the STS and the inferior parietal lobule are active during the observation of hand movements (see Rizzolati et al. 2001 for a review). Furthermore, imaging studies using both action observation and observation/execution tasks have shown that the left inferior frontal cortex and the right anterior parietal region are active both when a gesture (lifting a finger) had to be executed following the observation of the same gesture and when the gesture had just to be observed. The same area did not respond when the finger movement had to be done after the observation of a control stimulus (a cross), or when participants just attended to the cross (Iacoboni et al. 1999; see also Rizzolati et al. 2001 for review). The parieto-frontal circuit was also found to activate in other fMRI studies when participants observed a human or robot hand grasping an object (Gazzola et al. 2007), in answer to action related (Lewis et al. 2005) and hand and mouth related sounds (Gazzola et al. 2006), and when aplasic individuals (born without arms and hands) both watched motor acts using hands and moved their feet (Gazzola et al. 2007) (see Rizzolati et al. 2010 for a review). It should be noted that, while in monkeys MN did not respond to pantomimes and they could not be involved in imitation as imitation is not part of the behavioural repertoire of adult monkeys, several experiments on MNs in humans have used recognition and imitation of pantomimes (Kosky et al. 2002, 2003; Iacoboni et al. 1999; Grèzes et al. 1998;) as well as the imitation of meaningless gestures (Iacoboni et al. 1999; Rizzolati & Craighero 2004). These studies have often revealed activation in the inferior frontal gyrus and the inferior precentral gyrus, which has been interpreted as proof of the existence of a MN system in

humans that has evolved to include both action recognition and production (see Hickok 2009 for a review).

The MN system has been argued to have a main role in action understanding (Gallese et al. 1996; Rizzolati et al. 2001). Rizzolati et al. (2001) defined “action understanding” as “the capacity to achieve the internal description of an action and to use it to organize appropriate future behaviour”, however other definitions exist (e.g. see Gallese et al. 1996). In the present work I will consider action recognition and “action understanding” as synonymous, as the action recognition employed in the thesis requires the perception and comprehension of learned motor actions. Apart from questions over definitions, the assertion that mirror neurons are involved in action understanding was based on observation that (i) those neurons in monkeys responded specifically on execution and presentation of actions towards objects (e.g. lift an object/piece of food and put it in a container, or take a piece of food and put it in the mouth), (ii) the neurons did not fire to pantomimes (without the object present, and so having not a goal) but (iii) fired again to actions toward hidden objects, if the monkey could see the object before it was hidden by a screen, as well as (iv) responding when the stimulus was not visual, as when sounds related to purposeful actions were presented (e.g. cracking a peanut shell or ripping paper). All this evidence has led to the claim that mirror neurons were not simply visuo-motor association neurons, linking a visually presented object to its appropriate action, but coded the meaning of the actions. However in a review Hickok (2009) has pointed out that all the findings could be interpreted in more straightforward way, in terms of audiovisual associative neurons, matching the representation of the object to its target action, with this representation retrieved from the sound of the object itself or from working memory (as when monkeys attended actions to hidden objects), rather than of neurons having ‘semantics’ (Hickok 2009).

Another argument put forward in favour of the MN system being related to recognizing the meaning of an action comes from a study by Gallese et al. (1996). These authors simultaneously

recorded the activity in monkeys' F5 and in the hand area of primary motor cortex (M1), as well as recording EMG activity from several mouth and limb muscles. The results did not show any activity from M1 and from limb and mouth muscles during action observation while mirror neurons were responding (Gallese et al. 1996). This suggested that no covert movement were involved, and cells in F5 were not mere motor-related neurons. However this result could be not replicated in humans, in a transcranial magnetic stimulation (TMS) study that showed an increase in distal muscle motor-evoked potentials (MEPs) during action observation (Fadiga et al. 1995). Inconsistent results have come also from two recent studies using neural adaptation. Adaptation is a decrease in the blood-oxygen-level dependent (BOLD) response from a brain area when a given sensory stimulus is presented repeatedly several times, and adaptation across two separate stimuli is considered to be evidence for the stimuli involving the same process and neural correlate. A first fMRI study on healthy participants failed to show populations of neurons undergoing adaptation for executed actions that were subsequently observed and vice versa (Dinstein et al. 2007) while a second study pointed out the right inferior parietal lobe shows adaptation across action execution and perception (Chong et al. 2008).

Neurophysiological evidence from the monkey points to action recognition and production sharing neural and functional processes even though other possible, and more straightforward explanations may be proposed (Hickok 2009, see above). Also the neuroimaging studies in humans fail to give conclusive answers on the issue and it is clear that distinct component processes must also contribute to each task. This is indicated perhaps most clearly by evidence of dissociations between the tasks in neuropsychological patients.

For example, dissociations have been documented between patients who show spared recognition of actions and gestures but who are impaired at producing the actions themselves (not concomitant on a motor impairment, in cases of ideomotor apraxia; see Chainay & Humphreys, 2002). Also it cannot be argued that the dissociation exists only because recognition tasks are easier than

producing gestures or imitating, as the reverse pattern of deficit, a syndrome labelled as “pantomime agnosia” (Rothi et al. 1986), has also been reported (Bell 1994; Rothi et al. 1986; Cubelli et al. 2000; see also Mahon et al. 2005 for a review). For instance Negri et al. (2007) obtained case-level dissociations in a study where they tested an unselected group of 37 unilateral brain damaged patients for object use, object recognition, pantomime imitation and pantomime recognition. Although at group level they found significant correlations between each pair of task, they also pointed out subsets of patients demonstrating dissociations between each test pairs (Negri et al. 2007).

Gesture recognition has been linked to inferior frontal regions (Pazzaglia et al. 2008) as it has pantomime imitation (Goldenbeg 2007). However the recognition of particular aspects of transitive actions can be linked not to frontal regions but to inferior parietal (recognition of spatial aspects of action) and posterior middle temporal cortex (recognition of semantic aspects of action). Parietal regions have also been shown to be linked to ML action imitation (Rumiati et al. 2005; Goldenberg et al. 2009).

Patients with lesions in the left parietal lobe have been reported to have poorer performance at gesture to command than at imitation while patients with lesions in the left occipital and temporal cortex have been documented with the opposite pattern, being almost normal when producing actions on verbal command (Merians et al. 1997). Also, as described in the previous paragraph, when gesture production is considered alone, there are dissociations in the production of different types of action - for example, patients who can imitate familiar but not unfamiliar actions (see Tessari et al. 2007 for a review). These dissociations point to there being separable components in the system for processing actions as sensory stimuli for imitation and for learned gesture execution, and they are compatible with a dual route account of action (see Tessari et al. 2007 and Rumiati et al. 2010 for a review). The dual route model involves a semantic system where motor schemas of already known gestures are stored and used for execution but not necessarily for action imitation (as

suggested by the double dissociations in patients who cannot recognize but can imitate and vice versa). Also, a crucial point of the model is that access to the semantic system, needed to recognize or understand the goal of an action, is not necessary for correctly imitating a gesture, as any gesture can be processed through the direct route, and the representation of the action, before being translated in motor terms is sustained by working memory.

Neural correlates of action imitation of MF and ML transitive and intransitive gestures

Data on the neural correlates of praxis also come from neuropsychological observations on patients. Traditionally the left hemisphere was considered dominant for controlling gesture production (see Rothi et al. 1997) in right-handed people. However, even though there is a large consent on the major involvement of the left hemisphere in action production, some authors suggest that this depends upon the type of actions that have to be implemented. So, while the execution of transitive (tool-related) actions seems to rely more on the left-hemisphere (Bartolo et al. 2001; Tessari et al. 2007), both right and left cortical areas are involved in the production of intransitive gestures (Buxbaum et al. 2001, see also Tessari et al. 2007 and Rumiati et al. 2010 for a review). Also a role for sub-cortical structures has been suggested by some studies (see Tessari et al. 2007; Leiguarda et al. 1997, 2001; De Renzi et al. 1980), even though there is still not yet consent about which type of gesture may be more impaired after lesions or deterioration in those structures.

One piece of evidence comes from the observation of patients suffering of ideomotor apraxia. In right handed people ideomotor apraxia has classically been described in relation to lesions of the left posterior parietal cortex (Liepmann, 1900, 1905)(see Rothi et al. 1991 for a review), though other different studies point to the role of right brain areas as well as sub-cortical structures (see Tessari et al. 2007; Leiguarda et al. 1997, 2001; De Renzi et al. 1980), especially when finger configurations (Goldenberg & Strauss 2002; Della Sala et al. 2006) or movement sequences

(Canavan et al. 1989) have to be copied. While there is also neuropsychological data (e.g. Goldenberg & Hagmann 1997; Peigneux et al. 2000; Cubelli et al. 2000; Bauxbaum et al. 2001; Tessari et al. 2007) supporting the idea of two separate neural systems for imitating MF and ML gestures, there is inconsistency with respect to the specific neuro-anatomical structures involved in each (particularly concerning their hemispheric localisation). Lesions involving the parietal cortex, especially the left angular gyrus, are reported to cause a deficit in the imitation of meaningless (ML) as compared to meaningful (MF) actions in left-brain damaged patients (LBD) (Mehler 1987; Goldenberg & Hagmann 1997; Peigneux et al. 2000; Tessari et al. 2007). In contrast Tessari et al. (2007) reported two right brain damaged patients (RBD) who were more impaired in imitating ML relative to MF gestures. For these two patients the lesions included the caudal portion of the pallidum, the putamen and the posterior limb of the internal capsule.

Goldenberg (2008), in a review of apraxia, also argues for a role of parietal lesions in the imitation of meaningless gestures, as well as on the use of tools and objects, and actually states that parietal lesions have an impact on those functions and not on other aspects of praxis. Goldenberg further points out that the role of the parietal lobes concerns the apprehension of spatial relationships between body-parts, tools and objects rather than representations of motor acts (Goldenberg 2008). Goldenberg et al. (2007) used lesion subtraction procedures to determine the locations specifically associated with defective pantomime of tool use in patients with left-brain damage and aphasia. Their results showed that damage to the left inferior frontal cortex was associated with a deficit in pantomiming action, even though the area of lesion overlap further extended into the underlying white matter (WM) and it is possible that damage of WM projections contributed to the deficit (Liepmann 1905; Geschwind 1976; Catani and Ffytche 2005).

Observations of neuropsychological deficits also indicate a role of subcortical structures on imitation that do not relate to peripheral neurological symptoms. For instance data from Leiguarda et al. (1997, 2001) suggest that the basal ganglia are necessary for the imitation of transitive actions,

while intransitive actions may operate through cortical regions – with this holding even for meaningless actions based on intransitive gestures. In patients with sub-cortical lesions then imitation may be spared for meaningless actions, but the production of familiar transitive actions may be disrupted (Hanna-Pladdy et al. 2001). In contrast, Tessari et al. (2007) described two right – brain damaged patients whose lesions involved the basal ganglia. These individuals were more impaired in imitating meaningless (ML) as compared to meaningful (MF) transitive (or tool-related) pantomimes and their lesions overlapped on basal ganglia. The report from Leiguarda et al. (1997, 2001) gives the opposite picture to this, but in their case the MF transitive gestures could have been more difficult than the ML gestures. There are data too suggesting that access to long-term semantic memories for action may involve middle temporal regions, while deficits in access to (and possibly planning for production) the spatial aspects of action link to inferior parietal damage (Buxbaum et al. 2010). The implementation of learned transitive actions may operate through sub-cortical routines (though see Tessari et al. 2007), while left inferior frontal regions are involved in aspects of action production where lesions become most pronounced when there is a lack of convergent input from holding the actual objects (see Chainay & Humphreys, 2002, about the use of convergent sensory input into motor output and selection processes).

Consistent with the above argument, neuropsychological data show dissociations between transitive and intransitive actions suggesting that the two classes of gestures can be functionally and neutrally separable. In the majority of cases patients have been described with deficits in which transitive actions are more impaired than intransitive actions (e.g., Buxbaum et al. 2007) and it has been proposed that transitive actions relying on a repository of action engrams in the left inferior parietal cortex (Buxbaum, 2001; Buxbaum et al. 2007; Liepmann, 1900-1905) and/or sub-cortical structures (Leiguarda et al. 1997, 2001) whereas familiar intransitive actions may be supported by fronto-parietal regions that respond to fine-grained dynamic properties of action (Buxbaum et al. 2007; Haaland & Flaherty, 1984; Mozaz, 2002; Rapcsak et al. 1993).

Recent work by Stamenova, Roy and Black (2010) compared transitive and intransitive actions in stroke patients. Selective deficits in transitive actions were associated with left hemisphere damage and problems with intransitive action with right hemisphere damage, consistent with prior arguments for the necessary involvement of the right hemisphere in intransitive action, perhaps because these actions depend more on fine-grained spatio-temporal modulation of action. On the other hand, the same investigators (Stamenova et al. 2009) have reported data on cortical-basal degeneration patients showing selectively greater changes on the left or right side of the brain and failed to find evidence for intransitive actions ever being more impaired than transitive. Hence the case for a functional and neural distinction between these different classes of learned actions remains inconclusive.

Behavioural and imaging studies on healthy participants (e.g. Rumiati et al. 2009; Tessari & Rumiati 2004; Peigneux et al. 2004) show different brain areas to be active for MF and ML actions, even though also in this case there is not unequivocal consent on the structures that are involved. In studies using positron emission tomography (PET), imitation of MF actions has been observed to be associated with activation in the left angular and middle frontal gyri, as well as the right supramarginal gyrus and inferior parietal lobule (Peigneux et al. 2004), and also in the inferior temporal, angular and parahippocampal gyri in the left hemisphere (Rumiati et al. 2005). The parieto-occipital and occipito-temporal junctions on the right, the superior temporal gyrus on the left, and the superior parietal cortex bilaterally have also been shown to have increased activation linked to imitation of ML actions (Rumiati et al. 2005). Other studies though suggest considerable overlap in the brain areas used to make transitive and intransitive gestures, consistent with all familiar gestures relying on a common neural network involving parietal and frontal cortices (e.g., Kroliczak & Fray, 2009).

Reasons for the present work

As the above review indicates, many studies have investigated action imitation and recognition, and different fields of neuroscience have addressed the issue. However there is still not unanimous consent on how imitation and recognition take place, especially in relation to the brain regions involved. Neuropsychological and clinical observations can reveal symptom correlations and dissociations that sometimes highlight different components involved in praxis, according to the task (imitation or action recognition) and the type of action involved (MF or ML).

One caveat however is that neuropsychological studies using lesion-symptom mapping frequently rely on categorical subdivisions of patients based on a given cut off as well as on observer-dependent lesion demarcations. The use of a cut off, especially in tasks where each answer is scored either 1 or 0, introduces the risk that patients having scores differing only for one point are treated differently (e.g. scores that equal the cut off will be considered as defective, while scores higher than the cut off for one point will be treated as borderline or not defective at all). Also manual demarcations of lesions sites may lead to under- or over- estimation of differences in tissues according to the strictness of the observer's criteria. The present study aims to investigate the neural substrates of action imitation, production to name and recognition using a complementary VBM analysis based on segmented grey matter (GM). VBM uses the general linear model to statistically assess the relations between brain tissue integrity and behavioural performance. Here, imitation, action production and recognition scores were used as predictors of change in the signal intensity coming from each voxel across the whole brain in groups of consecutively sampled patients, not pre-selected on the basis of having apraxia, but using continuous scores on tests of gesture imitation in order to characterise their abilities. This approach also allows us to control in the model covariates of no interests such as age, gender, neglect, which may otherwise contaminate the results.

VBM analysis provides an instrument to test movement production offline and then to look for neural correlates from brain images in unbiased samples of participants. Of course VBM works only if brains differ in voxel intensity signal, and in adults that means that brains entered in the analysis should have a lesion. Also, being based on correlation, VBM requires quite big samples to give results. For this reason I have attempted to test large samples of participants on tasks that may be considered to test praxis and then to use the performance of individual patients as a predictor of the density of brain GM. I have also assessed patients at different stages of their disorder – including patients scanned at a sub-acute stage (Chapter 5 and 6) and patients with chronic deficits (Chapter 4), and I have analysed both MRI (Chapter 4) and CT (Chapter 5 and 6) data. Scanning at different stages of recovery, and using different imaging procedures, both raise questions about the comparability of the results, but they also allow conclusions to be drawn with greater confidence when converging results emerge. The data from across the thesis point to both common patterns of deficits across different tasks and action types, and also to some instances of dissociation – both in behavioural and in imaging terms. The General Discussion chapter tries to draw the results together to make general conclusions about the action production and recognition system.

2. GENERAL METHODS

This thesis presents five neuropsychological studies focusing on the performance of patients with acquired brain lesions in gesture production and recognition Chapter 3 compares patients with chronic acquired injury, involving either the left or the right hemisphere, and healthy volunteers in the imitation and recognition of different types of action (familiar or unfamiliar transitive actions to objects and familiar or unfamiliar intransitive, not-object-related, gestures).

Chapter 4 uses chronic brain injured patients' scores in the imitation of familiar and unfamiliar transitive and intransitive gestures to predict MRI signal changes from gray matter or white matter segmented images. In this chapter voxel-based morphometry was performed on patients' scores and MRI signal values entered as continuous measures. However healthy controls' data were also used to describe the patient sample at a behavioral level (see the paragraph below and chapter 2 for more details).

Chapter 5 analyzes the relation between GM and WM integrity and the skills to produce gestures on verbal command, to imitate and to recognize actions, in a sample of acute stroke patients using voxel-based morphometry on CT scans. In this chapter the data for the patients were not compared to healthy controls' scores.

Chapter 6 investigates the GM and WM correlates of production on verbal command of transitive and intransitive familiar gestures, again on acute stroke patients using voxel-based morphometry on CT scans. As in Chapter 5 the patients' scores were not compared to controls.

Chapter 7 reports a neuropsychological investigation where we tested the ability of Parkinson's disease patients in imitation of familiar and unfamiliar transitive and intransitive gestures as compared to healthy controls.

This section of the thesis reports a description of the samples of patients and healthy volunteers that took part in the studies reported in this thesis, along with the materials and the tasks administered.

In some cases only some patients or controls from a main sample are included in a study. Also, some tasks are included in more than one study while others are unique for one or two studies. For this reason, in those cases where it may not be clear, tables are presented summarizing which subjects or tasks are included in each chapter.

Also, the two final paragraphs describe the imaging data used in the present work for the analyses using voxel-based morphometry (VBM), how they had been acquired and prepared for the analyses and the tools used to run the VBM.

PATIENTS

Patients- Chapters 3 (comparing right and left brain damaged patients) and 4 (VBM on MRI scans of patients in chronic phase)

Twenty-four patients (mean age= 67.9, SD= 10.9, age range= 36-82) were recruited at the Behavioural Brain Science at the school of Psychology of the University of Birmingham. All the patients had acquired brain lesions (twenty-three had a stroke, while one had a bilateral lesion caused by encephalitis), and all were in the chronic stage (> 9 months after the occurrence of the lesion). According to the Edinburgh Handedness Inventory (Oldfield, 1971) twenty-one patients were right handed before the stroke and three were left-handed. Patients' demographic data and their Edinburgh Handedness Inventory scores are summarized in Appendix 1 (see Table 1 in Appendix 1).

From this sample, the data of fifteen patients were used in the two studies presented in chapter 3 and chapter 4, three patients were included only in the study in chapter 4 and six patients were included only in the study in chapter 3. Table 1 shows which patients were included in each chapter (3 or 4 or both), the patients' lesion side, handedness and the hand used to imitate (dominant or not dominant).

In total, eighteen right-handed patients (sixteen male, two female) were included in the study described in chapter 3. Nine patients had a lesion involving the right side of the brain (Right Brain Damaged, RBD) (mean age= 69.22, SD= 8.07, age range= 55-78) and nine had a lesion on the left (Left Brain Damaged, LBD) (mean age= 67.2, SD= 13.7, age range= 36-82), confirmed on either MRI or CT scans. From the main sample of twenty-four patients, six were excluded from the first study because of one of the following reasons: i) three patients resulted to be left-handed before the stroke; ii) two patients had a bilateral brain lesion.

In a first version of the present work one patient (MMcD, highlighted in red in Table 1) was included by mistake in the sample of LBD, and so his data were analysed also in chapter 3.

However, when we checked again the patient's scan he resulted to have a bilateral lesion, which was also likely to influence his behaviour. For this reason he was then excluded from the sample in chapter 3. A final section of chapter 3 will describe briefly MMcD results and a picture of his lesion will be reported.

Twenty-one patients (20 males and 1 female, 18 right-handed, 3 left-handed) (mean age: 68.18; SD: 11.13. Age range: 36-82) were included in the study reported in chapter 4. Seven patients had a lesion involving the left side of the brain (Left Brain Damaged, LBD), eleven had a lesion on the right (Right Brain Damaged, RBD) and three had bilateral brain lesions (BBL).

None of the patients who took part in the studies of chapter 3 and 4 were included in chapter 5, 6 and 7.

Table 1. Cortical patients in chapter 3 and chapter 4 (all native English patients recruited among those regularly attending the school of psychology of the University of Birmingham)

	lesion side	chapter 3	chapter 4	handedness	hand used
MP	RBD	✗	✓	left	n-d
JW	RBD	✓	✓	right	d
JQ	RBD	✓	✓	right	d
AS	RBD	✓	✓	right	d
JM	RBD	✓	✓	right	d
AK	RBD	✓	✓	right	d
JE	RBD	✓	✓	right	d
PW	RBD	✓	✓	right	d
JB	RBD	✗	✓	left	n-d
MC	RBD	✓	✓	left	n-d
QJ	RBD	✓	✓	right	d
BL	LBD	✓	✗	right	d
DS	LBD	✓	✓	right	d
PH	LBD	✓	✓	right	n-d
MM	LBD	✓	✓	right	d
PJ	LBD	✓	✓	right	d
DE	LBD	✓	✓	right	n-d
BR	LBD	✓	✓	right	d
RH	LBD	✗	✓	left	d
DL	LBD	✓	✗	right	d
DT	LBD	✓	✗	right	d
MMcD	BBD	✗	✓	right	d
GA	BBD	✗	✓	right	d
PM	BBD	✗	✓	right	d

Table 1 shows for each patient: lesion side (LBD= left brain damage, RBD= right brain damage, BBD= bilateral brain damage); chapter in which the patient was included (included= ✓, excluded= ✗); handedness before stroke (right, left); hand used for imitation (d= dominant; n-d= non-dominant). The BBD patient highlighted in red was included by mistake in the LBD group in chapter 3 in a first version of the study.

Alongside the experimental tasks, the patients in chapter 3 underwent a general neuropsychological assessment with the Birmingham Cognitive Screen (BCoS) covering the domains of language, mathematical/number abilities, praxis/control and planning of action, memory, attention and executive functions (Humphreys, Bickerton, Samson & Riddoch, 2012). A description of the BCoS

is reported in Appendix 1, along with the patients' results (Table 2 in Appendix 1). The results on the BCoS tests were used to perform correlations with the imitation scores.

Patients- chapters 5 and 6 (VBM on CT scans of acute patients)

CT scans and behavioural results from 233 stroke patients (110 male and 123 female; mean age= 70.64, SD= 14.40) were taken from the dataset collected by the Birmingham University Cognitive Screen Trial group (<http://www.bucs.bham.ac.uk>) in 12 local stroke units, and were used for the analyses. Each patient's age, gender, education level, and the hand used to perform for gestures production and imitation are reported in Appendix 2 (Table 1 in Appendix 2). All the patients had ischemic stroke and were at a sub- acute stage (>2 days, ≤3 months after the stroke) at the time of both behavioural testing and CT scan acquisition. At the time of testing all were alert and had sufficient English comprehension to follow the instructions. As the data were taken from a very large database, this allowed us to further filter the data, and to include only those patients who reported to be pre-morbidly right-handed (based on self report or as reported by relatives). Patients having bad quality CT scans as well as those who underwent CT on the same day of the stroke were excluded from the sample. From the initial database of 539 patients 306 were discarded for the following reasons: bad quality scan (N= 37); missing data on tasks used as covariates (N= 54); scan acquisition was performed in the same day as the patient was admitted (N= 144); hemorrhagic stroke (N= 38); the patient was left-handed (N= 33).

In chapters 5 and 6 patients' scores were used as continuous measures, and data from controls were not needed.

All patients gave informed consent.

The data of the same 233 acute patients were used in both chapters 5 and 6.

None of the patients in chapters 5 and 6 took part in the studies presented in the other chapters.

Parkinson's patients- chapter 7 only

Nineteen native Italian speaking PD patients (9 male, 10 female; mean age= 66.37, SD= 6.95) participated in the study. All the patients were right handed according to the Edinburgh Handedness Inventory (Oldfield 1971). PD patients' age, gender, the Edinburgh Handedness Inventory scores and hand used for gestures imitation are reported in Appendix 3 (Table 1 in Appendix 3). The patients were recruited according to the following criteria: diagnosis for idiopathic (unknown aetiology) PD, absence of major cognitive decline, presence of asymmetric symptoms, having normal or corrected to normal vision. The diagnosis was made by a neurologist on the basis of the patients' symptoms as well as of the results of anatomical scans of their brains (SPECT) proving the presence and the asymmetry of the lesion. Twelve patients showed more pronounced symptoms on the left and seven were more impaired on the right side of the body. PD patients' neurological and motor symptoms (rigidity or tremor) were assessed with scale III of the United Parkinson Disease Rating Scale (see Table 1 in Appendix 3). All patients were under pharmacological treatment with L-Dopa.

PD patients were first given the Mini Mental State Examination (MMSE) in order to exclude those who could have shown a major cognitive decline. Also, PD patients were administered a battery of neuropsychological tests, standardized for the normal Italian population, assessing general intelligence, attention, language functions, visual perception, short-term memory for verbal material and locations in space. A description of the tests is in Appendix 3 along with the summary of the patients' results (Table 2 in Appendix 3).

Only one PD patient obtained a MMSE score that was just below the cut-off for the normal Italian population (cut-off= 24) when corrected for age and education (raw score = 26; score corrected for age and education = 23.2); however as his performance on all the other tests (see Table 2 in Appendix 3) was in the normal range, he was not excluded from the sample.

CONTROL SUBJECTS

Table 2 (see below) summarizes the composition of the control samples used in chapters 3, 4 and 7, along with handedness and the hand used for imitation and tasks performed.

Controls- Chapters 3 and 4

Eighteen English-speaking healthy participants (mean age= 65.56, SD=10.18, age range= 37-78) with no reported history of neurological and/or psychiatric disease served as controls for the studies presented in chapters 3 and 4. Fifteen controls reported to be right-handed while three reported to be left-handed. All had normal or corrected to normal vision. Only the fifteen right-handed (mean age= 66.80, SD=7.72, age range= 50-78) were included in the study in chapter 3, while data for all the eighteen healthy subjects were used in chapter 4¹.

The imitation scores (for transitive actions only) of seven of these eighteen English controls were also used in chapter 7 (see next paragraph).

Controls- Chapter 7

Two different groups of healthy participants were used to compare the PD patients' scores on the intransitive and transitive action imitation tasks. The first group had been tested on the intransitive actions prior to the present examination and these data were used again here. The second group was tested on the transitive actions only.

For the intransitive actions we used data collected with 31 Italian native speaking controls, 10 female and 21 male (range = 53-75; mean age = 65.35; SD: 6.5). A t-test comparing the age of PD and controls did not reveal any significant difference ($t(48) = 0.52$; $p = 0.60$, 2-tailed). None of the controls had a history of neurological or psychiatric disorders and all had normal or corrected to

¹ In chapter 4 the controls' data were used to establish the cut-offs for the experimental tasks. The cut-offs were used only to describe the patients' sample imitation behaviour. In the VBM analyses patients' imitation scores were used as continuous measurements to predict voxel signal intensity.

normal vision. All individuals in this control group were right handed and used their right hand/arm for imitation. The data for those 31 controls were used only in chapter 7 to compare to the performance of the PD patients.

For the transitive actions 21 healthy participants served as controls (mean age = 63.35 years, SD = 7.30; fourteen were native Italian-speaking and seven native English-speaking²); these individuals had no neurological and/or psychiatric disorders. All controls had normal or corrected to normal vision and all but one were right-handed. The controls did not differ in age from the PD patients ($t(38) = 1.35; 0.183, 2$ -tailed). The fourteen Italian native speaking controls took part only in the study in chapter 7 while the seven English speaking also took part in the study in chapters 3 and 4.

Table 2. Healthy controls in chapters 3, 4 and 7

chapter	controls	handedness	hand used	tasks performed
3	15 native English speaking	Right handed only	10 dominant 5 non-dominant	imitation transitive; imitation intransitive (adapted for English participants); recognition transitive; recognition intransitive
4	18 native English speaking (15 also in chapter 1)	15 right-handed; 3 left-handed	12 dominant 6 non-dominant	imitation transitive; imitation intransitive (adapted for English participants)
7	14 native Italian speaking AND 7 native English speaking (also in chapter 2)	20 right-handed; 1 left-handed	14 dominant 7 non-dominant	imitation transitive
7	31 native Italian speaking, tested by Tessari et al. (submitted)	31 right-handed	31 dominant	imitation intransitive only- Italian version by Tessari et al. (submitted)

Table 2 summarizes the composition of each control sample in chapters 3, 4 and 7 along with the handedness, hand used to imitate (dominant, non-dominant) and tasks performed by each sample.

² There was no significant difference ($p = 0.64$) between the overall scores of native Italian-speaking and native English-speaking subjects. Additionally, those seven English controls were given the tasks used in the study in chapter 3 and 4 and served as controls also in the studies in chapter 3 and 4. The Italian controls were not included in chapters 3 and 4 as they were not administered many of the tasks used in those two chapters.

TASKS

Table 3 shows a summary of the tasks used in each of the five experimental chapters.

Imitation tasks in chapters 3, 4 and 7

Transitive actions: For the transitive actions we presented 20 meaningful (MF) pantomimes of objects being used (e.g. hammering or drinking from a glass) and 20 unfamiliar meaningless (ML) control actions derived from the MF actions (e.g. a action maintaining the grasp and arm configuration for hammering but performed in an unusual direction; for details about the stimuli see Tessari & Rumiati 2004). These stimuli were employed because they were already used in previously published studies on the topic, with both patients and controls, and they have been utilized in studies across different nationalities (e.g., in Italy (Tessari et al. 2004) and Germany (Rumiati et al. 2005)). The list of the 20 MF and 20 ML actions is reported in Appendix 4. Pictures showing a sample of MF and ML transitive stimuli are in Figure 1.

Each transitive action was presented once to each participant and scored as 1 if performed correctly or 0 if it was performed incorrectly (maximum MF score= 20, ML= 20; total= 40).

The same list of actions was administered to patients and controls in chapters 3, 4 and 7.

Figure 1. Imitation MF and ML transitive gestures- stimuli- chapters 3, 4 and 7



Figure 1 shows an example of an MF pantomime (left), in this case “drinking from a glass”), and its ML version (right).

Intransitive actions: The stimuli were taken from the original set of 18 MF and 18 ML intransitive gestures by Tessari et al. (submitted). The intransitive MF actions were a sample of those gestures people commonly use for communication (e.g. waving “hallo”) and were selected as 10 Italian independent raters easily recognized them. The intransitive ML actions were created in order to match the MF for complexity of execution and were judged as unrecognizable by the 10 Italian independent raters (Tessari et al. submitted). The same list of MF and ML actions had already been used in previous studies on healthy Italian-speaking participants (Carmo & Rumiati 2009; Rumiati et al. 2009). One half of the MF and ML actions involved movement of the hand (i.e. distal) while the other half involved the use of an arm (i.e. proximal). In chapter 7 (studies on Italian Parkinson’s patients) the whole set of 18 MF and 18 ML actions was used. In chapters 3 and 4, to adapt the task to the English patients and controls, 3 MF gestures were removed from the original MF list (Tessari, in prep.) as eighteen healthy English controls consistently failed to indicate that they had a meaning. The remaining 15 MF stimuli were easily recognized and named correctly by the healthy English native raters. Three actions were also discarded from the original ML list in order for this list to equal the MF list length. The discarded ML actions matched for complexity the gestures eliminated from the MF set according to the data from ten native English independent raters. The 18

MF and 18 ML stimuli are listed in Appendix 4. The 3 MF and 3 ML stimuli that were removed to adapt the task for the English participants are reported in bold (see Appendix 4). Two examples of the stimuli are in Figure 2 in this chapter.

In chapters 3 and 4, using the task adapted to test English participants, each intransitive action was shown only once and performance was scored 1 if the action was correctly executed and 0 if it was done incorrectly (maximum MF score= 15, ML= 15; total= 30).

In chapter 7, using the Italian version of the task to test Italian PD participants, the intransitive actions could be presented twice, if the patient failed to reproduce an action at the first attempt. In this chapter the intransitive actions were administered following the same procedure to the one previously used by Tessari et al. (submitted.) to test the Italian controls whose data also served to calculate cut-offs for MF, ML and total performance (cut-offs are reported in Appendix 4 below the list of intransitive gestures). This allowed us to identify those PD patients scoring below the cut-off for the normal population, beside the group analyses. Each action was rated 2 if correct at the first presentation, 1 if correct after the second presentation and 0 if incorrect both at the first and at the second attempt (maximum MF score= 36, ML= 36; total= 72).

Figure 2. Imitation MF and ML intransitive gestures- stimuli- chapters 3, 4 and 7



Figure 2 shows one of the MF intransitive gestures (i.e. “mad”) used as stimuli (left) and one of the ML (right).

Procedure, common to transitive and intransitive gestures in chapters 3, 4 and 7: Each type of action was presented in a separate block to maximize the use of differential imitation processes,

with the order of presentation randomized within each list. There were four blocks of stimuli: i) MF transitive; ii) ML transitive; iii) MF intransitive; iv) ML intransitive. The block of MF pantomimes was administered before the ML pantomimes. After a short break, the intransitive actions were presented, again with the MF followed by the ML block. The MF actions were administered before the ML stimuli in order to reduce the likelihood of selecting the common ‘direct’ route for imitation of MF as well as ML actions, given that MF actions could be reproduced using the same, direct imitative route as ML actions (Tessari & Rumiati, 2004).

The experimenter demonstrated each action using always the right (dominant) hand. This was done to maximize the consistency of stimulus presentation across participants. We avoided using video stimulus presentations as it could have jeopardized patients’ performances because of reasons unrelated to a praxis deficit (e.g. if patients could not clearly see the stimuli because of the relative small size of the computer screen). Patients and controls were instructed to reproduce the action as similarly as possible to the model. The cortical patients in chapters 3 and 4 performed the pantomimes using either their dominant hand or the ipsilesional hand if having a paresis of the contralesional limb. Nineteen of the twenty-four cortical patients who participated in the studies in chapters 3 or 4 (or both) used their dominant limb while five used their non-dominant limb (see Table 1 above in this method section for details).

The PD patients in chapter 7 used the hand that was less affected by the disease. Twelve PD patients performed the imitation task using their right arm/hand while seven imitated using their left (non dominant) arm/hand.

In all three chapters (i.e. chapters 3, 4 and 7), to control for the hand used, some controls were asked to use their dominant hand while other used their non-dominant hand when responding³ (see Table 2 in this method section for details on hand used by controls to imitate).

³ On average there was not an effect of the hand used ($p > 0.1$) on both patients and controls’ performance.

The performance of each participant was video-recorded and later scored by two independent raters blind to the experimental conditions⁴. For both transitive and intransitive actions, an action was scored as incorrect if the participant performed a spatial error of the hand or the arm; a visual error (i.e. the action was: i) a combination of two items included in the list; ii) a action that was visually similar to the target; iii) a meaningful action, visually similar to the meaningless target), or an omission (for a detailed description of the errors see Tessari and Rumiati, 2004).

Chapter 3 only- Recognition of transitive and intransitive gestures

In addition to the imitation tasks patients and controls were tested for their ability to recognize the MF transitive and intransitive actions they imitated. The MF action recognition tasks were given at the end of the examination protocol. This was done in order to minimize the possibility that the performance in the imitation and recognition tasks influenced each other.

Recognizing MF transitive and intransitive actions

Stimuli: The same 20 MF transitive and 15 MF intransitive gestures previously imitated were presented for recognition. The stimuli in each list were given in a pseudo-random order.

Procedure: Actions were showed one at a time by the experimenter using her right hand.

Participants had to provide either the action name or any information that demonstrated unequivocally that they knew its meaning (e.g. description of circumstances where the gesture was usually performed). Correct answers were scored 1 otherwise 0. Each gesture was shown only once (transitive maximum score= 20, intransitive maximum score= 15).

⁴ The Cohen's k agreement coefficient was calculated on the scores provided by the two independent raters for all the three chapters. The coefficient was computed for MF and ML actions taken separately, and for the total action scores. The analysis was performed separately for PD, cortical patients and controls. As the coefficient was ≥ 0.80 in all the cases considered, the scores of only one rater (the same for patients and controls) were used.

Chapter 7 only- MF transitive and MF intransitive gestures naming

After being tested for imitation, PD patients were showed again the same MF transitive and MF intransitive actions they just imitated. As the PD performance was at ceiling (i.e. all the PD easily recognized and correctly named all the actions) the results at this task were not further considered in the analyses.

Table 3. Tasks used in this thesis

	Imitation transitive	Imitation intransitive (Italian version- 18M & 18ML)	Imitation intransitive (adapted English version- 15M & 15ML)	Recognition-transitive actions	Recognition-intransitive actions	MF transitive actions naming	MF intransitive actions naming	BCoS Gesture Production	BCoS Imitation	BCoS Actions Recognition
chapter 3	✓		✓	✓	✓					
chapter 4	✓		✓							
chapter 5								✓	✓	✓
chapter 6										✓
chapter 7	✓	✓				✓	✓			

Table 3 shows the tasks included or not included in each chapter (included= ✓; not-included= blank).

Chapters 5 and 6- Birmingham Cognitive Screen- Gestures Production, Imitation and Actions Recognition

The tasks were drawn from the Birmingham Cognitive Screen (BCoS; Humphreys et al. 2012 (see www.BCoS.bham.ac.uk)).

Gesture Production: Three meaningful (MF) intransitive gestures (hitch hiking; military salute; stop) and three MF transitive gestures (to drink from a glass; to shake a salt cellar; to use a hammer) had to be reproduced on verbal command. Intransitive and transitive actions were presented in separate blocks with the intransitive action performed before the transitive.

For the intransitive gestures, the examiner at first showed an example (i.e. the gesture for ‘be quiet’) along with the sentence: “This is the gesture for ‘be quiet’. Now, I will ask you to carry out some gestures for me. Can you please be as precise as possible?”. For each gesture the following instruction was provided verbally and in writing: “Could you show me the gesture for...?”

Performance was given a score of 0 if no response was given after 15 seconds, or if the patient produced an unrecognizable gesture (e.g. for hitch-hiking, shaking open palm forwards) or a perseveration from the previous action. A score of 1 point was given if a gesture was recognizable but contained spatial errors (e.g. for the salute, the hand touches the cheek instead of the forehead) or movement errors (e.g. for hitch-hiking, correct hand gesture but with wrist rotation instead of forearm oscillation), while 2 points were given to correct and accurate gestures.

For the transitive pantomimes the following instruction was provided: “I will give you the name of an object and ask you to pretend that you have the object in your hand. I will then ask you to show me how to use it. For example, if you have to show how you would use a toothbrush, you could make a gesture like this (show gesture)”. Each pantomime was preceded by the question: “how would you use ...?”

As for the intransitive gestures, answers delayed more than 15 seconds after the question; unrecognizable actions and perseverations were scored 0. A gesture was scored 1 if recognizable but containing errors [spatial errors (e.g. for glass, pouring gesture towards the chest instead of the mouth); incorrect grip (e.g. for hammer, the grip indicates that the hammer is held perpendicular to forearm); movement errors (e.g. for hammer, the oscillation is too small to be effective for a hammer); incomplete sequence of action (e.g. for salt cellar, correct grip but no shaking of salt); or concretization (i.e. use of body part as object)]. Recognizable and correct performances were scored 2 (maximum intransitive score= 6, transitive= 6, total= 12).

Patients had to reproduce both type of action using their most effective hand.

Imitation: Two ML hand sequences and two ML finger postures were presented for imitation.

Patients were informed that they were to imitate gestures that had no particular meaning. The two hand sequences were presented before the two finger postures. The stimuli used for Imitation are displayed in Figure 2.

Figure 3. BCoS Imitation- stimuli

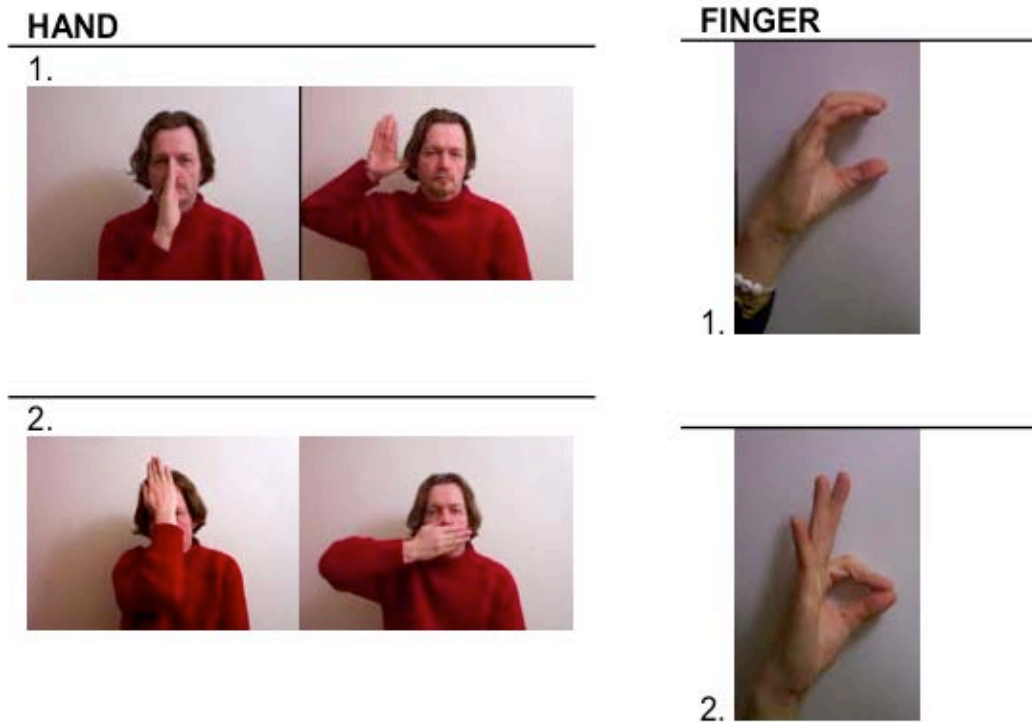


Figure 3 shows the two ML hand sequences (left) and the two ML finger postures (right) from BCoS Imitation.

The experimenter sat in front of the patient and showed each action using the right or left hand according to which hand the patient preferred to use, so that the actions were presented in a mirror configuration. For each item in the list patients were instructed to wait until the experimenter had finished the demonstration and then to copy the gesture as accurately as possible using the hand they were best able to act with. An example was provided (i.e. lifting an hand). Each action sequence or finger posture was presented for two seconds. If the patient's performance was incorrect at the first attempt, the gesture was presented a second time.

Performance was scored as follows: i) 0 point if the action produced contained more than one error, ii) 1 point if it contained only ONE error after the second presentation, iii) 2 points if the action was correct and precise after the second presentation, iv) 3 points if the action was correct & precise at the first presentation. Possible errors were: incorrect finger/hand position, incorrect spatial

relationship between hand and head, incomplete movement sequence. The maximum possible score was 12.

Action Recognition: Three MF intransitive gestures (come over; good; goodbye) and three MF transitive pantomimes (to drink from a cup; to use a key; to use a lighter) were presented to be recognized (see an example of the stimuli in Figure2). Intransitive and transitive gestures were presented in two separate blocks, with the intransitive presented before the transitive.

Patients were told they were going to see gestures/pantomimes of object use presented along with four possible names for each target action (e.g. the experimenter demonstrated the hand gesture for “come over” while verbalizing four possible names: 1) come over; 2) salute; 3) go away; 4) no, and patients were instructed to indicate which among the four names matched the gesture executed by the experimenter).

Figure 4. BCoS Actions Recognition- stimuli



Figure 4 shows an example of the stimuli presented for Action Recognition (the gesture for “good”) along with the list of possible choices given to the patients.

The block of intransitive gestures was preceded by an example that was presented with the following instruction: “if I show you this gesture (the gesture for ‘be quiet’ was shown) and give you these meanings: counting, be quiet, hello, it’s crazy; be quiet is the meaning that best matches the gesture”. The same was done before the block of transitive pantomimes using the gesture for “toothbrush”.

The experimenter demonstrated the actions using the dominant hand.

For each item a maximum time of 15 seconds was allowed for the patient to produce the answer.

Answers received a score of 1 point if correct and 0 if incorrect or omitted, so the maximum possible score was 6.

NEUROIMAGING ASSESSMENT

Chapter 4- MRI scans

The MRI scans of patients were taken at the Birmingham University Imaging Center (BUIC) on a 3T Philips Achieva MRI system with 8 channels phased array SENSE head coil. A sagittal T1-weighted sequence (sagittal orientation, echo time/time to repetition, TE/TR = 3.8/8.4 ms, voxel size 1 x 1 x 1 mm³) was used to acquire the anatomical scans.

Pre processing of the T1 data

All images were pre-processed as part of the neural Birmingham University Cognitive Screen project following the below steps. The T1 scans were converted and reoriented with MRICro (Chris Rorden, University of South Carolina, Columbia, SC, USA) and then preprocessed using SPM5 (Statistical Parametric Mapping; Friston, Ashburner, Kiebel, Nichols, & Penny 2007, Wellcome Department of Cognitive Neurobiology, London, UK). The scans were transformed into the standard MNI space (Montreal Neurological Institute) using a modified unified-segmentation procedure (Ashburner & Friston 2005; Seghier et al. 2008), designed to be optimised for patients with brain lesions by including a fourth tissue type that depicts abnormal tissue. The procedure output four classified tissues maps for grey matter (GM), white matter (WM), cerebrospinal fluid (CSF) and abnormal tissue, on the basis of the intensity of the signal in each voxel using a priori knowledge of the expected location of that tissue, with each map representing the probability that a given voxel belonged to GM, WM, CSF or, with low probability, to an abnormal class. A brain lesion causes a change in the signal intensity from the damaged tissue, so this tissue is mapped as a

region of reduced likelihood of representing either GM or WM (notice that, as we tested patients at a chronic stage, the damaged brain regions could have been replaced by CSF if not classified as abnormal). After segmentation, the resulting images were smoothed using a 12-mm FWHM Gaussian filter.

Chapters 5 and 6- CT scans

Computed Tomography (CT) images were acquired for each patient as part of their clinical assessment. The CTs were taken on average 3.4 days after the stroke, with 94% of cases within a week from the stroke. We obtained the image in the digital DICOM format. The CTs were acquired using the following scanners: Siemens sensation 16; GE medical system LightSpeed 16 and LightSpeed plus. The images covered the whole brain with an in-plane resolution of $0.5 \times 0.5 \text{ mm}^2$ and a slice thickness varying between 4-5 mm. CT images depict the density of the tissue and as such have a clear biological interpretation and provide an undistorted image of the brain tissue density.

Pre processing of the CT data

The quality of the CT scans was assessed by eye; bad quality data due to head movement, enlarged ventricles or other image artefacts were removed from the analysis. The CT images were pre-processed using SPM5 (www.fil.ion.ucl.ac.uk/~spm). Images were first converted to Nifti format then normalized to an in-house CT template (Ashburner and Friston, 2003). This initial normalization stage was mostly based on skull shape and aimed to linearly transform the images into MNI space to optimize the following procedures. Next we used the unified-segmentation algorithm as implemented in SPM5 (i.e. Seghier, Ashburner and Friston, 2005). In the unified model, the priors of the tissue class, from which intensities are drawn, are encoded by deformable tissue probability maps. The a-priori tissue class maps indicate the probability of finding expected signal sources: grey matter (GM), white matter (WM), cerebrospinal fluid (CSF), bone, fat and air at each voxel. To account for the presence of an abnormal tissue due to the stroke condition we

adapted a similar approach to Seghier et al. (2008) and added a seventh tissue class. In creating the extra abnormal tissue we assumed that in each grey or white matter voxel there is 10% chance of it being an abnormal tissue class. Furthermore, for the grey and white matter tissue classification, we assumed a single Gaussian distribution for the underlying intensities. To account for potential inhomogeneity of the abnormal tissue two different Gaussian distributions were used to model the intensities in this tissue class. Finally CT images as opposed to MRI do not suffer field bias due to field strength inhomogeneity, therefore we did not correct for that in the model. The segmented white and grey matter images were then smoothed using a 12 mm^3 FWHM Gaussian kernel to accommodate random field theory assumptions of continuity (Worsley and Friston, 1995).

VBM analyses- tools- common to chapters 4, 5 and 6

In chapters 2, 3 and 4 voxel-based morphometry was carried out analyzing the data with SPM8 (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, London, UK) using parametric statistics in the framework of general linear model (Ashburner & Friston, 2000).

The anatomical localization of the lesions was done using AAL3 toolbox and confirmed using the Duvernoy human brain atlas (Duvernoy, Cabanis, & Vannson, 1991). The brain coordinates are presented in the standardized MNI space.

3. Imitating transitive and intransitive gestures: An analysis of lesion side and associated cognitive impairments.

ABSTRACT

The ability to imitate gestures has traditionally been considered to be supported by brain structures in the left hemisphere, even though neuropsychological studies, as well as behavioural and imaging studies in healthy participants, suggest a role for right hemisphere and sub-cortical structures too. The present study tested a group of patients with unilateral brain damage on the imitation of meaningful (MF) and meaningless (ML) transitive and intransitive gestures, and on recognition of the same gestures. The results showed that right brain damaged (RBD) patients generally performed better than left brain damaged (LBD) patients on transitive actions, while the two groups did not differ when imitating intransitive actions. Also, at group level, the relative ease of intransitive actions was demonstrated when compared to transitive, and of action recognition compared to imitation. However, at single subject level, there were dissociations with sometimes better performance for transitive relative to intransitive action imitation, as well as good performance in imitating MF intransitive actions that could not be recognized. The implications for understanding action recognition and production are discussed.

INTRODUCTION

Ideomotor apraxia is syndrome that impairs the ability to voluntarily reproduce gestures in imitation and/or on verbal command. Traditionally the left hemisphere of the human brain has been considered dominant for controlling gesture production (see Rothi et al. 1997) in right-handed people, depending perhaps upon the type of action that has to be implemented. So, while the execution of transitive (tool-related) actions seems to rely more on the left-hemisphere (Bartolo et al. 2001; Tessari et al. 2007), both right and left cortical areas have been linked to the production of

intransitive gestures (Bauxbaum et al. 2001, see also Tessari et al. 2007, and Rumiati et al. 2010 for a review). Also a role for sub-cortical structures has been suggested by some studies (see Tessari et al. 2007; Leiguarda et al. 1997, 2001; De Renzi et al. 1980), even though there is still not consensus yet about which type of gestures are more impaired after lesions to those structures.

Several neuropsychological studies have shown that ideomotor apraxia is not a unitary syndrome – there are symptom dissociations between patients in relation to the type of actions to be executed and the body part required for the task (see Rumiati et al. 2009 for a review). For instance, some studies report patients who are more impaired when imitating meaningful (MF) compared to meaningless (ML) gestures (Goldenberg & Hagmann 1997; Peigneux et al. 2000; Tessari et al. 2007), while others report the opposite result (Bartolo et al. 2001; Tessari et al. 2007). Such double dissociations suggest that the imitation of MF and ML actions may depend on distinct neural structures.

A dual route model of action production has been proposed to account for the double dissociation between abilities to reproduce MF and ML gestures (Rothi et al. 1997; Rumiati and Tessari, 2002). This model involves a semantic route, relying on Long Term Memory, which supports the reproduction of MF (known) gestures, and a direct route, depending on Short Term Memory, which allows ML (new) actions to be imitated (see Figure 1 in the general introduction). Input into both routes is provided by a visual analysis component, through which the visual properties of actions are processed. Output from both routes operates through a common motor system supporting the actual implementation of the action.

Alongside the neuropsychological observations, the argument for different mechanisms for transitive and intransitive actions has been confirmed by several behavioural investigations in healthy participants as well as by imaging studies (e.g. Rumiati et al. 2009; Tessari & Rumiati 2004; Peigneux et al. 2004). For instance, Peigneux et al. (2004) reported that the imitation of MF actions was associated with activation in the left angular and middle frontal gyri, as well as the right

supramarginal gyrus and inferior parietal lobule. Activity in the inferior temporal, angular and parahippocampal gyri in the left hemisphere has also been noted for MF actions (Rumiati et al. 2005). In contrast, observation of ML actions has been associated with the parieto-occipital and occipito-temporal junctions on the right, the superior temporal gyrus on the left, and the superior parietal cortex bilaterally (Rumiati et al. 2005).

On the other hand, arguments can also be made against the different actions being fully dissociated. For example, neuropsychological studies have reported that apraxic patients have more difficulties in imitating transitive than intransitive gestures (Haaland et al. 2000; Buxbaum et al. 2005, 2007), but the reverse dissociation has not been convincingly reported. This suggests that intransitive actions are merely easier to perform, and indeed these actions are typically easier for normal participants too (Carmo & Rumiati, 2009). If arguments are to be made about the functional dissociation between transitive and intransitive actions, then evidence is needed that more clearly shows that intransitive actions can be impaired when transitive are not.

A crucial point for the model is the suggestion that access to the semantic system in order to recognize or understand the goal of an action is not necessary for correctly executing a gesture, as any gesture can be processed through the direct route, where representation of the action before being translated into motor terms is sustained by working memory. This happens for novel gestures as well as for MF gestures if the semantic route is unavailable. On the other hand, the consequences of impairment of the direct route are less clear. For example, if damage affects visual analysis processes then there may be problems in imitating MF as well as ML gestures, along also with impairments to MF gesture recognition. In contrast, if the deficits are more on the output side then problems may affect MF action production as well as imitation, though action recognition should be spared. The problems may also affect ML more than MF gestures, if the representations of learned gestures (on the input or output side) are more robust to brain lesion. Thus a variety of different dissociations may be expected. Double dissociations have been shown between imitation and

recognition tasks, with patients being impaired in imitation but not in recognition and vice versa (Negri et al. 2007, see also Mahon et al. 2005 and 2008), which does support the general architecture of the dual route model, but the neural underpinnings of these effects has still be exactly established. For example, are production deficits more apparent after left hemisphere damage? Are recognition deficits contingent on the presence of right as well as left hemisphere lesions? To examine these questions in more detail, and to assess how imitation and recognition operate for transitive and intransitive gestures, and imitation for MF and ML actions, a group study was conducted with patients with chronic deficits following brain lesion. The aim was to look at the pattern of deficits of patients according to the side of their lesion, for action recognition as well as for imitation, and for MF and ML transitive and intransitive actions (here the ML actions were derived from transitive and intransitive real actions). The deficits in action recognition and production in the patients were also related to the cognitive profile of the patients derived from the Birmingham Cognitive Screen (BCoS; Humphreys et al. 2012).

GENERAL METHODS

This study compares right-brain damaged (RBD) and left-brain damaged (LBD) patients in the imitation and recognition of transitive and intransitive MF and ML gestures. For details on the patients and control samples and on the tasks employed in this study see the method chapter (pgs. 21- 38).

As already mentioned in the method chapter, in a previous version of this chapter one bilateral brain damaged (BBD) patient was included by mistake among the LBD (patient MMcD, see Table 1 in the method chapter). In the present version MMcD scores were excluded from the group analyses however, as a matter of honesty, his results will be briefly presented and discussed at the end of the chapter and a picture reporting his lesion will be reported. MMcD scores are shown in Table 1 of the present chapter below the main table showing the results of the unilateral patients.

RESULTS

Patients' scores and cut offs for the transitive and intransitive imitation tasks and at the transitive and intransitive action recognition tasks are reported in Table 1. Defective performance is given in bold.

Table 1. Patients' scores- action imitation and recognition

Patient	Lesion Side	IMITATION						RECOGNITION	
		transitive MF	transitive ML	transitive TOT	intransitive MF	intransitive ML	intransitive TOT	transitive	intransitive
JW	RBD	16	15	31	12	12	24	18	15
JQ	RBD	6	6	12	11	8	19	11	12
AS	RBD	17	14	31	14	14	28	17	13
JM	RBD	15	9	24	12	11	23	18	13
AK	RBD	12	13	25	12	12	24	17	13
JE	RBD	16	12	28	14	12	26	18	14
PW	RBD	12	9	21	9	11	20	16	13
MC	RBD	14	12	26	10	8	18	17	14
QJ	RBD	14	10	24	12	13	25	15	14
BL	LBD	5	2	7	2	3	5	1	0
DS	LBD	8	4	12	11	14	25	14	15
PH	LBD	9	7	16	10	11	21	19	15
MM	LBD	7	7	14	6	12	18	na	na
DL	LBD	18	9	27	13	13	26	15	15
DT	LBD	15	9	24	10	8	18	19	13
DE	LBD	13	12	25	13	10	23	19	13
BR	LBD	13	11	24	13	14	27	14	13
PJ	LBD	5	0	5	13	11	24	13	8
MMcD	BBD	9	7	16	2	3	5	17	13

cut off imitation
transitive

MF	12
ML	9
TOT	22

cut off imitation
intransitive

MF	10
ML	11
TOT	21

cut off recognition

transitive	15
intransitive	12

Table 1 shows the scores obtained by patients in transitive and intransitive MF and ML gesture imitation (separate blocks presentation), and in discriminating MF gestures when shown intermingled with the ML. Scores below the cut off (calculated on the basis of controls means and standard deviations) are in **bold**. The scores of MMcD are reported in the red box at the bottom, as he was included by mistake in a previous version of this chapter as LBD but then it was revealed that he had a bilateral lesion. In the current version MMcD's scores were excluded from the group analyses.

IMITATION

Figure 2 reports the proportion of accuracy scores obtained by LBD, RBD (Fig.2a, 2b) and controls (Fig.2c) at the transitive and intransitive imitation tasks.

Transitive action imitation deficits and dissociations

At first each patient was treated as a single case in order to see who among them failed in the imitation of MF, ML actions or both. Cut offs for transitive MF, ML and totals were established on the basis of the means and standard deviations of the controls (MF (mean= 15.67; SD= 1.95); ML (mean= 13.53; SD= 2.10); totals (mean= 29.20; SD= 3.65)) using the modified t-test by Crawford and Garthwaite (2002). Scores having a probability $p \leq .05$ (1-tailed) as being in the control sample were considered as impaired.

Seven patients (5 LBD and 2 RBD) had scores below the cut off for MF and ML and total actions; 1 RBD fell below the cut off only for the MF; three (2LBD 1RBD) were defective only when imitating ML actions.

The possibility of dissociations between the MF and ML actions was investigated using the revised tests for dissociations by Crawford and Garthwaite (2005). Differences between scores that had a probability $p \leq .05$ (2-tailed) in the control sample were considered as abnormal. Only one LBD reported a classic dissociation between MF and ML, having a score at the control level for MF and below the cut off for ML actions. The other RBD and LBD patients did not report classic or strong significant dissociations (see Table 1).

Figure 2a. Proportion of correct actions imitated by LBD

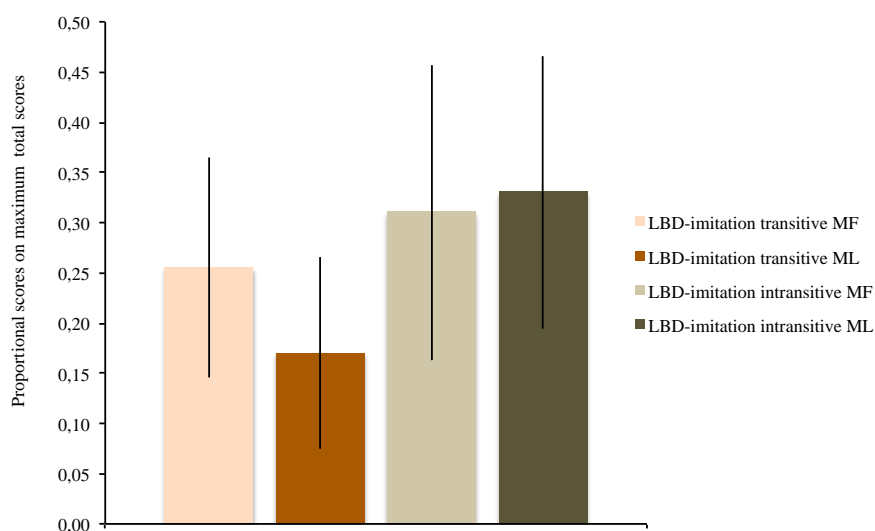


Figure 2b. Proportion of correct actions imitated by RBD

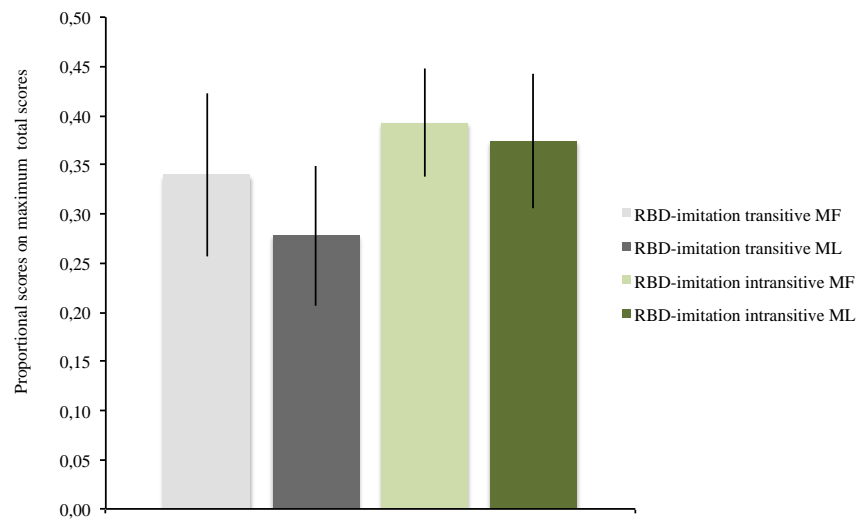


Figure 2c. Proportion of correct actions imitated by controls

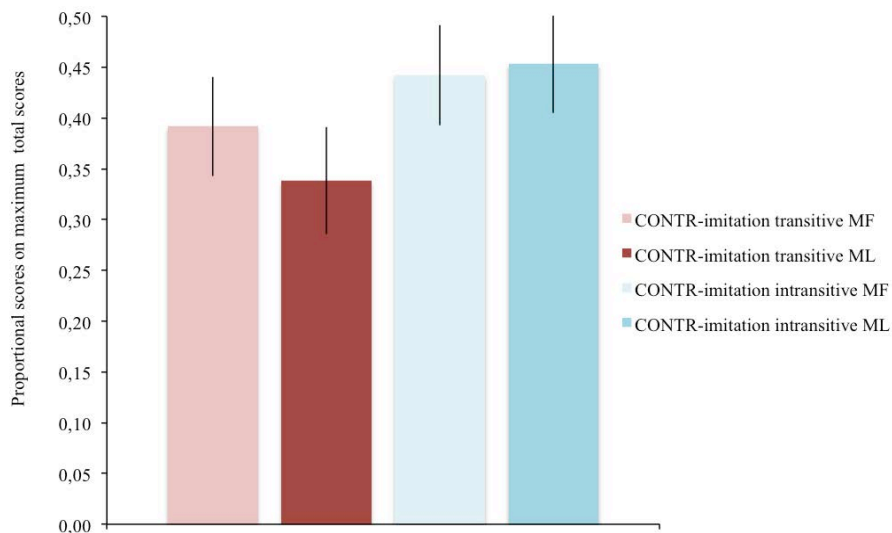


Figure 2- LBD (2a) and RBD (2b) performed worse than controls (2c) with both transitive and intransitive actions.

However, t tests showed that RBD had higher total and ML scores than LBD for the transitive gestures. Also, RBD did not differ from controls when executing MF intransitive gestures. Finally, all the three groups had higher scores for the intransitive than for the transitive.

Transitive action imitation group analyses (group as between subject factor)

Accuracy scores

A repeated measures ANOVA was performed on the accuracy scores, using Action Meaning (MF versus ML) as a within-subject factor and Group (RBD, LBD and controls) as between-subject

factor. The analysis revealed a significant main effect of Group ($F(2, 30) = 12.39$; $p \leq 0.0001$) and Action Meaning ($F(1, 30) = 47.65$; $p \leq 0.0001$). Generally controls had higher total accuracy scores (mean= 29.20; SD= 3.65) than both LBD (mean= 17.1; SD= 8.23) and RBD patients (mean= 24.67; SD= 5.79), and all the three groups, when considered together, imitated MF actions (mean= 13.50; SD= 3.86) better than ML actions (mean= 10.91; SD= 4.01). The interaction between Action Meaning and Group was not significant ($F(2, 30) = 1.05$; $p = 0.36$).

Independent samples t-tests showed significant differences between controls and LBD patients for MF ($t(\text{corr. df.} = 11.43) = 3.72$; $p = 0.003$, 2-tailed), ML ($t(22) = 5.69$; $p \leq 0.0001$, 2-tailed) and total action performance ($t(\text{corr. df.} = 11.69) = 4.64$; $p = 0.001$, 2-tailed). RBD patients differed significantly from controls for ML ($t(22) = 2.4$; $p = 0.026$, 2-tailed) and total action scores ($t(22) = 2.37$; $p = 0.027$, 2-tailed), while the difference for the MF was close to the full significant threshold ($t(22) = 1.97$; $p = 0.061$, 2-tailed). Also significant differences emerged between RBD and LBD for ML ($t(16) = 2.76$; $p = 0.013$, 2-tailed) and total action scores ($t(16) = 2.42$; $p = 0.027$, 2-tailed), but not for MF ($t(16) = 1.87$; $p = 0.1$, 2-tailed).

Paired-samples t-tests were assessed if MF and ML actions differed within RBD, LBD and control groups. MF and ML differed significantly for all the three groups (LBD ($t(8) = 4.02$; $p = 0.003$); RBD ($t(8) = 3.36$; $p = 0.01$) and controls ($t(14) = 4.68$; $p \leq 0.0001$)), with MF pantomimes performed more accurately by all the three groups.

Intransitive action imitation deficits and dissociations

Each patient was treated as a single case in order to see who among them failed in imitating intransitive actions. Cut offs for intransitive MF, ML and totals were established on the basis of the means and standard deviations for the controls (MF (mean= 13.27; SD= 1.49); ML (mean= 13.60; SD= 1.45); totals (mean= 26.87; SD= 2.83)) using the modified t-test by Crawford and Garthwaite (2002). Scores having a probability $p \leq .05$ (1-tailed) of being found in the control sample were considered as defective.

Five patients (3 LBD and 2 RBD) had scores below the cut-off for MF and ML and total action scores; one RBD patient had normal performance with MF but fell below the cut off for the ML stimuli and total actions; two LBD⁵ and one RBD patient were defective only when imitating ML actions while having normal total action scores; one LBD patient had MF and total action scores below the cut off.

Also, the presence of dissociations between MF and ML action scores were investigated using the revised test for dissociations by Crawford and Garthwaite (2005). Differences between scores that had a probability $p \leq .05$ (2-tailed) relative to the control sample were considered as outside the normal limits. Three LBD (one of them reported a strong dissociation) and two RBD (one of them reported a strong dissociation) patients imitated MF better than ML actions, while one LBD did better on ML than MF actions (classic dissociation). All the other patients did not report any classic or strong dissociation (see Table 1).

Intransitive action imitation group analyses (group as between subject factor)

RBD and LBD patient's scores were compared to those of the controls, as well as relative to each other.

Accuracy scores⁶

An ANOVA was run on accuracy scores for RBD, LBD and controls with Group (RBD, LBD, controls) as a between-subject factor and Action Meaning (MF Vs ML) as a within-subject factor. The analysis showed a significant main effect of Group ($F(2, 30) = 7.01$; $p = 0.003$) but no effect of Action Meaning ($F(1, 30) = 0.173$; $p = 0.68$). Also the interaction between the two main factors was

⁵ One of the two LBD having a deficit only for ML intransitive actions had a score= 11 that had a probability of $p = .052$ to be found in a normal sample, based on our controls data distribution. This was the only patient having this score.

⁶ The Cohen's k agreement coefficient was calculated on the participants' scores provided by the two independent raters. The coefficient was computed for Totals and separately for MF and ML. As the k was ≥ 0.80 in all the cases considered, the scores of only one rater were used.

not significant ($F(2, 30) = 1.18; p = 0.32$). Both LBD (mean = 19.20; SD = 8.08) and RBD (mean = 23.00; SD = 3.35) patients had generally poorer performances than controls (mean = 26.87; SD = 2.83), even though RBD did slightly better than LBD. Overall MF (mean = 11.71; SD = 3.13) actions were imitated as accurately as ML (mean = 11.88; SD = 3.01).

Independent samples t-tests revealed differences between LBD patients and controls for MF ($t(\text{corr. df.} = 10.37) = 2.74; p = 0.02$, 2-tailed), ML ($t(\text{corr. df.} = 10.55) = 2.76; p = 0.019$, 2-tailed) and total action scores ($t(\text{corr. df.} = 10.48) = 2.89; p = 0.016$, 2-tailed). Also RBD patients had significantly lower performance than controls for MF ($t(22) = 2.29; p = 0.032$, 2-tailed), ML ($t(22) = 3.33; p = 0.003$, 2-tailed) and total actions ($t(22) = 3.03; p = 0.006$, 2-tailed). A comparison between RBD and LBD did not reveal any significant differences for the MF ($t(\text{corr. df.} = 1.66) = 1.65; p = 0.126$, 2-tailed), ML ($t(16) = 0.88; p = 0.39$; 2-tailed), totals ($t(16) = 1.31; p = 0.21$; 2-tailed))⁷.

Finally, paired samples t-tests did not reveal significant differences between MF and ML within the LBD ($t(8) = -0.72; p = 0.49$), RBD ($t(8) = 1.05; p = 0.33$) and control groups ($t(14) = -1.58; p = 0.14$)⁸.

Comparison between imitation of transitive and intransitive gestures

At first the presence of dissociations between transitive and intransitive action imitation scores was investigated using the revised tests for dissociation of Crawford and Garthwaite (2005). Differences between scores that had a probability of $p \leq .05$ (2-tailed) as belonging to the control sample were considered as being outside the normal range. See Table 1 for the scores at the imitation tasks.

Two LBD patients showed a classic dissociation where they generally performed better on intransitive than on transitive gestures (respectively inside and outside the normal range). For one of

⁷ Independent samples t-tests and non-parametrical tests (Mann-Whitney for controls and Kruskal-Wallis for LBD) did not show any difference between participants using the dominant or non-dominant hand within controls and LBD ($p > 0.1$). RBD all imitated using the dominant hand.

⁸ The results of the t-tests were all confirmed by non-parametrical tests (all $p < 0.05$).

these LBD patients the deficit was clearer for MF stimuli for the other it was most apparent with ML stimuli. One RBD patient had dissociations between MF transitive and ML intransitive actions, as well as between ML transitive and ML intransitive, with scores in the normal range when imitating both transitive MF and transitive ML actions, but he did not showed dissociation between MF or ML transitive and MF intransitive even though his score with the MF intransitive were just below the cut off.

Also, two LBD had a classic dissociation when MF transitive and ML intransitive actions were compared. One performed at control level with the MF transitive pantomimes while being defective with the ML intransitive gestures, while one had the opposite pattern. It is to be noted that this last patients had scores within the normal range only for the ML intransitive actions, and that he was the only patient in the sample whose aphasia was so severe that it was not possible to test him for the action recognition task.

Finally, one RBD had a dissociation between MF transitive and MF intransitive, being impaired in execution of MF transitive while doing at control level with the MF intransitive.

Proportional scores

As the scores for the transitive and intransitive action tasks were based on different scales, proportional scores were calculated based on accuracy relative to the total maximum score for transitive and intransitive gestures, summed over the MF and ML stimuli (maximum scores= 40 and 30 respectively). After being transformed in this way, the patients' results were subjected to an ANOVA, with Group (RBD and LBD) as a between subject factor, Type of Action (Transitive and Intransitive) and Action Meaning (MF and ML) as within-subjects factors. The analysis showed a significant between-subject effect of Group ($F(1, 16) = 4.53; p = 0.05$), significant main effects of Action Type ($F(1, 16) = 14.12; p = 0.002$) and Action Meaning ($F(1, 16) = 7.91; p = 0.012$) and a significant interaction between Action Type and Action Meaning ($F(1, 16) = 17.73; p = 0.001$). All the other interactions were not significant (Action Type x Group ($F(1, 16) = 0.39; p = 0.54$); Action

Meaning x Group ($F(1, 16) = 0.08$; $p = 0.79$); Action Type x Action Meaning x Group ($F(1, 16) = 3.4$; $p = 0.08$)).

The interaction arose because the drop from MF to ML actions was greater for transitive than for intransitive actions. For intransitive actions there was no difference between the MF and ML actions and for transitive actions there was a reliable advantage for MF over ML actions (t tests reported in above section).

The data for the controls were also transformed as for the patients and then entered into a 2x2 ANOVA with Type of Action (Transitive and Intransitive) and Action Meaning (MF and ML) as within-subjects factors. The analysis showed significant main effects of Action Type ($F(1, 14) = 30.82$; $p \leq 0.0001$) and Action Meaning ($F(1, 14) = 12.38$; $p = 0.003$) and a significant interaction between Type of Action and Action Meaning ($F(1, 14) = 18.21$; $p = 0.001$). Generally intransitive gestures (mean = 0.9, SD = 0.09) were reproduced more accurately than transitive (mean = 0.73; SD = 0.09), and both MF (mean = 0.44; SD = 0.05) and ML (mean = 0.45; 0.05) intransitive gestures were executed better than transitive MF (mean = 0.39; SD = 0.05) and ML (mean = 0.34; SD = 0.05) (Fig2b). As for the patients, there was an effect of meaningfulness for transitive actions (MF > ML) but not for intransitive actions (MF = ML) (t tests reported above).

RECOGNITION

Patients' scores and cut offs for the transitive and intransitive action recognition tasks are reported in Table 1. Defective scores are highlighted in bold. Figure 3 reports the proportion of accuracy scores obtained by RBD, LBD and controls for transitive and intransitive actions. One LBD patient could not be given the tasks because of expressive aphasia that made his answers for the most part incomprehensible.

Figure 3. RBD, LBD and controls- Proportional accuracy scores

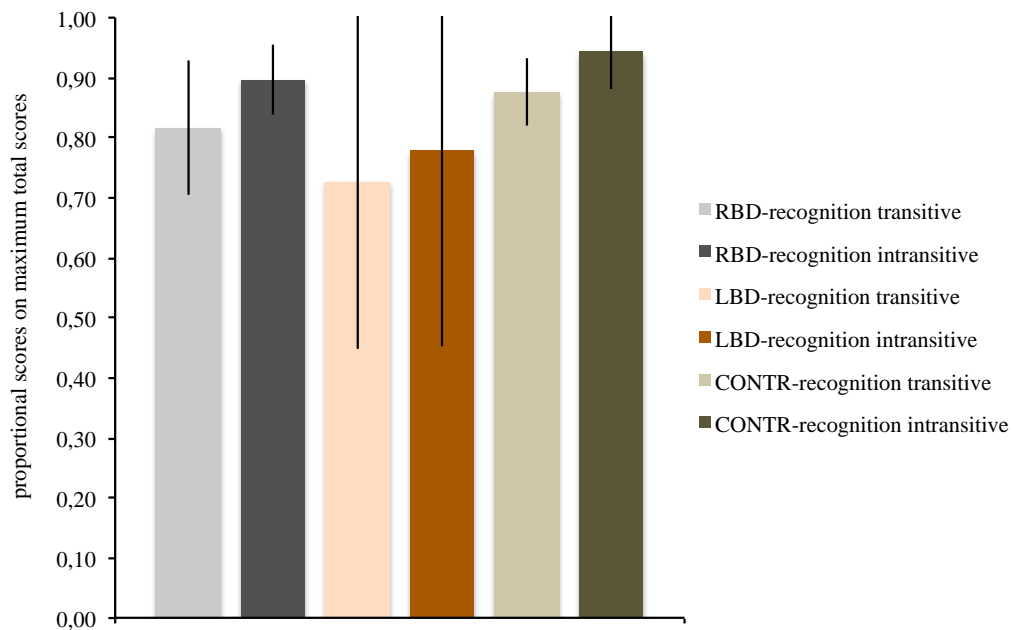


Figure 3 shows the average proportional accuracy in each group. Proportional scores were calculated dividing each participant score by the maximum possible score (i.e. transitive maximum total= 20, intransitive maximum total= 15). The intransitive actions proved to be easier to be recognized within all the three groups. Also, the analyses did not reveal a significant main effect of group.

Transitive and intransitive action recognition deficits (Accuracy scores)

The patients' data were examined at single case level in order to assess dissociations on transitive and intransitive actions recognition tasks. The cut offs were calculated on the basis of the control's means and standard deviations (transitive (mean= 17.53; SD= 1.13); intransitive (mean= 14.13; SD= 0.92) using the modified t-test by Crawford and Garthwaite (2002). Scores having a probability $p \leq .05$ (1-tailed) as belonging to the control sample were considered as defective.

Two LBD patients and one RBD patient performed below the cut off when they had to recognize both transitive and intransitive actions, and one RBD and three LBD individuals had scores below the cut off only when tested with the transitive actions.

The presence of dissociations between the ability to correctly identify either transitive or intransitive actions was investigated using the revised tests for dissociations by Crawford and

Garthwaite (2005). Differences between scores that had a probability $p \leq .05$ (2-tailed) in to be found in the control sample were considered as suggesting dissociating performances. Three LBD revealed a classic dissociation, two of them having scores below the cut off for the transitive but performing at control level with the intransitive. One LBD showed a strong dissociation, having scores below the cut off in both tasks but did better when he had to recognize transitive pantomimes.

In addition to examining problems in recognition only, dissociations between imitation and recognition of MF transitive pantomimes were tested. Two LBD patients showed a classic dissociation between recognition and imitation of MF transitive pantomimes. One of them had scores in the normal range in imitation and defective scores in recognition, one showed the opposite pattern (defective imitation and normal recognition imitation). This last LBD patient also had a classic dissociation, with normal scores in recognition but defective imitation for intransitive MF actions. Finally, another LBD had normal scores in intransitive MF action imitation and defective score in MF intransitive action recognition (the same patient did not have a dissociation between imitation and recognition of MF transitive gestures, and was defective in both).

Proportional scores for gesture recognition

As the scores for the transitive and intransitive action recognition tasks were based on different scales, a proportional score was calculated based on accuracy relative to the total maximum score for transitive and intransitive gestures (maximum scores= 20 and 15 respectively). An ANOVA was conducted with Group (LBD, RBD, controls) as between-subject factor and Action Type (transitive and intransitive) as a within -subject factor. The analysis revealed a significant main effect of Action Type ($F(1, 30) = 12.37; p = 0.001$), with intransitive actions (mean= 0.88; SD= 0.18) identified correctly more frequently than transitive (mean= 0.82; SD= 0.17). There was not a main effect of Group ($F(2, 30) = 2.66; p = 0.09$) or a significant interaction between the two factors ($F(2, 30) = 0.18; p = 0.84$).

Imitation and recognition tasks (correlations)

To provide a finer-grained analysis of performance in the different conditions, correlations were conducted including all the participants but one (who could not be given the recognition task because his production aphasia was too severe to obtain any understandable answer). Significant correlations emerged between transitive action recognition and imitation of transitive MF actions (Pearson Correlation (N= 32) = 0.66; $p \leq 0.0001$, 2-tailed) and of transitive ML actions (Pearson Correlation (N= 32) = 0.64; $p \leq 0.0001$, 2-tailed). This was also the case for intransitive action recognition and the imitation of both MF intransitive actions (N= 32) = 0.56; $p \leq 0.0001$, 2-tailed) and ML intransitive actions (N= 32) = 0.60; $p \leq 0.0001$, 2-tailed).

When only the data for patients were analyzed, the correlations remained. For transitive gesture recognition there were correlations with the imitation of MF transitive actions (Pearson Correlation (N=17) = 0.62; $p = 0.006$, 2-tailed) and ML transitive actions (Pearson Correlation (N=17) = 0.62; $p = 0.006$, 2-tailed). For intransitive action recognition there were correlations with MF intransitive actions (Pearson Correlation (N=17) = 0.54; $p = 0.02$, 2-tailed) and ML intransitive actions (Pearson Correlation (N=17) = 0.58; $p = 0.01$, 2-tailed).

For the control group alone, there was a reliable correlation between transitive action recognition and transitive action imitation for MF stimuli (Pearson Correlation (N=15) = 0.67; $p = 0.006$, 2-tailed) but not for ML stimuli (Pearson Correlation (N= 15) = 0.45; $p = 0.1$, 2-tailed). The correlations with intransitive action recognition were not reliable (Pearson Correlation (N=15) = 0.23; $p = 0.4$, 2-tailed relative to MF intransitive imitation, and Pearson Correlation (N= 15) = 0.31; $p = 0.26$, 2-tailed relative to ML intransitive imitation).

Birmingham Cognitive Screen (BCoS) and imitation

The relations between imitation performance and the scores on sub-tests of the BCoS assessing personal orientation, control functions, naming and praxis were explored. A description of the normative samples, tasks and the results of the patients (scores below the cut offs are in bold), along

with the cut offs, are reported in Appendix 1. The scores at the BCoS tasks of five patients were not available, so those patients could not be included in this analysis.

Imitation of transitive MF actions correlated significantly with Picture Naming (Pearson Correlation (N=13) = 0.67; $p= 0.01$, 2-tailed) and Action Recognition (Pearson Correlation (N=13) = 0.6; $p= 0.03$). Also, there was a reliable correlation between the imitation of ML transitive actions and BCoS Gesture Production (Pearson Correlation (N=13)= 0.57; $p= 0.04$). BCoS Picture Naming also significantly correlated with imitation of MF intransitive actions (Pearson Correlation (N=13) = 0.55; $p= 0.05$). Moreover, there was a significant correlation between MF and ML intransitive action imitation and BCoS Figure Copy (Pearson Correlation (N=13) = 0.65; $p= 0.02$, 2-tailed and Pearson Correlation (N=13)=0.74; $p=0.004$ respectively), Imitation (MF (Pearson Correlation (N=13) = 0.73; $p< 0.001$, 2-tailed), Gesture Production (Pearson Correlation (N= 13)= 0.6; $p= 0.03$) and Personal Information (Pearson Correlation (N= 13)= 0.56; $p= 0.04$). Intransitive ML did not relate significantly with any of the BCoS tasks.

DISCUSSION

The patients overall performed worse than the controls in transitive and intransitive action imitation but not in transitive and intransitive action recognition. This might arise because the recognition task was easier than the production task (imitation). The recognition tasks tended to correlate with the production tasks, suggesting that they did tap some common underlying processes. But in addition at a single case level there were two patients whose dissociations were in an opposite direction. Indeed one LBD patient (patient DL, see Table 1) had scores within the normal range when imitating MF transitive actions but failed in the MF transitive action recognition task. This patient also performed at a control level when she had to execute MF transitive and intransitive, as well as ML intransitive gestures, but was impaired in reproducing ML transitive actions. During the testing session patient DL failed with the ML transitive gestures because as soon as the presentation

of the gesture terminated she was no longer able to remember it and asked for more presentations, overtly admitting that she did not remember them. According to the dual route model, ML gestures require short-term memory to sustain the representation of the action and the ML transitive actions we used were more demanding than the ML intransitive, as proved by the fact that they were systematically performed worse than all the other actions. So it is possible that the patient had difficulties in remembering gestures only when the task was more demanding. It is interesting that deficits in visual short-term memory have previously been reported in this patient (Gillebert & Humphreys, 2009). In our investigation we did not include tasks tapping short-term and long-term memory for actions so we cannot draw more detailed conclusions on patient DL's specific memory skills nor about the relationship between her apparent deficit in remembering the actions in the short term and her failure in the action recognition task. The main point here is that this patient showed accurate performance in imitating gestures that later she could not name or give information about (not due to speech problems, see Table 2 in Appendix 1, Picture Naming, patient DL). However it is worth noting that this same patient was not impaired in the BCoS Gesture Recognition. This last task is a multiple-choice task (four names of actions are provided for the patient to choose the correct answer between them), and this could have facilitated her to access the information about the actions presented. Another patient (patient PJ) showed a similar dissociation with scores in the normal range for imitation of MF intransitive gestures and defective scores in MF intransitive gesture recognition. This patient was impaired in all tasks apart from the imitation of MF intransitive actions. Unfortunately the BCoS scores for patient PJ were not available. Nevertheless, his performance suggests a certain degree of independence between imitation and action recognition.

For action imitation, there were no reliable differences between the two patient groups when asked to imitate intransitive gestures. Instead RBD patients had better total scores than LBD individuals with the transitive gestures, even though RBD showed an actual advantage only for the transitive

ML but not for the MF. This suggests that a general impairment in reproducing actions can be present after damage confined to the right hemisphere, especially for the intransitive gestures. At a single case level more LBD patients fell below the control norms, but in almost all cases there were instances where at least one RBD patient performed the same way. Failures in imitation may occur for different reasons that should be analyzed more deeply at single case level. Possibly selecting patients with very focal lesions in a specific part of the right or left hemisphere may be helpful here in order to give a better insight into the involvement of specific structures in the two hemispheres in praxis. However the fact that some RBD patients showed an impairment in copying visually presented actions fits with previously reported data (Peigneux et al. 2004; Rumiati et al. 2005; see Tessari et al. 2007, for a review). As pointed out in the introduction, RBD patients have been shown to be defective in imitating intransitive gestures (Buxbaum et al. 2001; Tessari et al. 2007). Also studies using positron PET reveal that imitation of MF actions are associated with activation in the right supramarginal gyrus and inferior parietal lobule (Peigneux et al. 2004), and in the parieto-occipital and occipito-temporal junctions on the right (Rumiati et al. 2005).

In general intransitive actions were performed and recognized better than transitive actions, even though dissociations in the opposite directions were revealed, both for imitation and recognition. Two LBD patients (DS and PJ) showed a general advantage for intransitive actions, being impaired in transitive but not in the intransitive imitation task. Opposite to this, one RBD (patient MC, see Table 1) had scores at control level for MF and ML transitive actions while being below the cut off for both MF and ML intransitive gestures. Moreover MC performance with MF and ML transitive gestures significantly dissociated from imitation of the ML intransitive. Together, the pattern of dissociations in the LBDs and RBD suggests that different processes may underlie imitation of transitive and intransitive gestures. Also the results are compatible with previous studies indicating a main role of left-brain areas in imitation of transitive gestures (Stamenova et al. 2010; Buxbaum, 2007; Buxbaum et al. 2001; Liepmann, 1900-1905) and of right-brain areas in imitation of the

intransitive (Stamenova et al. 2010; Peigneux et al. 2004; Rumiati et al. 2005; see Tessari et al. 2007, for a review).

Beside the dissociations in overall performance with the transitive and intransitive actions, more specific dissociations also emerged. For instance, one LBD case (patient DT) performed better with MF transitive than ML intransitive actions. Further investigations are required to understand why this dissociation emerged; however it indicates that the difference between transitive and intransitive actions may be not relate only to the difficulty of the tasks. There is strong evidence that intransitive actions used in imitation tasks to date were easier than the transitive tasks, but this does not exclude the possibility that stimuli more balanced in term of difficulty may help to point out differential mechanisms involved in the imitation of transitive and intransitive gestures.

Intransitive actions were also recognized more frequently than transitive by all but one LBD patient (patient PJ) who, despite being impaired with in both transitive and intransitive recognition tasks, did significantly better with the transitive. It is possible that transitive actions were more robust in this patient because: i) transitive gestures were supported by an additional mechanism, independent of the mechanisms supporting intransitive action, and this additional mechanism was relatively spared in this patient; ii) his lesion involved areas relating to social communication (notice that MF intransitive actions were all communicative gestures, e.g. waving “hallo”), or iii) for some personal reason (may be he was particularly keen for tool use, e.g. DIY). Nonetheless this demonstrates that transitive and intransitive actions are not necessarily impaired equally and it is not always the case that intransitive are more robust than transitive.

The issue of tasks tapping different processes or being simply more or less difficult to perform emerges also for the distinction between MF and ML actions. At group level, transitive MF pantomimes were generally executed better than ML gestures while there was no difference between MF and ML intransitive. At the level of single patients, only one LBD (DL, already mentioned above) had a classic dissociation between the two types of transitive gestures, with better

performance for the MF, while for the intransitive two RBD (JQ, classic dissociation, and MC, strong dissociation) and three LBD (PJ and DE, classic dissociation; DT, strong dissociation) were significantly advantaged when imitated the MF than the ML. Opposite to this however, one LBD patient (patient MM) had a significant dissociation where there was normal performance with the ML gestures along with a deficit with MF intransitive gestures. MM also had poor performance with both MF and ML transitive actions. This was the only dissociation found in favour of ML gestures, when gestures of the same type (i.e. MF intransitive versus ML intransitive or MF transitive versus ML transitive) were directly compared at single subject level. So, in the present study the advantage for the ML gestures was less frequent than for the MF. Similarly, previous studies reported less frequent dissociations in favour of ML gestures (Bartolo et al. 2001; Tessari et al. 2007) compared with MF gestures (see Tessari et al. 2007 and Rumiati et al. 2009 for a review). Nonetheless, this evidence does not fit well with an explanation of MF and ML gestures differing only in terms of difficulty, instead suggesting that they may involve at least some different processes. It is true that for the transitive gestures MM did not show a significant dissociation, performing the ML only slightly better than the MF gestures (ML 20% correct and MF 18% correct). This result may be due to several reasons. For instance MM performed below the cut-off on many of the BCoS test administered (see Table 2 in Appendix 1), with his results suggesting a general loss of cognitive resources. So, it may be possible that transitive gestures were generally too demanding for MM regardless from them having a meaning or not, and so regardless from the cognitive processes MM could activate to accomplish the task.

It should be pointed out that, although there were dissociations between the tasks, the tasks generally correlated across the participants (even for control subjects). This favours the hypothesis that there is a strong relation between the different actions and between recognition and imitation, and also a single rather than a dual route account (where the same knowledge representations are called upon irrespective of whether the action is familiar or unfamiliar). It also remains possible

though that the correlations emerged from the contribution of some co-varying factor such as the processing resources the patient could bring to the task. Correlations with the tasks from the BCoS across the whole group of patients showed that both MF transitive and intransitive action imitation correlated with BCoS picture naming while ML transitive and ML intransitive actions did not. The correlations could come about due to the anatomical overlap of both processes. For example, damage to the inferior frontal cortex in the left hemisphere will disrupt picture naming and possibly also action coding, because this brain region supports both functions rather than because there are common processes involved. Other two interesting correlations emerged between: i) imitation of MF transitive gestures and BCoS Action Recognition and ii) imitation of MF and ML intransitive actions and BCoS Figure Copy. Those correlations suggest that the transitive actions may rely more on a semantic representation of the target action while the intransitive may rely more on the correct processing of spatial configuration of the limb.

Patient MMcD

As stated previously, a patient (MMcD) was included by mistake in the LBD group in a previous version of this chapter, reflecting an earlier error in data entry into a patient database. Because the imitation behaviour of MMcD was unusual for a patient with unilateral left brain damage, we checked his MRI scan⁹ using the binary lesion map (see chapter 4 for details of on how we proceeded) and noticed that MMcD actually had damage involving both hemispheres (see Figure 4).

⁹ The scans of the other patients were checked as well with the same procedure. For those patients who did not have MRI scans available we could only visually check their CT scans. Even though visual checking, being observer dependent, may be prone to errors, here we did not look for fine-grained lesions of specific brain structures. Also, those patients did not show behaviors that clearly contrasted with the observed lesions.

Figure 4. Patient MMcD- Lesion

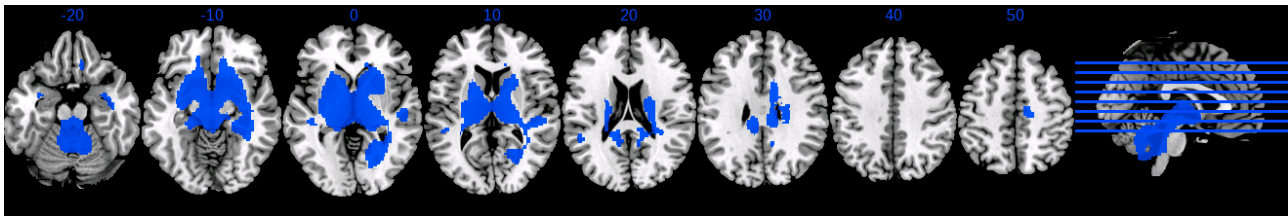


Figure 4 shows the bilateral lesion of patient MMcD on the axial slices in standard MNI space.

MMcD – imitation results

Here we report MMcD's results, along with a picture of his lesion (Figure 4), in order to account for his exclusion from the LBD group.

MMcD's imitation and recognition scores are reported in Table 1, highlighted in red, at the bottom of the main table containing the other patient's scores.

MMcD proved to be defective on both transitive and intransitive imitation tasks; regardless of the actions being MF or ML. Nonetheless MMcD reported a significant disadvantage for intransitive gestures, as indexed by the strong dissociation between his performances on the two tasks (i.e. defective scores with both transitive and intransitive gestures, though significantly lower with the intransitive). This result is consistent with previous claims of lesions on right brain areas having a role in causing a deficit with intransitive gestures (e.g. Stamenova et al. 2010; Peigneux et al. 2004; Rumiati et al. 2005; see Tessari et al. 2007, for a review).

It is also possible that MMcD had a more general praxic deficit, as evidenced by his defective performance in all the imitation tasks, as well as some difficulties in processing visuo-spatial information. Indeed, some intransitive gestures presented as stimuli required pointing to a direction, to reach a precise point of the body (e.g. the gesture for "mad" required to hit the upper side of the head, see MF and ML stimuli in Figure 2 in the method chapter) or to assume a precise postural configuration of the limb (e.g. the military salute) or of the fingers (e.g. the gesture for "good

luck”/”finger crossed”). In the present work we did not formally analyzed the patients’ errors, as in general they were too sparse to make meaningful analyses. However, at single patient level, we did notice that MMcD errors were compatible with a difficulty in processing of the visuo-spatial properties of the actions. For instance, for the gestures for “mad”, which require hitting the temple with the tip of the index finger, MMcD started the gesture correctly but then he failed do hit his head, moving instead toward a different point in the space. Also, in the distal gestures (hand gestures), he constantly failed to move his fingers in order to reach the correct configuration. For instance he was not able to move his middle finger above the index finger when he had to reproduce the gesture for “good luck”.

Despite the possible visuo-spatial problems MMcD was not categorized as having a deficit in the BCoS Figure Copy. However, it is to be noticed that MMcD performance was at the limit for being considered as normal, as he reported a score of 37 that is the cut-off below which a performance must be considered as pathological. More testing, possibly administering more tasks assessing visuo-spatial abilities are needed to draw conclusions on MMcD’s deficits.

4. Neural correlates of transitive and intransitive action imitation:

An investigation using voxel-based morphometry (VBM)

ABSTRACT

The ability to reproduce visually presented actions has been studied through neuropsychological observations of patients with ideomotor apraxia while attempts to understand the neural basis of action reproduction have been made through lesion-symptom mapping with discrete patients groups (classified according to the presence of different forms of apraxia). Lesion-symptom mapping studies have reported that areas in the parietal and frontal lobes in the left hemisphere are involved respectively in the imitation of meaningless actions and meaningful pantomimes of object use. However there is still not consent on this issue, and there is also a question if the results can be generalized to all meaningful and meaningless actions, regardless of whether actions are related or not to tool use, and whether they have a strong grasping component. In the present study I report a first attempt to use voxel –based morphometry (VBM) to evaluate the relations between brain lesions and the symptoms of apraxia. The imitation of meaningful (familiar) and meaningless (unfamiliar) tool-related (transitive) and intransitive (not-tool related) actions were examined in a consecutive series of brain-lesioned patients. The analysis showed that the left parietal cortex was involved in the imitation of novel gestures, regardless of whether they were transitive or intransitive. Also, familiar transitive actions and both types of unfamiliar actions were associated with damage to the right frontal cortex and right supplementary motor areas. Although surprising, the result in the right hemisphere may be explained by possible attention deficits of some of our patients. There were no reliable correlations between the lesions and performance on MF intransitive actions.

INTRODUCTION

Imitation is an innate tendency in humans (Meltzoff & Moore, 1977, 1983, 1989) as well as in newborn chimpanzees (Myova 1996; Bard & Russel 1999; Myowa-Yamakoshi et al. 2005) and macaques (Ferrari et al. 2006). The ability to reproduce gestures may provide one of the foundations of social communication and it may have an important role in learning effective tool use (e.g. how to use a hammer etc.).

Following a brain lesion people can suffer from a deficit in their ability to imitate visually presented actions, characterized neuropsychologically in the syndrome of ideomotor apraxia. In right handed people this syndrome has classically been described in relations to lesions of the left posterior parietal cortex (Liepmann, 1900-1905)(see Rothi et al. 1991 for a review), though other different studies point to the role of right brain areas as well as sub-cortical structures (see Tessari et al. 2007; Leiguarda et al. 1997, 2001; De Renzi et al. 1980), especially when finger configurations (Goldenberg & Strauss 2002; Della Sala et al. 2006) or movement sequences (Canavan et al. 1989) have to be copied.

Prior neuropsychological evidence indicates that ideomotor apraxia is not a unitary phenomenon, with symptom dissociations reported among patients (see Rumiati et al. 2009 for a review). For instance, neuropsychological observations suggest a double dissociation between the production of meaningful and meaningless gestures, with some studies reporting patients who are more impaired when imitating meaningful (MF) compared to meaningless (ML) gestures (Goldenberg & Hagmann 1997; Peigneux et al. 2000; Tessari et al 2007), and others showing the opposite pattern (Bartolo et al. 2001; Tessari et al. 2007). Double dissociations have also been observed between finger and hand gestures, with patients able to imitate hand postures but not finger configurations and other with the opposite pattern (Goldenberg & Karnat 2006).

A cognitive neuropsychological model of praxis was first proposed by Rothi et al. (1991) and then modified by other authors (e.g. Goldenberg & Hagmann 1997; Cubelli et al. 2000; Bauxbaum et al. 2001; Tessari et al. 2007). This model postulates (i) a *semantic route to action*, relying on long-term memory representations which allow the reproduction of MF (known) gestures, and (ii) a *direct route*, depending on short-term memory (i.e. the *innervatory pattern* in the original model from Rothi et al. (1991)), which supports the reproduction of ML (new) actions (see Figure 1 in the general introduction). The starting point of both routes is a *visual analysis* component, through which the visual properties of actions are processed. Also both semantic and direct processes end at the level of the *motor system* involved in the actual implementation of the action.

Neuropsychological observations on unilateral brain damaged patients (e.g. Goldenberg & Hagmann 1997; Peigneux et al. 2000; Cubelli et al. 2000; Bauxbaum et al. 2001; Tessari et al. 2007), as well as behavioural and imaging studies on healthy participants (e.g. Rumiati et al. 2009; Tessari & Rumiati 2004; Peigneux et al. 2004), support the idea of two separate neural systems for imitating MF and ML gestures but are inconsistent with respect to the neuro-anatomical structures involved in each (particularly concerning their hemispheric localisation). Lesions involving the parietal cortex, especially the angular gyrus, are reported to cause a deficit in the imitation of meaningless (ML) as compared to meaningful (MF) actions in left-brain damaged patients (LBD) (Mehler 1987; Goldenberg & Hagmann 1997; Peigneux et al. 2000; Tessari et al. 2007). In contrast Tessari et al. (2007) report two right brain damaged patients (RBD)(with lesions including the caudal portion of the pallidum, the putamen and the posterior limb of the internal capsule) who were more impaired in imitating ML vs. MF gestures.

In studies using positron emission tomography (PET), imitation of MF actions has been observed to be associated with activation in the left angular and middle frontal gyri, as well as the right supramarginal gyrus and inferior parietal lobule (Peigneux et al. 2004), and also in the inferior temporal, angular and parahippocampal gyri in the left hemisphere (Rumiati et al. 2005). The

parieto-occipital and occipito-temporal junctions on the right, the superior temporal gyrus on the left, and the superior parietal cortex bilaterally have also been shown to have increased activation linked to imitation of ML actions (Rumiati et al. 2005).

Goldenberg et al. (2007) used lesion subtraction analysis to determine the locations specifically associated with defective pantomime of tool use in patients with left-brain damage and aphasia. Their results showed left inferior frontal cortex to be associated with a deficit in pantomime, even though the area of lesion overlap further extended into the underlying white matter - it is possible that damage of white matter projections contributed to the deficit (Liepmann 1905; Geschwind 1976; Catani & Fytche 2005).

One caveat with the neuropsychological studies described above is that they rely on categorical subdivisions of patients based on a given cut off as well as on observer-dependent lesion demarcations. The use of a cut off, especially in tasks where each answer is scored either 1 or 0, introduces the risk that patients having scores differing only for one point are treated differently (e.g. scores that equal the cut off will be considered as defective, while scores higher than the cut off for one point will be treated as borderline or not defective at all). Also manual demarcations of lesions sites can lead to under- or over- estimation of differences in tissues according to the strictness of the observer's criteria. The present study aims to investigate the neural substrates of action imitation using a complementary VBM analysis based on segmented grey matter (GM) and white matter (WM) tissue. VBM uses the general linear model to statistically assess the relations between brain tissue integrity and behavioural performance. Here, MF and ML imitation scores were used as predictors of change in signal intensity coming from each voxel across the whole brain in a group of consecutively sampled patients, not pre-selected on the basis of having apraxia, but using continuous scores on tests of gesture imitation in order to characterise their imitation abilities. This approach also allows us to control in the model covariates of no interests such as age, gender, neglect, which may otherwise contaminate the results.

The dual route model can be applied to both symbolic and non-symbolic intransitive (not-tool related) gestures (Rumiati et al. 2009), however the neural substrates of MF and ML intransitive actions, relative to MF and matched ML transitive actions, have not been tested together in the same study. Here we used the scores patients obtained in imitation of MF transitive and intransitive pantomimes, along with matched ML transitive and intransitive actions, as predictors of voxel signal intensity.

METHODS

The sample of 21 patients, the imitation tasks, the MRI scans acquisition and preprocessing as well as the tools used for the analyses and the anatomical localization of the regions highlighted by the analyses are described in the method section of this thesis (pgs. 21-38).

A final section of the chapter will present the lesion overlap maps in the GM and WM showing the number of patients having a lesion in the regions highlighted by the analyses. Patients' lesions were identified using the automated lesion identification procedure described by Seghier et al. (2008).

The 21 patients' MRI structural images were segmented, normalized and smoothed (8mm). Then outlier voxels were detected by comparing the segmented GM and WM of the patient to the ones of 150 controls using fuzzy clustering (Seghier et al. 2008) and the outlier voxels in each tissue class were assigned to the lesion. The image showing the number of patients whose lesion overlap in the GM and WM were created using the "image calculator" function of SPM5 (Statistical Parametric Mapping; Friston, Ashburner, Kiebel, Nichols, & Penny, 2007, Wellcome Department of Cognitive Neurology, London, UK) using the expression: 'i1 + i2 + i3 + i4 + ... + i21'.

The images for GM and WM were displayed with MRICRON (Chris Rorden, University of South Carolina, Columbia, SC, USA) and saved as bitmap files.

BEHAVIOURAL RESULTS- transitive (MF & ML) and intransitive (MF & ML) actions

Figure 1 illustrates the proportional scores for transitive and intransitive gestures for LBD, RBD and BBD and control participants¹⁰. Patient's scores are in Appendix 2 (Table 1 in Appendix 2; defective scores are in bold).

Figure 1- imitation of transitive MF&ML and intransitive MF&ML- proportional scores from patients and controls

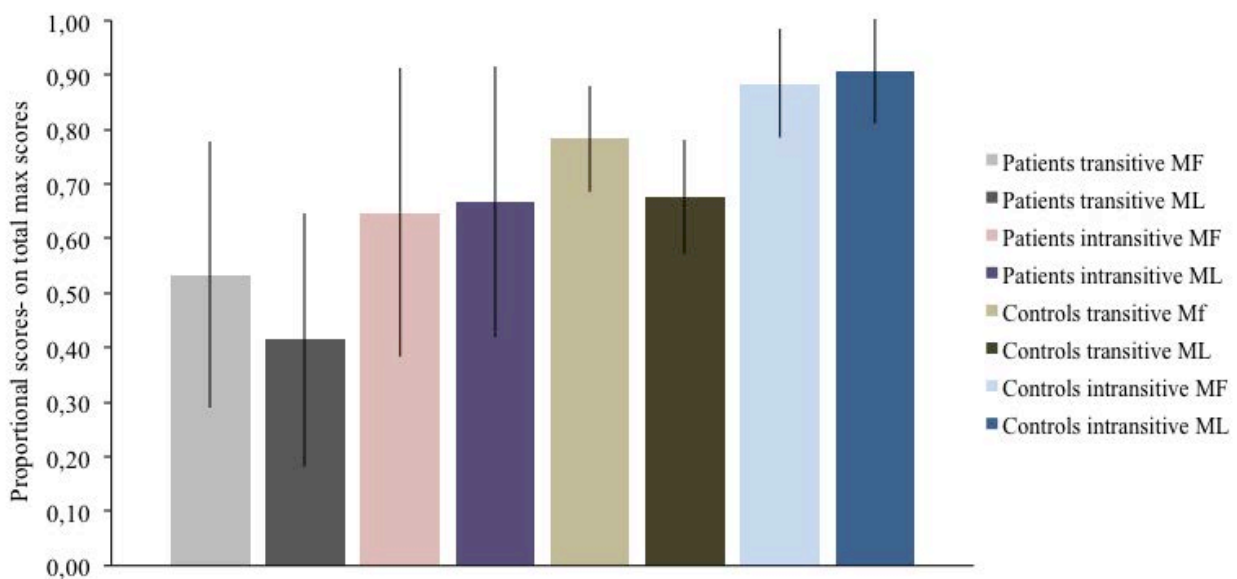


Figure 1. The graph illustrates the performance of patients (left half of the graph) and controls (right half of the graph). Controls' data were used to compare patients' performance at a single case level (see main paragraph). The data were not statistically analyzed at group level, however it can be seen that patients had generally better performance with the intransitive than with the transitive actions and that the difference between MF and ML was more evident for the transitive actions. Also, lowest performance was reported with the MF transitive actions.

¹⁰ The Cohen's k agreement coefficient was calculated on a sample of patients and controls' scores provided by the two independent raters. The coefficient was computed for Totals and separately for MF and ML transitive and ML intransitive actions. As the k was ≥ 0.80 in all the cases considered, the scores of only one rater were used.

To provide an initial descriptive analysis of the behavioural data, cut offs were established on the basis of the control's means and standard deviations for the transitive (MF (mean= 15.78; SD= 1.93; ML (mean= 13.89; SD=2.30); totals (mean= 29.67; SD=3.50)) and intransitive (MF (mean= 13.44; SD= 1.42) ML (mean= 13.72; SD= 1.36); totals= 27.17; SD= 2.66) actions using the modified t-test by Crawford and Garthwaite (2002). For the transitive action imitation task eleven patients (6 LBD, 4 RBD and 1 BBD) performed below the cut off for MF (≤ 12); ML (≤ 9) and total action performance (≤ 23); one LBD had normal performance with MF but fell below the cut off for the ML and total action scores; one RBD was defective only when imitating MF actions and one RBD was below the cut off only for the ML actions. At the intransitive action imitation task four LBD, three RBD and one BBD performed below the cut off for MF (≤ 10) and ML (≤ 11) and total actions (≤ 22); one LBD and one RBD were below the cut-off for MF and totals; one RBD was defective for ML and total action scores and one RBD and one BBD were defective only for the ML actions.

VOXEL-BASED MORPHOMETRY

The MRI scans of 21 patients were used to investigate the relationship between GM and WM integrity and scores for the transitive MF and ML and intransitive MF and ML imitation tasks on a voxel-by-voxel basis.

ANALYSES

The patients' raw scores at imitation of transitive MF and ML and intransitive MF and ML gestures were used as the covariates of interest. Two models were estimated including either GM or WM segmented images along with the four covariates of interest: i.e. i) transitive MF, ii) transitive ML, iii) intransitive MF, iv) intransitive ML. Also, eight further models were estimated, each including only one covariate of interest at a time and either GM or WM: 1) transitive MF and GM; 2)

transitive ML and GM; 3) intransitive MF and GM; 4) intransitive ML and GM; 5) transitive MF and WM; 6) transitive ML and WM; 7) intransitive MF and WM; 8) intransitive ML and WM. Age, handedness¹¹, education and gender were used covariates of no interest in all the models. T- contrasts were run on each model using a mixed peak and cluster threshold with at least 50 voxels showing a $Z > 2.6$ (i.e. $p \leq 0.005$, uncorrected). Here we decided to use a p- value a bit less restrictive than a $p \leq 0.001$ (uncorrected) because of the size of the patients sample, as well as to have the same threshold as the in the next two chapter where CT scans, instead of MRI scans, were used for the VBM analyses (see chapter 5 and 6 for more details).

VBM RESULTS

GREY MATTER

Table 1 (below) shows the MNI coordinates and the statistical values of the results obtained from the contrasts run on all the models including GM scans.

GM- transitive MF&ML and intransitive MF&ML

The model including all the four covariate of interest along with GM scans was analyzed and revealed a significant cluster ($p \leq 0.05$ FWE-corr, cluster level) within the parietal cortex, including the precuneus and extended to the cuneus in the left hemisphere.

A plot of the results on the main peak on this cluster showed that the imitation of intransitive gestures had the stronger relation with the intensity of the signal (Figure 2).

¹¹ Patients were divided in right-handed and left-handed according to the scores they received at the Edinburgh Handedness Inventory (Oldfield, 1971).

Figure 2. GM- transitive MF&ML and intransitive MF&ML- Plot of results on the main peak (i.e. precuneus)

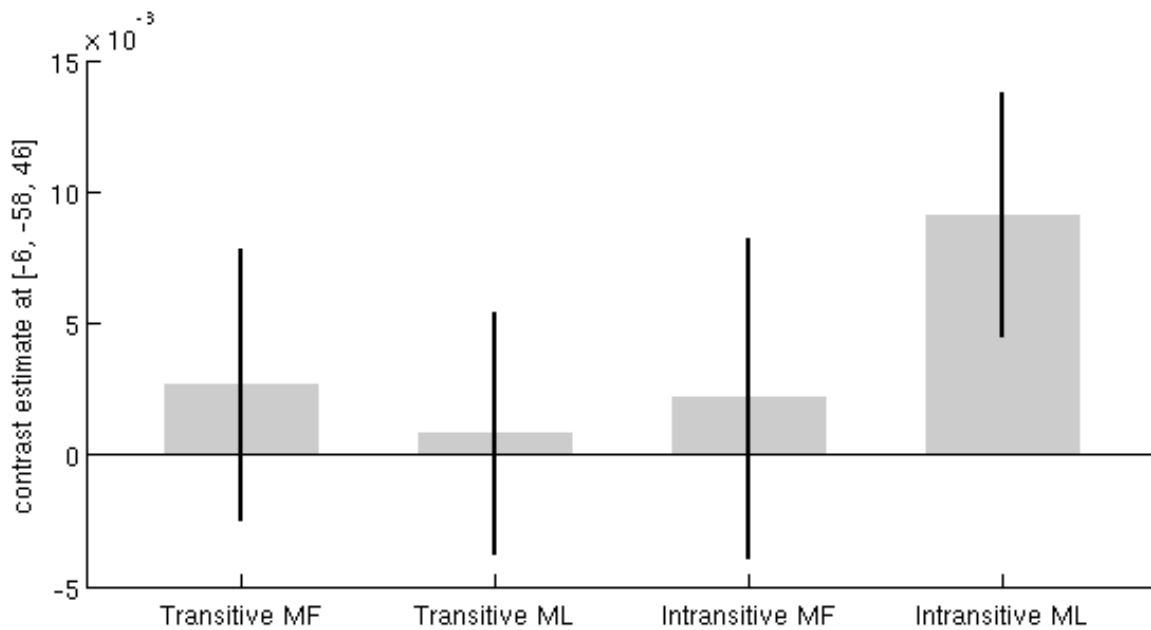


Figure2 imitation of intransitive ML gestures showed the strongest relation with the signal from GM in correspondence of the main peak in the cluster highlighted by the contrast run on the model including all four covariates of interest.

GM- transitive MF

The contrast on the model with the scores at imitation of MF transitive gestures as unique covariate of interest highlighted a large cluster ($p \leq 0.05$, FWE-corr, cluster level) in the frontal cortex including the supplementary motor area (SMA) on the right (Figure 3a) and extending to the left hemisphere on the posterior cingulate cortex (PCC) (Figure 3b).

Figure 3a. GM- transitive MF- Right frontal cortex and SMA

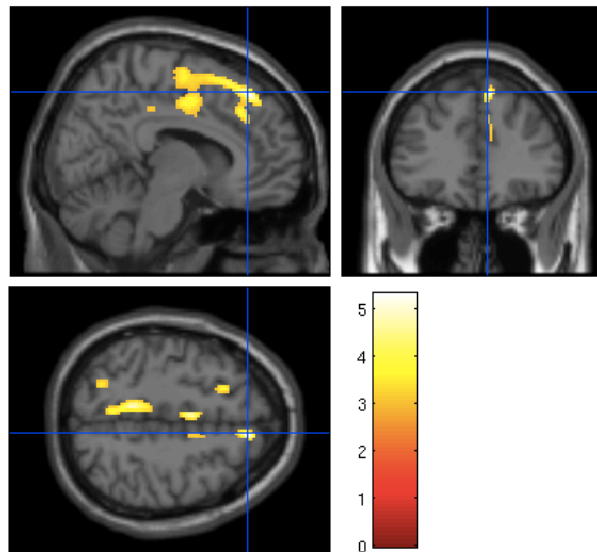


Figure 3b. GM- transitive MF- Left PCC

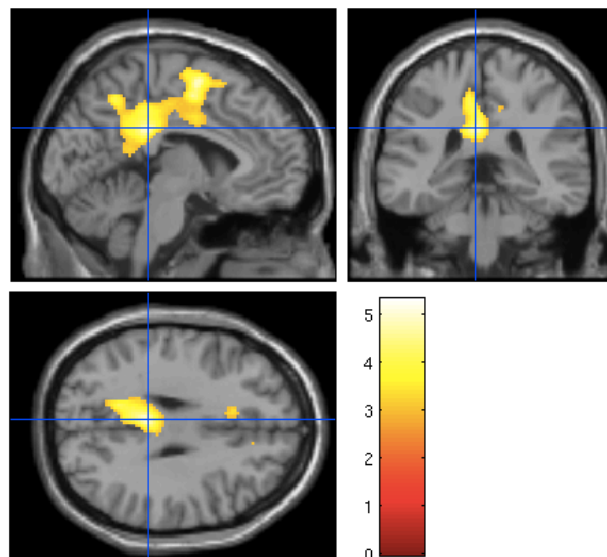


Figure 3a and 3b- imitation of transitive MF gestures correlated with a large cluster ($p \leq 0.05$, FWE-corr, cluster level) encompassing GM areas on the frontal cortex and SMA on the right hemisphere (3a) as well as the posterior cingulate cortex on the left (3b).

GM- transitive ML

The analysis on the model including patient's GM segmented images along with the ML transitive actions' scores as the only covariate of interest revealed one large cluster ($p \leq 0.05$ FWE-corr, cluster level) on the left superior parietal cortex including the left precuneus and extending on the

left middle occipital cortex (Figure 4a). Another cluster was highlighted in the right hemisphere including the middle cingulate cortex as well as the frontal cortex and the supplementary motor areas (Figure 4b), although this cluster had a $p = 0.08$ (FWE-corr, cluster level) and so the result did not reach the full significance level when corrected.

Figure 4a. GM- transitive ML- left parietal and occipital cortex

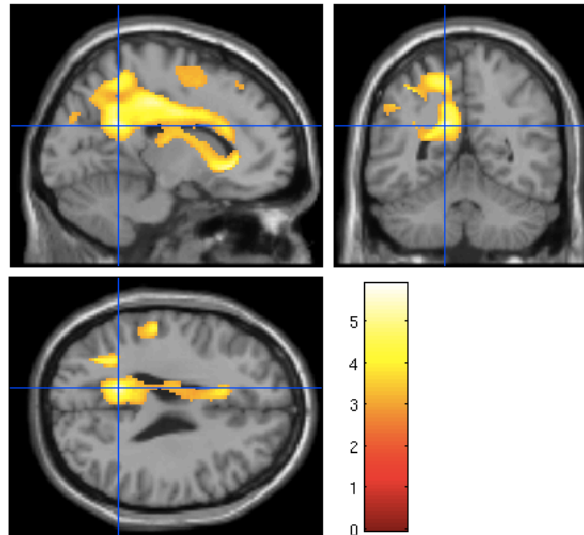


Figure 4b. GM- transitive MF- right frontal cortex and SMA

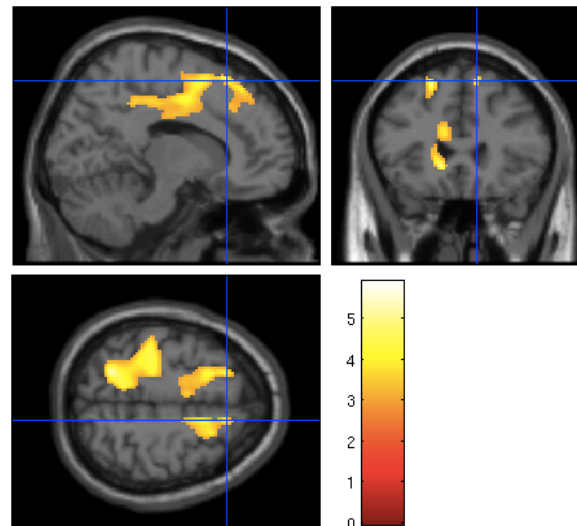


Figure 4a and 4b- imitation of transitive ML gestures appeared to involve parietal areas and partly extending to the occipital cortex on the left hemisphere (4a). Moreover the analyses gave results on the right frontal cortex and SMA (4b) that were also revealed by the analyses for the transitive MF gestures.

GM- intransitive ML

The t contrast on the model with scores for ML intransitive gestures as covariate of interest and GM scans showed a significant cluster ($p \leq 0.05$ FWE-corr, cluster level) in the left parietal cortex peaking on the precuneus and extending into the supplementary motor area and superior frontal cortex on the right hemisphere. Finally a cluster on the left supramarginal gyrus was revealed, although not significant after correction (in red on Table 1). It is reported here though because clusters in the same area were obtained for Imitation and Production (on verbal command) on intransitive ML and MF gestures in the studies in chapter 5 and 6. This was not the case for the other actions types here.

Figure 5a. GM- intransitive ML- left parietal cortex

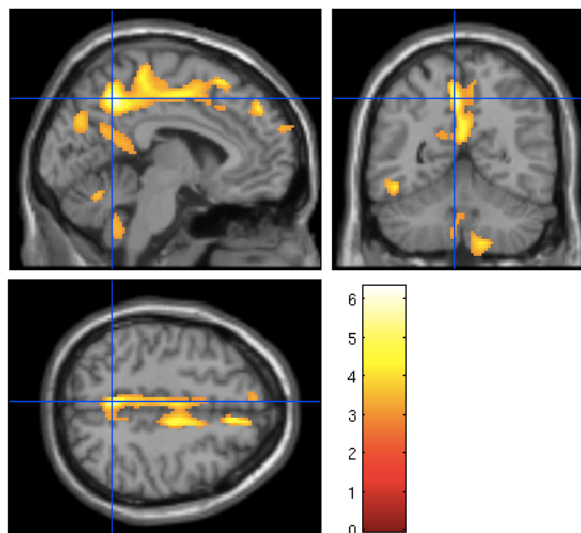


Figure 5b. GM- intransitive ML- right frontal cortex and SMA

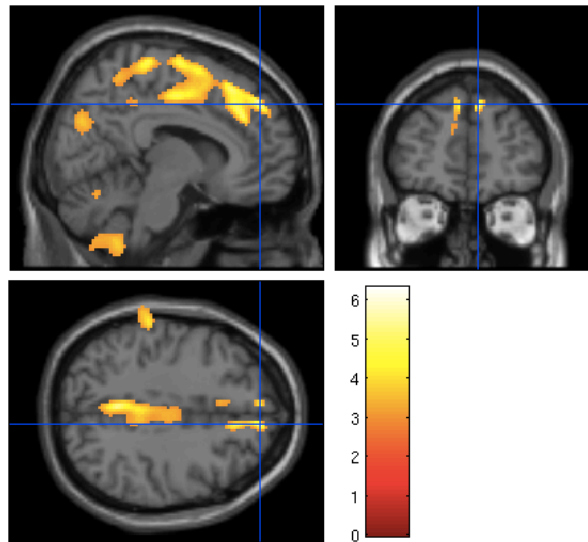


Figure 5a and 5b- similarly to transitive ML, intransitive ML gestures were associated with damage to the left parietal cortex (5a). The cluster also extended to the right frontal cortex and SMA (5b) – areas that were also revealed by the analyses for the transitive MF and ML gestures (the significance threshold for the transitive ML was not violated).

GM- intransitive MF

The analysis on the model with only MF intransitive actions' scores showed clusters on the left cuneus and also involving the left superior occipital cortex, but they were not above the significance threshold. The results will be only shortly mentioned in the discussion and they must be taken cautiously.

Table 1. GM- MNI coordinates and stats. All $p \leq 0.005$, uncorrected

ALL CONTRASTS P=0.005

GM												
<i>Imitation- transitive MF & ML and intransitive MF & ML</i>												
cluster	cluster	cluster	cluster	peak	peak	peak	peak	peak	x	y	z	
p(FWE-corr)	p(FDR-corr)	equivk	p(unc)	p(FWE-corr)	p(FDR-corr)	T	equivZ	p(unc)				
0.005	0.007	2198	0.000	0.357	0.867	6.23	4.09	0.000	-6	-58	46	precuneus_L
				0.852	0.867	4.89	3.56	0.000	-22	-46	62	Parietal_Sup_L
				0.860	0.867	4.86	3.55	0.000	-6	76	28	cuneus_L
<i>Imitation- transitive MF</i>												
cluster	cluster	cluster	cluster	peak	peak	peak	peak	peak	x	y	z	
p(FWE-corr)	p(FDR-corr)	equivk	p(unc)	p(FWE-corr)	p(FDR-corr)	T	equivZ	p(unc)				
0.001	0.002	3481	0.000	0.414	0.869	5.32	3.93	0.000	8	34	50	Frontal_Sup_Medial_R
				0.453	0.869	5.24	3.89	0.000	10	20	58	Sup_Motor_Area_R
				0.622	0.869	4.89	3.72	0.000	-6	-36	28	Cingulum_Post_L
<i>Imitation- transitive ML</i>												
cluster	cluster	cluster	cluster	peak	peak	peak	peak	peak	x	y	z	
p(FWE-corr)	p(FDR-corr)	equivk	p(unc)	p(FWE-corr)	p(FDR-corr)	T	equivZ	p(unc)				
0.000	0.000	8210	0.000	0.221	0.354	5.90	4.18	0.000	-24	-60	54	Parietal_Sup_L
				0.283	0.354	5.68	4.09	0.000	-14	-52	24	Precuneus_L
				0.285	0.354	5.68	4.09	0.000	-32	-64	18	Occipital_Mid_L
<i>0.080</i>	<i>0.042</i>	<i>1251</i>	<i>0.007</i>	<i>0.834</i>	<i>0.387</i>	<i>4.46</i>	<i>3.50</i>	<i>0.000</i>	14	-6	42	<i>Cingulum_Mid_R</i>
				<i>0.869</i>	<i>0.394</i>	<i>4.37</i>	<i>3.46</i>	<i>0.000</i>	10	32	50	<i>Frontal_Sup_Medial_R</i>
				<i>0.909</i>	<i>0.399</i>	<i>4.25</i>	<i>3.39</i>	<i>0.000</i>	12	24	56	<i>Sup_Motor_Area_R</i>
<i>Imitation- intransitive ML</i>												
cluster	cluster	cluster	cluster	peak	peak	peak	peak	peak	x	y	z	
p(FWE-corr)	p(FDR-corr)	equivk	p(unc)	p(FWE-corr)	p(FDR-corr)	T	equivZ	p(unc)				
0.000	0.000	4133	0.000	0.137	0.522	6.31	4.34	0.000	-6	-56	46	Precuneus_L
				0.267	0.522	5.75	4.12	0.000	10	-8	70	Sup_Motor_Area_R
				0.327	0.522	5.57	4.04	0.000	8	46	40	Frontal_Sup_Medial_R
0.868	0.901	274	0.157	0.431	0.522	5.31	3.92	0.000	-62	-30	34	Supramarginal_L
<i>Imitation- intransitive MF</i>												
cluster	cluster	cluster	cluster	peak	peak	peak	peak	peak	x	y	z	
p(FWE-corr)	p(FDR-corr)	equivk	p(unc)	p(FWE-corr)	p(FDR-corr)	T	equivZ	p(unc)				
0.453	0.959	605	0.050	0.654	0.902	4.81	3.68	0.000	-6	-74	32	Cuneus_L
				0.854	0.902	4.38	3.46	0.000	-4	-68	24	Cuneus_L
				1.000	0.992	3.34	2.84	0.002	-12	-88	20	Occipital_Sup_L

Table 1. VBM results on GM. The significant clusters found ($p = 0.005$ uncorrected; $p \leq 0.05$ FWE-corr) are in bold. One cluster for imitation of transitive ML gestures had a $p = 0.08$ (FWE-corr), and it is in italic. One cluster was revealed also for the MF intransitive gestures, although it was not significant when FWE-corrected. The cluster in red for the intransitive ML was not significant. We reported it because a cluster in the same areas was reported also in the study in chapter 5 and 6 for Imitation of ML intransitive actions and for intransitive MF gestures production.

WHITE MATTER

As for GM, contrasts were run on models with WM scans and the covariates of interest (i.e. scores at the imitation tasks). As for GM the covariates were included together in a unique models as well as they were taken individually in separate models for each task.

The analyses on the models including: i) all the four covariates, ii) transitive MF gestures only, iii) intransitive MF gestures only, iv) intransitive ML gestures only did not give any results nor significant or not significant.

Instead, results were obtained from the contrast on the model with ML transitive gestures only¹².

WM- transitive ML

The contrast on the model with transitive ML gestures as the only covariate of interest showed a significant cluster ($p \leq 0.05$ FWE-corr, cluster level) in the left corticospinal tract and WM tract within the left superior temporal gyrus (Figure 6). The statistical values and the MNI coordinates for this contrast are in Table2.

¹² The same covariates of no interest as the ones used for the models with GM scans were entered also in the models for WM (i.e. age, handedness, education and gender). The threshold used was the same as the one used for contrast on GM (i.e. at least 50 voxels showing a $Z = 2.6$, $p \leq 0.005$, uncorrected).

Figure 6. WM- transitive ML- left corticospinal tract.

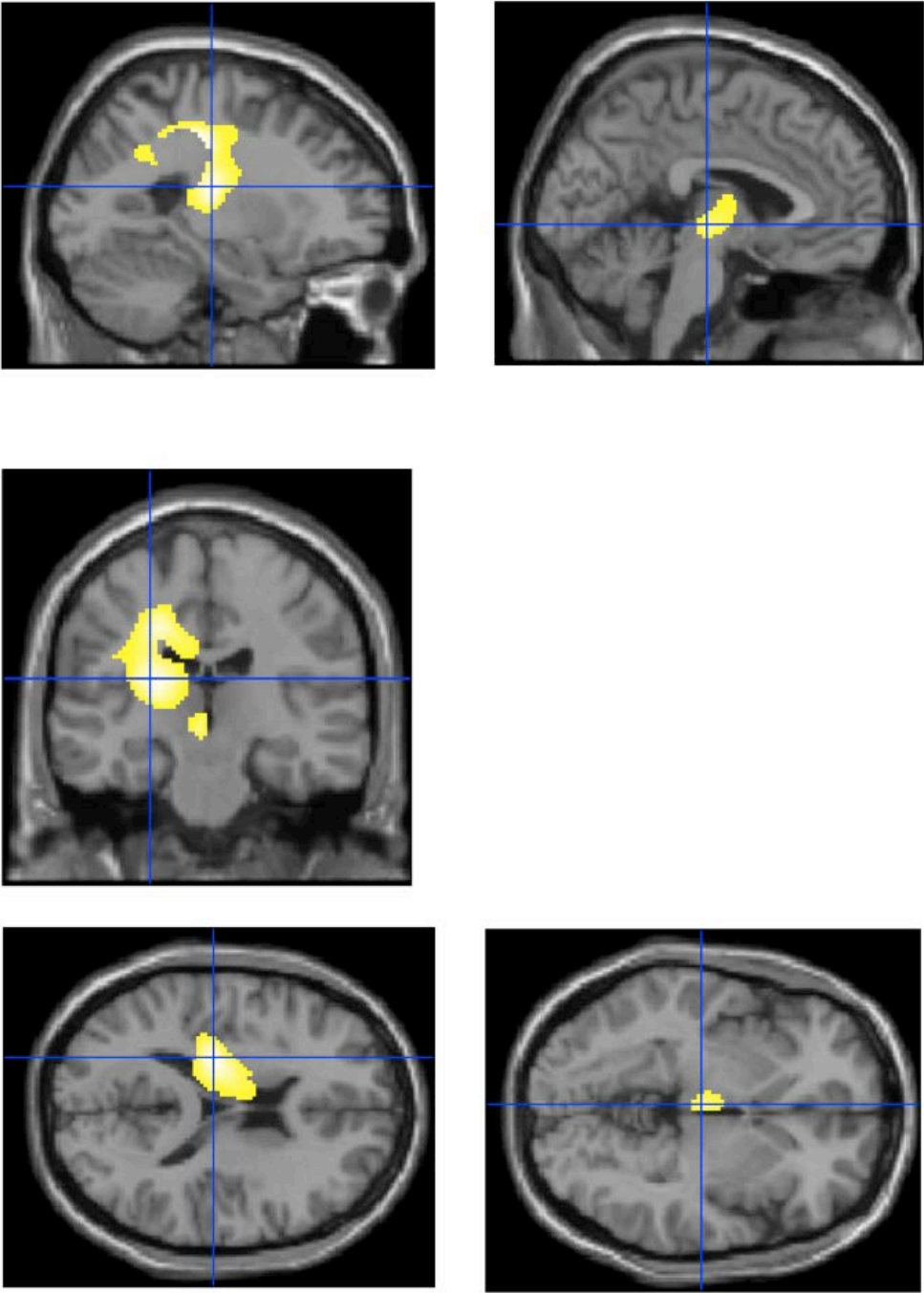


Figure 6- only the contrast on the model with WM and scores in imitation of ML transitive gestures gave results and highlighted a significant cluster into the corticospinal tract on the left hemisphere.

Table 2. WM- MNI coordinates and stats. All $p \leq 0.005$, uncorrected

WM												
<i>Imitation- transitive ML</i>												
cluster	cluster	cluster	cluster	peak	peak	peak	peak	peak				
p(FWE-corr)	p(FDR-corr)	equivk	p(unc)	p(FWE-corr)	p(FDR-corr)	T	equivZ	p(unc)	x	y	z	
0.007	0.002	3689	0.002	0.460	0.587	4.44	3.49	0.000	-24	-28	40	Left corticospinal tract
				0.539	0.587	4.28	3.40	0.000	-26	-22	16	
				0.771	0.667	3.82	3.14	0.001	-4	-20	-4	

Table 2. VBM results on WM. Only the model for transitive ML gestures gave results in WM, and showed a significant cluster ($p \leq 0.05$ FWE-corr, cluster level) on the left corticospinal tract.

LESION OVERLAP MAPS

The lesions overlap map is showed in Figure 7 (GM).

Figure 7- GM- Lesion overlap map

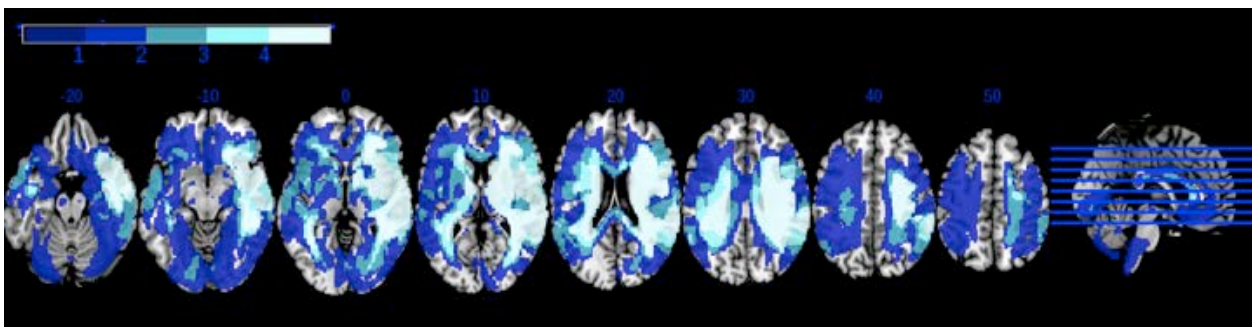


Figure 7- Lesion overlap map for the 21 patients on the axial slices in standard MNI space. Patients' lesions overlap on the blue coloured voxels. The bar on top of the figure shows the number of patients corresponding to each colour shade (range 1–4).

DISCUSSION

The present study investigated the link between GM and WM lesions and performance in gesture imitation, according to the (i) type of action to be executed (transitive or intransitive) and (ii) the familiarity of the action (MF or ML). The brain lesion data were analyzed using voxel-based morphometry, an unbiased approach that treats patients' behavioural scores as predictors of change in the intensity of the signal from each voxel of segmented GM or WM tissue. Reliable correlations

were found between impairments in gesturing and neural changes on GM for the contrasts run on the model including all the four imitation tasks, as well as on three of the models with individual tasks as unique covariate of interest (i.e. imitation of i) MF transitive, ii) ML transitive, iii) ML intransitive gestures).

A cluster in the left superior parietal cortex involving the precuneus, and extending also to the cuneus in the occipital cortex, appeared to relate on average to all the four tasks, even though the plot of the results showed a stronger relation between signal change in this cluster and the imitation of ML intransitive gestures. However the contrasts run on models with single covariate of interest showed that both ML transitive and ML intransitive actions related to the reduced signal from the left parietal cortex. Lesions involving the left parietal cortex were already indicated as causing the symptoms of ideomotor apraxia (see Rothy et al. 1991 for a review), and observations on unilateral brain damaged patients showed that LDB patients with lesions on superior parietal structures had poorer performance in the imitation of ML as compared to MF gestures (Mehler 1987; Goldenberg & Hagmann 1997; Peigneux et al. 2000; Tessari et al. 2007). Also brain imaging studies indicate that the left superior parietal cortex shows increased activation when ML actions were imitated (Rumiati et al. 2005). Moreover, the cluster we found in the left parietal cortex for both types of ML gestures involved the left precuneus, a structure that was reported to be involved in shifting attention between different locations in space (see Cavanna et al. 2006 for a review). Those data suggest that the parietal areas highlighted by our analyses may play a role in processing visuo-spatial information that can be necessary for imitating ML unfamiliar actions. Moreover, the extension of the cluster in the occipital cortex for the ML transitive gestures suggests that imitation of those actions may rely also on basic visual processes.

No cluster in parietal and occipital cortex was found for the transitive MF gestures. So, it may be possible that imitation of MF gestures is based on information available from other components in the system (e.g. representations in long term memory), which are activated instead of visuo-spatial

attention and basic visual processes. However, in the present study we could not find areas involved for MF gestures only, so it is not possible to draw strong conclusions about the neural substrates and the processes that are unique to this type of action. Also, the cluster in the occipital cortex was revealed for MF intransitive gestures that also can rely on information stored in memory. However, this last cluster was not significant when corrected and it is possible that it was mainly due to the presence of few patients who also had a deficit specific to recognition of communicative intransitive actions, and hence processed these gestures as ML.

Imitation of MF transitive gestures appeared to correlate only with the integrity of the frontal cortex and SMA in the right hemisphere. Also, the same areas were revealed by the contrasts run on the two models including either ML intransitive or ML transitive action imitation scores, although the cluster was not fully significant for the ML transitive. Frontal areas and SMA have previously been found to be involved in praxis. For instance Peigneux et al. (2004) included SMA together with the superior parietal lobule in a set of brain areas serving innervatory motor patterns common to both MF actions, implemented through the lexical route, and ML actions, processed through the direct route. Also, SMA has been reported to be crucial for implementing organized and smooth action sequences (Goldenberg 1985) and Grèzes et al. (1998) reported selective activation of the SMA when participants saw actions and had the intention to imitate them as compared to mere observation. Moreover, in the study by Gèzes et al. (1999) SMA was activated for MF gestures only and not for ML movements. Those previous studies indicate that the SMA may have a role in imitation, particularly for MF gestures, however our results differ from the previous investigations in that the clusters found by our analyses were on the right and not on the left hemisphere. For our data we propose that the cluster on the right frontal cortex and SMA was less related to imitation and more to attention and control processes that are necessary to correctly perform the task. It may be possible that, when an actor displays an action, there is automatic activation of a set of representations that are the most similar to the action displayed, in order to retrieve the target action

meaning (if MF) or to categorize it as ML. If an action has to be imitated the viewer must modulate the representation of the MF action, in order to perform it as similarly as possible to the model, avoiding a “prototypicalization” error (i.e. a gesture that is the prototypical version of the target gesture), or, in the case of a MF gesture, inhibit any representation and switch to a direct imitation process, avoiding the production of a “lexicalization” error (i.e. execution of a MF gesture somehow similar to the ML target). So, it may be that our patients who had a lesion to right frontal areas and SMA were not able to deal with the conflict between their mental representation and the actual action displayed. Here the patients’ errors were quite sparse (i.e. patients did not report consistently a specific type of errors) and were not further analyzed. Nonetheless, it is still possible that their problem in dealing with the conflict generally distracted them from the task leading them to produce wrong actions.

Results from the WM analysis indicated a large cluster on the corticospinal tract running within the left hemisphere. At the best of our knowledge little is still known about the role of the different WM tracts in cognitive functions, however this finding is coherent with the role of this WM tract in connecting the cortical motor areas to the spinal cord and so allowing the impulses to pass from the brain to the peripheral motor system. The role of WM in praxis, as well as in other cognitive functions, still needs more investigation, possibly using Diffusion Tensor Imaging on larger groups of patients and controls.

Due to time limits the present study included a relatively small sample of patients (three more patients were tested, however it was not possible to have their MRI scans in time to meet the deadline for thesis submission and so they had to be excluded from this study). The reduced patient sample size led to the decision to use a $p \leq 0.005$ instead of a $p \leq 0.001$, as a stricter threshold could have caused a loss of information from our data. This decision was made also in order to have the same p value used in the next two chapters where CT scans of acute patients, instead of MRI scans of chronic patients, were used for VBM.

Finally, the lesion overlap map showed that up to 4 patients had overlapping lesions. Nonetheless, here continuous behavioural scores and continuous values associated to grey or white matter were analyzed. This made possible to account also for those areas of minor volume loss, due for instance to dendritic loss on areas connected to damaged regions, and that could not be identified by methods that assign binary values to damaged or intact tissues.

5. Recognizing and executing movements: An investigation using Voxel-Based Morphometry (VBM)

ABSTRACT

The skills to execute and understand actions are crucial for everyday life and likely depend on both overlapping and distinct processes (Rothi et al. 1991; Rumiati et al. 2002). Action execution and recognition was investigated in the present study by carrying out a large-scale lesion-symptom analysis of deficits in action recognition, generation to command and imitation in stroke patients. Voxel-based morphometric analysis revealed distinct regions of neural change associated with each key symptom, along with some overlapping regions in parietal and temporal cortex, and the underlying white matter, for gesture recognition production on command and imitation. Also, as the three praxis tasks used here are part of a new battery of test aimed at acute stroke patients, a further aim of the present study is to look at the areas that are likely to be involved in those three tasks, as well as to have a baseline for a large number of stroke patients in the acute phase that will be re-tested in a follow up when in the chronic phase. The implications are discussed for understanding the neural control of action recognition and production in acute stroke patients.

INTRODUCTION

In the past decade several studies have advocated the existence of a common neural system involved in representing actions, both when actions are merely observed and when they are executed. The key initial evidence came from physiological studies in monkeys. These studies demonstrated the existence of a class of visuo-motor neurons (the so-called mirror neurons, MNs), that responded when the animals saw actions as well as when they had to produce them (see Rizzolati et al. 2001 for a review). At first MNs were found in area F5 in the monkeys' ventral premotor cortex (Gallese et al. 1996; Rizzolati et al. 1996) but they have also been reported in a

variety of regions (e.g., in a portion of the superior temporal sulcus (the STSa) that responds also to biological motion and the inferior parietal lobule (area PF) that has been shown to respond strongly to the observation of action). Together these regions comprise the MN system which has been argued to play a critical role in a range of processes, from action understanding through to intention encoding (Iacoboni et al. 2005; see also Rizzolati et al. 2001, 2010 for a review).

Supportive evidence for a MN system in humans has been come from various sources.

Electrophysiological evidence (e.g., EEG) has shown activity in motor regions when gestures are observed (Gastaut et al. 1954; Cohen-Seat et al. 1954; see also Cochin et al. 1998, 1999; Altschuler et al. 1997, 2000; Salmelin et al. 1994; Hari et al. 1997; Salenius et al. 1997; Hari et al. 1998). This is been supported by evidence from brain imaging investigations showing that ventral premotor/inferior frontal areas (including Broca's region), the STS and the inferior parietal lobule are active when hand movements are observed (see Rizzolati et al. 2001 for review). Furthermore imaging studies using both action observation and execution tasks have shown that the left inferior frontal cortex and the right anterior parietal region are active both when a gesture (lifting a finger) has to be executed following the observation of the same action and when the gesture has just to be observed. The same area does not respond when the finger movement has to be enacted after the observation of a control stimulus (a cross), or when participants just attend to a cross (Iacoboni et al. 1999; see also Rizzolati at al. 2001 for review). The same parieto-frontal circuit also activates in other fMRI studies when participants view a human or robot hand grasping an object (Gazzola et al. 2007) and even when aplasic individuals (born without arms and hands) watch hand actions and moved their feet (Gazzola et al. 2007) (see Rizzolati et al. 2010 for a review).

It has been argued that the MN system has an important role in action understanding (Gallese et al. 1996; Rizzolati et al. 2001). In the present work we will consider action recognition and "action understanding" as synonymous, and an action recognition task is examined which required the perception and comprehension of motor gestures. The assertion that MNs are involved in action

understanding is based on the finding that MNs in monkeys respond both on execution and presentation of actions toward objects (e.g. lift an object/piece of food and put it in a container, or take a piece of food and put it in the mouth). However, these same neurons have not been found to fire to pantomimed action (without the object present, and so having not a goal) but do fire again to actions toward hidden objects, if the monkey could see the object before it was hidden by a screen. This evidence has led to the claim that MNs are not simply visuo-motor association neurons, linking a visually presented object to its appropriate action, but rather MNs code the meaning of actions. Other interpretations (e.g., Hickok 2009) suggest that MNs are cross-modal associative neurons, reflecting the presence of an object, and an action, irrespective of whether the object is present or represented in working memory (as when monkeys attend to actions to hidden objects). Another argument put forward in favour of the MN system being related to recognizing the meaning of an action comes from a study by Gallese et al. (1996). These authors simultaneously recorded activity in region F5 in the monkey and in the hand area of primary motor cortex (M1), as well as recording EMG activity from several mouth and limb muscles. The results showed that there was activity in MNs but not in cells in primary motor cortex (Gallese et al. 1996). This suggests that no covert movement were involved, and hence that MNs in F5 are not 'merely' motor-related. However in humans there is evidence for an increase in activity in distal muscle motor-evoked potentials (MEPs) evoked by trans-cranial magnetic stimulation during action observation (Fadiga et al. 1995). Inconsistent results have also come from two recent studies using neural adaptation and fMRI. fMRI adaptation is the decrease in the blood-oxygen-level dependent (BOLD) response from a brain area when stimuli or responses are repeatedly presented. Adaptation across two separate stimuli is considered to be evidence for the same processes and neural correlates being recruited. It follows that, if action execution and recognition involve the same processes, then the neural response to action execution should 'adapt' after action observation and vice versa. Dinstein et al. (2007) failed to find this and concluded that action recognition and execution do not involve

common neural populations. In contrast, Chong et al. (2008) reported that there was adaptation in the right inferior parietal lobe across action execution and perception (Chong et al. 2008).

This review suggests that (i) there is neurophysiological evidence from the monkey suggesting that action recognition and production share neural and functional processes - though the exact account of the role of these processes remains in debate (Hickok 2009, see above), but (ii) there is inconclusive neuroimaging evidence on the issue while (iii) it is clear that distinct component processes must also contribute to each task. This latter argument is indicated perhaps most clearly by evidence of dissociations between the tasks in neuropsychological patients. For example, dissociations have been documented between patients who show spared recognition of actions and gestures but who are impaired at producing the actions themselves (not concomitant on a motor impairment, in cases of ideomotor apraxia; see Chainay & Humphreys, 2002). Also it cannot be argued that the dissociation exists only because recognition tasks are easier than action production or imitation as the reverse pattern of deficit has also been documented (in the syndrome “pantomime agnosia”, Bell 1994; Rothi et al. 1986; Cubelli et al. 2000; see also Mahon et al. 2005 for a review). In one study Negri et al. (2007) obtained case-level dissociations within an unselected group of 37 unilateral brain damaged patients who undertook object use, object recognition, pantomime imitation and pantomime recognition tasks. Although at group level there were significant correlations between each pair of tasks, the authors also pointed out subsets of patients demonstrating dissociations between each test pairing (Negri et al. 2007).

Patients with lesions in the left parietal lobe are reported to have particularly poor performance at gesturing to command compared to imitation with recognition spared, while those with lesions in the left occipital and temporal cortex present with the opposite pattern, being almost normal when producing actions on verbal command but impaired at action recognition (Merians et al. 1997).

Also, even when gestures production is considered alone, there are dissociations in the production of different types of action for example, patients who can imitate familiar but not unfamiliar actions

(see Tessari et al. 2007 for a review). These dissociations point to there being separable components of the action recognition and production systems.

The 'dual route' cognitive neuropsychological model of praxis (e.g. Rothi et al. 1991; Goldenberg & Hagmann 1997; Cubelli et al. 2000; Buxbaum et al. 2001; Rumiati and Tessari 2002) distinguishes between a *semantic route*, relying on Long Term Memory (LTM), which supports the reproduction of MF (known) gestures, and a *direct route*, dependent on a Short Term Memory (STM) system (i.e. the *innervatory pattern* in the original model from Rothi et al. (1991)), which supports the reproduction of ML (new) actions (see Figure 1 in the general introduction). The starting point of both routes is a *visual analysis* component, through which the visual properties of actions are processed. Both the semantic and direct processes end at the level of the *motor system* involved in the generation of the motor pattern for action. This framework explains impaired action recognition in terms of poor access to, or impaired representation of, LTM for action. Poor LTM for action should also result in problems in producing actions to names, a problem that could also reflect impairment in output from the LTM system. Deficits in imitation should stem from damage to the indirect route.

Although the neuropsychological literature indicates functional dissociations between patients, there is much less consensus about the underlying lesion pathologies. Classically, ideomotor apraxia (reflecting poor action production specifically) has been associated with lesions involving the left inferior parietal lobe (Liepmann, 1900-1905, Heliman et al. 1982). However, the subsequent literature has pointed to the involvement of a variety of other cortical structures (inferior frontal, posterior middle temporal, and also sub-cortical structures) that can be linked to different apraxic deficits. For example, it has been argued that the left inferior cortex is particularly implicated in pantomime (acting without an object) whereas deficits in actual use of objects is linked to inferior parietal damage (Weiss & Fink, 2010; see also Goldenberg et al. 2007). Gesture recognition too has been linked to inferior frontal regions (Pazzaglia et al. 2008) while recognition of particular aspects

of transitive (object-oriented) actions have been linked not to frontal regions but to inferior parietal (recognition of spatial aspects of action) and posterior middle temporal regions (recognition of semantic aspects of action). In patients with sub-cortical lesions imitation may be spared for meaningless actions, but the production of familiar transitive actions may be disrupted (Hanna-Pladdy et al. 2001). Taken together these neuropsychological results suggest that access to long-term semantic memories for object-related actions may involve middle temporal regions. Deficits in access to (and possible planning for production) spatial aspects of action link to inferior parietal damage. The implementation of learned transitive actions may operate through sub-cortical routines, while left inferior frontal regions are involved in aspects of action production, with lesions to this region producing their most pronounced effects when patients pantomime action (when they lack convergent input from holding the actual objects; see Chainay & Humphreys, 2002, about the use of convergent sensory input into motor output and selection processes).

The present study used a voxel-based morphometric (VBM) analysis to assess effects of brain lesion on action recognition and production in a large, unbiased sample of stroke patients. Three tasks were assessed:

- (1) Gesture Production (the generation of meaningful, learned actions to names),
- (2) Imitation (the replication by the patient of meaningless gestures made by the examiner), and
- (3) Action Recognition (the identification by the patient of meaningful, learned actions by the examiner).

The Gesture Production task was chosen in order to require access to LTM prior to production (stressing output section of the semantic route to production). The Imitation task was used in order to assess the indirect route (which must be used for meaningless actions, according to the model in Figure 1). The Action Recognition task was chosen to assess input from observed action into the LTM system.

Regions where damage leads to problems in both Action Recognition and Imitation tasks are likely to support these input processes. Action Recognition and Gesture Production differ in the stimulus input (hand movements vs. name) and in their output demands (output only required for the production task), but they both call on long-term memories for actions (with familiar actions being tested in each case). Regions of damage linked to both problems can be linked to the common LTM-based processes. Imitation and Gesture Production both required motor output but differ in input processing (arm movements vs. names) and in their demands on LTM (not required for imitation but required for production). For this it can be argued that areas that lead to problems on both tasks are those involved in access to motor output.

Alongside the analyses of the regions that on average relate to all the three tasks, we also assessed deficits linked to single tasks, to evaluate lesion sites linked to ‘classical’ task impairments in apraxia.

The VBM analysis was performed on segmented grey matter (GM), to focus on the grey-level correlates of impaired action recognition and execution. Differently from VBM, other approaches to analyzing lesion-symptoms associations use techniques that could be biased, as they require subdivisions of patients based on a given cut off or according to observer-dependent lesion demarcations. The use of a cut off, especially in tasks where each answer is scored categorically, raises the possibility that patients having scores differing only for one point are treated differently (e.g. scores that equal the cut off will be considered as defective, while scores higher than but still close to the cut off will be treated not defective). Also making a priori demarcations of lesions sites can lead either to critical areas being ignored or overestimated according to the strictness of the used criteria. VBM uses the covariates of interest, in this case the three BCoS tests’ raw scores, as predictors of changes in the signal intensity coming from each voxel across the whole brain in the patient group and it does not require to make subdivisions based on performances or lesions.

METHODS

The patients' sample, the tasks, the neuroimaging assessment and the preprocessing of the CT scans are described in the methods section of this thesis (see pgs. 21-38).

VOXEL-BASED MORPHOMETRY

The segmented GM and WM maps of the 233 patients were used to look at the relation between the intensity of the signal from GM or WM across the whole brain and abilities in three domain of praxis: i.e. producing MF actions on verbal command (Gesture Production); imitating ML hand sequences and ML finger postures (Imitation); recognizing MF pantomimes and MF communicative gestures (Action Recognition).

ANALYSES

Analyses were carried out separately on GM and WM segmented images. At first two models were estimated including all the three covariates of interest, corresponding to the raw scores at the three tasks: i) Gesture Production; ii) Imitation; iii) Action Recognition. Analyses were run on the models in order to look at the average contribution of the three covariates in predicting changes in the signal intensity in either GM or WM.

Further models were estimated for each covariate of interest taken individually (i.e. i) Action Recognition only; ii) Gesture Production only; iii) Imitation only), both for GM and WM. Age, gender, years of education and hand (used for imitation/gestures production, dominant or non dominant) were introduced as covariates of non-interest¹³ in all the models analysed.

After models estimation the t contrasts were run using a mixed peak and cluster threshold with at least 50 voxels showing a $Z \geq 2.6$ (i.e. $P \leq 0.005$, uncorrected). The same threshold was used for all the contrasts reported below. The p-value threshold was set at $p \leq 0.005$, instead of a $p \leq 0.00$, for two reasons: 1) here we used CT scans that are a bit more noisy; 2) the tasks could have proven

¹³ Handedness was not included as only right-handed patients were included in the sample (see also above).

quite easy for some of the patients, and so the distribution of the data slightly skewed toward the higher values. With these conditions a p-value $p \leq 0.001$ was judged to lead to a possible loss of information from the present data.

RESULTS

The proportional scores, calculated on maximum possible score for each task, are reported on Figure 2.

Figure 2. Proportional scores at Gesture Production, Imitation and Action Recognition

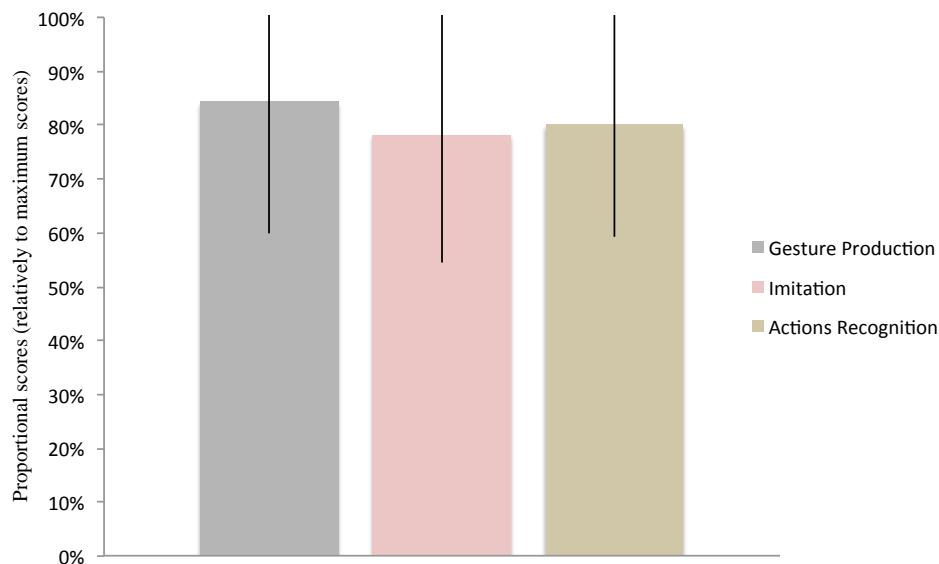


Figure 2 reports the mean percentage scores at the 3 praxis tasks (i.e. (mean score/max possible score)*100)

GREY MATTER

The MNI coordinates and the statistics for all the main results on GM are reported on Table 1 (see below).

GM- Gesture Production, Imitation, Actions Recognition

Two clusters were significant when corrected for familywise error (FWE). On average, low performance in the tasks tapping the praxis domain (i.e. gestures production on verbal command, imitation, action recognition) was associated with lesions in the left hemisphere, clustering around the anterior cingulate (ACC) and middle temporal cortex ($p < .05$, FWE corrected).

A plot of the results however revealed that the effect almost completely related to the Action Recognition task both in ACC (Figure 3a) and in the middle temporal cortex (Figure 3b).

Figure 3 a GM- Gesture Production, Imitation, Actions Recognition-Plot of results on ACC

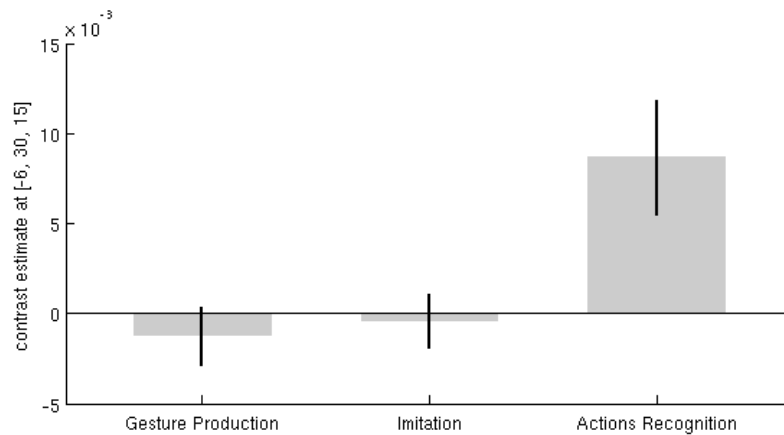


Figure 3 b GM- Gesture Production, Imitation, Actions Recognition-Plot of results on the middle temporal cortex

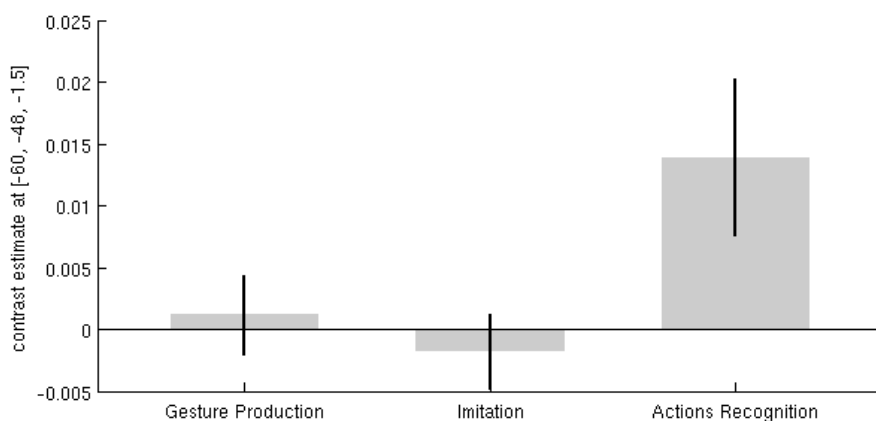


Figure 3a and **Figure 3b** show the contribution of each covariate of interest in predicting changes in the signal from GM.

GM- Action Recognition

The analysis highlighted the same two clusters of voxels on the left ACC (Figure 4a) and on the left middle temporal cortex (Figure 4b) as the ones found previously for the contrast including all the three covariates. Again the two clusters were both significant at cluster level after correction for multiple comparisons ($p < .05$, FWE, corrected).

Figure 4a GM- Action Recognition- left ACC

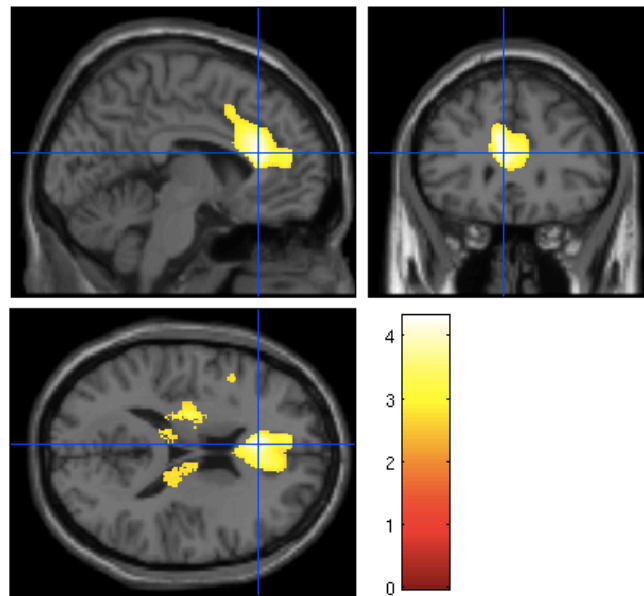


Figure 4b GM-Action Recognition- left middle temporal cortex

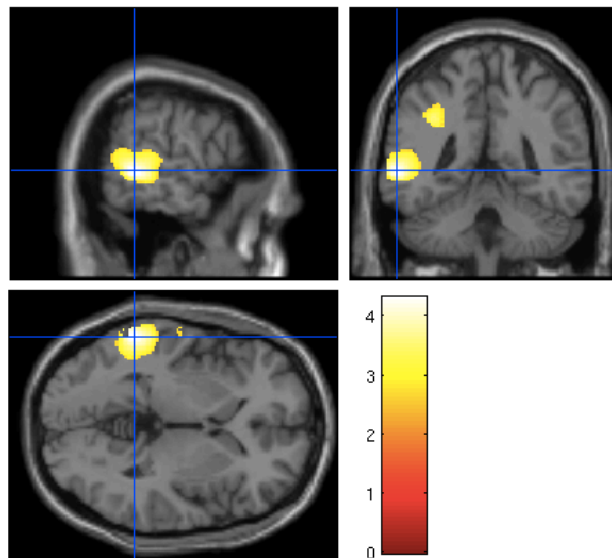


Figure 4a and **Figure 4b** shows the significant clusters ($p < 0.05$ FWE-cor) obtain for Action Recognition. The same clusters were revealed by the contrast run on the model including all the three covariate of interest (i.e. Gesture Production, Imitation, Action Recognition).

Table 1. Main findings on GM: MNI coordinates and stats. All $p \leq 0.005$, uncorrected

GM												
<i>GM areas for Gesture Production, Imitation and Actions Recognition</i>												
cluster	cluster	cluster	cluster	peak	peak	peak	peak	peak	x	y	z	
p(FWE-cor)	p(FDR-cor)	equivk	p(unc)	p(FWE-cor)	p(FDR-cor)	T	equivZ	p(unc)				
0.000	0.000	5993	0.000	0.122	0.288	4.37	4.27	0.000	-6	30	15	Cingulum_Ant_L
				0.149	0.288	4.31	4.22	0.000	-9	30	24	Cingulum_Ant_L
				0.406	0.528	3.96	3.89	0.000	-12	11	43	Cingulum_Mid_L
0.018	0.016	2447	0.001	0.239	0.382	4.16	4.07	0.000	-60	-48	-2	Temporal_Mid_L
<i>GM areas for Actions Recognition</i>												
cluster	cluster	cluster	cluster	peak	peak	peak	peak	peak	x	y	z	
p(FWE-cor)	p(FDR-cor)	equivk	p(unc)	p(FWE-cor)	p(FDR-cor)	T	equivZ	p(unc)				
0.008	0.006	2888	0.001	0.146	0.323	4.31	4.22	0.000	-60	-45	-2	Temporal_Mid_L
				1.000	0.952	2.96	2.93	0.002	-64	-18	3	Temporal_Sup_L
0.000	0.001	4836	0.000	0.180	0.323	4.25	4.16	0.000	-6	28	16	Cingulum_Ant_L
				0.249	0.323	4.14	4.06	0.000	-9	27	25	Cingulum_Ant_L
				0.683	0.742	3.70	3.64	0.000	-12	11	43	Cingulum_Mid_L
<i>GM areas for Gesture Production</i>												
cluster	cluster	cluster	cluster	peak	peak	peak	peak	peak	x	y	z	
p(FWE-cor)	p(FDR-cor)	equivk	p(unc)	p(FWE-cor)	p(FDR-cor)	T	equivZ	p(unc)				
<i>0.115</i>	<i>0.077</i>	<i>1499</i>	<i>0.008</i>	<i>0.932</i>	<i>0.826</i>	<i>3.40</i>	<i>3.35</i>	<i>0.000</i>	<i>-56</i>	<i>-28</i>	<i>21</i>	Supramarginal_L
				0.992	0.826	3.17	3.13	0.001	-58	-37	-3	Temporal_Mid_L
				0.997	0.826	3.10	3.07	0.001	-60	-27	6	Temporal_Sup_L
<i>GM areas for Imitation</i>												
cluster	cluster	cluster	cluster	peak	peak	peak	peak	peak	x	y	z	
p(FWE-cor)	p(FDR-cor)	equivk	p(unc)	p(FWE-cor)	p(FDR-cor)	T	equivZ	p(unc)				
0.651	0.669	625	0.066	0.818	0.932	3.57	3.51	0.000	-54	-28	21	Supramarginal_L
0.887	0.669	391	0.137	0.951	0.932	3.35	3.31	0.000	-40	0	34	Precentral_L

Table1. MNI coordinates and p-values of the clusters revealed by the analyses on GM. Significant clusters are in bold. All the contrasts were run with a mixed peak and cluster threshold of 50 voxels having a $z = 2.6$ (i.e. $p \leq 0.005$, uncorrected).

GM- Gesture Production

The analysis highlighted one large cluster (Figure 5), encompassing the supramarginal gyrus and portions of the middle and superior temporal cortex extending into the middle and superior temporal cortex, although it showed $p = 0.077$, false discovery rate (FDR) corrected and a $p = 0.115$, FEW corrected.

Figure 5 GM- Gesture Production- left parietal and temporal cortex

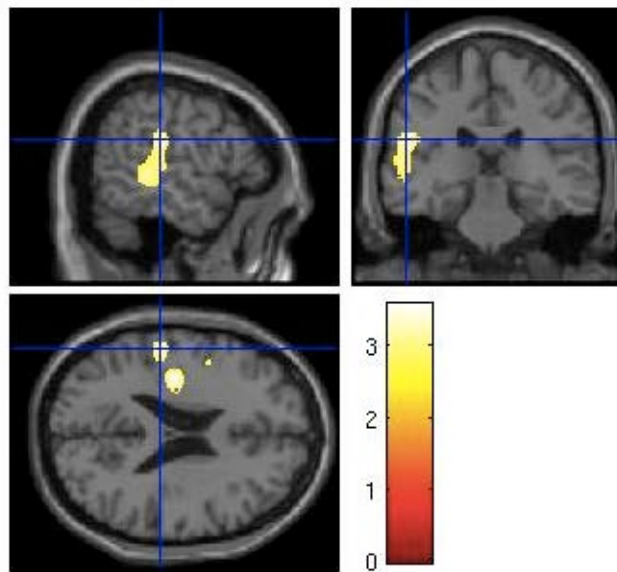


Figure 5 shows the most significant cluster obtained on GM ($p= 0.077$ FDR-cor, cluster level and $p= 0.115$ FWE-corr cluster level) for Gesture Production that encompassed the area around the left supramarginal gyrus, middle temporal and superior temporal cortex.

GM- Imitation

The two bigger clusters that were highlighted by this contrast encompassed the supramarginal and postcentral gyri on the left hemisphere (Figure 6a and 6b). However, as reported in Table 1, both clusters were not significant after correction ($p > 0.1$ both FWE and FDR corrected).

Figure 6a GM- Imitation- left supramarginal gyrus

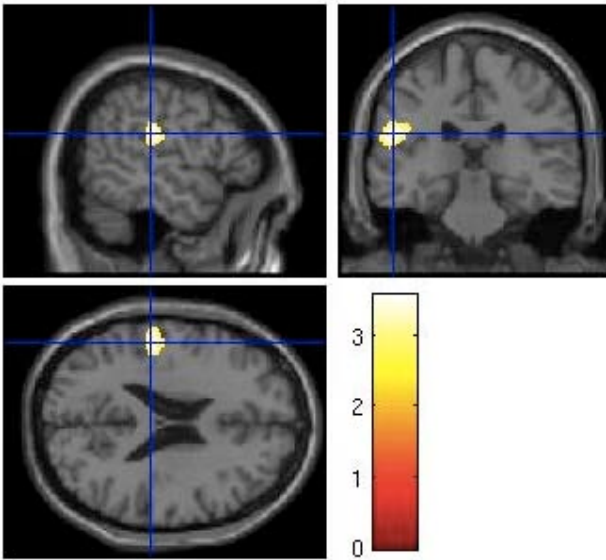
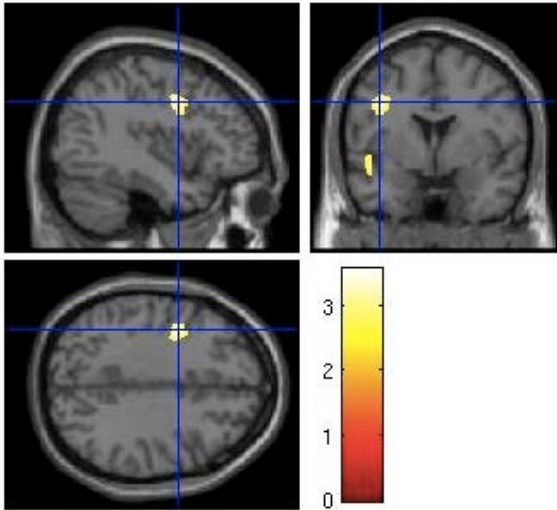


Figure 6b GM- Imitation- left precentral gyrus



Figures 6a and 6b show the two larger clusters on GM relating to Imitation and that involved parietal and frontal areas.

WHITE MATTER

Table 2 reports the statistical value and the MNI coordinates for all the main results obtained on WM (see below).

WM- Gesture Production, Imitation, Recognition

The contrast showed one significant cluster ($p < 0.05$, FEW-corr) involving the WM tract within the superior temporal gyrus.

As for GM, a plot of the results highlighted the predominant role of Action Recognition in predicting a decrease in the signal at WM level (Figure 7).

Figure 7. WM- Gesture Production, Imitation, Actions Recognition-Plot of results on WM

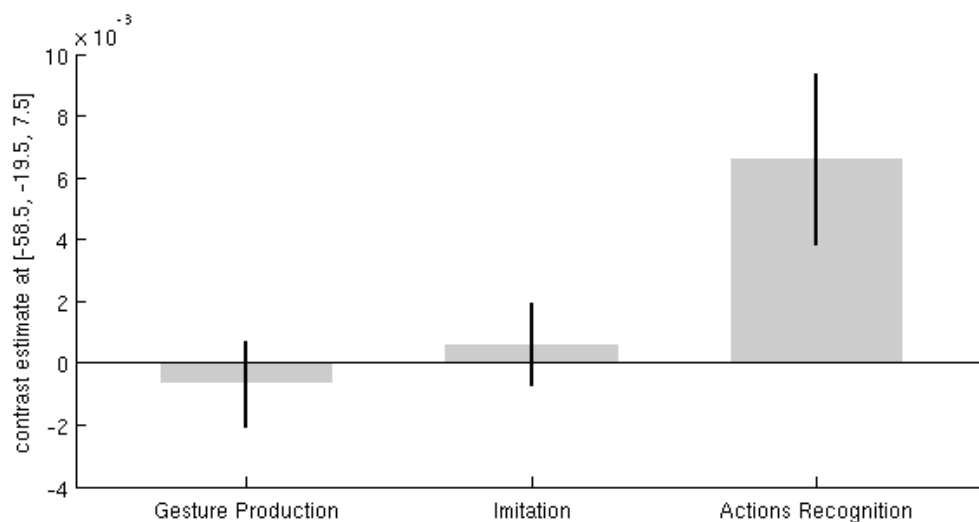


Figure 7 shows the relative contribution of each covariate in predicting the signal strength from the WM tract within the superior temporal gyrus.

WM- Action Recognition

The contrast on WM pointed out a cluster, significant after correction ($p < .05$, FEW corrected), in the WM tract within the left superior temporal gyrus (Figure 8). This result matched the one we found when Action Recognition was used as covariate together with the scores at the other two tests.

Figure 8. WM-Action Recognition- WM within the left superior temporal gyrus

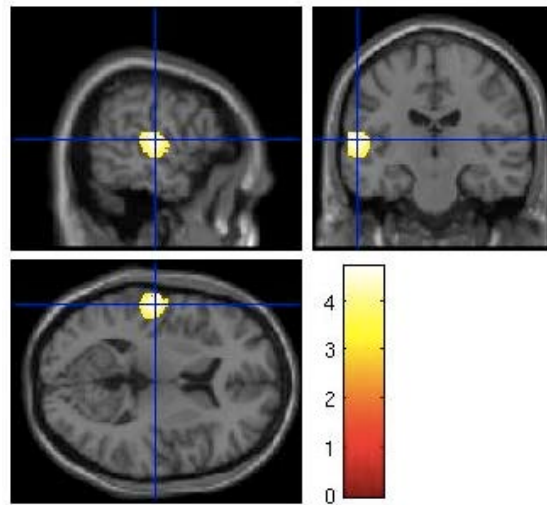


Figure 8 shows the significant cluster ($p < 0.05$ FWE-cor and FDR-cor, cluster level) in the WM tract within the superior temporal gyrus. The result match the one found for the contrast run on the WM model including Actions Recognition together with Gesture Production and Imitation

Table 2. Main findings on WM: MNI coordinates and stats. All $p \leq 0.005$, uncorrected

WM												
<i>WM areas for Gesture Production, Imitation and Actions Recognition</i>												
cluster	cluster	cluster	cluster	peak	peak	peak	peak	peak	x	y	z	
p(FWE-cor)	p(FDR-cor)	equivk	p(unc)	p(FWE-cor)	p(FDR-cor)	T	equivZ	p(unc)				
0.048	0.042	2277	0.004	0.031	0.047	4.70	4.58	0.000	-58	-19	7	WM tract within the left superior temporal pole
				1.000	0.951	2.69	2.66	0.004	-60	-3	0	
<i>WM areas for Actions Recognition</i>												
cluster	cluster	cluster	cluster	peak	peak	peak	peak	peak	x	y	z	
p(FWE-cor)	p(FDR-cor)	equivk	p(unc)	p(FWE-cor)	p(FDR-cor)	T	equivZ	p(unc)				
0.035	0.027	2479	0.003	0.036	0.050	4.65	4.54	0.000	-58	-19	7	WM tract within the left superior temporal pole
				0.999	0.997	2.90	2.88	0.002	-60	-3	0	
				1.000	0.997	2.79	2.76	0.003	-50	-4	-2	
<i>WM areas for Gesture Production</i>												
cluster	cluster	cluster	cluster	peak	peak	peak	peak	peak	x	y	z	
p(FWE-cor)	p(FDR-cor)	equivk	p(unc)	p(FWE-cor)	p(FDR-cor)	T	equivZ	p(unc)				
0.059	0.023	2161	0.005	0.606	0.610	4.10	4.05	0.000	-40	6	-15	WM tract within the left temporal pole
				0.926	0.610	3.33	3.29	0.000	-52	3	-14	
				0.958	0.610	3.26	3.22	0.001	-62	-1	-3	
0.042	0.023	2371	0.003	0.618	0.610	4.09	4.03	0.000	33	-58	12	Right Corpus Callosum
				0.977	0.610	3.19	3.15	0.001	27	-42	18	
				1	0.894	3.11	3.09	0.004	34	-37	3	
<i>WM areas for Imitation</i>												
cluster	cluster	cluster	cluster	peak	peak	peak	peak	peak	x	y	z	
p(FWE-cor)	p(FDR-cor)	equivk	p(unc)	p(FWE-cor)	p(FDR-cor)	T	equivZ	p(unc)				
<i>0.068</i>	<i>0.119</i>	<i>2065</i>	<i>0.005</i>	<i>0.779</i>	<i>0.993</i>	<i>3.54</i>	<i>3.49</i>	<i>0.000</i>	<i>40</i>	<i>-39</i>	<i>-5</i>	Right Corpus Callosum
				0.962	0.993	3.25	3.21	0.001	24	-34	19	
				0.964	0.993	3.24	3.20	0.001	39	-57	1	

Table2. MNI coordinates and p-values of the clusters revealed by the analyses on WM. Significant clusters are in bold. All the contrasts were run with a mixed peak and cluster threshold of 50 voxels having a $z= 2.6$ (i.e. $p \leq 0.005$, uncorrected).

WM- Gesture Production

The analysis on WM revealed a significant cluster ($p < 0.05$, FWE corrected) involving the caudal part of the corpus callosum on the right hemisphere (Figure 9a), as well as a cluster having a $p= 0.059$, FEW corrected and a $p \leq 0.05$, FDR corrected, overlapping the WM tracts within the left superior temporal cortex (Figure 9b).

Figure 9a WM-Gesture Production- right corpus callosum

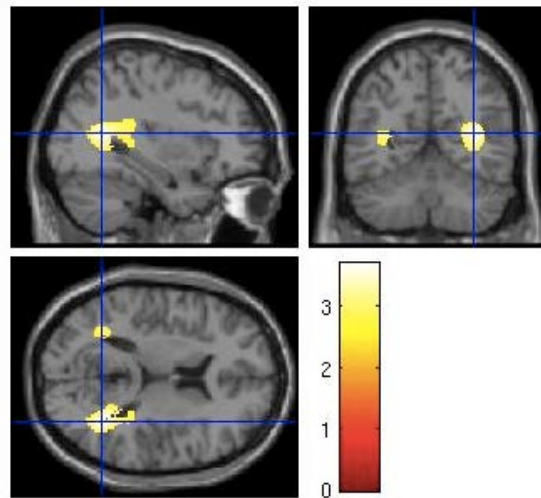


Figure 9b WM-Gesture Production- WM within the left superior temporal gyrus

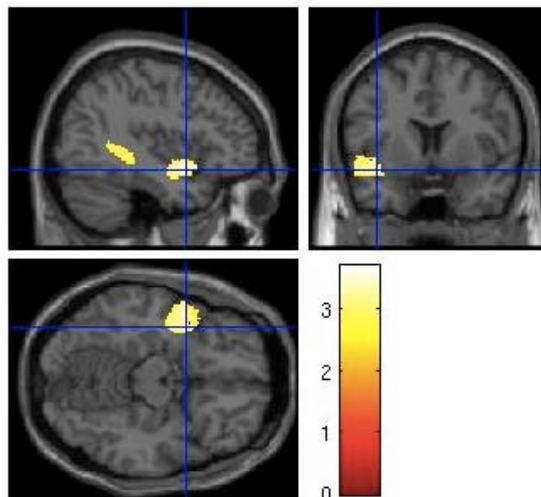


Figure 9a shows the significant cluster ($p \leq 0.05$ FWE-corr) involving the corpus callosum and the optical tract on the right hemisphere. **Figure 9b** shows the cluster encompassing the WM tract within the left temporal lobe ($p = 0.059$, FWE-corr; $p \leq 0.05$, FDR-corr).

WM- Imitation

Imitation appeared to relate to signal intensity on the posterior part of the corpus callosum on the right hemisphere (Figure 10). As reported in Table 2, the cluster showed a $p = 0.068$, FWE corrected, and a $p = 0.119$, FDR corrected.

Figure 10 WM-Gesture Production- right corpus callosum

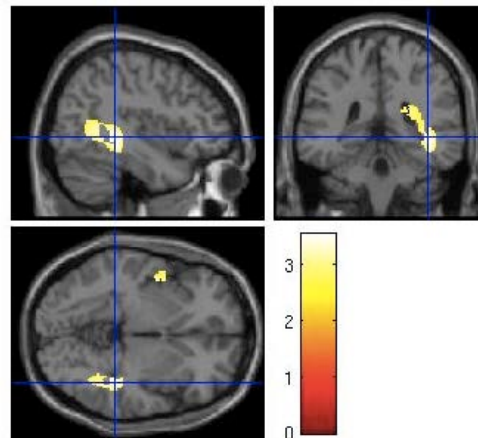


Figure 10 shows the WM tract on the right corpus callosum. The same tract appeared also for Gesture Production, however for Imitation it was less significant ($p= 0.068$ FWE-cor, cluster level).

DISCUSSION

Of central interest for this study was the relation (if any) between different apraxic symptoms in action recognition, production and imitation. To this end, the BCoS Action Recognition, Gesture Production and Imitation were analysed in a unique model examining their average contribution in predicting the signal intensity from GM and WM, and so indicating which areas are involved when generally doing a praxis related task. Secondly, each set of scores was analysed in individual models.

On average the three covariates of interest appeared to relate to changes in the signal on the left anterior cingulate (ACC) and medial temporal cortex, even though a plot of the results suggested that the intensity of the signal from GM was almost completely predicted by Action Recognition. The analysis on Action Recognition as the only covariate of interest confirmed this, revealing the same GM regions that were found when the contrast was run on the model including all the three covariates. The left middle temporal cortex was reported to be active in a PET study when participants observed gestures either for later imitation or recognition but only when the actions had

a meaning (Decety et al. 1997). Also in other research, the same region has been found to be damaged in two patients who were not able to produce actions to objects, while still retaining the knowledge of the objects they could not use (Price et al. 2010). Moreover, Price et al. (2010) reported higher incidence of impairment in gesture production among patients whose lesion extended into left temporal (and middle temporal) cortex. This also fits with our finding of a cluster extending to the left middle temporal cortex for Gesture Production, where the patients had to reproduce meaningful gestures on verbal command, although this cluster showed only a trend for significance when FDR-corrected, and an even higher p-value when FWE-corrected. As both successful recognition and production of meaningful gestures may require retrieving information from LTM, those results point to a role of the medial temporal cortex in the action retrieval process. This interpretation is supported by previous investigations that indicated the medial temporal cortex as having a role in encoding the right sequence of events within episodes stored in LTM (Tubridy et al. 2011). To activate a representation of the right movement sequence may be crucial not only to execute a movement correctly but also to recognize a gesture, especially in the case of pantomimes where the actual object is not present to help gesture identification.

A cluster in the left ACC was revealed only for Action Recognition. This result was unexpected and does not clearly relate to lesions reported in studies of apraxia. The ACC has most typically been linked to action monitoring and response selection (e.g. Dehance et al. 1994; Pardo et al. 1990). However, the ACC keeps a great number of interconnections between different cortical areas. Moreover, it has been proposed that ACC could be divided into two parts: i) a more posterior part primarily connected to areas appointed to monitoring behaviour, response selection and motor control (e.g. prefrontal, parietal, premotor and supplementary motor areas); ii) a more anterior part connected to the hippocampus, and to other structures belonging to the limbic system, that is involved in assessing the salience of motivational and emotional/affective information (see Bush et al. 2000 for a review). It should also be noted that the hippocampus was previously indicated as a

structure involved in the retrieval of semantic information about pantomimes of object use (e.g. Tessari et al. 2007). The present results do not enable us to identify fine-grained subdivisions within the ACC, however it is possible that a lesion on the more anterior part impaired action recognition in our patients because the ACC could not pass information to the hippocampus. Alternatively the patients may have failed in the task because of a deficit in identifying the motivation or the intention of the actions. The Action Recognition task administered in the present study was composed of both transitive pantomimes of object use and intransitive communicational gestures. Here the total scores were considered, so it is not possible to distinguish which between the two types of gestures is more responsible for the results. For instance, if the relation between ACC and performance holds true only for the transitive pantomimes, this may support the hypothesis of a disconnection from the hippocampus, which can be involved in the retrieval of information about those actions (e.g. Rumiati et al. 2005, Tessari et al. 2007). Conversely, if the relation is due only to the intransitive communicative gestures, it is more likely that a lesion on ACC led to a failure in recognizing the intentions of the actor. More analyses may address this issue.

The strongest results on the GM analysis emerged for Action Recognition, however also Gesture Production and Imitation gave some results, although they are not as strong and must be taken cautiously. The results on GM for Gesture Production, besides partially overlapping with the results for Action Recognition in the middle temporal cortex, also extended more superiorly on the left supramarginal gyrus, an area that was also related to performance in Imitation and that was reported to be damaged in patients with ideomotor apraxia (e.g. Heliman et al. 1982). Moreover a small cluster on the frontal cortex, although not significant, appeared to be linked to Imitation only.

For the WM analysis the contrast revealed an average contribution across the tasks predicting signal changes in tracts within the superior temporal gyrus in the left hemisphere. Similarly to the GM analysis, a major contribution of Action Recognition emerged. The analysis of the three covariates taken separately confirmed a relation between the integrity of the WM tract within the left superior

temporal gyrus and performance in Action Recognition, and revealed also a relation between this same WM tract and Gesture Production, even though it was less significant than for Action Recognition. Gesture Production appeared to relate also to the signal changes from a WM tract overlapping the posterior part of the corpus callosum in the right hemisphere and the same tract appeared also for Imitation. At the best of our knowledge there are no studies in literature discussing the role of white matter tracts in processing and producing action. The mapping of the different WM tracts is quite novel, and more studies are needed to understand the role of WM in praxis, as well as in the other cognitive functions. Moreover, other techniques would be more appropriate than VBM for investigating white matter damage (e.g. Diffusion Tensor Imaging (DTI)). Nonetheless the interesting point that emerges from our data is the overlap between areas involved in the three tasks has a similar pattern in WM and GM. Indeed, common WM tracts were revealed for Action Recognition and Gesture Production and for Gesture Production and Imitation. Also, Action Recognition and Imitation, in this case imitation of meaningless intransitive gestures, did not overlap, for either the GM or the WM analysis. Future studies could be performed relating DTI signal to the performance of patients in tasks tapping different abilities involved in praxis. In recent years, investigations on praxis have been boosted by the discovery of the MN in monkeys. Some studies have claimed proof of the existence of the MN in humans, though often from indirect evidences of common neurophysiological phenomena (e.g. EEG signal or activations in fMRI studies) relating both to imitation and observation or recognition of different kinds of gesture (see Rizzolati et al. 2001, 2004 for a review). However, to imitate a meaningful gesture is also likely to require recognition of the gesture itself and a common activation, for instance, can possibly be due to common memory processes. In the present study Action Recognition and Gesture Production showed at least some partially overlap both in GM and WM areas that could have a role in retrieving semantic representations of meaningful gestures. Also the overlapping on GM and WM between Gesture Production and Imitation seems to be better explained by the fact

that both require the actual production of a movement that is accomplished through a common motor-output process. Together, those results seem to fit more with a dual-route model of praxis (Rothi et al. 1991; Rumiati et al. 2002) than with the hypothesis of a unique population of neurons serving both gesture production and recognition or understanding.

Finally, consideration must be given as to why we choose a statistical threshold with a p-value ≤ 0.005 (instead of $p \leq 0.001$). As already mentioned, this was done because the analyses were run on CT scans that could have some noise. Also the tasks used to test the patients could have been easy for some of them, thus generating ceiling effects. Given these conditions, the use of a very strict threshold (as $p \leq 0.001$) may have caused a loss of information. However, there are two main reasons for which CT scans and BCoS tasks, instead of MRI and longer or more difficult tasks, were employed. First, this investigation used the scores at the praxis tasks taken from the Birmingham Cognitive Screening (BCoS; Humphreys et al. 2012), a new battery of tests aimed at stroke patients in the acute phase. Beside the wish to understand praxis functions and to have data to compare with previous findings, our further aim was to explore the brain areas correlating with performance at three of the praxis BCoS sub-tests in patients who just suffered from a stroke (i.e. when other compensation mechanisms, at behavioural or neural level, were not established). The BCoS was built to be an efficient screening tool for a population of patients who may not be able to endure long and hard testing sessions and for this reason only a few items were included in each task. It should be noted that the BCoS praxis tasks correlate highly with other praxis assessments more frequently used and also relate to measures of patients' general functioning in everyday life, both in a sub-acute phase and in a follow up done nine month later (see Bickerton et al. 2012). In addition, the present investigation was carried out on sub-acute patients (i.e. the population of patients for which the BCoS was created), and for this kind of patient only CT scans were available, as they were taken routinely when patients were admitted into the hospital, and collecting MRI scans for all our patients was not possible.

As already done for the behavioural data (Bickerton et al. 2012), it would be useful to follow up on the same patients as it could help to obtain a clearer picture of the neural substrates tapped by the BCoS praxis tasks, and to understand how these substrates reorganize over time or in relation to the rehabilitation programs (if any) underwent by the patients. .

6. Distinct and Common Neural Correlates of Apraxia for Transitive and Intransitive Gestures: An investigation using Voxel-Based Morphometry (VBM)

ABSTRACT

Previous neuropsychological investigations suggest that intransitive gestures are typically maintained better than transitive gestures after brain lesion. However it is not clear which are the common and distinct neural mechanisms that underlie the production of those two types of gestures. The present study tried to clarify this issue using a lesion-symptom approach (voxel-based morphometry, VBM) based on transitive and intransitive gestures performed by a large group of subacute stroke patients and clinical computed tomography scans. At a behavioural level, the analyses of the patients' scores revealed significantly higher performance for transitive than intransitive gesture production. This contrast with prior results may reflect a difference between gesture production to name (used here) and imitation (used previously). At a neural level, VBM analyses revealed that, on average, producing a gesture on verbal command involved the insula and inferior parietal areas on the left. The results indicating damage within the insula were driven by the production of transitive gestures, while both types of gesture seemed to involve, at least to some extent, the parietal cortex. Analyses run independently for transitive and intransitive gestures showed that, at gray matter level (GM), distinct regions of neural change were associated with each key symptom. Impairments in intransitive gestures were associated with damage to left frontal and parietal cortex, while lesions within deeper brain regions including the left insular cortex were related to transitive gestures to objects. Distinct regions for intransitive and transitive gestures were also revealed in the white matter (WM), in the corpus callosum and in the WM within the temporal

cortex respectively. Also, transitive actions had at least some relation with damage to the corpus callosum.

All together, the behavioural scores and their correlations with the neuroimaging data suggest that both common and discrete neural mechanisms are involved when transitive and intransitive gestures have to be performed.

INTRODUCTION

Within the neuropsychological syndrome of apraxia, people can suffer from impairments in the ability to execute actions that are not caused by a primary motor deficit (Liepmann, 1900-1905). Apraxia is not a unitary phenomenon and there are dissociations reported between patients in relation to the type of action to be executed and the body part involved in the task (see Rumiati et al. 2009 for a review). For instance, neuropsychological observations have been made of patients who are more impaired when imitating meaningful (familiar) compared to meaningless (unfamiliar) gestures (Goldenberg & Hagmann 1997; Peigneux et al. 2000; Tessari et al 2007), as well as patients showing the opposite pattern (Bartolo et al. 2001; Tessari et al. 2007), and also between impairments in imitation as opposed to actual use of the same objects (e.g., Chainay & Humphreys, 2002). These differences (e.g., between the production of familiar and unfamiliar gestures) also appear to reflect the involvement of different brain structures (e.g. Goldenberg & Hagmann 1997; Peigneux et al. 2000; Cubelli et al. 2000; Buxbaum et al. 2001; Tessari et al. 2007). Whether differences occur in the production of different kinds of familiar gestures, and whether different familiar gestures depend on contrasting neural structures, remains a moot point however. The most studied contrast is between transitive pantomimes of object use and intransitive (communicative) gestures (e.g., miming how to use a hammer vs. waving to greet someone).

Functional imaging studies in normal participants suggest considerable overlap in the brain activity used to make transitive and intransitive gestures, consistent with all familiar gestures relying on a

common neural network involving parietal and frontal cortices (e.g., Krolczak & Fray, 2009). On the other hand, neuropsychological data showing dissociations between the two classes of patient indicate that the actions may be functionally and neutrally separable. In the majority of cases patients have been described with deficits in which transitive actions are more impaired than intransitive actions (e.g., Buxbaum et al. 2007) and it has been proposed that transitive actions relying on a repository of action engrams in the left inferior parietal cortex (Buxbaum, 2001; Buxbaum et al. 2007; Liepmann, 1900-1905). In contrast, familiar intransitive actions may be supported by bilateral fronto-parietal regions that respond to fine-grained dynamic properties of action (Buxbaum et al. 2007; Haaland & Flaherty, 1984; Mozaz, 2002; Rapcsak et al. 1993). The preponderance of impairments in producing transitive over intransitive actions, however, may reflect the greater difficulty of transitive actions, as better performance in imitating intransitive over transitive actions has been reported (Carmo & Rumiati, 2009).

A stronger argument for a distinction between transitive and intransitive actions comes from recent work by Stamenova, Roy and Black (2010). These investigators assessed the production (to name) and imitation of transitive and intransitive gestures in patients with unilateral left or right hemisphere damage after stroke (Stamenova et al. 2010). Although no cases were found demonstrating a complete double dissociation between transitive and intransitive gestures (e.g., with both gesturing to name and imitation for one class of action affected while both tasks were preserved for the other class), there were instances of selective dissociation for one type of action (either gesturing to name or imitation) or for either transitive or intransitive actions. Selective deficits in transitive actions were associated with left hemisphere damage and problems with intransitive action with right hemisphere damage, consistent with prior arguments for the necessary involvement of the right hemisphere in intransitive action, perhaps because these actions depend more on fine-grained spatio-temporal modulation of action. On the other hand, the same investigators (Stamenova et al. 2009) have reported data on cortical-basal degeneration patients

showing selectively greater changes in the left or right hemisphere and failed to find evidence for intransitive actions ever being more impaired than transitive. Hence the case for a functional and neural distinction between these different classes of learned actions remains inconclusive.

In the present paper, a different approach is taken in which a non-selected sample of stroke patients was examined for the presence of deficits in transitive or intransitive action production to name, and the underlying lesions were examined using voxel-based morphometry. Voxel-based morphometry (VBM) is an unbiased means of assessing the correlation between neural change after brain lesion and behavioural symptoms of interest. The procedure requires data from patients who do and also patients who do not show the cardinal symptoms being assessed so that the latter can serve as ‘lesion controls’ – enabling the analysis to extract out damaged areas in the critical patients which might reflect anatomical constraints on the brain lesion (e.g., after occlusion of the middle cerebral artery) rather than the necessary role of the brain structure in behaviour (see Rorden & Karnath, 2004). The analysis used VBM based on continuous measures of performance in patients within a set time period post lesion to provide a fine-grained measure of brain-behaviour relations (see Chechlacz et al. 2010, for a similar approach). Given prior reports on the relations between deficits in transitive relative to intransitive actions then it can be expected that selective impairments in transitive actions will be associated with unilateral damage in the left inferior parietal cortex (Buxbaum et al. 2007). On the other hand, selective deficits in familiar intransitive actions may be result from more bilateral (and particularly more right hemisphere damage) in patients. Lesions linked to both classes of action may reflect common processes in programming for motor output, for instance involving pre-motor cortex and sub-cortical systems (e.g., Stamenova et al. 2010, 2011).

METHODS

The same patients and the same Gesture Production task taken from the Birmingham Cognitive Screen (BCoS) (Humphreys et al. 2012) were used as in chapter 5, with the difference being that here we split the Gesture Production task into its two components: i.e. transitive (asking to produce pantomimes actions to objects on verbal command) and intransitive (asking to produce communicational actions on verbal command) gestures. For a description of the patient sample, the task, the neuroimaging assessment and the preprocessing of the CT scans see the method section (pgs. 21-38).

BEHAVIOURAL RESULTS- transitive versus intransitive gestures

Figure 1. Mean scores at GP transitive and GP intransitive. Patient scores are in Appendix 1.

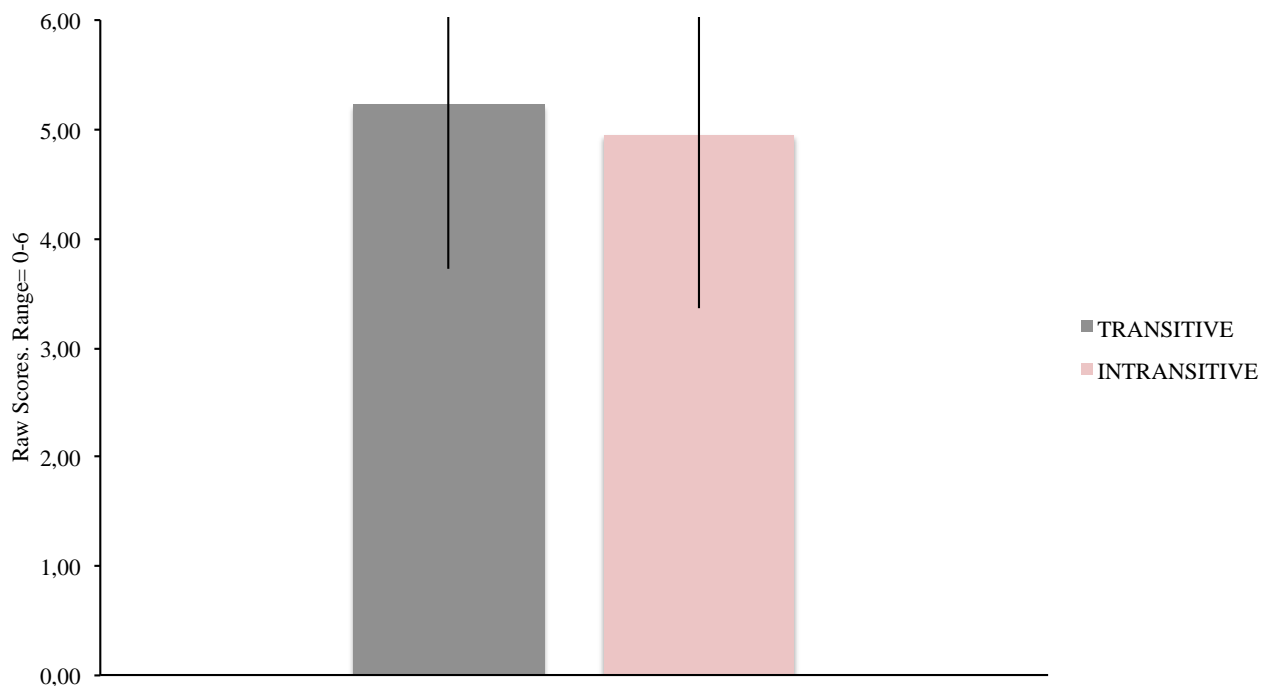


Figure1. Transitive gestures were executed significantly better than the intransitive.

At first a paired samples t-test compared the patients' behavioural scores (Figure 1). The analysis revealed a statistically significant difference in the production of the two type of gesture ($t(232) > 3.29$, $p < .000$, 2-tailed), with GP transitive (mean= 5.22; SD= 1.5) being performed better than GP intransitive (mean= 4.94; SD= 1.58).

Although the two types of actions differed in difficulty, they also correlated with each other (Pearson correlation = .93, $p < .0000$, 2-tailed).

VOXEL-BASED MORPHOMETRY

As in the study presented in chapter 5, the CT scans available for the 233 acute stroke patients were used for the analyses. The aim of the present study was to explore the relations between the changes in the signal intensity from either gray matter (GM) or white matter (WM) across the whole brain and performance at production of meaningful intransitive and transitive gestures on verbal command.

ANALYSES

The raw scores for producing intransitive and transitive gestures were included together in two models as the two covariates of interest, along with GM and WM respectively. In addition, four models were including one covariate of interest at a time (i.e. i) scores for the production of intransitive gestures and GM; ii) scores for the production of transitive gestures and GM; iii) scores for the production of intransitive gestures and WM; iv) scores for the production of transitive gestures and WM) were estimated in order to analyse the discrete effect of each covariate on GM and WM. Age, gender, years of education and hand (used for imitation/gestures production, dominant or non dominant) were included as covariates of non-interest in all the models¹⁴. T-contrasts were run on the models estimated. As in the study presented in chapter 5, CT scans of acute patients were used, along with the same BCoS Gesture Production task that was designed for screening cognitive functions in patients who just survived a stroke. As already stated in chapter 5, CT scans can be noisy and the performance of some patients was at ceiling. Accordingly we used a mixed peak and cluster threshold with at least 50 voxels showing a $Z \geq 2.6$ (i.e. $P \leq 0.005$,

¹⁴ Handedness was not included as only right-handed patients were included in the sample (see also above).

uncorrected), instead of a stricter $p \leq 0.001$. The same threshold was used for all the contrasts run on GM and WM.

VBM RESULTS

GRAY MATTER

The MNI coordinates and the statistical values of the results obtained for all the contrast run on GM are reported in Table 1 (see below).

GM- transitive and intransitive Gesture Production

The t-contrast looking at the average effect of production of intransitive and transitive gestures revealed one significant cluster of voxel in the insula (Figure 2a) ($p \leq 0.05$, FWE-corr), also extending to the supramarginal gyrus within the left parietal cortex (Figure 2b).

Figure 2a GM- transitive and intransitive- left insula

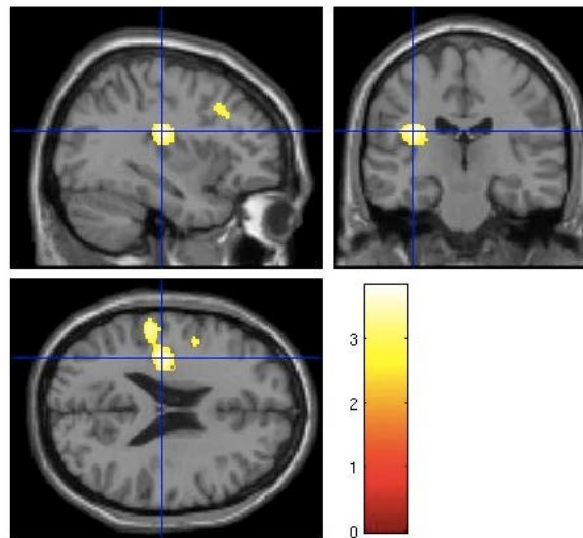


Figure 2b GM- transitive and intransitive- left parietal cortex

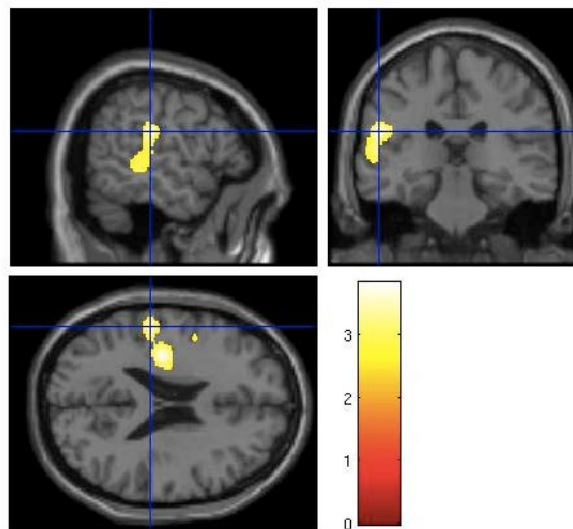


Figure 2a shows the significant cluster in the left insula. **Figure 2b** The cluster extended into the supramarginal gyrus. A plot of the results showed that, in correspondence of the MNI coordinates in the left insula the signal intensity was almost completely predicted by performance on transitive gestures (Figure 3a), while the effect on the left supramarginal gyrus was explained more by intransitive gesture production, even though also scores with the transitive gestures showed at least some relation with the integrity of this area (Figure 3b).

Figure 3a GM- transitive and intransitive- Plot of results on the left insula

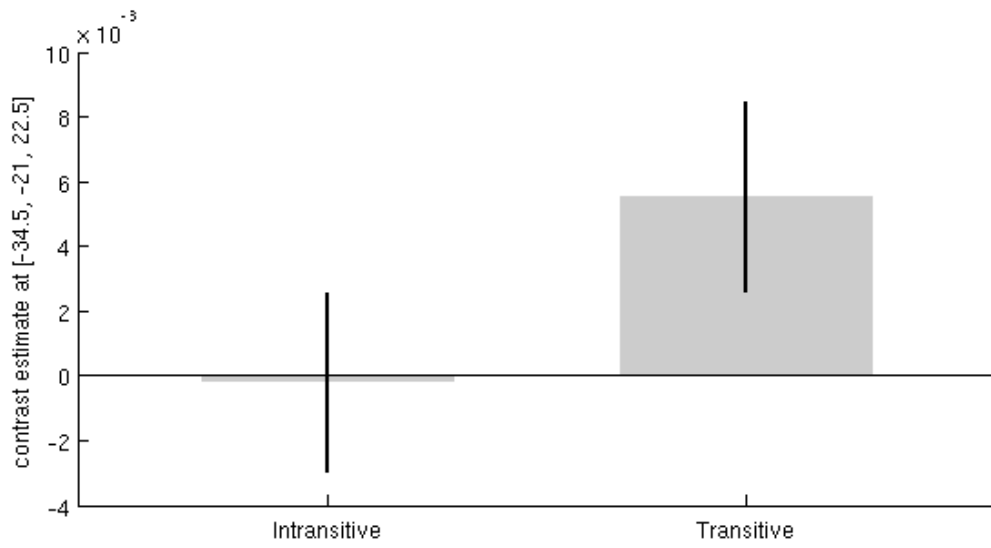


Figure 3b GM- transitive and intransitive- Plot of results on the left supramarginal gyrus

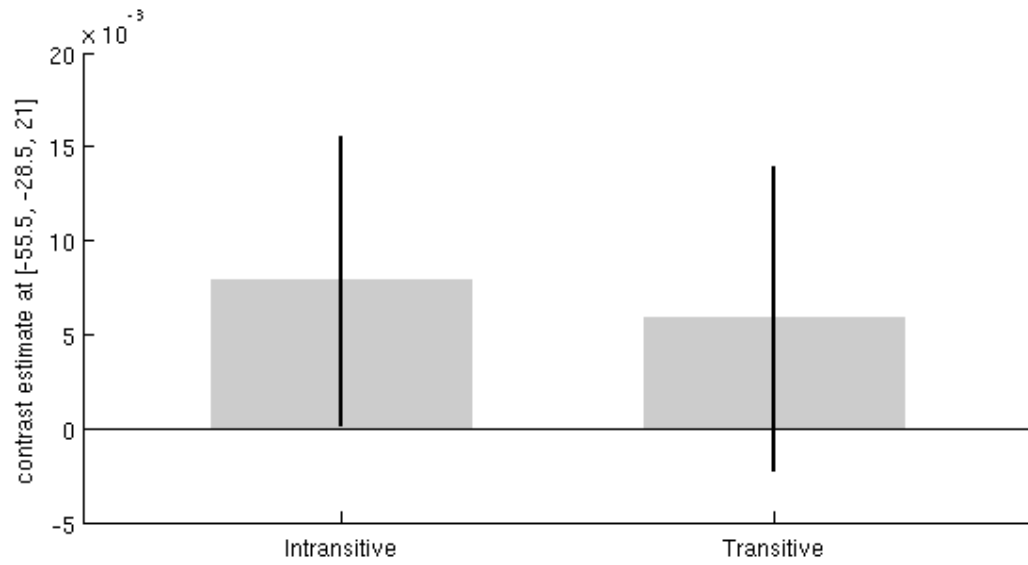


Figure 3a and **Figure 3b** illustrate the contribution of each covariate to determine the effect in the insula (**Figure 3a**) and on the supramarginal gyrus (**Figure 3b**).

Table 1. GM- MNI coordinates and stats. All $p \leq 0.005$, uncorrected

GM												
<i>GM areas for Gesture Production- intransitive and transitive</i>												
cluster	cluster	cluster	cluster	peak	peak	peak	peak	peak	x	y	z	
p(FWE-cor)	p(FDR-cor)	equivk	p(unc)	p(FWE-cor)	p(FDR-cor)	T	equivZ	p(unc)				
0.038	0.02	2060	0.002	0.555	0.732	3.82	3.75	0.000	-34	-21	22	Insula_L
				0.828	0.732	3.55	3.50	0.000	-56	-28	21	Supramarginal_L
				0.852	0.732	3.52	3.47	0.000	-28	-16	25	Insula_L
<i>GM areas for Gesture Production-transitive</i>												
cluster	cluster	cluster	cluster	peak	peak	peak	peak	peak	x	y	z	
p(FWE-cor)	p(FDR-cor)	equivk	p(unc)	p(FWE-cor)	p(FDR-cor)	T	equivZ	p(unc)				
0.004	0.001	3344	0.000	0.202	0.347	4.21	4.13	0.000	-32	-21	24	Insula_L
				0.777	0.382	3.61	3.56	0.000	-26	-21	16	Thalamus_L
				0.782	0.382	3.60	3.55	0.000	-66	-45	-2	Temporal_Mid_L
<i>GM areas for Gesture Production-intransitive</i>												
cluster	cluster	cluster	cluster	peak	peak	peak	peak	peak	x	y	z	
p(FWE-cor)	p(FDR-cor)	equivk	p(unc)	p(FWE-cor)	p(FDR-cor)	T	equivZ	p(unc)				
0.720	0.594	560	0.080	0.936	0.873	3.39	3.34	0.000	-46	33	-2	Frontal_Inf_Tri_L
0.794	0.594	490	0.100	0.942	0.873	3.38	3.33	0.000	-56	-28	21	Supramarginal_L

Table 1. VBM results on GM. The significant clusters found ($p = 0.005$ uncorrected; $p \leq 0.05$ FWE-corr) for transitive and intransitive gestures considered together, and for transitive gestures are in bold. The two bigger clusters relating to intransitive gestures alone are reported as well, even though they were not significant when corrected.

GM- transitive Gesture Production

The t-contrast confirmed a reliable relation between production of transitive gestures and a decrease in the signal intensity on the insula ($p \leq 0.05$, FWE-corr), also extending to the thalamus and the middle temporal cortex in the left hemisphere (Figure 4).

Figure 4 GM- transitive - left insula

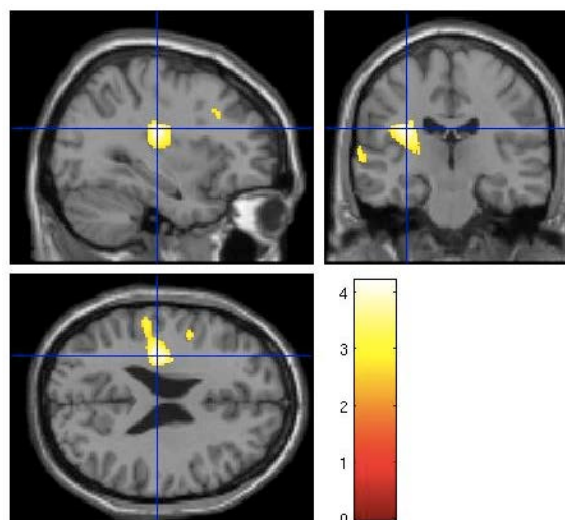


Figure 4 shows the reliable effect of transitive gestures peaking in the insula.

GM- intransitive Gesture Production

The t-contrast showed two clusters in the left inferior frontal cortex and around the supramarginal gyrus, both in the left hemisphere (Figure 5a and 5b). Even though these two clusters were not significant when corrected for multiple comparisons ($p \geq 0.1$, FWE-corr), we report them because they replicate a result we found in the previous chapter (see chapter 5) for imitation of meaningless intransitive gestures (also taken from BCoS). Also the fronto-parietal path was indicated as serving the mirror-neuron system in previous investigations (see Rizzolati et al. 2004). However, conclusions should be cautious.

Figure 5a GM- intransitive – left frontal cortex

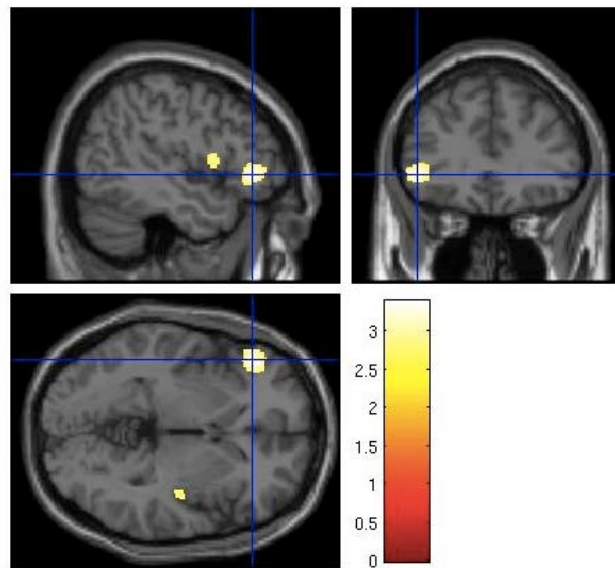


Figure 5b GM- intransitive – left supramarginal gyrus

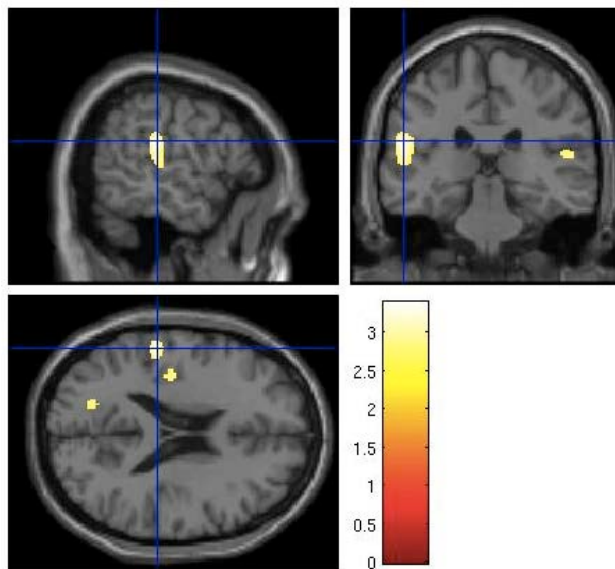


Figure 5a and **Figure 5b** show the effects of GP intransitive in the inferior frontal cortex (Figure 5a) and in the left supramarginal gyrus (Figure 5b). Both clusters were not significant ($p \geq 0.1$) after being corrected for multiple comparisons.

WHITE MATTER

The MNI coordinates and the statistical values concerning the contrasts run on WM are reported in Table 2 (see below).

WM- transitive and intransitive Gesture Production

The t-contrast showed an average significant effect of production of transitive and intransitive gestures on the corpus callosum on the right hemisphere ($p \leq 0.05$, FWE-corr) (Figure 6a). Also, a cluster was revealed on the WM tract within the left temporal pole ($p = 0.058$, FWE-corr) (Figure 6b).

Figure 6a WM- transitive and intransitive- corpus callosum

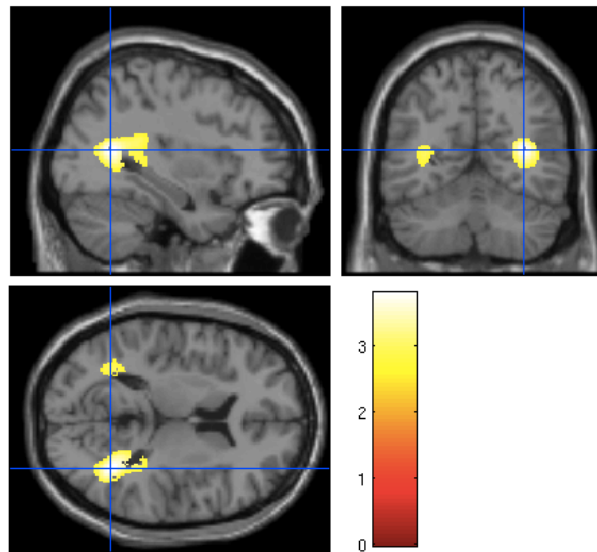


Figure 6b WM- transitive and intransitive- WM tract within the left temporal pole

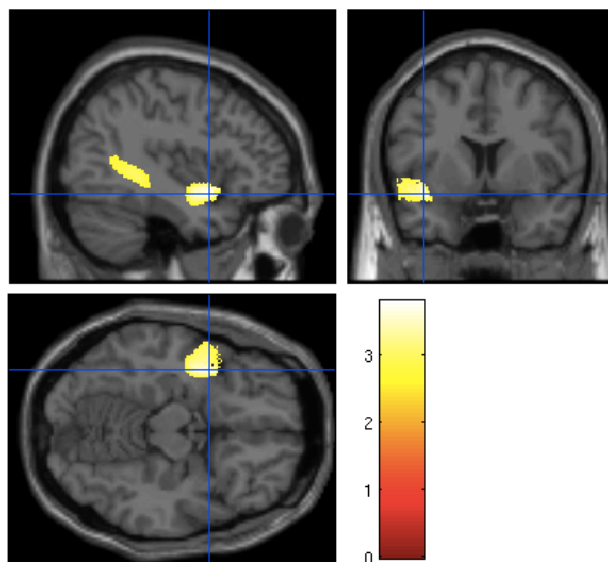


Figure 6a shows the cluster in the corpus callosum that was revealed by the contrast on the model including both transitive and intransitive gestures. The same contrast revealed a cluster in the WM tract within the left temporal pole (**Figure 6b**).

When the results were plotted it appeared that the effect on the right corpus callosum was mainly driven by the production of intransitive gestures (**Figure 7a**), while the effect on the WM within the left temporal pole was explained by production of intransitive gestures (**Figure 7b**). The results in

the corpus callosum also related to transitive gestures production, even though at a lower extent (Figure 7a).

Figure 7a WM- transitive and intransitive- plot of the results on the corpus callosum

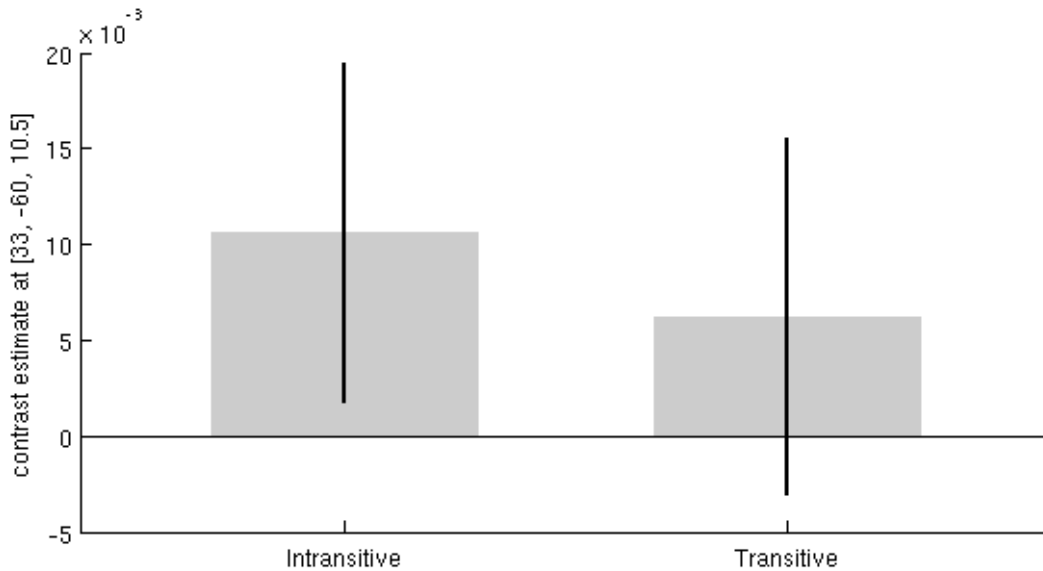


Figure 7b WM- transitive and intransitive- plot of the results on the WM within the left temporal pole

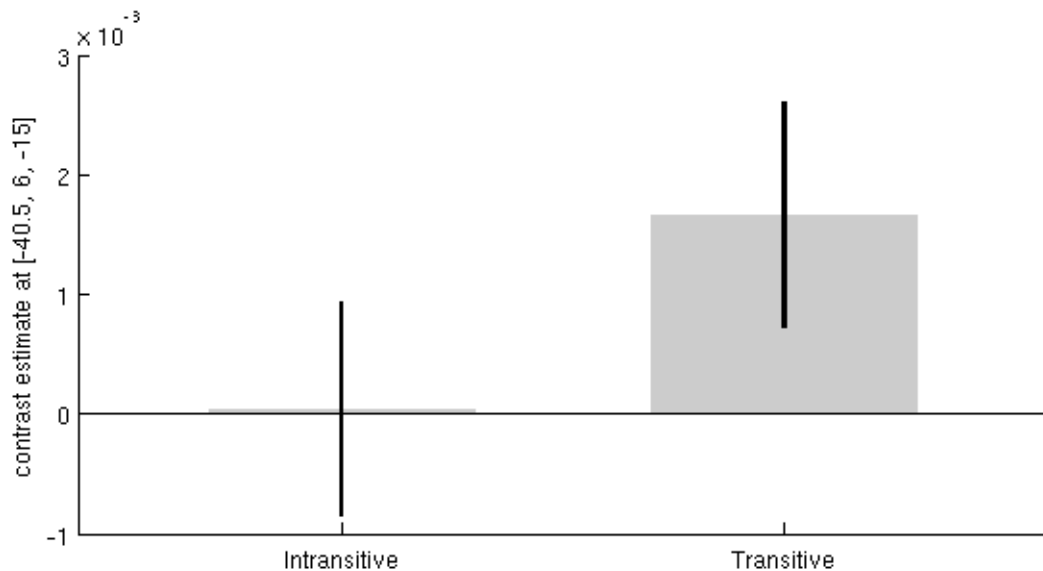


Figure 7a. The plot reports the effect of each covariate of interest in predicting the signal intensity in the corpus callosum. Production of intransitive gestures appears to have the stronger relation with neural changes on this region, however also transitive gestures seem to have at least some correlation. **Figure 7b** shows that only production of transitive gestures relates to signal changes on the WM tract within the left temporal pole.

Table 2. WM- MNI coordinates and stats. All $p \leq 0.005$, uncorrected

WM												
<i>WM areas for Gesture Production- intransitive and transitive</i>												
cluster	cluster	cluster	cluster	peak	peak	peak	peak	peak	x	y	z	
p(FWE-corr)	p(FDR-corr)	equivk	p(unc)	p(FWE-corr)	p(FDR-corr)	T	equivZ	p(unc)				
0.023	0.025	2770	0.002	0.522	0.275	3.78	3.72	0.000	33	-60	10	
				0.877	0.275	3.42	3.37	0.000	27	-40	16	Right_Callosal
				1.000	0.290	2.81	2.78	0.003	33	-39	3	_Body
<i>0.058</i>	<i>0.020</i>	<i>2177</i>	<i>0.005</i>	<i>0.512</i>	<i>0.275</i>	<i>3.79</i>	<i>3.73</i>	<i>0.000</i>	<i>-40</i>	<i>6</i>	<i>-15</i>	
				0.928	0.275	3.33	3.29	0.001	-62	-1	-3	<i>Left_Temporal_</i>
				0.931	0.275	3.32	3.28	0.001	-52	3	-14	<i>Pole</i>
<i>WM areas for Gesture Production-transitive</i>												
cluster	cluster	cluster	cluster	peak	peak	peak	peak	peak	x	y	z	
p(FWE-corr)	p(FDR-corr)	equivk	p(unc)	p(FWE-corr)	p(FDR-corr)	T	equivZ	p(unc)				
0.015	0.019	3050	0.001	0.293	0.263	4.02	3.95	0.000	-40	6	-15	
				0.490	0.263	3.81	3.75	0.000	-62	-1	-3	Left_Temporal
				0.594	0.263	3.71	3.66	0.000	-52	3	-14	_Pole
0.615	0.321	733	0.073	0.915	0.326	3.35	3.31	0.000	34	-63	10	Right_Callosal_Body
<i>WM areas for Gesture Production-intransitive</i>												
cluster	cluster	cluster	cluster	peak	peak	peak	peak	peak	x	y	z	
p(FWE-corr)	p(FDR-corr)	equivk	p(unc)	p(FWE-corr)	p(FDR-corr)	T	equivZ	p(unc)				
0.017	0.005	2983	0.001	0.277	0.167	4.04	3.97	0.000	32	-55	13	Right_Callosal
				0.998	0.763	2.95	2.92	0.002	33	-36	1	_Body

Table 2. VBM results on WM. The significant clusters ($p = 0.005$ uncorrected; $p \leq 0.05$ FWE-corr) are in bold. The cluster on the WM within the left temporal pole revealed by the contrast on the model including both the covariates of interest, having a $p = 0.058$, was close to full significance level, and it is reported in italic. The cluster on the corpus callosum for transitive gestures production is not significant but it was reported here as transitive actions appeared to relate to this area, at least to some extent, when considered in the same model as intransitive actions.

WM- transitive Gesture Production

Producing transitive gestures significantly related to a decreased signal from the WM within the temporal pole on the left hemisphere ($p \leq 0.05$, FWE-corr) (Figure 8). As reported in Table 2, a small cluster appeared also in correspondence of the right corpus callosum, although not significant ($p \geq 0.1$, FWE-corr).

Figure 8 WM- transitive- WM tract within the left temporal pole

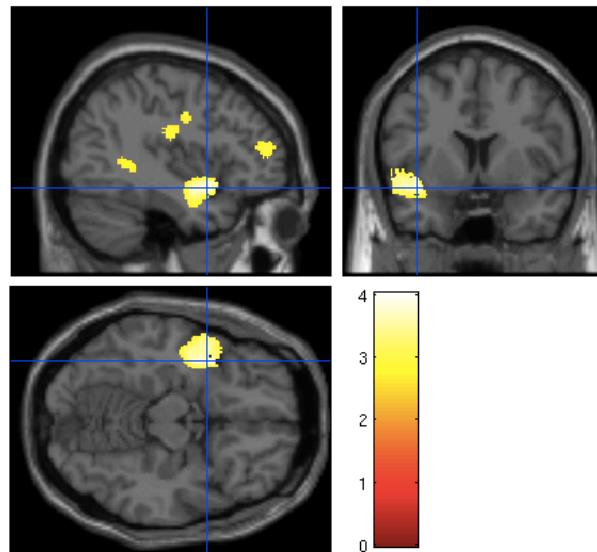


Figure 8. Producing transitive gestures on verbal command related significantly to the WM tract within the left middle temporal lobe. This is coherent with the results obtained previously when the results of the contrast we run on the model including both transitive and intransitive gestures were plotted (see Figure 7b).

WM- intransitive Gesture Production

A reliable association was present between intransitive gestures and lesions to the corpus callosum in the right hemisphere, revealed by the t-contrast run on the model including the scores for GP intransitive only (Figure 9).

Figure 9. WM- intransitive- corpus callosum

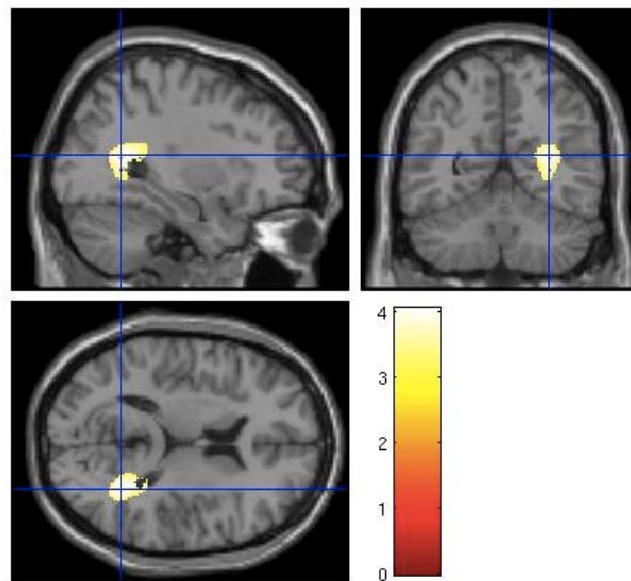


Figure 9. Production of intransitive gestures showed a reliable relation to signal changes in the right corpus callosum. This is coherent with the results of the analysis on the model including both intransitive and transitive gestures. The same WM tract was also found in the previous chapter for Imitation, where intransitive meaningless gestures had to be imitated.

DISCUSSION

Behavioural data

Intransitive and transitive gestures were performed differently, with transitive gestures being reproduced more accurately than intransitive. This result is relatively uncommon, at least at a group level, though some dissociations in this direction have been reported in the literature (Stamenova, Roy & Black 2010). This result is suggestive of the two types of actions being performed through at least partially separate mechanisms. However, there could also be effects here based on the relative difficulty of the relatively small numbers of gestures that were assessed. Additionally it should be noted that, in contrast to previous investigations that used imitation tasks (i.e. actions presented by an actor had to be copied), in the present study patients had to reproduce the gestures on verbal command. This opens the possibility that the action schema for intransitive gestures are

not generally more robust than those for transitive gestures but that the representations of the two types of gestures are more easy to be accessed by different input systems, i.e. visual or verbal respectively.

VBM

The contrasts examined areas associated with greater deficits on transitive than intransitive actions, and vice versa. The analyses revealed that contrasting lesion patterns were associated with the different problems, along with some overlapping brain regions. Most notably, there was evidence for subcortical regions involving the left inferior insula being associated with deficits in producing transitive actions to a name. In contrast, deficits in producing intransitive actions were linked to frontal and parietal lesions, although this result was not strong. Differences emerged also in terms of WM damage, with transitive gestures being related to WM lesions within the left temporal cortex, while the corpus callosum on the right hemisphere appeared to have a role in processing intransitive gestures. Transitive gestures also appeared to have at least some correlation with the signal intensity on the right corpus callosum.

Beside those differences, overlapping areas seemed to relate to both types of gesture in the left supramarginal gyrus (most strongly related to intransitive gestures).

The evidence for distinct neural sites associated with impairments in transitive and intransitive actions is interesting and supports the case for these two classes of action being supported by different functional and neural processes.

In terms of GM damage, the results indicated that transitive actions were selectively affected by lesions to sub-cortical structures (basal ganglia and thalamus). This result is compatible with findings on Parkinson's patients who have been found to have poorer performance than controls when reproducing MF pantomimes but not intransitive gestures (Leiguarda et al. 1997, 2001). The role of the basal ganglia in action execution will be discussed further in the next chapter. Beside subcortical areas, the cluster found to relate significantly to transitive gesture production also

extended to the left middle temporal cortex, an area that was reliably associated also to the BCoS Actions Recognition task analysed in the previous chapter (see chapter 5). This same area has also been found to be active in a PET study when participants observed meaningful but not meaningless actions (Decety et al. 1997), and it has been reported among the lesions of patients with a deficit in action production (Price et al. 2010). Moreover, two of the patients reported by Price et al. (2010) were impaired in gesturing object use, on presentation of the pictures of the target objects, but still retained the ability to recognize the objects (Price et al. 2010). As already suggested in the previous chapter, those data indicate a role of the left middle temporal cortex in retrieving information about actions that are stored in long-term memory. Also, as here, the same area did not appear for the intransitive gestures. This suggests that the left middle temporal cortex may be more crucial for actions involving tools.

For the production of intransitive gestures the results in the GM analysis indicated a role of the inferior frontal cortex and the supramarginal gyrus in the left hemisphere. These results were not strong, but they do replicate the findings in the previous chapter for the BCoS Imitation task, where intransitive meaningless actions visually presented by the examiner had to be imitated. Also, in the present chapter, the cluster centred on the left supramarginal gyrus appeared to relate, at least to some extent, to both transitive and intransitive gestures, even though the relation was stronger for the intransitive gestures. The cluster on the frontal area instead was not reported for transitive actions. However it should be recognized that neither the frontal nor the parietal areas related to Action Recognition in Chapter 5.

The involvement of the left supramarginal gyrus for transitive, intransitive meaningful and intransitive meaningless gesture production and imitation supports the role of this area in gesture execution, regardless the meaning or the modality of presentation of the action (i.e. demonstration by an actor or verbal command), and these data fit with reports that associate lesions in this region with ideomotor apraxia (e.g. Heliman et al- 1982). The left inferior frontal regions, that were shared

by the intransitive meaningful actions used here and the intransitive meaningless actions used in chapter 5, may have a role in coding the motor properties of intransitive gestures only. For instance intransitive gestures may be linked to the need to compute fine-grained spatio-temporal action codes to generate intransitive actions (Buxbaum et al. 2007), regardless the meaning and the way they are presented. The schema for transitive gestures instead may be triggered automatically by the information about the object itself, even in pantomimes where an actual object is not present (e.g. to put the hand in the grasping posture may automatically trigger the whole action sequence for the target object). However, as stated above, the results obtained in the present study for intransitive gestures on GM were not robust enough to draw strong conclusions, and future studies, using for instance a longer list of both MF and ML stimuli having different levels of difficulty, are needed to clarify this issue.

Results were obtained also when the analyses were run on models based on WM damage. To date just the main WM tracts have been mapped, and a only few studies have tried to explore WM involvement in gesture execution, and cognitive functions in general. However a few points about the present data can be discussed. For instance, transitive gestures appear to relate significantly to WM tracts within the left temporal pole, while the intransitive related significantly to the signal from the corpus callosum. The cluster in the corpus callosum was also related to transitive gestures, though the relation was lower than it was for intransitive gestures. Moreover the signal in the corpus callosum correlated with the scores at the BCoS Imitation task in the previous chapter (chapter 5). More studies, for instance using MRI scans on GM together with Diffusion Tensor Imaging (DTI) sequences, should be run to look at the areas that are connected by this portion of the corpus callosum and the possible role of this circuit in action execution.

In contrast with a previous fMRI study on healthy participants (e.g. Kroliczak & Fray, 2009) the current data point in the direction of differential processes in the production of intransitive and intransitive gestures. This remains to be clarified, nonetheless it should be said that in prior fMRI

studies only relatively limited distal movements of the fingers have been used (due to the constraints on movement in the scanner). It may be possible these restrictions mean that the stimuli were not clearly tapping more “typical” transitive and intransitive actions (e.g. hammering (transitive), waving hello (intransitive)). In contrast, the present study used naturalistic actions and tested for the necessary role of the brain regions affected in the patients.

Finally, as in the previous chapter, the data were analysed using a statistical threshold with a $p \leq 0.005$, instead of $p \leq 0.001$. This was done in order to reduce the risk of losing information from the data. The reasons guiding this choice have been elaborated in chapter 5.

In chapter 5 we suggested a follow up on the same patients in order to understand how the pattern of association between behaviour and brain lesions evolved for the effect of time and rehabilitation (see discussion in chapter 5). The follow up should consider the gesture production task as a whole, as well as the split into transitive and intransitive gesture production sub-tasks.

7. The Role of the Basal Ganglia in Action Imitation:

Neuropsychological Evidence from Parkinson's disease Patients

ABSTRACT

Though previous studies have suggested that the basal ganglia are necessarily involved in gesture imitation, their precise role is unclear. Leiguarda et al. (1997, 2001) report that Parkinson's Disease patients (PD) have poor execution of observed meaningful (MF) transitive (tool-related) actions, despite normal performance with intransitive (non tool-related) MF and meaningless (ML) gestures. In contrast, Tessari et al. (2007) described two right –brain damaged patients with ideomotor apraxia, whose lesions involved the basal ganglia, who were more impaired in imitating ML as compared to meaningful MF transitive pantomimes. This inconsistency was assessed here by testing a group of PD patients with MF transitive and intransitive pantomimes and matched ML movements. The data indicate a double dissociation, with PD reporting higher scores when imitating MF transitive actions than ML matched gestures, while performing better with the ML than the MF intransitive actions. Performance on ML intransitive gestures also related to the performance of the patients on the Corsi block test of visuo-spatial memory. The results are discussed in terms of the factors that load on visual memory for gesture reproduction, as well as the possible role of the basal ganglia in communicative gestures (for MF intransitive actions).

INTRODUCTION

Previous studies have suggested that the basal ganglia are necessarily involved when participants perform gestures on verbal command or on imitation (e.g. Pramstaller et al. 1996; Roy et al. 2000; Leiguarda et al.; 1997, Leiguarda et al. 2001; Tessari, Canessa, Ukmar, Rumiati, 2007). For instance, Tessari et al. (2007) described two right –brain damaged patients whose lesions involved the basal ganglia. These individuals were more impaired in imitating meaningless (ML) as

compared to meaningful (MF) transitive (or tool-related) pantomimes and whose lesions overlapped on basal ganglia. In contrast to this, though, Leiguarda et al. (1997, 2001) report that Parkinson's disease (PD) patients were impaired on the execution of transitive MF pantomimes both on imitation and on verbal command, while performance with both symbolic (MF) and non-symbolic (ML) intransitive gestures were normal. Unlike Tessari et al. (2007), performance on ML transitive gestures was not tested.

Rumiati et al. (2002) proposed a 'dual route' model of action imitation in which learned actions can be imitated via either of two 'routes' – a lexical route based on the recognition of a learned action and the retrieval of a learned action programme, and a non-lexical route based on direct mapping between perceived motor actions and output motor commands, that does not depend on having learned representations for the actions (see Figure 1 in the general introduction). According to Tessari et al. (2007), the basal ganglia modulate the direct (non-lexical) route to action. In contrast they suggest that the lexical route operates through posterior parietal and pre-frontal brain regions, particularly in the left hemisphere (see Rothi et al. 1991, 1997; Peigneux et al. 2001, for a similar account). These arguments are supported by data from functional brain imaging (Peigneux et al. 2004; Kareken et al. 1998) and from lesion overlap analyses of patients with problems in imitating meaningful or meaning less gestures (Tessari et al. 2007). On the other hand, the data from Leiguarda et al. (1997, 2001) suggest that the basal ganglia are necessary for the imitation of transitive actions, while intransitive actions may operate through cortical regions – with this holding even for meaningless actions based on intransitive gestures.

To attempt to reconcile these apparently conflicting results, we examined a group of PD patients on tasks requiring the imitation of both MF and ML transitive and intransitive gestures. Is the involvement of the basal ganglia most apparent in the performance of ML relative to MF gestures, or are they most required to carry out transitive MF gestures? The performance of these different gestures was tested here using sets of matched stimuli, and the relations between imitation scores,

object and action recognition, neuropsychological assessment and neurological exam were considered.

METHODS

In this chapter we tested a sample of PD patients in imitation of MF and ML transitive and intransitive gestures. The PD patients' scores were also related to an index of their peripheral neurological symptoms and to the neuropsychological evaluation.

The PD patients and controls sample and the tasks are described in the method chapter (see pgs. 21-38).

The tests employed in the neuropsychological evaluation are described in Appendix 3.

RESULTS

Figure 1 illustrates the proportion accuracy scores for imitating transitive and intransitive, meaningful and meaningless gestures, for the PD patients and the controls. For the gesture and object recognition tasks the PD patients scored at ceiling. This indicates that any problems in imitating MF gestures were not due to poor perceptual processing or access to stored visual-perceptual knowledge. Since separate control participants were used for the transitive and intransitive gestures the data were analysed first for transitive and intransitive gestures separately, comparing the PD patients and each set of controls; subsequently the data were compared between transitive and intransitive gestures for the PD patients and the controls separately.

Imitating transitive (object-related) gestures

Accuracy scores¹⁵

¹⁵ The Cohen's *k* agreement coefficient was calculated on the scores provided by the two independent raters. The coefficient was computed for MF and ML actions taken separately, and for the total action scores. The analysis was

A repeated measures ANOVA was performed on the accuracy scores, using Action Meaning (MF Versus ML) as a within-subject factor and Group (PD Versus Controls) as a between-subject factor. The analysis revealed a significant within-subject effect of Action Meaning ($F(1, 38) = 9.86$; $p = 0.003$), with MF actions (mean = 13.15, SD = 2.03) performed better than ML actions (mean = 12.10, SD = 3.35). There was also a significant effect of Group ($F(1, 38) = 13.2$; $p = 0.001$), with Controls generating higher total scores (mean = 27.67; SD = 4.40) than PD patients (mean = 22.74; SD = 4.16) (Figure 1). There was a significant interaction between Action Meaning and Group ($F(1, 38) = 7.51$; $p = 0.009$); while controls performed similarly with the two kinds of actions ($t < 1.0$), the PD had poorer performance with ML compared with MF actions, ($t(18) = 3.65$; $p = 0.002$, 2-tailed) (mean MF gestures = 12.42; SD = 1.84; mean ML gestures = 10.32; SD = 2.91).

Figure 1. Parkinson's patients and controls' proportional accuracy

performed separately for PD and controls. As the coefficient was ≥ 0.80 in all the cases considered, the scores of only one rater (the same for PD and controls) were used.

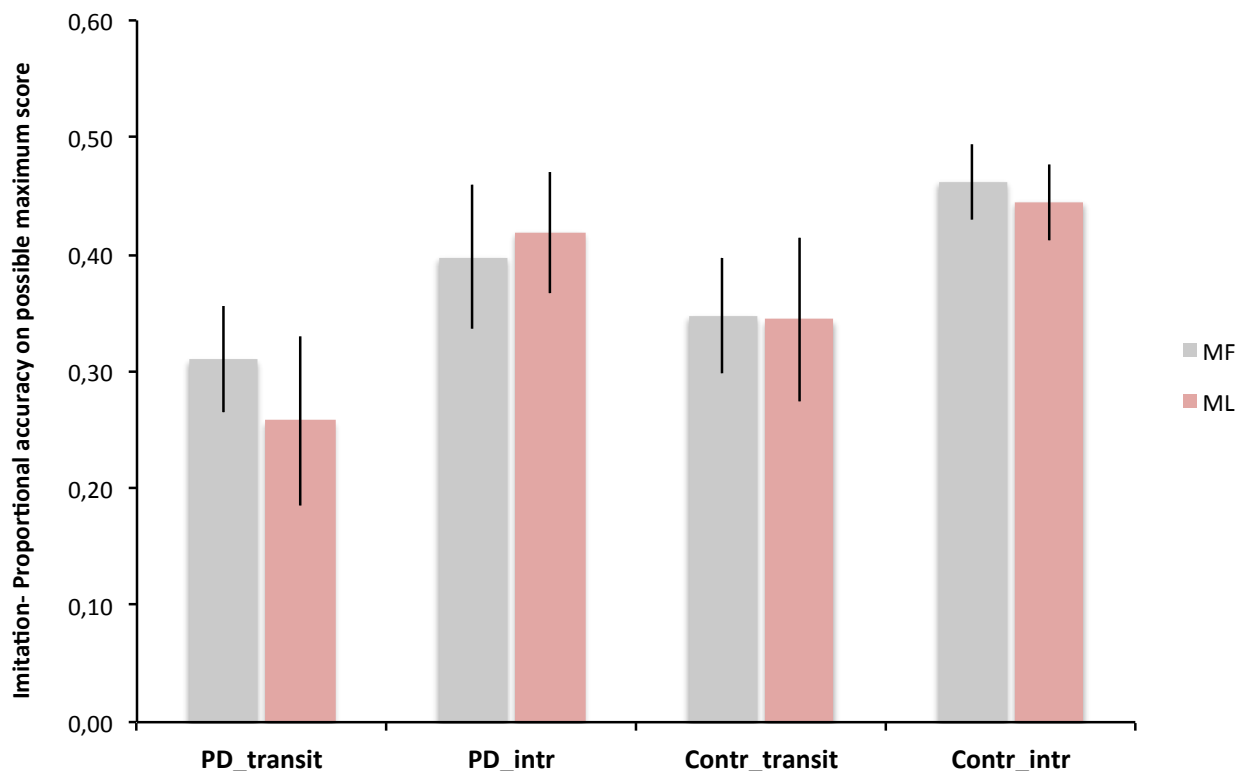


Figure 1 shows the mean proportional accuracy at the MF and ML, transitive and intransitive, actions imitation tasks for PD patients (i.e. PD_transit and PD_intr; left half of the graph) and controls (i.e. Contr_transit and Contr_intr; right half of the graph).

Relative to the controls, the PD patients were worse at both MF gestures ($t(38) = -2.45$; $p = 0.019$, 2-tailed; mean PD = 12.42; SD = 1.84; mean control = 13.90; SD = 1.97). The PD patients were also reliably worse at ML gestures ($t(38) = -3.82$; $p < 0.0001$, 2-tailed; mean PD = 10.32; SD = 2.91; mean controls = 13.76; SD = 2.79).

Imitation of transitive gestures and UPDRS III scores

The performance of the patients when imitating transitive gestures was correlated to the scores the patients obtained on scale III of the United Parkinson Disease Rating Scale that assesses neurological and motor symptoms (i.e. tremor or rigidity). There were no reliable correlations for either MF gestures (Pearson Correlation = -0.24; $p = 0.33$, 2-tailed) or ML gestures (Pearson Correlation = -0.165; $p = 0.5$, 2-tailed).

Imitating intransitive gestures

Eleven out of nineteen patients had a total score under the cut-off for the normal Italian population. Of these, four showed impairment only when imitating the symbolic gestures while seven reported scores defective scores for both symbolic and non-symbolic gestures. None showed impairment for the non-symbolic movements alone. PD patients' scores are reported in Table 1.

Table 1. PD patients- imitation of intransitive gestures

PD	MF	ML	TOT
1	34	32	66
2	18	24	42
3	33	36	69
4	25	29	54
5	26	29	55
6	32	31	63
7	28	24	52
8	32	36	68
9	32	32	64
10	26	30	56
11	26	28	54
12	30	32	62
13	31	35	66
14	35	34	69
15	30	26	56
16	27	28	55
17	25	28	53
18	22	26	48
19	32	33	65

cut off for the normal Italian population:

età`	cut-off MF	cut-off ML	cut-off Tot
30-50	≤32	≤31	≤63
51-70	≤31	≤28	≤59
≥71(Education≤ 6)	≤25	≤24	≤50
≥71(education≥7)	≤30	≤24	≤58

Table 1 reports the scores obtained by the PD patients when imitating intransitive actions. The performance of the patients was compared to the cut offs calculated for the normal Italian population. Scores equal to or less than the cut off were considered defective and are reported in bold.

An ANOVA was run on PD and control scores with Action Meaning as a within-subject factor and Group as the between-subject factor. There was a significant between-subject effect of Group ($F(1, 48) = 15.92; p < 0.0001$), with PD (mean= 58.79; SD= 7.67) obtaining lower total scores than controls (mean= 65.32; SD= 3.90), but there was no overall effect of Action Meaning ($F(1, 48) = 0.113; p = 0.74$). Action Meaning and Group interacted ($F(1, 48) = 12.15; p = 0.001$). PD patients

generated better scores when imitating ML (mean= 30.16; SD= 3.75) than MF gestures (mean= 26.63; SD= 3.75)($t(18) = -2.33$; $p = 0.032$, 2-tailed). In contrast, controls performed better with MF (mean= 33.29; SD= 2.36) than ML gestures (mean= 32.03; SD= 2.37) ($t(30) = 2.62$; $p = 0.014$, 2-tailed).

Further comparisons between the PD and controls when PD and Controls confirmed that the control advantage was reliable for MF actions alone ($t(\text{corr. } df = 24.4) = 4.25$; $p < 0.0001$, 2-tailed), while there was a borderline effect for ML scores ($t(\text{corr. } df = 26.97$; $p = 0.061$, 2-tailed).

Intransitive actions and UPDRS III scores

There was no significant correlation between the part 3 of the United Parkinson's Disease Rating Scale (UPDRS III) and the total imitation score for intransitive gestures (Pearson Correlation= -0.36; $p = 0.14$, 2-tailed); nor were there effects for MF or ML considered alone (MF: Pearson Correlation= -0.38; $p = 0.11$; ML: Pearson Correlation= -0.29; $p = 0.23$, both 2-tailed).

Comparison between transitive and intransitive actions

As the scores for the transitive and intransitive action tasks were based on different scales, a proportional score was calculated based on accuracy relative to the total maximum score for transitive and intransitive gestures, summed over the MF and ML stimuli (maximum scores= 40 and 72 respectively), MF and ML. The patients' results, after being transformed as described above, were subjected to 2 X 2 Analysis of Variance (ANOVA), with Type of Action (Transitive vs Intransitive) and Action Meaning (MF versus ML) as within-subjects factors. The analysis revealed both significant main effects of the Type of Action ($F(1, 18) = 119.05$; $p < 0.0001$)(transitive mean= 0.57; SD= 0.1; intransitive mean= 0.82; SD= 0.11), and of Action Meaning ($F(1, 18) = 4.54$; $p = 0.047$) (MF mean= 0.35; SD= 0.07; ML mean= 0.34; SD= 0.1) actions. Also the interaction between Type of Action and Action Meaning was significant ($F(1, 18) = 16.28$; $p = 0.001$). For transitive gestures there was more accurate performance with MF than ML actions ($t(18) = 3.78$),

while for intransitive actions there were more accurate gestures to ML than MF stimuli ($t(18) = -2.14$) (both $p < 0.05$).

The data for the controls were first transformed as for the patients and then entered into a 2-factor ANOVA with Type of Action (Transitive versus Intransitive), Action Meaning (MF versus ML) as between-subjects factors. The analysis revealed a significant between-subject effect of Type of Action ($F(1, 50) = 81.91$; $p < 0.0001$) and a trend for an effect of Action Meaning ($F(1, 50) = 3.37$; $p = 0.072$). The interaction between the two factors was not significant ($F(1, 50) = 1.45$; $p = 0.23$). Intransitive actions (mean = 0.91; SD = 0.05) were imitated more accurately than transitive action (mean = 0.69; SD = 0.11). MF actions tended to be reproduced more accurately than ML actions (mean MF = 0.42; SD = 0.07; mean ML = 0.40; SD = 0.07) actions.

Gesture imitation and neuropsychological assessment

The relations between imitation performance and the general neuropsychological screening tests were also considered. Relative to the norms established for the standard neuropsychological tests, the PD patients did not show an impairment when evaluated for general intelligence, language functions, visual perceptive functions, short-term memory for verbal material and locations in space, and attention (see Table 1, also Appendix 1). However 2 PD patients showed a borderline score at the Corsi block task, and 3 showed borderline performance at the Verbal Fluency test (FAS), so correlations between those tests and the imitation tasks were conducted. For the correlation only the patients having available scores in the Corsi block task and FAS were considered.

Corsi block task, FAS and gesture imitation

A significant correlation emerged between total scores on imitating transitive actions and the Corsi test (Pearson Correlation ($n = 13$) = 0.63; $p = 0.02$, 2-tailed). This result was confined to ML actions (Pearson Correlation ($n = 13$) = 0.49; $p < 0.001$), and the correlation was not reliable for MF

transitive actions (Pearson Correlation ($n=13$) = 0.38; $p= 0.21$). The correlations between transitive actions and verbal fluency were not reliable ($p>0.05$).

For intransitive actions (MF and ML), none of the correlations were reliable (all $p>0.05$).

DISCUSSION

The present results were collected from a group of PD patients who showed good recognition of gestures and objects implied in transitive actions, but who were nevertheless impaired at action imitation. Our results match previous findings, whilst also painting a more complex picture of imitation deficits in PD. Similarly to Tessari et al. (2007) we found that the PD patients were impaired at imitating ML relative to MF transitive gestures. Tessari et al. used this result to argue for PD patients having an impaired direct, non-lexical route in imitation, inferring from this that the direct, non-lexical route is mediated by the basal ganglia. In contrast, Leiguarda et al. (1992, 2001) reported that PD patients were impaired at imitating transitive relative to intransitive gestures.

Consistent with this, our PD patients were poor at transitive gestures and obtained higher accuracy scores on intransitive gestures. Our data go beyond the previous results though by assessing both the type of action (transitive or intransitive) and the familiarity of the gesture (MF vs. ML).

Through this we were able to demonstrate a form of double dissociation in which ML gestures were impaired for transitive actions whilst MF intransitive gestures were disrupted more than ML gestures. This pattern of results goes against a simple account of PD patients as either having an impaired direct, non-lexical route to imitation, or against them having a deficit specific to transitive actions. We consider both points.

While the results for transitive gestures concur with the argument that PD patients have a deficit in a direct, non-lexical route to imitation (MF>ML), the results for intransitive actions do not (since ML>MF). We also found that the ability to imitate ML transitive actions correlated with performance on the Corsi blocks task – a test of visuo-spatial memory. This last finding suggests

that transitive ML stimuli placed a particular load on visuo-spatial memory, and that the PD may have had difficulty reproducing these actions for this reason. The lack of correlation for ML intransitive actions may have occurred because these actions placed a lesser load on Visuo-spatial STM. A previous study found some PD patient to be impaired in an n-back task tapping visuo-spatial STM (Costa et al. 2010;), as well as in a delayed-response test in a spatial condition as compared with a non-spatial (object) condition (Postle et al. 1997). This also meshes with controls also finding these actions the most difficult to re-produce (see Figure 1). It is possible that demands on visuo-spatial memory contributed to previously reported deficits in PD patients imitating ML actions (Tessari et al. 2007).

In contrast to their performance with transitive actions, the patients and controls generally performed better with intransitive actions. This could be due to these actions being less complex than transitive actions, despite our attempts to match the action types. Alongside this, the PD patients were relatively impaired, compared with the controls, at re-producing MF intransitive actions. In absolute terms, this effect was small and so we need to be cautious in any interpretations. However, it is suggestive that the basal ganglia may be particularly involved either in communicative gestures or in making gestures in relation to the body as opposed to another object (as required for transitive actions). Consistent with this, a previous study reported that PD patients were impaired in their pragmatic communication abilities and this deficit correlated with measures of frontal lobe functions (Mc Namara et al. 2002).

In sum, the current data go against an account of initiation deficits in PD purely in terms of a loss of a direct, non-lexical route to action. The results suggest instead that factors such as load on visuo-spatial memory and requirements either to make communicative or body-related gestures may be particularly important in eliciting problems in imitation.

8. GENERAL DISCUSSION

The goal of the present work was to try to assess the functional and neural mechanisms underlying action production and recognition, and in doing this, to reconcile some inconsistencies in the literature on praxis. One specific aim was to assess the relations between the processes involved in the reproduction of different types of gesture (transitive and intransitive, MF or ML), and a second was to evaluate the relations between gesture recognition, action production and imitation.

The first empirical chapter (Chapter 3) presented a neuropsychological investigation of a group of patients having unilateral lesions either in the left (Left Brain Damaged, LBD) or the right (Right Brain Damaged, RBD) hemisphere. Previous similar investigations have typically involved only a small range of tasks (e.g. comparing imitation of MF pantomimes with imitation of ML intransitive actions, or the recognition MF gestures and imitation of only MF gestures) and often assessed only small groups of patients. In contrast to this I sampled a large group of patients, and give them a battery of tasks including MF and ML transitive and MF and ML intransitive actions, as well as two tasks where they had to demonstrate knowledge of the MF actions they previously imitated.

Imitation and recognition tasks were also administered to a group of healthy participants and compared to the LBD and RBD patients. In this study all patients and controls were right handed.

The results showed that the patients generally had poorer action production than the controls, regardless of the side of the lesion, while on average the patients did not differ significantly from controls when they had to recognize MF actions. On imitation, LBD and RBD differed in their total scores with transitive gestures, although this difference was driven by the performance with the transitive ML only, as the two groups did not differ when they had to reproduce transitive MF pantomimes. Also there were no reliable differences between the two groups for the intransitive gestures. At single case level more LBD patients fell below the norms for control participants, but in almost all cases there were instances where at least one RBD patient performed the same way.

Significant differences between MF and ML transitive gestures emerged within both the patient and control groups, while intransitive actions did not show a significant difference between MF and ML gestures (neither for the patients nor the controls). In addition, intransitive gestures were always easier to perform than the transitive gestures, regardless whether the actions were MF or ML, and there was also better recognition of intransitive gestures for both patients and controls.

Although there were dissociations between the imitation tasks, in the patient group the performance of MF and ML transitive actions correlated with each other and the MF transitive also correlated with MF and ML intransitive actions. MF and ML intransitive actions also correlated within each other. Within controls MF and ML transitive actions correlated with each other as were MF and ML intransitive actions, but performance on transitive and intransitive actions did not correlate (note though that this result can arise because the intransitive actions were found particularly easy to perform by controls). Also correlations emerged between the imitation and recognition tasks.

Finally the generation of MF transitive and MF intransitive actions correlated with Picture Naming from the BCoS, a task that uses mixtures of animate and inanimate objects. Also the accuracy of MF transitive gestures correlated with scores on the BCoS Action Recognition test, suggesting that the retrieval of action meaning is crucial for imitating those actions. In contrast ML intransitive gesture performance correlated with the BCoS Figure Copy task, indicating the importance of spatial coding when ML actions have to be reproduced.

The second study (Chapter 4) employed scores on the same MF and ML transitive and intransitive imitation tasks as used in Chapter 3 as predictors of changes in voxel intensity in MRI T1 images of segmented grey matter (GM) in a group of brain damaged patients with acquired brain lesions. The data were then analyzed using voxel-based morphometry. For all kinds of gestures apart from the MF intransitive actions, reliable correlations were found between impairments in gesturing and neural changes in both the left and the right hemispheres. MF and ML transitive and ML intransitive gestures related to the signal in the left superior parietal cortex involving the precuneus,

and, for the ML transitive actions, the cluster also extended into the left occipital cortex. Moreover, MF and ML transitive, as well as ML intransitive actions, related to clusters in the right frontal cortex and SMA (though for the ML transitive actions this cluster did not reach full significance after correction). In chapter 4 results were also obtained in the WM, but only for the ML transitive gestures, with the contrast revealing a large significant cluster in the corticospinal tract running within the left hemisphere. MF intransitive gestures failed to give any significant result and this may reflect a lack of variation for these stimuli, due to generally good performance across the patients.

The brain areas involved in the production of MF gestures on verbal command, imitation of ML actions and action recognition were investigated in the third empirical chapter (Chapter 5). A VBM approach was again used on a large sample of acute stroke patients, but in this case combining the data for learned transitive and intransitive actions. The analysis used CT scans as images and the scores at Gesture Production, Imitation and Action Recognition from the BCoS as predictors of changes in GM signal intensity. In this study reliable results were obtained only for Action Recognition, which was associated with the signal from the left anterior cingulate cortex and the left middle temporal lobe. The results obtained for Gesture Production and Imitation did not survive to FEW/FDR corrections, suggesting that other factors (e.g. general impairment) may determine performances. Nonetheless it can be noticed that Gesture Production related to a cluster that also involved the left middle temporal cortex - so partially overlapping the results obtained for Action Recognition. Moreover Gesture Production and Imitation both indicated effects related to the superior parietal cortex in the left hemisphere. However these results must be treated cautiously. The study presented in chapter 5 also highlighted significant results in WM. Both Action Recognition and Gesture Production significantly related to WM change within the left superior temporal pole. Gesture Production also significantly correlated with the signal from the posterior

part of the corpus callosum, and a cluster in the same WM tract was also revealed for Imitation (although it did not reach the full significance level after correction).

The fourth empirical chapter (Chapter 6) focused on the Gesture Production task from the BCoS that was split into two subtests: i) production of MF transitive pantomimes, and ii) production of intransitive MF symbolic gestures. The same patient sample was used as in the previous chapter. The aim was to look at different neural correlates of production on verbal command of transitive and intransitive gestures. A preliminary analysis compared the patients' accuracy in producing the two types of gestures, highlighting an advantage for transitive with respect to the intransitive actions. This is strange if compared with the results in chapter 3, where intransitive gestures were produced more accurately than the transitive. However the tasks in chapter 3 and 6 differed in that in chapter 3 patients imitated visually presented gestures, while in chapter 6 they had to execute the gestures on verbal command. At a neural level, only the transitive gestures gave results surviving cluster correction. This analysis revealed a cluster centred on the insula in the left hemisphere. Also production of intransitive gestures revealed two clusters in the left supramarginal gyrus and left frontal cortex. Though these last results they did not survive cluster correction, they did overlap the results found for Imitation (chapter 5) (where intransitive ML gestures had to be produced in imitation). The left supramarginal gyrus was also associated to intransitive ML action imitation in chapter 4. Note however that all the results for intransitive Gesture Production, BCoS Imitation (chapter 5) and intransitive ML actions imitation in chapter 4 were not significant after correction and they must be taken cautiously.

In the final empirical study (Chapter 7) a group of patients with idiopathic Parkinson's Disease (PD) with minimal cognitive decline, was tested. The imitation of MF and ML transitive and intransitive gestures was probed. Generally the PD patients showed lower performance than the controls but also demonstrated different patterns of performance with transitive and intransitive actions. There was worse performance with the ML transitive actions as compared to the MF

transitive actions, and worse performance with the MF intransitive than the ML intransitive actions. The performance of these patients did not relate to their peripheral neurological symptoms but may (to some degree) reflect the differential overall difficulty of the different tasks.

Implications for models and the neuroanatomy of action recognition and production

Generally the results obtained in the five studies indicate that tasks involving praxis functions are highly correlated and may differentiate mainly because of the difficulty of the task. These data do not fit terribly well with the existence of separate processes for action production to name, imitation or command. At group level, in Chapter 3, the results mainly suggested that the different tasks varied in difficulty, even though some patients behaving opposite way to the rest of the group were reported (i.e. one right-brain damaged patient who imitated better transitive than intransitive actions; one patient left-brain damaged patients being at control level for imitation of transitive MF gestures but who was impaired in recognizing them; one left-brain damaged patient who was impaired in recognition but not on imitation of MF intransitive gestures; one left-brain damaged patient having normal scores when imitating ML intransitive actions but being below the cut off for MF intransitive gestures) suggesting the involvement of at least some separate process. However, these behaviours were reported only on few patients and they cannot be considered as final proof in favour of the existence of a dual process. At group level, the comparison between transitive and intransitive gestures in chapter 6 revealed an advantage for transitive actions, with this result going in the opposite direction to the data in chapter 3 (and from the majority of the other studies) where an advantage for intransitive gestures has been noted. However, in chapter 6 the gestures had to be produced on verbal command while in chapter 3 they had to be imitated. It is possible that differences in performance may depend by on how the stimuli are presented. It is possible that actions schemas for intransitive gestures are more easily activated from a visual input while the transitive are more easily activated via auditory input. Nonetheless this also suggests that different types of information may be crucial for the execution of transitive or intransitive gestures, with one

type of information more automatically linked to the visual system (intransitive) while the other type (for transitive) is linked to the auditory system. This remains speculative however, especially given that transitive gestures reflect tool use, and there have been shown to be strong visually-driven responses to tools in various imaging studies (REFS).

Also, the analyses in chapter 4 (VBM on MRI scans and imitation scores of chronic patients) revealed common areas, as well as some differences in brain regions, involved in the processing of different action types. The right frontal cortex and SMA were associated with MF and ML transitive as well as ML intransitive gestures. Also, the cluster for MF transitive gestures mainly involved those frontal areas in the right hemisphere, only slightly extending to the left posterior cingulate cortex. This result is not standard in relation to the literature, and I have proposed that it was mainly driven by a few patients having a right frontal lesion who failed in imitation because of an attentional deficit or an impairment in controlling their motor behaviour, when imitating both MF or ML, transitive or intransitive actions. ML transitive and ML intransitive gestures were also related to a cluster in the parietal cortex having its peak in the precuneus. The precuneus was previously reported to sustain the ability to shift attention between different locations in space and spatially guided behaviours (see Cavanna et al. 2006 for a review). The intervention of visuo-spatial processes in ML intransitive gestures is compatible with the correlation found at behavioural level in chapter 3 between imitation of those gestures and the BCoS Figure Copy. Though a correlation with Figure Copy was not found for ML transitive gestures, ML transitive gestures shared a cluster with ML intransitive gesture performance in this brain area putatively involved in visuo-spatial processing. Moreover, BCoS Figure Copy taps the ability to put elements in their correct position in order to give to the figure its proper configuration. This ability may be important in intransitive gestures, as they mainly require moving the limb in a required direction in order to reach the target configuration. In contrast, transitive gestures mainly require repeated movements with the limb

never stopping in a precise configuration). So, it is possible that both transitive and intransitive ML actions share those processes needed to correctly understand the direction of action.

In Chapter 5 (VBM on CT scans and BCoS scores of acute patients) Action Recognition was the only task giving strong results – with an association to the left anterior cingulate cortex (ACC) and the middle temporal gyrus. The ACC is an area that has interconnections with the hippocampus and the structures belonging to the limbic system and has been reported to have a role in cognitive functions as well as in emotion and motivation (see Bush et al. 2000 for a review). We proposed two possible explanations of our result for BCoS Action Recognition: i) the lesion in the ACC contributed to a deficit in recognizing actions because of its relation to the hippocampus where information about known actions may be stored; ii) the ACC has a role in identifying the motivation or the intention of the actions and this may be crucial for correctly recognize them. Gesture Production (on verbal command) and Imitation did not give strong results; nonetheless they may suggest something about the processes through which actions are executed. Indeed a cluster for Gesture Production extended into the left middle temporal cortex, which was also found for Action Recognition, but not for Imitation. As Action Recognition and Gesture Production both used MF actions as stimuli it may be possible that the left middle temporal cortex had a role in retrieving long-term memories for gestures. The cluster found for Gesture Production had its peak on the left supramarginal gyrus and this was also found for Imitation but not for Action Recognition. Also, when Gesture Production was split in its transitive and intransitive components (chapter 6), it appeared that the intransitive but not the transitive gestures related to the left supramarginal gyrus. Summarizing, Imitation of ML intransitive actions and production of MF intransitive gestures on verbal command related to clusters on the left supramarginal gyrus on sub-acute patients (chapters 5 and 6), and the same cluster was also found for chronic patients imitating ML intransitive in chapter 4. Additionally impairments for the BCoS Imitation of ML intransitive gestures task, and the intransitive MF Gestures Production task, showed a cluster on the frontal cortex (chapter 5 and 6).

In all three studies these clusters did not survive to corrections, nonetheless they suggest that frontal and parietal areas may have a role in the execution of intransitive gestures, regardless of their meaning and the modality of stimulus presentation. However this conclusion must be made very cautiously, and further investigation is needed, for instance testing patients in imitation and production on verbal command using the same set of MF and ML intransitive actions. Also it would be useful to carry out those studies on the same patients in both acute and chronic phases to assess the stability of the results..

Stronger findings were obtained in chapter 6 (VBM with CT scans and BCoS Gesture Production, transitive and intransitive, scores of acute patients) for the production of MF transitive gestures, which were related to a cluster centered on the insula in the left hemisphere. This result matched findings in chapter 7 where Parkinson's patients were tested on the imitation of MF and ML, transitive and intransitive gestures. The study on Parkinson's patients gave the results that best supported the dual route model for action imitation, with patients showing opposite patterns of performance according to the type of gestures that had to be executed. PD patients generally had lower gesture scores than controls, but while they did worse with the ML transitive than the MF transitive pantomimes, the pattern was the opposite when intransitive actions were considered (ML>MF). This is difficult to explain in terms of overall task difficulty but suggests the possibility of a further subdivision of action imitation according to other characteristics of the actions.

However even if several pieces of data in the present work are consistent with a distinction between MF and ML actions it is still unclear if a distinction exists also between actions involving or not a tool (transitive vs. intransitive actions). Some results pointed in that direction. To assess the dissociation between transitive and intransitive actions the stimuli tended to differ in difficulty – a problem that pervades the literature and not just the current data. In particular, intransitive actions tended to be easier than transitive, for controls as well as patients, and this may make it difficult to demonstrate a double dissociation (as opposed to the one-way dissociation in favour of intransitive

actions. It may be easier to generate double dissociations between patients (as groups and not only at single subject level) if transitive and intransitive gestures could be more balanced in terms of difficulty. The current analysis was limited in this respect since it used a standard neuropsychological screening test for at least some of the analyses.

Some methodological issues

VBM was used in the investigations of the neural correlates of action production, an approach that uses the general linear model to statistically assess the relations between brain tissue integrity and behavioral performance. Here, the MF and ML imitation scores were used as predictors of change in the signal intensity coming from each voxel across the whole brain in a group of consecutively sampled patients, not pre-selected on the basis of having apraxia. In addition the analysis used continuous scores on tests of gesture imitation in order to characterize imitation abilities. This approach also allows controls over covariates of no interests such as age, gender, neglect, which may otherwise contaminate the results. VBM also has the advantage to allow offline testing (at least compared with on-line measurement techniques, such as fMRI). This can facilitate investigations about praxis when the tasks require to execute actual movements as, differently from the most part of the others neuroimaging approaches, where movements create artifacts.

However VBM can fail to give results if the data are not normally distributed, a quite common characteristic of data with patients. There can also be problems in segmenting and normalizing patients with large lesions or where there has been substantial enlargement of the ventricles. In general, though, these problems proved relatively slight. The scans were also independently verified by eye, to ensure that segmentation and normalization was accurate.

One of the interesting aspects of the VBM analyses here is that CT as well as MRI was used. CT may have the disadvantage of having more noise in the signal and being lower resolution although it also has some benefits (e.g., less distortion). Despite the possible noise, the current study indicates that CT analyses can be useful, at least when large numbers of patients are involved. Also, the aim

of the chapter where CT scans were used was to test a sample of sub-acute patients who had just survived from a stroke, also in order to explore the neural correlates of a new neuropsychological screen that is mainly aimed at obtaining quick, but efficient, evaluations of patients when they are admitted following a stroke. Only CT scans were available for those patients, taken as routine when patients were first seen in the hospital. Since the scans were taken from a very large sample of patients, it is likely to be quite representative of the stroke population.

Other implications

Understanding how movement production works may be critical for creating tests able to assess movement deficits that are due to a cognitive (as opposed to motor) impairment and that can go undiagnosed (because the test is too easy or because it does not tap the component that is impaired). For instance if the double dissociation between MF and ML gestures and the existence of a double route mechanism for imitation is true, and if the direct route allows the subject to reproduce both MF and ML gestures, then a problem to the semantic route could remain undiagnosed as the patient is still able to imitate the MF actions through the direct route. Nevertheless the patient can suffer from subtle manifestations of the deficit in everyday life when actions need to be produced from long-term memory. The BCoS test is interesting in this respect because it attempts to tap different parts of the action system, using ML actions for imitation and MF actions for production from name, as well as action recognition. In extensions of the current work it would be interesting to assess how well the analyses of ideomotor apraxia in patients predict their function in everyday life, when objects are handled rather than pantomimed in action. Very often patients perform better when using real objects than when pantomiming (Chainay & Humphreys, 2002), but nevertheless subtle problems may emerge particularly when the tasks become more taxing (e.g., with multi-steps). This should be analysed.

In addition, it would be interesting to evaluate whether there is differential success in rehabilitating the different symptoms in patients – can training on one route transfer to performance using the

other route? If this is the case, then an argument can be presented that the routes are not modular but more distributed, so that retraining one component can generalise to other forms of action. This suggests that fine-grained analyses of action rehabilitation may be a useful way to further probe the nature of the action processing system.

Finally, the data suggest that gesture execution is a quite complex function where different core processes may intervene. Also, it is possible that gestures themselves can be divided into components. In the same way spoken language is composed of single letters that combine together according to language rules to give shape to morphemes, lexemes, syllables, and words etc., movements may be divided into minimal motor units that become complete gestures having different meaning according to the rules through which they are associated together.

9. SUMMARY

The present work investigated production and recognition of meaningful and meaningless transitive and intransitive gestures.

The first experimental chapter reported a neuropsychological investigation on patients with unilateral lesions on the right or on the left side of the brain revealing a praxic deficit for patients after both left and right hemisphere lesions. The second study used voxel-based morphometry to look at the neural correlates of actions imitation. This study showed common areas in the right frontal cortex associated with meaningful transitive, meaningless transitive and meaningless intransitive gestures. Moreover, the left precuneus related to meaningless transitive and meaningless intransitive gestures. Imitation of meaningless intransitive gestures also showed a cluster in the left supramarginal gyrus. Although not significant after correction this result was replicated in the third and fourth experimental studies (voxel based morphometry on CT scans of sub-acute patients) for imitation of meaningless intransitive actions, along with imitation and gesture production for meaningful intransitive actions – two tasks taken from the Birmingham Cognitive Screen. This suggests that this area may have a role for intransitive gestures, regardless of their meaning. None of those results on the supramarginal gyrus survived the corrections and must be treated very cautiously.

The third and fourth experiments also gave significant results for Action Recognition and transitive Gesture Production, again taking data from the Birmingham Cognitive Screen. Action Recognition related to clusters centered on the Anterior Cingulate cortex and the middle temporal cortex, with this last cluster also present (although not significant) for Gesture Production (performances for transitive and intransitive gestures summed up together). Transitive Gesture Production was associated to a significant cluster centered on the insula. This result also fits with one of the findings in the last experimental study that was carried out on a sample of Parkinson's patients that proved to

be impaired in imitation of transitive gestures. Beside this, Parkinson's patients also had significantly different performance when imitating different types of actions. Overall, the results point to a complex network of structures that support action, depending on factors such as the meaningfulness of the stimuli, whether actions are communicative or tool-based (for intransitive and transitive actions), whether they are imitative, made to command to simply recognized.

APPENDIX 1- chapters 3 and 4

Table 1. Patients in chapters 3 and 4

patient	age	gender	education	Edinburgh Handedness Inventory
BL	82	F	5	na
DS	76	M	4	90
PH	36	M	5	100
MP	62	M	na	-100
MM	75	M	2	100
MMcD	77	M	1	90
JW	77	M	2	100
JQ	63	M	5	100
AS	73	M	3	90
GA	45	M	2	100
PJ	70	M	na	100
DE	68	M	3	100
BR	69	M	2	100
JM	67	M	na	100
AK	74	M	4	100
JE	61	M	na	100
PM	68	M	2	100
PW	78	M	2	na
JB	74	F	2	-70
MC	75	M	4	100
RH	75	M	2	-100
QJ	55	M	na	100
DL	56	M	3	100
DT	73	M	na	100

Table 1 shows the age, gender, education and the scores on the Edinburgh Handedness Inventory (Oldfield 1971) of patients who participated in the studies presented in chapters 3 and 4. Levels of education based on categorization of the 2001 Census (Level 0 - no academic, vocational or professional qualifications, including those with City and Guilds, RSA/OCR, BTEC/Edexcel qualifications and including unknown qualifications; Level 1 – 1+ O and A levels, NVQ level 1 to 3, Foundation GNVQ to advance GNVQ, up to higher school certificate; Level 4-5 – degree +, NVQ level 4-5, NHD, NHC, qualified teacher status, qualified medical or allied health professional status). The entries labeled as “na” means that the data was not available.

Birmingham Cognitive Screen- Tasks administered to patients in chapter 3

Normative sample

The Birmingham Cognitive Screen (BCoS) was administered to adult healthy participants that had been selected according to age, gender and education level, in proportions that should be representative of the English adults population according to the 2001 Census (Office for National Statistic website accessed on 18th July 2008). Age and education level were divided in ranges as follows: i) age: 50-64, 65-74, 75 or above; ii) education: Level 0 - no academic, vocational or professional qualifications, including those with City and Guilds, RSA/OCR, BTEC/Edexcel qualifications and including unknown qualifications; Level 1 – 1+ O and A levels, NVQ level 1 to 3, Foundation GNVQ to advance GNVQ, up to higher school certificate; Level 4-5 – degree +, NVQ level 4-5, NHD, NHC, qualified teacher status, qualified medical or allied health professional status. The education levels were based on the categorization of the 2001 Census.

The cut off were obtained from 100 participants divided according to the three age range: 50-64 (N= 34); 65-74 (N= 33); 75 or above (N= 33). The cut offs for the tasks considered in the present study are reported in Figure 1.

Figure 1. Cut offs at the BCoS tasks administered to patients in chapter 3

		cut offs points		
		impairment = less than the given score		
		50- 64	65-74	75≤
	Personal Information	8	8	8
	Time & Space	6	6	6
	Picture Naming	11	11	10
Rule Finding and Switching	Accuracy	<6	<5	<4
	Rule Finding	<1	<1	<1
	Multi-Step Object Use	11	10	10
	Gesture Production	10	9	9
	Action Recognition	5	5	4
	Imitation	9	9	9
	Figure Copy	42	41	37

Figure 1. Performance is considered as defective in falling below the scores reported for each age range.

BCoS- Patients testing

The following subtests from the Birmingham Cognitive Screen (BCoS) (Humphreys, Bickerton, Samson and Riddock 2012) were administered to the patients who took part in the present study: Gesture Production, Imitation and Action Recognition are described in the methods chapter (chapter 2).

Long-term memory¹⁶- Personal Information: This subtest is composed by eight questions concerning age, job, home address etc.. Each question is presented verbally, while the patient can answer in a verbal or written form, in case of unreliable verbal production. For written answers the patient can use his/her favourite hand.

Each correct answer is scored 1, incorrect answers or answers delayed more than 15 seconds are scored 0, for a maximum score = 8.

Long-term memory-Time and Space: it assesses the patient's time and space awareness. It is composed by 6 questions, 3 concerning the actual moment and place (i.e. where are you right now; in which city; what time of the day is it now); the other 3 refer to a more general temporal dimension (i.e. what month is it; what day of the week is it; what year is it). The patient should answer verbally, but in case of error or non-response multiple-choice questions are presented, with the right response presented among two distracters

Each correct answer is scored 1, while incorrect or delayed (<15secs) answers are scored 0, for a maximum score = 0.

Picture Naming: The task includes fourteen pictures of objects belonging to different categories (i.e. seven inanimate objects, seven living things (3 fruits; 2vegetables; 2animals)). The items were

¹⁶ Both Personal Orientation and Time and Space consist of open verbal questions (e.g., where are you now? What month is it?). For the orientation in time and space, in addition, there is a multiple choice (4 choice responses) to be presented in the case of a non-response by the patient, an error in the initial question or in cases where aphasia prevents answers to the open questions.

presented in the format of grey shaded hand drawings (see figure 2 for examples of the stimuli).

Also half of the stimuli had a “long name” (6 to 9 letters) and half had a “short name” (3 to 5 letters), in order to detect speech production deficits sensitive to word length.

Patients were presented with the pictures and were instructed to name them. If the patient did not answer or did errors with the first four items the test stopped. A maximum time of 15 seconds was allowed to name each item.

Correct answers were scored 1, incorrect or delayed (>15 seconds) answers were scored 0, for a maximum score = 14.

Figure 2. Example of the items used in Picture Naming



Figure 2. In Picture Naming grey shaded hand drawings of seven living things (fruits, vegetables, animals) and of inanimate objects were presented to be named.

Birmingham Rule Finding and Switching test: Stimuli consisted in 19 grids (plus 3 grids for practice trials) of 6 columns and 6 lines, for a total of 36 cells (32 grey, 2 red, 2 green). In each grid a black dot was placed inside one of the cells (see figure 3 for an example), and through the task it moved from one position in the grid to another.

When the first grid was displayed patients were required to point the black dot to see if they were able to point to it. Then they were asked again to point to the black dot, to ensure that the previous pointing response was reliable. If this second answer was not reliable the test was stopped. Patients were told that in the next pages the dot would move in different cells following a precise rule. The rules determining the movement of the dot were three: 1) from right to left, and vice versa; 2) from a red cell to the other red cell, and vice versa; 3) from a red to a green cell, and vice versa.

The rule by which the dot moved sometimes changed, but patients were not warned about that.

Patients were asked to predict the position of the dot in each consequent grid. To do this they had to find the rule determining the position of the dot in the next item, as well as to detect if the rule had changed.

Each grid was presented one at a time. The preceding grid was always left visible in order to reduce memory problems.

The task started with a practice trial: a first grid was followed by a second where the dot had changed its position. The patient was asked to indicate where the dot would have moved in the subsequent grid. Then the third grid was showed, for feedback. If necessary the patient response was corrected by the experimenter. The actual task followed.

Each correct answer was scored 1, incorrect or delayed (> 15 seconds) answers were scored 0, for a maximum score = 18 (i.e. Accuracy). Each correct rule detection was scored 1, for a maximum score = 3 (i.e. Rule Detection).

Figure 3. Example of the items used in Birmingham Rule Finding and Switching test

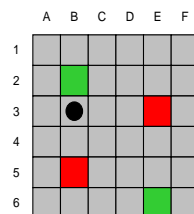


Figure 3. Patients had to predict the position of the dot on subsequent grids on the basis of the previous moves of the dot. The rule by which the dot moved sometimes could change.

Multi-Step Object Use: This task required the patients to perform a sequence of actions on objects in order to carry out the task. Two target objects and three distracters were displayed: matches (objects placed nearest to patient), batteries, glue stick, screwdriver, torch (object placed furthest from patient). The task was to light the torch.

Patients were also showed a picture of a lighted torch and were told that everything they needed was in front of them. In case of unilateral weakness the experimenter could help the patient (e.g. helping to hold the torch) if the patients demonstrated to initiate the correct action.

The action sequence was scored on the basis of the presence of 12 criteria: 1) unscrewing the top of the torch after checking if it already works; 2) fill the barrel (after it is open); 3) insert the right number of batteries (i.e. 2); 4) close the barrel (once the batteries are in); 5) screw in again the top of the torch; 6) switch the torch; 7) need of maximum of two attempts to correctly insert the batteries; 8) accomplishment of the final goal of the task (i.e. light the torch); 9) irrelevant objects were not used; 10) irrelevant actions with distracters were not performed; 11) irrelevant actions with the target objects were not performed; 12) absence of perseverations.

One point was given for each reached criteria, for a maximum score = 12.

Complex Figure Copy: The figure displayed in Figure 4 was presented to be copied, along with the instructions “I will show you a figure. Please copy the figure the best you can”.

The patients’ drawings had been scored as follows: one point was given for the presence of the main middle square and one point was given for its correct shape and proportion. For each of the 15 elements inside the main middle square, one point was given for its presence, one for its correct shape and proportion, and one for its position. The total maximum score was 47.

Figure 4. Complex Figure Copy

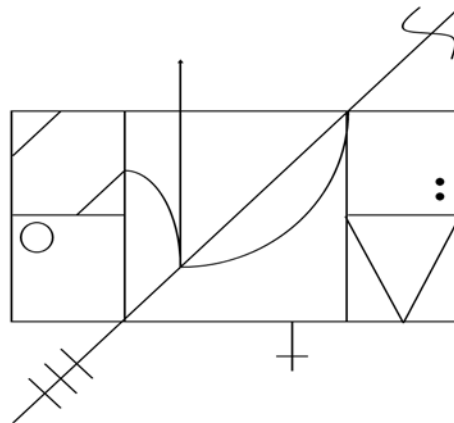


Figure 4. Patients were asked to reproduce the figure reporting all the elements in their correct position.

Table 2. BCoS scores obtained by patients in chapter 3

Patient	Personal Info	Time & Space	Bham Frontal-Accuracy	Bham Fron-tRule	Picture Naming	Multiple Object	Gesture Production	Actions Recognition	Imitation	Figure Copy
JW	8	6	3	0	13	9	11	5	9	38
JQ	7	6	16	3	11	11	11	4	11	43
AS	8	6	16	3	13	9,00	10,00	5,00	9,00	39,00
JM	na	na	na	na	na	na	na	na	na	na
AK	8	6	12	2	9	11	9	5	8	38
JE	na	na	na	na	na	na	na	na	na	na
PW	8	6	13	2	14	11	11	4	9	44
MC	8	6	6	0	13	8	11	6	8	33
QJ	na	na	na	na	na	na	na	na	na	na
BL	6	6	3	1	5	2	7	4	4	9
DS	8	6	16	2	8	12	7	5	11	44
PH	8	6	15	2	6	12	10	5	9	42
MM	0	5	1	0	0	11	5	3	6	45
DL	8	6	16	3	14	11	9	6	9	47
DT	na	na	na	na	na	na	na	na	na	na
DE	7	5	10	3	5	2	12	4	8	44
BR	8	5	2	0	11	12	12	6	10	37
PJ	na	na	na	na	na	na	na	na	na	na
MMcD	8	6	9	2	9	12	12	5	9	37

Table 2 shows the scores obtained by patients at the BCoS tasks. Scores falling below the cut off are in bold. Missing entries are indicated as “na” (i.e. the score was **not available**). The BCoS scores of patient MMcD are reported in the red box below the main table. MMcD was later revealed to have a bilateral lesion and was excluded from the group analyses in chapter 3.

APPENDIX 2- chapters 5 and 6

Table 1. Patients in chapter 5 and 6

	GENDER		HAND USED		EDUCATION					
	Male	Female	Right	left	level1	level2	level3	level4	level5	na
N	110	123	191	42	6	169	30	7	14	7

N Tot= 233

Table1 summarize gender (male female), hand used for imitation and educations level of the 233 acute patients whose data were used in chapter 5 and 6. Notice that all the patients in this sample were right-handed. Education levels were based on the categorization of the 2001 Census. The information on the education of 7 patients was **not available** (i.e. “**na**”).

APPENDIX 3- chapter 7

Table 1- Parkinson's patients

PD	AGE	GENDER	EDUCATION	HANDEDNESS	HAND USED
1	54	Male	18	83,3	Right
2	68	Male	8	100	Right
3	74	Male	13	75	Left
4	66	Female	11	91,6	Right
5	75	Male	17	75	Right
6	63	Male	7	83,3	Right
7	70	Male	12	100	Right
8	66	Female	8	91,7	Right
9	75	Female	8	100	Left
10	63	Male	13	100	Right
11	52	Female	8	83,3	Right
12	73	Male	18	66,6	Right
13	71	Female	12	100	Left
14	60	Female	10	83,3	Left
15	55	Female	9	83,3	Right
16	69	Female	7	100	Left
17	69	Female	5	100	Left
18	69	Female	8	100	Left
19	69	Male	10	100	Right

Table 1 reports age, gender, education (total years in education) and the Edinburgh Handedness Inventory (Oldfield 1971) scores and the hand used for imitation.

Neuropsychological Evaluation

Mini Mental State Examination: The Italian version of the Mini Mental Estate Examination

(Magni et al. 1996) was administered to both PD patients and controls to evaluate the integrity of their general cognitive abilities. All participants who scored (corrected for age and education) less than 27 were discarded.

Corsi block test (Italian normative data, Orsini et al. 1987): Evaluating short-term memory for locations in space.

Forward and reverse Digit Span (from the Italian version of the WAIS-R, Orsini et al. 1987):

Evaluating the short-term memory and the working memory for verbal material, words retrieval ability.

VOSP screening test and VOSP object decision from Visual Object and Space Perception Battery (VOSP) (Warrington et al. 1991): Assessing visual perception abilities.

Verbal Fluency for Phonemic Categories (Spinnler et al. Standardizzazione e taratura italiana dei test neuropsicologici 1987): Assessing words retrieval ability.

Token and Naming subtest from the **Aachener Aphasia Test** (Italian version, Luzzati et al. 1994): Evaluating patients' language comprehension and naming abilities.

Trail Making Test A and B (Italian normative values, Giovagnoli et al. 1996): Evaluating spatial and visual attention and the abilities to switch from alphabetical to numerical stimuli.

Table 2- Parkinson's patients- neuropsychological evaluation

PD	MMSE	VOSP		AAT		DIGIT		CORSI	Trail making			Verbal fluency score	UPDRS III score
	score	1 score	2 score	token T score	naming T score	fwd score	bwd score	score	A score	B score	B-A score		
1	29 (26,2)	20	18	78	80	na	na	na	na	na	na	40 (31,2)	12,00
2	29 (27)	16	15	na	na	na	na	na	na	na	na	18 (21,9)	31,00
3	30 (27,7)	20	19	74	80	5 (4,75)	3	4 (4)	45 (26)	130 (96)	85 (47)	31 (29,5)	10,00
4	30 (28)	20	17	70	80	na	na	na	na	na	na	28 (31,2)	15,00
5	30 (28,3)	20	15	70	71	na	na	na	na	na	na	28 (22,3)	16,00
6	29 (27,9)	20	17	74	80	5 (5)	3	5 (5)	38 (21)	239 (181)	201 (160)	20 (23,2)	25,00
7	30 (28,4)	19	17	74	76	4 (4,25)	4	na	na	na	na	34 (31,6)	16,00
8	28 (26)	20	15	67	71	6 (6,25)	3	4 (4,25)	57 (37)	na	na	28 (31,2)	15,24
9	28 (26,4)	19	17	74	78	6 (6,25)	4	4 (4,5)	65 (39)	210 (122)	145 (84)	35 (39,7)	33,00
10	26 (23,2)	19	17	72	78	na	na	na	na	na	na	36 (32,9)	10,00
11	28 (26)	20	19	74	76	5 (5)	5	5 (5)	na	na	na	na	6,00
12	29 (26,7)	20	19	72	80	4 (3,5)	4	5 (5)	47 (34)	111 (79)	64 (46)	39 (33,3)	12,00
13	29 (27,4)	20	18	67	80	6 (5,75)	4	5 (5,25)	na	na	na	na	12,00
14	30 (28)	20	20	78	80	6 (6)	5	5 (5,25)	40 (23)	88 (30)	48 (7)	41 (43,5)	8,00
15	30 (28)	19	20	78	80	4 (4)	6	6 (6,25)	30 (17)	110 (62)	80 (46)	57 (59)	8,00
16	30 (28,9)	20	17	70	80	5 (5,25)	4	4 (4,5)	49 (26)	174 (96)	125 (70)	49 (52,9)	11,00
17	27 (25,9)	19	19	66	80	6 (6,5)	5	4 (4,5)	41 (14)	116 (19)	75 (6)	38 (46,6)	15,24
18	27 (25)	18	17	65	80	4 (4,25)	3	4 (4,5)	55 (32)	146 (68)	91 (36)	25 (28,9)	26,00
19	29 (27)	20	18	74	80	5 (5,25)	4	5 (5,25)	54 (31)	141 (63)	87 (32)	na	8,00

Table 2 reports the scores obtained by the Parkinson's patients at the neuropsychological evaluation and the United Parkinson's Disease Rating Scale- part 3 (UPDRS III). Scores below the cut offs for the normal Italian population are in bold. If required by the test scoring procedure, scores were corrected by age and/or education. The corrected scores are reported in brackets next to the raw scores. Some data were **not available** (i.e. "na").

10. References

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