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Mental motor representations across the adult life-span: behavioural and fMRI evidence in explicit and implicit motor imagery tasks.

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“Love is being stupid together”

A Stefano.

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Abstract

Motor imagery (MI) is a cognitive state in which movements are mentally evoked. There is behavioural evidence that MI declines with aging, but limited information on the functional anatomical correlates of these changes.

In my thesis, I present a systematic behavioural/fMRI investigation of this issue and demonstrate that aging is associated with modified brain responses ranging from successful compensation to failed compensation depending on the complexity of the motor imagery task.

After a theoretical introduction in **Chapter 1**, I describe the effects of early aging on explicit MI through a study of 24 young and 24 elderly subjects during two fMRI tasks requiring movement execution (ME) or MI of finger movements; temporal correlations between MI and ME were also measured **(Chapter 2).**

I found significant differences between the two groups: elderly subjects lost the behavioural temporal correlation between MI and ME; moreover, they over-recruited occipito-temporal areas. The temporal discrepancy between MI and ME in the elderly subjects correlated with brain regions that showed increased activations. These observations suggest that elderly subjects have qualitatively different explicit MI abilities.

MI can be elicited also by using implicit tasks, in which subjects are involved in *motorically driven decisions*. The hand laterality task is one such example: subjects are asked to decide whether a depicted hand is a left or a right one.

Chapter 3 illustrates the fMRI correlates of this task in 30 young subjects. I found stronger signals in left premotor and parietal cortices for palm-viewed stimuli, whereas back-view stimuli were associated with stronger occipital activations to suggest the existence of brain-encoded, view-dependent representations of body segments.

Chapter 4 reports the extension of the 2nd study to the assessment of the effects of early aging on implicit motor processes: I compared those data with the ones of 29 elderly subjects. While there was no specific aging related behavioural effect, I found significant additional activations in the elderly group in occipito-temporal regions, which were negatively correlated with RTs. These results reveal a pattern of *graceful aging* in the domain of implicit motor representations whereby cognitive performance remains at juvenile level thanks to some compensatory brain processes.

It remained to be seen whether the effect of early aging could be detected by using more complex implicit MI tasks, something addressed in **Chapter 5**, through the study of 22 young and 23 elderly subjects performing a Grip Selection Task in which they were asked to report whether they would grip a portrayed tool with an over- or an under-hand grip. I found a behavioural decline in the elderly group, with hyperactivations in the occipital cortices and hypoactivations in the superior parietal lobule, an area previously associated with object grasping. The greater complexity of the imagined movement may determine a pattern interpretable in terms of a failed attempt of compensation.

I conclude with Chapter 6, discussing my data in the light of neurocognitive models of healthy aging.

Chapter 1 – General introduction

Motor imagery as window on motor representations

Motor imagery (MI) is a mental state during which movements are mentally evoked and rehearsed without overt actions (Jeannerod and Decety, 1995).

A functional equivalence between MI and real movement execution is suggested by several lines of evidence: for example, (1) the isochronism of the physical and mental performances of the same action, (see for example Decety *et al.*, 1989) and the impact of biomechanical constraints on MI performance (2) the TMS and EMG evidence of a pre-activation of motor pathways during motor imagery tasks (Li *et al.*, 2004; Roosink and Zijdewind, 2010) and (3) the partial overlap of the neural networks activated during motor execution and imagination as revealed by PET and fMRI (see Hétu *et al.*, 2013 and Figure 1.1 for a systematic meta-analysis on the neurofunctional effects associated with MI).

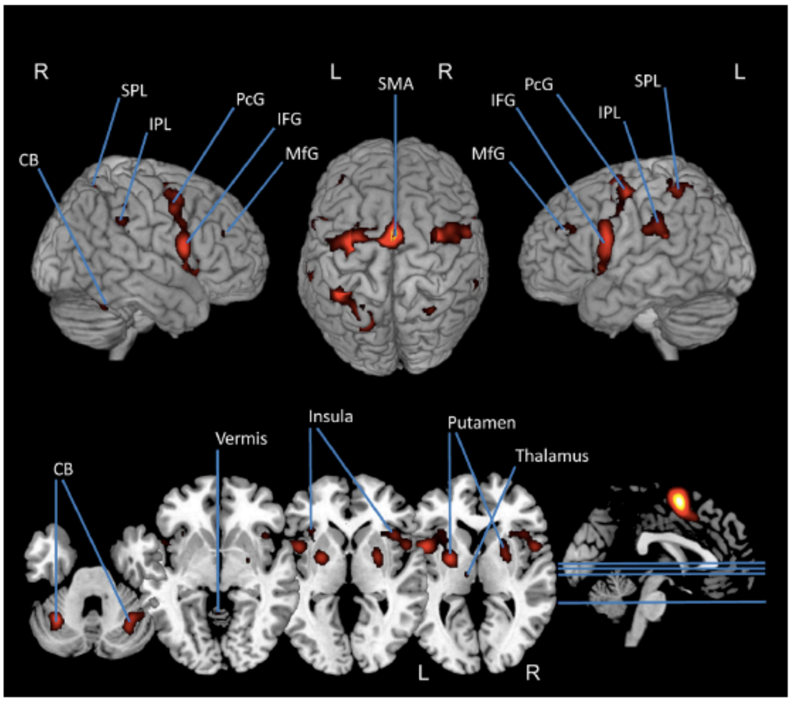

Figure 1.1. Regions consistently activated during motor imagery as seen in the meta-analysis by Hetu et al., 2013

Motor imagery is also being used as a Trojan horse to explore the organization of the motor system where the presence of an explicit motor outflow might be not desirable (e.g. in clinical conditions characterized by involuntary movements like, Gilles de la Tourette Syndrome – see Zapparoli *et al.*, 2015a; Zapparoli *et al.*, 2015b) or, in combination with fMRI, as a proxy for communication in patients unable to do so, like patients in apparent vegetative state (Owen *et al.*, 2006).

An exciting new exploitation of motor imagery activity is the one made in the area of neuroprosthetics: it has been shown that neural signals from posterior parietal cortex, decoded during a motor imagery behaviour, can govern a robotic limb in a tetraplegic patient and encode complex aspects of motor planning including motor goals (Aflalo *et al.*, 2015).

All this evidence is a clear vindication of the fact that during motor imagery subjects are capable of recruiting motoric representations and it provides the rationale for using MI in a variety of basic research and clinical domains for the study of motor neurocognition as well as in rehabilitation programs (for a review, seeMulder, 2007).

For example, MI trainings have been used in motor rehabilitation after stroke with variable fortunes (Page *et al.*, 2001a; Page *et al.*, 2001b; Jackson *et al.*, 2004), after brain injury (Braun *et al.*, 2011; Sacco *et al.*, 2011), in movement disorders (Braun *et al.*, 2011; Heremans *et al.*, 2011), but also as a complementary treatment of non-neurological patients to boost motor recovery after orthopaedic surgery (Christakou and Yannis, 2007; Lebon *et al.*, 2012).

MI has been also used to reinforce motor skills learning in healthy subjects (Lafleur *et al.*, 2002; Jackson *et al.*, 2003), including athletes (Moran *et al.*, 2012).

The growing interest in MI is confirmed by the important increase in publications related to MI since 1990 (see Figure 1.2).

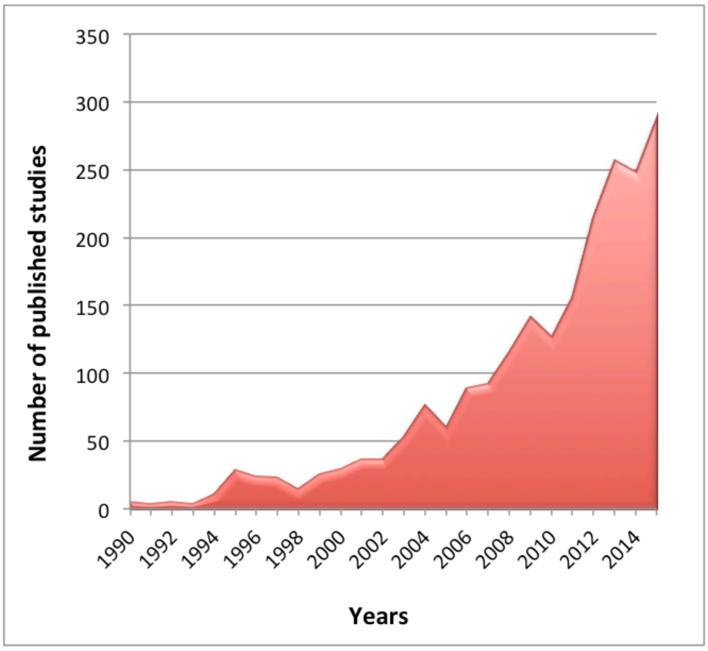

Figure 1.2. Increase of the number of published articles on MI between 1990 and 2015. Source: PubMed database (http://www.ncbi.nlm.nih.gov/pubmed/) using the term "motor imagery" as key word.

Explicit and Implicit Motor Imagery

The action simulation involved in MI can be triggered explicitly or an implicitly, depending on the instructions and task characteristics.

In Explicit MI, subjects are directly asked to imagine themselves while executing the required actions (Ehrsson *et al.*, 2003) and to focus on kinaesthetic bodily sensory information by taking a first-person egocentric perspective.

Explicit MI skills are indirectly investigated with self-report questionnaires or mental chronometry paradigms; the isochronism of executed and imagined movements is taken as evidence that explicit MI has motoric components (Collet *et al.*, 2011).

On the other hand in implicit tasks, the MI process may be triggered without explicit reference to the concept of MI during "prospective action judgements" (Jeannerod and Frak, 1999), as in the Grip Selection Task (GST), where subjects are asked to judge whether a tool is oriented conveniently for being grasped with the right or with the left hand (Johnson, 2000; Daprati *et al.*, 2010); another example of an implicit MI task is the Hand Laterality Task (HLT): subjects are asked to decide whether hands portrayed in a picture (rotated at different angles) are the left or right one. It is believed that during this task subjects unconsciously simulate a mental rotation of their own hand to match the position of the depicted hand stimulus, hence producing “motorically driven perceptual decisions” (Parsons, 1987a; Parsons, 1987b).

The contribution of a motoric component during these tasks is supported by PET and fMRI studies showing the involvement of the premotor cortices (the lateral premotor cortex and the SMA), of posterior parietal cortices (the superior parietal lobule and intraparietal sulcus) and the cerebellum (Bonda *et al.*, 1995; Parsons *et al.*, 1995; Vingerhoets *et al.*, 2002; Seurinck *et al.*, 2004; de Lange *et al.*, 2005; de Lange *et al.*, 2006; de Lange *et al.*, 2008).

Because of the implicit nature of the mechanisms whereby motor representations are evoked by tasks like the HLT or GST, a specific potential use in rehabilitation could be envisaged for clinical conditions like hemiplegia accompanied by anosognosia in which patient cooperation with explicit strategies may lack in spite of some sparing of cortical motor regions and their function (Gandola *et al.*, 2014).

Motor Imagery in the life cycle

There is a rich body of literature documenting age-related patterns of brain activity associated with the changes in cognitive function that are typical of normal aging (Park and Reuter-Lorenz, 2009). Several cognitive models have been proposed to interpret these findings.

The HAROLD model (hemispheric asymmetry reduction in older adults) hypothesizes that older adults have a more bilateral pattern of activations in the prefrontal cortex, in order to compensate for age-related cognitive decline (Cabeza, 2002). Based on a similar logic, the PASA model (posterior–anterior shift in aging) suggests that aging is associated with a significant reduction of neural activity in posterior areas (mainly occipito-temporal) together with a significant increment of activations at the level of the frontal lobe (Davis *et al.*, 2008).

The CRUNCH hypothesis (compensation-related utilization of neural circuit hypothesis) proposes that, in tasks with lower cognitive load, older adults recruit greater neural resources to compensate and reach the same level of performance of young people; however, when the cognitive load is higher, they show equivalent or lower activation and worse behavioral performance compared with young adults (Reuter-Lorenz and Cappell, 2008).

The Scaffolding Theory of Aging and Cognition (STAC) model (Park and Reuter-Lorenz, 2009) integrates compensation and dedifferentiation and include factors that may influence brain activation, such as neural challenges, behavioral performance and neuroplasticity. This model proposes that older subjects may maintain a good level of performance, despite neural impoverishment, thanks to the engagement of compensatory scaffolding that would manifest itself with the recruitment of additional brain regions shoring up "*the declining structures whose functioning has become noisy, inefficient or both*" (Park and Reuter-Lorenz, 2009). This theory represents the first attempt of linking functional, structural, cognitive changes in aging, with particular attention to the concept of compensatory processes in healthy seniors.

Neurofunctional compensatory processes have been previously described also in the domain of motor functions, using a variety of motor tasks, ranging from simple to complex movements (Mattay *et al.*, 2002; Ward and Frackowiak, 2003; Heuninckx *et al.*, 2005). These studies showed age-related differences, especially in non-motor brain regions associated with more cognitively demanding tasks, like pre-SMA, which may reflect increased cognitive monitoring of performance (for a review, see Nachev *et al.*, 2008); these differences are usually greater when complex tasks are used (Heuninckx *et al.*, 2005). These findings are usually interpreted as a sign of ''*an adaptable motor network able to respond to age-related degenerative changes in order to maintain performance levels*'' (Ward and Frackowiak, 2003).

Given the vast functional equivalence between motor execution and motor imagery at the cortical level, one would expect a similar scenario also for the MI domain.

To date, only few studies investigated the influence of ageing on MI processes; the details of these studies will be discussed in the next Chapters.

It is worth noting that the aforementioned studies are based on elderly subjects in their mid seventies on average. It remains unknown what happens in *younger* elderlies, one and a half decade earlier[1]. Do they have preserved motor imagery skills, and if so, are these subserved by the same functional anatomical patterns as in younger adults?

No study has yet investigated these issues nor it is known whether the eventual preservation of their imagery abilities is based on compensatory mechanisms of some kind. Given the rich literature on neurofunctional compensation processes in ageing, one could expect to observe different pattern of activation in young elderly subjects, which could be considered as a successful compensatory process or as a compensatory attempt, depending on whether the performance reaches a level similar to that of younger subjects (Berlingeri *et al.*, 2010).

The present thesis was designed to study the effects of early aging on MI, using different explicit and implicit tasks with different level of complexity, by means of behavioural and fMRI measurements.

In Chapter 2 I will address this issue through the study of 24 young and 24 elderly subjects during two fMRI tasks requiring real movement execution or explicit MI of hand movements.

In Chapter 3 will introduce implicit MI, reporting the neurofunctional effects in 30 young healthy subjects associated with a classic implicit MI task, the Hand Laterality Task; in Chapter 4 these data will be compared with those of 29 elderly subjects, in order to assess the effects of early aging on implicit motor processes.

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[1] For a long time the seventh decade, perhaps because it coincides with retirement for most people, was considered synonymous of old age. The socio-economical and medical progress, the increased proportion of surviving late elderlies may have moved the popular definition of senescence to the 8th decade in the economically developed countries (Orimo H, Hideki I, Suzuki T, Araki A, Hosoi T, Sawabe M. Reviewing the definition of "elderly". Geriatrics & Gerontology International 2006; 6(3): 149-58.)

Finally, in Chapter 5 I will investigate whether the effects of early aging could be better detected by using a more complex implicit MI task, through the study of 22 young and 23 elderly subjects performing a Grip Selection Task.

Because much of this work is already published or in-press in peer-reviewed articles (Zapparoli *et al.*, 2013; Zapparoli *et al.*, 2014; Zapparoli *et al.*, under second review), some sections (e.g. Methods, Results) are taken from the papers. Yet, the overall document is adapted to the narrative structure that is normally expected in a PhD thesis. In particular, the discussion of each experiment is shorter when compared with the one published in each paper. Shared comments that are relevant for all experiments are rather presented in a final general discussion.

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Chapter 2 - Mental images across adult life-span: a behavioural and fMRI investigation of motor execution and explicit motor imagery.

1. Introduction

As already pointed out in chapter one, explicit MI can be defined as a mental state in which real movements are explicitly evoked without an overt action (Jeannerod and Frak 1999). The simulation theory proposed by Jeannerod et al. (2001) postulates a functional equivalence between this specific cognitive process and the execution of real movements, arguing that imagined actions are actually actions, except for the fact that they are not executed. Several studies have confirmed the existence of neurocognitive similarities between explicit MI and M.E. (Decety et al. 1989; Georgopoulos and Massey 1987; Gerardin et al. 2000; Hanakawa et al. 2003; Jeannerod and Frak 1999; Sirigu et al. 1996). Interestingly, the mental simulations involved in explicit MI can be conducted without noticeable electromyographic activity (see for example Personnier et al. 2010a), suggesting that individuals are able to mentally rehearse covert actions with a minimal outflow of motor commands to the second motor neuron. Behavioural studies have also shown that the physical performance and the mental performance of the same action are generally temporally correlated (see Guillot and Collet 2005 for a review). For example, Decety et al. (1989) compared the time taken by subjects to walk either physically or mentally to targets located at different distances. They found that subjects took the same time in the M.E. and in the MI condition with a similar increase of the actual or imagined walking time with target distance. However they also made the very interesting observation that the MI time for the action of walking with a 25kg weight increased to a larger extent than the actual execution of the same action (Decety et al. 1989). Similar observations have been replicated several times for a variety of tasks. This difficulty effect conforms to Fitts' law for both executed and imagined movements (Decety and Jeannerod 1995; Sirigu et al. 1996; Stevens 2005). These findings suggest that explicit MI and M.E. may depend on partially overlapping neural systems, a prediction supported by several functional imaging studies on overt and imagined movements. This shared neural network includes the dorsal premotor cortex, the supplementary motor area (SMA), the ventral lateral premotor cortex, the cortex of the intraparietal sulcus and the supramarginal gyrus (Decety 1996; Gerardin et al. 2000; Hanakawa et al. 2003; Jeannerod and Frak 1999; Mattay et al. 2002; Stephan et al. 1995).

Differences between explicit MI and M.E. activation patterns have also been recorded. The posterior superior parietal cortex (Stephan et al. 1995) and a zone anterior to the lateral premotor cortex and to the SMA (pre-SMA) are the cortical areas that were more active in MI than during M.E. (Deiber et al. 1998; Gerardin et al. 2000; Lafleur et al. 2002). The cortical areas that were more active during movement than during imagery were located in the motor cortex proper, in the posterior part of the lateral premotor cortex (Stephan et al. 1995), in the posterior part of the SMA, in the parieto-temporal operculum and in the anterior parietal cortex (de Lange et al. 2005).

At the moment in which this study was conceived, only a few experiments had investigated age-related changes in explicit MI skills, with only one study to document the neural correlates of these changes. Some studies have combined transcranial magnetic stimulation (TMS) with measurements of motor-evoked potentials (MEP) and determined that the ability to produce corticomotor facilitation in association with a MI task is largely preserved with aging (Hovington and Brouwer 2010), even though the facilitations may be less muscle-selective in the elderly (Leonard and Tremblay 2007). On the other hand, behavioural experiments have shown that declining explicit MI ability is associated with normal aging (Mulder et al. 2007; Personnier et al. 2010a; Personnier et al. 2010b; Personnier et al. 2008; Skoura et al. 2005; Skoura et al. 2008). Other studies reported a stronger correlation between the real execution of movements and MI in healthy young subjects compared to older ones (Skoura et al. 2008). Notwithstanding these observations, Malouin et al. (2010) found that the vividness of MI is not affected by aging, they also found a change in the quality of MI in elderly subjects: with aging there is a reduction of the dominance of visual MI whereby kinaesthetic imagery becomes as relevant. The authors suggested that this effect could be due to a decline in visuospatial and kinesthetic working memory associated with aging.

This is not the only possible interpretation of the reasons for the deterioration of MI with aging; it has also been suggested that this decline might occur because sensory information from the periphery is not as efficiently available to the motor system during MI as it is during the actual execution of movements. This lack of sensory information might prevent the elderly subjects from verifying whether the imagined movements are similar to the actual ones (Skoura et al. 2008; Zwergal et al., 2012). Finally, another possible explanation is that feed-forward simulations of motor acts become less effective with aging (Personnier et al. 2008). These hypotheses will be further addressed in the discussion section of this Chapter.

There is a rich body of literature documenting age-related patterns of brain activity associated with the changes in cognitive function that are typical of normal aging (Park and Reuter-Lorenz 2009). Motor functions are no exception; neuroimaging studies have revealed that elderly subjects exhibit different brain activation patterns while making simple finger movements (Calautti et al. 2001; Hutchinson et al. 2002; Mattay et al. 2002), hand movements (Ward and Frackowiak 2003) or more complex interlimb coordination tasks (Heuninckx et al. 2005).

Only two imaging studies have addressed explicit MI and aging. One study (Nedelko et al. 2010) documented that the level of activation in the regions relevant for the mirror system (Rizzolatti and Craighero, 2004), the ventral premotor and inferior parietal cortex, was preserved when elderly subjects imagined movements previously seen in a video. Hyperactivation among the elderly participants was interpreted as indicative of compensatory activity for the age-related decline of neural structures. On the other hand, the study by Zwergal et al. (2012) on MI for walking, has been interpreted along the lines of the hypothesis that sensory information from the periphery is not available as efficiently in the elderly. Neurofunctional activities increased in the what the authors call vestibular cortices[2], in the motion-sensitive visual cortices and in the somatosensory areas. However, none of the previous studies has measured explicit correlations between behavioural variables and the brain response, nor the correlation of MI and M.E. of the same acts in aging.

The present study was designed to study the effects of aging on explicit MI using both behavioural and fMRI measurements and also to make explicit comparisons with motor execution of the same task. The subjects completed a finger opposition motor task and the same task performed in a kinaesthetic MI modality. The tasks were conducted separately for each hand. Moreover, to explore the correlation between executed and imagined movements and to compare those correlations across groups, subjects were also studied using a mental chronometry paradigm outside of the MRI scanner.

Because they have been seen in other cognitive domains in graceful aging (Berlingeri et al. 2010; Buckner 2004; Grady et al. 1994), I expected to observe quantitatively or topographically different patterns of activation (i.e., age-specific activations) in our normal elderly subjects. When present, these were tentatively interpreted according to the framework of compensatory processes (see Berlingeri et al. 2010 for further discussion); they were classified as a successful compensatory process or as a compensatory attempt, depending on whether the performance reached a juvenile-like level.

Because much is known about the functional properties of the different cortical areas, and because there was also an actual motor task to test the "motoric nature" of the MI patterns observed, I expected that a careful scrutiny of the differences in the patterns of brain activation between the young and the elderly participants would have helped to test some of the hypotheses that behavioural studies have offered related to the qualitative changes of MI of the elderly. To make one extreme example about one of the possible anticipated scenarios, the complete absence of

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[2] Contrary to what can be done for primary visual cortex and surrounding areas, by definition vestibular cortices cannot be identified as such only on the basis of topographic considerations as they are all multi-modal in nature (Guldin and Grusser, 1993). Accordingly, the Authors' functional attributions of those cortices are mere speculations.

motor/premotor activations for MI in the elderly might have brought support to the hypothesis that (forward) motor simulation becomes less possible, if not impossible, with aging (Personnier et al. 2008). As the reader shall see, a relatively more complex and yet still interpretable pattern of age-related differences emerged for both the M.E. and the MI task.

2. Materials and methods

2.1 Participants and neuropsychological assessment

The participants included 24 young subjects (12M/12F; age: 27±5.6 years) and 24 elderly subjects (11M/13F; age: 60±4.6 years). All the participants were right-handed; handedness was determined by using the Edinburgh Handedness inventory (Oldfield 1971). All the participants were in good health, with no past medical history for neurological, psychiatric or cognitive disorders. The subjects participated in the study only after the nature of the procedure had been fully explained and they had signed an informed consent form in compliance with the Declaration of Helsinki (1964).

All the young subjects were university students; the education level was balanced across groups (elderly group: 14±3.4 years; young group: 15±2.2 years).

To exclude age-related cognitive deficits, the elderly subjects also completed a neuropsychological assessment. The neuropsychological battery included a summary index of cognitive functioning, the Mini-Mental State Examination (Folstein et al. 1975), and a series of more specific neuropsychological tests assessing memory functions: short story recall (Spinnler and Tognoni 1987), delayed recall of the complex Rey’s figure (Carlesimo et al. 2002), Corsi’s block test (Orsini A. et al. 1987), digit span (Wechsler 1945); the Token test for language (Spinnler and Tognoni 1987), phonemic fluency (Novelli et al. 1986), semantic fluency (Novelli et al. 1986), the Trail Making Test parts A & B to test executive functions (Giovagnoli et al. 1996), attentional matrices (Spinnler and Tognoni 1987) and Raven’s Coloured Progressive Matrices to test abstract reasoning (Raven 1984). None of the subjects had pathological scores on this battery of tests.

2.2 Behavioural tasks

The aim of these tests was to establish the MI skills of participants and to assess the impact of aging on these skills. I examined the effects of normal aging on the temporal correspondence between overt and covert (imagined) movements with a mental chronometry task. The behavioural task was performed by all subjects half an hour after the fMRI scan. There were three classes of executed or imagined movements: the same finger opposition task[3] used for the fMRI scans; a pronosupination of the forearm, keeping the hand extended; and a fist-making movement. Each class of movement included 8 trials for each limb. Each trial involved a variable number of cycles (2, 3, 4 or 5 cycles). Each trial (e.g., 4 cycles of the pronosupination of the left forearm) was repeated twice so that there were 24 trials overall for each upper limb. The entire protocol was performed separately for each hand. The order of the tasks and the number of cycles in each trial were counterbalanced. Half of the subjects started with the right upper limb. For all conditions, the subjects sat comfortably in front of an examination desk. For the finger opposition task, the basic cycle involved four taps (thumb-to-index, thumb-to-middle, thumb-to-ring and thumb-to-little finger) with the forearm lying in a supinated position. For the pronosupination of the forearm, each subject laid a forearm on the desk in a half-pronated position (starting position). For the fist-making movements, the forearm was placed in a supinated position. The tasks were performed while the subjects' eyes were closed. For the MI tasks, the subjects were invited to perform the same tasks performed during the fMRI scans using a kinaesthetic imagery modality.

Each trial was triggered by the experimenter, who gave the "go-signal" to begin the execution/imagination of the requested movement; the M.E. and MI durations were measured by an

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[3] For the finger opposition task, there were minor differences between the fMRI and the task performed outside the scanner (during the behavioural task we varied the number of repetitions of the finger tapping (from 2 to 5 cycle). These were needed in order to collect meaningful behavioural data outside the scanner while keeping the subjects sufficiently involved in the task.

electronic stopwatch; in particular, the duration of the trial was measured from the "go-signal" (given by the experimenter) to the "stop-signal" (self-reported by the participant). All the subjects were first trained at the task to reach the require speed (approximately 1 Hz), by imitating the experimenter who performed the movement at the required speed.

The chronometry tests were available for 36 out of 48 subjects (18 for each group).

For each subject, I calculated the mean duration of the movements; subsequently, I examined whether the duration of the overt movements correlated with the duration of the covert movements.

Statistical analyses of the behavioural data

The M.E. and MI durations for the behavioural tasks performed outside the scanner were analysed as follows: the differences among the groups and the tasks were first analysed with a 2 (elderly vs young) x 3(opposition, fist-making, pronosupination) x 2 (motor execution vs. motor imagery) x 2 (hand) ANOVA. This analysis was followed by three 2 (group) x 2 (motor execution vs. motor imagery) x 2 (hand) ANOVAs for each task. A Greenhouse-Geisser correction for non-sphericity was used when needed. Correlation analyses using the Pearson coefficient were also performed to assess the temporal congruence between the motor execution tasks and the MI tasks.

2.3 fMRI experiment

MRI scans were performed using a 1.5 T GE Signa scanner and with a 1.5 Siemens Avanto scanner, equipped with echo-planar hardware for imaging. The same fMRI parameters were used for both scanners (for both scanners: flip angle 90°, TE=60 msec, TR=3000 msec, FOV=280x210 mm and matrix= 96 x 64 for both scanners). The slice thickness was 5 mm. All the subjects were also scanned with an MP-RAGE high-resolution (1x1x1 mm) T1-weighted volumetric scan for further visualisation of the results. To control for any scanner effect, there was an equal number of subjects scanned with the two scanners for each group.

The fMRI experiment consisted of one M.E. task and one MI task. The participants practiced the tasks before the beginning of the scanning session until they reached good accuracy (for the M.E. task) and the required speed (approximately 1 Hz). During the training session, all the participants performed and imagined each requested movement for two periods of 30 seconds each, alternating with resting periods, to simulate the fMRI experiment. All the subjects were able to perform the tasks flawlessly (i.e., at an asymptotic level) after two trials at most, and there were no differences between the groups in the time taken to learn the exceedingly simple finger tasks. The subjects kept their eyes closed for the entire experiment, and they were asked to concentrate on the task and to perform the task as accurately as possible.

The subjects performed the following tasks[4]:

- *Cued finger opposition*. Subjects were asked to alternately move the right or the left hand. The movements, performed at a frequency of approximately 1 Hz, involved touching the thumb to the fingers in sequence: thumb to index, thumb to middle finger, etc. After a few practice trials, the subjects were able to perform the actual motor task accurately at the desired rate. The subjects were monitored throughout the experiment for movement precision and speed. The task was self-paced, but the subjects were loosely cued in that they were given verbal reminders to perform the task once every 6 seconds. The performance of the tasks was alternated with resting state scans according to a block design. During the rest baseline control condition, the subjects were instructed to relax and to think of nothing. As before, the subjects were loosely cued and received a verbal reminder to remain in a resting state once every 6 seconds. Each block was 30 seconds long (10 scans in each period). There were 6 motor blocks and 6 rest blocks for each hand in alternating order.

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[4] When determining the ideal task for the experiments inside and outside the MRI scanner, a number of factors were taken into account, including compatibility with the fMRI environment and the magnitude of the cortical representation within the motor and premotor cortex for the body segment under investigation. I chose the finger opposition tasks because these tasks have been widely used in functional neuroimaging experiments (see for a review: Witt et al. 2008) and in MI investigations using both behavioural (see for example Sirigu et al. 1996) and neurofunctional techniques (see for example Guillot et al. 2009). Based on the same considerations, I decided not to use some interesting motor behaviours, such as pointing (Skoura et al. 2008), lifting one arm (Personnier et al. 2008), or walking (Skoura et al. 2005), despite the potential contribution these tasks could make to the investigation of MI in behavioural experiments.

- *Cued explicit MI of finger opposition*. The subjects were asked to imagine the same movements they had performed for the previous task. The subjects were instructed to avoid overt motion. The design, as before, involved 30 seconds alternating blocks of motor planning/imagery and rest, including the same verbal cues. The task was self-paced, but the subjects were loosely cued in that they were given verbal reminders to perform the task once every 6 seconds. The subjects were instructed to imagine movements from a kinaesthetic perspective, not from a third-person point of view, and not to count nor to assign numbers to each finger. The subjects were carefully observed by one of the experimenters in the scanner room who monitored for the correct execution of the actual motor tasks and the presence of spurious motor acts during the MI tasks. The subjects were debriefed after each experimental session (behavioural or fMRI) about their experiences. They all confirmed that they had performed the task as instructed, and there were only some anecdotal complaints by some elderly volunteers that they had had difficulty refraining from using a visual strategy.

2.4 fMRI data acquisition and analysis

For each condition, I collected 158 complete brain volumes.

Pre-processing

After image reconstruction, raw data visualisation and conversion from DICOM to the NIFTI format were performed with the software MRIcron (www.mricro.com).

All subsequent data analyses were performed in MATLAB 7.1 (Math Works, Natick, MA, USA), using the software Statistical Parametric Mapping (SPM8, Wellcome Department of Imaging Neuroscience, London, UK). First, fMRI scans were realigned to account for any movement during the experiment, and then they were stereotactically normalised into the MNI-EPI fMRI template space to permit group analyses of the data (Ashburner and Friston 1999; Friston et al. 1995). At this stage, the data matrix was interpolated to produce voxels with the dimensions 2 x 2 x 2 mm. The stereotactically normalised scans were smoothed using a Gaussian filter of 10 x 10 x 10 mm to improve the signal-to-noise ratio.

Statistical analyses

The BOLD signal associated with each experimental condition was analysed by a convolution with a canonical hemodynamic response function (Worsley and Friston 1995). Global differences in the fMRI signal were removed from all voxels with proportional scaling. High-pass filtering (128 seconds) was used to remove artifactual contributions to the fMRI signal, such as physiological noise from cardiac and respiratory cycles. First, a fixed-effect block-design analysis was performed for each subject to characterise the BOLD response associated with each task as opposed to rest. I created a contrast image for the effect of M.E. and MI for each hand, for each subject of each group. For example, for the motor execution task, I created the following contrast images for both groups: "M.E. with right hand > rest" and "M.E. with left hand > rest". To permit generalisation to the population level using group-based statistical inference, the individual contrast images generated by the fixed-effect analyses were entered in second-level ANOVAs conforming to random effect analyses (Holmes and Friston 1998; Penny and Holmes 2004). I assessed the following effects:

a) across-group effects: regardless of the experimental group, I first evaluated the commonalities and the differences between the M.E. task and the MI task. The commonalities were assessed as conjunction effects (Friston et al. 1999; Worsley and Friston 2000), and the differences were assessed as interaction effects;

b) within-group effects: the same effects were then calculated for each group separately;

c) between-group differences: activation patterns associated with MI or M.E. were compared across the groups;

d) correlation between behavioural indexes and fMRI patterns: the difference between the time taken to imagine rather than to perform a movement was used as a predicting covariate over the fMRI patterns for the two groups separately. This analysis included the data from the 36 subjects from whom the post-scan behavioural data were available.

The results of the statistical comparisons are visualised at the uncorrected $p < 0.001$ threshold. In the tables, I indicate which statistical effect survived one of the multiple comparisons corrections (family-wise error (FWE) offered by SPM8 (Worsley et al. 1996)), as complementary information to further explain the data[5]. These coordinates are marked by a *.

3. Behavioural results

The Greenhouse-Geisser corrected 3x2x2x2 ANOVA yielded the following results:

Main effects

Group: F(1, 34)=0.13; p=0.7. Hand F(1, 34)=0.7; p=0.4. Nature of the movement (finger opposition, pronosupination, fist-making) F(1.2, 42.1)=136.4; p<0.001, with the longest duration for the finger tapping task. Nature of the task (M.E., MI) F(1, 34)= 16.5; p<0.001, the motor imagery tasks being more time consuming.

Within group interactions

Nature of the movement*Nature of the task: F(1.1, 37.6)=12.8; p=0.001; the difference between execution and imagery was largest for the finger tapping task. Nature of the movement*hand: F(1.3, 44.1)=1.2; p<0.3. Nature of the task*hand: F(1, 34)= 0.1.; p=0.7. Nature of the movement*nature of the task*hand: F(1.4,47.4)=0.5; p=0.6.

By group interactions

Group*nature of the movement: F(1.2, 42.1)=5.7; p=0.02; the elderly were slower, particularly in the finger tapping task. Group*nature of the task: F(1, 34)=0.6; p=0.5. Group*hand: F(1, 34)=0.08; p=0.7. Group*nature of the movement*nature of the task: F(1.1, 37.6)=3.0; p=0.09. Group*nature

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[5] The group by task interaction effects are called "larger activations" or "additional activations," depending on whether the reference group had rather than not some activations in the given area.

of the movement*hand: F(1.3, 44.1)=0.7; p<0.4. Group*nature of the task*hand: F(1,34)=0.4; p<0.5. Group*nature of the movement*nature of the task*hand: F(1.4, 47.4)=0.8; p<0.4

To summarise, while there was no overall group effect, there was a clear task effect. The finger opposition task was the most time-consuming, given the nature of the task, and the MI tasks had longer duration overall. In addition, the finger opposition task produced the greatest difference between imagery and execution, shown by the significance of the Nature of the movement *Nature of the task interaction in the 3x2x2x2 ANOVA. The task-specific 2x2x2 ANOVAs showed no group effects. Rather, they showed the presence of motor imagery effects in all tasks. The significance of these effects was greatest for the finger opposition task: finger opposition F(1, 34)=17.1; p<0.001; pronosupination task F(1, 34)=5.1; p=0.03; fist-making task F(1, 34)=7.4; p=0.01. Exploration of the data shows that the size of this effect was largest for the finger opposition task (15% on average for this task, 5.6% for the pronosupination task and 1.5% for the fist-making task).

Group specific intersubject variability

We also assessed whether there were differences in the group-specific variability for the tasks by comparing the subject-specific SDs of the two groups for each task. This analysis showed that for the finger opposition task, there was a trend towards greater variability for MI among the elderly for both hands (right hand: one-tailed t(34)=1.4; p=0.07; left hand: one-tailed t(34)=1.3; p=0.09). The same analysis for M.E. showed no trends towards a difference (right hand: one-tailed t(34)=0,9; p=0.2; left hand: t(34)=0.2; p=0.4).

The same analysis for the other tasks showed no trends towards differences for the pronosupination task (MI right hand one-tailed t(34)=0.7, p= 0.2; MI left hand one-tailed t(34)=0.4, p=0.3; M.E. right hand one-tailed t(34)=1.1, p=0.2; M.E. left hand one-tailed t(34)=0.2, p=0.4) or for the fist-making task (MI right hand one-tailed t(34)=0.3, p=0.4; MI left hand one-tailed t(34)=0.3, p=0.4;

M.E. right hand one-tailed t(34)=0.3, p=0.4; M.E. left hand one-tailed t(34)=0.3, p=0.4).

Correlations between motor execution and motor imagery

Finally, I calculated the Pearson r-coefficient between the executed and imagined movement for each task and each hand in each group. For the finger opposition task, there was a strong significant correlation for the young participants ($r = 0.9$ for the right hand; $r = 0.9$ for the left hand; $p<0.001$ for both hands), but there was no correlation present for the elderly subjects ($r=0.4$ for the right hand; $r=0.5$ for the left hand; $p>0.05$ for both hands). See Figure 2.1.

On the contrary, for both the pronosupination task and the fist-making task, the temporal correlation was significant both for the young subjects (pronosupination task: $r=0.9$ for the right hand; $r=0.9$ for the left hand; $p<0.001$ for both hands; fist-making task: $r=1$ for the right hand; $r=1$ for the left hand; $p<0.001$ for both hands) and for the elderly subjects (pronosupination task: $r=0.7$ for the right hand; $r=0.7$ for the left hand; $p<0.05$ for both hands; fist-making task: $r=0.7$ for the right hand; $r=0.6$ for the left hand; $p<0.05$ for both hands).

To summarise, for the elderly participants, the correlation between executed and imagined movements is maintained for simple movements, while it is lost for tasks involving greater complexity, like the finger opposition task.

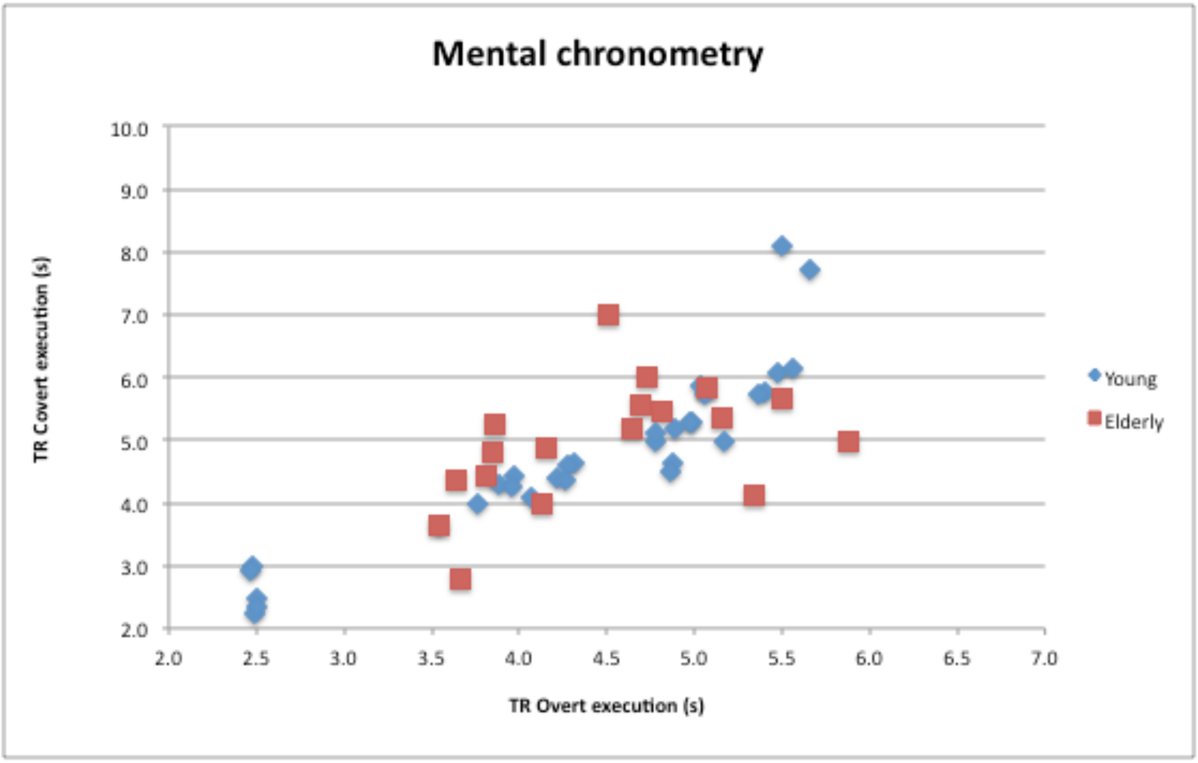

Figure 2.1. Behavioural results.

4. fMRI results

Having a 2x2x2 design with two within factors (M.E. and MI), two sides of the body (right and left) and one between-group factor (elderly and young subjects), there would be many results to report. In this Chapter, I focus on the most relevant ones; the effects not mentioned are not significant at the thresholds imposed on the statistical maps.

Brodmann areas and the coordinates of significant cluster maxima are reported in Tables 2.1 and 2.2.

I start by describing the within-group effects. I conclude this results section with the by-group interaction effects.

4.1 Commonalities and differences across M.E. and MI tasks.

As no hand-specific effects were observed for these analyses, the combined results are presented.

a) Conjunction of M.E. and MI

The areas of shared activation (across groups for both tasks and hands; see Figure 2.2a, areas in red) were the superior frontal gyrus, the SMA, the inferior temporal gyrus and the cerebellum in the left hemisphere. Further, shared activation was also found in the right hemisphere in the middle frontal gyrus, the insula, the angular gyrus and the superior temporal gyrus. Moreover, the shared pattern also includes, bilaterally, the precentral gyrus (area 6), the rolandic opercular gyrus, the parietal cortex (inferior and superior lobules), the supramarginal gyrus, the pallidum and the thalamus (see Figure 2.2a; areas in red).

b) M.E. task > M.I task.

The direct comparison between M.E. and MI showed that M.E. prompted stronger activation in the left supramarginal gyrus and in the left precentral gyrus (BA area 4) (see Figure 2.2a; areas in blue); differences were also observed in the right SMA and bilaterally in the cerebellum and in the postcentral gyrus (see Figure 2.2a; areas in blue).

These effects were common to the elderly participants and the young participants. There were no group-related interaction effects.

c) MI task > M.E. task. There were no brain regions showing a difference between MI and M.E. that was similar in magnitude across the two groups. The same comparison applied to the young subjects alone showed larger activations for MI in the left hemisphere in the frontal areas (superior, middle and inferior frontal gyri) and in the inferior parietal lobule (see Figure 2.2b, areas in green). In the elderly, the functional differences between M.E. and MI were much smaller; they were observed in the left frontal middle gyrus and the inferior frontal gyrus (triangular portion; see Figure 2.2b, areas in blue).

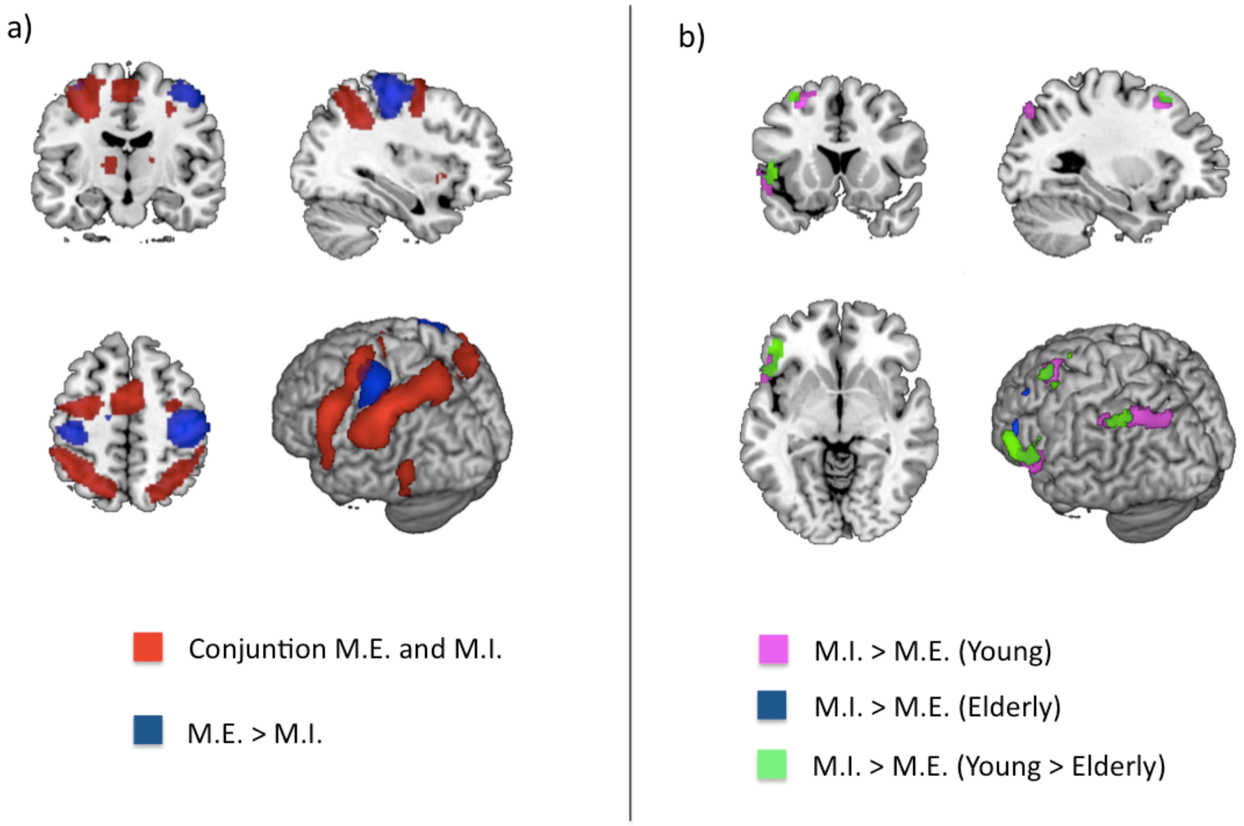

Figure 2.2. fMRI result: across group effects.

4.2 Commonalities related to M.E. tasks across both groups.

A conjunction analysis of M.E. effects, regardless of the hand in use, revealed that both groups showed activation in the precentral gyrus (primary motor cortex), the superior frontal gyrus, the rolandic opercular gyrus, the inferior parietal lobule and the superior temporal gyrus (see Figure 2.3a; areas in yellow).

Further shared effects were also found in the right SMA, the right pallidum, the right thalamus and bilaterally in the precentral gyrus (BA area 6), the inferior and the superior parietal lobules, as well as in the cerebellum (see Figure 2.3a; areas in yellow).

4.3 Commonalities related to MI tasks across both groups.

As for the results in section 4.2, no hand-specific effects (in terms of interactions) were observed. Therefore, combined results are presented.The conjunction analysis across groups for the MI tasks (see figure 2.3b, areas in violet) showed that both groups had activation in the left SMA, the left inferior frontal orbital gyrus, and bilaterally in the precentral gyrus (area 6), frontal areas (middle and superior gyri), the insula, parietal areas (inferior and superior lobules), the supramarginal gyrus, the pallidum, the thalamus, and in the cerebellum. During the MI tasks, both the young and elderly subjects also showed activation in the left inferior temporal gyrus, the right inferior frontal triangular gyrus, and right temporal areas, comprising the superior temporal gyrus and the superior temporal pole (see figure 2.3b, areas in violet).

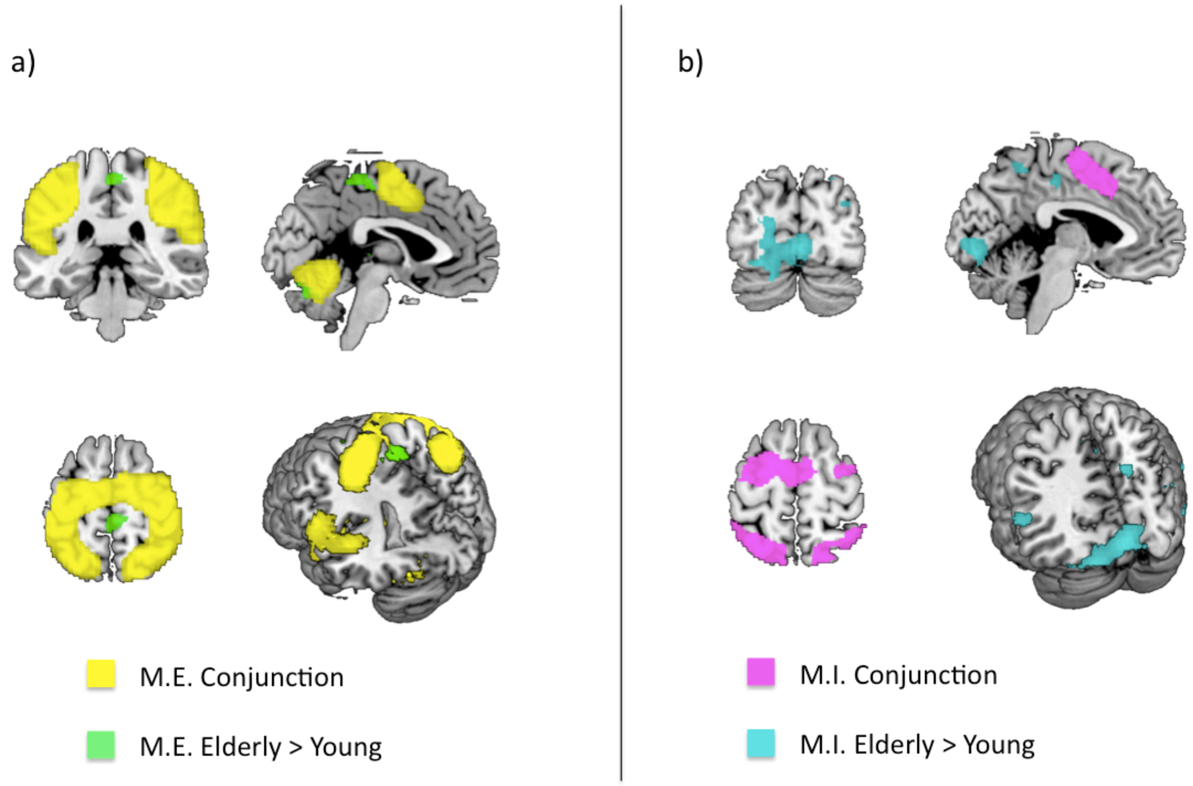

Figure 2.3. fMRI results: commonalities and differences between groups.

Table 2.1. fMRI results: across group effects.

Brain regions (BA)	MNI coordinates							
	x	y	z	Z-score	x	y	z	Z-score
	Left hemisphere				*Right hemisphere*			
Commonalities and differences across motor execution and motor imagery tasks								
a) M.E. and MI conjunction Elderly and Young								
Rolandic opercular gyrus (6)	-52	4	14	5.8*	--	--	--	--
Rolandic opercular gyrus	-48	4	4	6.3*	52	6	6	4.8*
Insula	--	--	--	--	46	6	4	5.0*
	--	--	--	--	50	4	-4	5.3*
Sup. frontal gyrus (6)	-26	-4	64	6.5*	--	--	--	--
Mid frontal gyrus	--	--	--	--	36	-4	60	5.0*
Precentral gyrus (6)	-52	2	34	7.5*	58	4	34	5.8*
	-40	-6	56	6.2*	56	10	4	4.9*
SMA (6)	-2	-2	56	7.1*	--	--	--	--
Sup. parietal lobule (7)	-24	-66	60	6.8*	24	-72	56	6.0*

Sup. parietal lobule (40)	--	--	--	--	44	-52	60	5.5*
Inf. parietal lobule (40)	-42	-40	40	Inf	36	-46	42	6.6*
	--	--	--	--	54	-38	58	4.5*
Supramarginal gyrus	-54	-26	26	6.5*	62	-36	32	4.8*
Angular gyrus (7)	--	--	--	--	28	-62	48	5.6*
Sup. temporal gyrus (42)	--	--	--	--	66	-30	16	4.8*
Mid. temporal gyrus (37)	-54	-60	0	5.5*	62	-52	-6	4.7*
Inf. temporal gyrus (37)	-54	-60	-16	4.7*	--	--	--	--
Cerebellum_6	-28	-60	-28	5.0*	--	--	--	--
Pallidum	-20	-4	8	5.3*	18	0	-2	5.4*
	--	--	--	--	22	-2	2	5.4*
	--	--	--	--	22	2	-2	5.3*
Thalamus	-12	-12	8	5.0*	14	-6	8	5.1*
	-10	-18	8	5.0*	--	--	--	--
b) M.E. > MI conjunction Elderly and Young								
Precentral gyrus (4)	--	--	--	--	28	-26	74	4.5*
	--	--	--	--	30	-30	74	4.4*
	--	--	--	--	40	-22	56	7.8*
Postcentral gyrus (3)	-38	-28	54	6.5*				
Supramarginal gyrus	--	--	--	--	54	-22	28	4.8*
	--	--	--	--	56	-22	24	4.7*
c) MI > M.E. (Young subjects)								
Inf. frontal gyrus, triang. part (45)	-46	38	0	5.2*	--	--	--	--
Inf. frontal gyrus, orbital part (47)	-46	36	-4	5.2*	--	--	--	--
Inf. frontal gyrus, operc. part	-50	14	12	4.3*	--	--	--	--
Sup. frontal gyrus (6)	-18	8	66	4.4*	--	--	--	--
Mid. frontal gyrus (6)	-42	6	56	4.5*	--	--	--	--
Mid. frontal gyrus (8)	-32	20	56	5.3*	--	--	--	--
Inf. parietal lobule (40)	-56	-52	48	5.1*	--	--	--	--
d) MI > M.E. (Elderly subjects)								
Inf. frontal gyrus, triang. part (45)	-52	34	18	5.1	--	--	--	--
Mid frontal gyrus (46)	-40	30	42	4.5	--	--	--	--
Commonalities during tasks across both groups								
a) M.E. conjunction Elderly and Young								
Rolandic opercular gyrus	-48	2	8	4.4*	--	--	--	--
Sup. frontal gyrus (6)	-24	-8	52	5.3*	--	--	--	--
Precentral gyrus (4)	-54	0	36	5.3*	--	--	--	--
Precentral gyrus (6)	-34	-10	58	5.8*	60	4	32	5.1*
	--	--	--	--	30	-10	56	5.3*

	--	--	--	--	32	-14	58	5.3*
	--	--	--	--	40	-6	60	5.5*
SMA (6)	--	--	--	--	6	-4	52	6.8*
Sup. parietal lobule (40)	--	--	--	--	36	-52	58	5.1*
	--	--	--	--	32	-54	56	5.1*
Sup. parietal lobule (7)	-24	-62	64	5.8*	22	-64	54	5.4*
	--	--	--	--	20	-62	60	5.4*
	--	--	--	--	24	-60	60	5.4*
Inf. parietal lobule (40)	-42	-36	40	6.7*	--	--	--	--
	-32	-50	50	5.6*	--	--	--	--
	-36	-48	48	5.5*	--	--	--	--
Supramarginal gyrus (40)	--	--	--	--	48	-34	40	6.6*
Supramarginal gyrus	-50	-28	30	5.5*	58	-20	24	5.6*
Sup. temporal gyrus (42)	-52	-30	14	4.6*	--	--	--	--
Sup. temporal gyrus	-52	-38	22	5.0*	--	--	--	--
Cerebellum_crus_1	--	--	--	--	32	-60	-28	5.1*
Cerebellum_6	-24	-54	-30	6.2*	20	-64	-22	5.3*
	--	--	--	--	28	-54	-34	5.5*
Vermis_6	--	--	--	--	0	-64	-16	6.5*
	--	--	--	--	0	-62	-12	6.4*
Pallidum	--	--	--	--	24	-2	0	4.5*
Thalamus	--	--	--	--	16	-18	12	4.5*
b) MI conjunction Elderly and Young								
Inf. frontal gyrus, orbital part (47)	-48	40	-4	4.6*	--	--	--	--
Inf. frontal gyrus, triang. part (45)	--	--	--	--	46	36	0	5.2*
Mid. frontal gyrus (46)	-38	38	32	5.9*	40	44	32	4.8*
Precentral gyrus (6)	-52	4	34	7.5*	58	4	34	5.8*
	-52	2	38	7.5*	--	--	--	--
	-50	2	48	7.4*	--	--	--	--
Sup. frontal gyrus (6)	-26	-2	64	6.7*	36	-4	60	5.0*
SMA (6)	-2	-2	56	7.1*	--	--	--	--
Insula	-46	10	-4	7.3*	42	18	-2	6.3*
	--	--	--	--	48	8	-4	5.8*
Sup. parietal lobule (40)	--	--	--	--	44	-52	60	5.5*
Sup. parietal lobule (7)	-24	-66	60	6.8*	24	-72	56	6.0*
	--	--	--	--	24	-60	62	4.5*
Inf. parietal lobule (40)	-42	-40	40	Inf*	36	-46	42	6.6*
	-38	-48	42	Inf*	54	-38	58	4.5*
Supramarginal gyrus (40)	--	--	--	--	62	-38	32	4.8*
Supramarginal gyrus	-52	-42	26	6.6*	66	-42	26	4.7*
	-54	-26	26	6.5*	--	--	--	--
Sup. temporal pole (38)	--	--	--	--	50	22	-16	5.1*

Sup. temporal gyrus (22)	--	--	--	--	66	-30	16	4.8*
Mid. temporal gyrus (21)	-52	-52	12	4.3*	66	-46	-4	5.7*
Inf. temporal gyrus (37)	-56	-58	-4	6.5*	--	--	--	--
Cerebellum_6	-28	-60	-28	5.0*	30	-68	-26	4.6*
Pallidum	-24	0	0	5.0*	22	-2	2	5.4*
	--	--	--	--	18	0	-2	5.4*
	--	--	--	--	22	2	-2	5.3*
Thalamus	-12	-12	8	5.0*	14	-6	8	5.1*
	-10	-18	8	5.0*	--	--	--	--

* FWE correct.

4.4 Between-group differences.

As before, I concentrate on the effects that were statistically significant. Any effect not mentioned was not significant.

a) MI task versus M.E. task.

Comparing these effects across groups (MI > M.E. for young > elderly) showed that among the young subjects, MI increased activations more than M.E., and the increase was greater than that observed in the elderly subjects. These effects were in the frontal areas (middle and frontal orbital gyri), the inferior parietal lobule, the angular gyrus, the superior temporal pole, and the putamen in the left hemisphere (see Figure 2.2b, areas in violet).

b) M.E. task

There were group-related differences: the elderly showed additional activations in the left inferior occipital gyrus, the right paracentral lobule, and in the right pre-SMA. Greater activations were found in the left SMA and in the right cerebellum.

No significant difference was found when comparing the M.E. effect (for both hands) in the young subjects with the elderly subjects (see Figure 2.3a; areas in green).

c) M.E. task: hand-specific effects.

Overall, the group-related differences can be summarised by stating that the activations for each hand (analysed separately) were more bilateral in the elderly subjects (see Figure 2.4). In fact, for both hands, compared with the younger subjects, the elderly subjects had greater activation in the S1 hand cortex in the same hemisphere as the moving hand (see figure 2.4a). When the left hand was moving, the greater ipsilateral activation was also present in the M1 hand cortex. These differences also proved to be significant when tested as reduced by hemisphere interaction effects in the elderly subjects as opposed to the younger ones. The effects are shown in the bar graphs in Figure 2.4b. In both S1 areas, the response for the ipsilateral hand is larger in the elderly subjects.

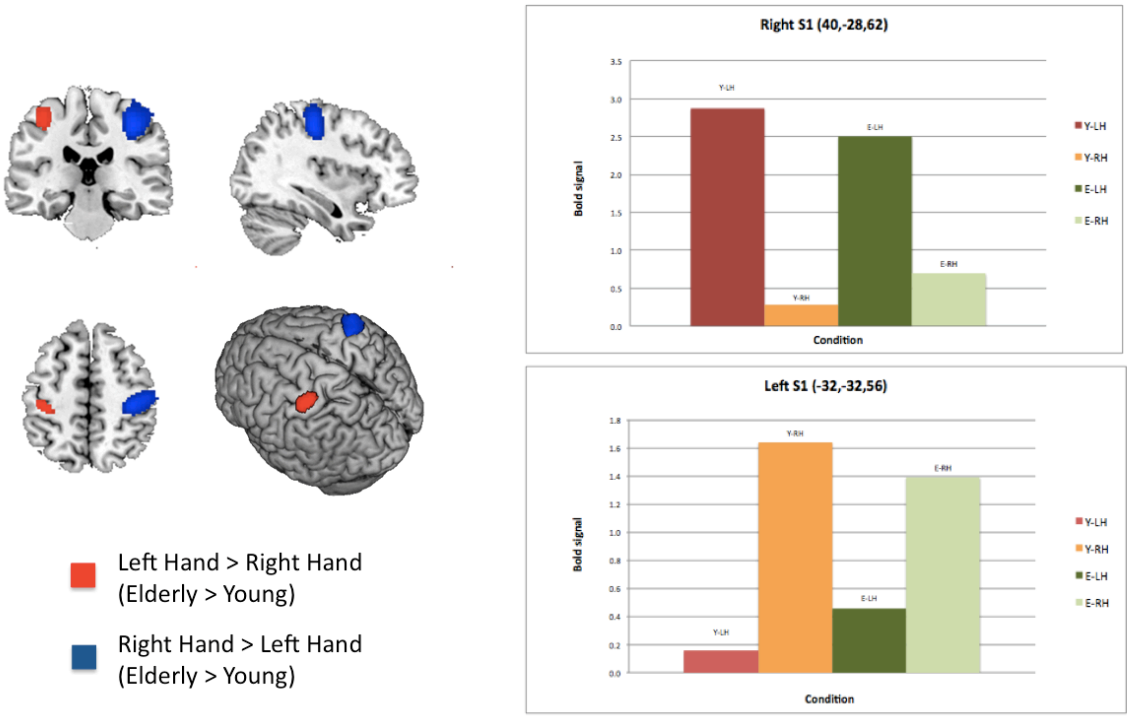

Figure 2.4. Reduced asymmetries in elderlies.

d) MI Task

The between-group comparisons showed additional activations in the elderly subjects: bilaterally in the occipital areas (calcarine fissure and inferior occipital gyrus), the left fusiform gyrus, the left subcortical structures (putamen and thalamus) and the left hippocampus. Greater activations were also found in the right hemisphere, in the superior and in the inferior temporal gyri (see Figure 2.3b, areas in light blue).

However, the opposite comparison (i.e., young subjects > elderly subjects) yielded no significant difference.

Table 2.2. fMRI Results: between group effects.

Brain regions (BA)	**MNI coordinates**							
	x	**y**	**z**	**Z-score**	**x**	**y**	**z**	**Z-score**
	Left hemisphere				**Right hemisphere**			
a) MI>M.E. for Young > Elderly								
Inf. frontal gyrus, orbital part (38)	-52	24	-10	2.4	--	--	--	--
Angular gyrus (39)	-40	-62	48	2.4	--	--	--	--
Putamen	-26	16	50	2.9	--	--	--	--
b) M.E. task: Elderly>Young								
SMA (6)	-16	6	66	4.4	--	--	--	--
Pre-SMA (6)	--	--	--	--	2	-28	58	5.0
Paracentral lobule (4)	--	--	--	--	10	-28	62	4.7
Inf. occipital gyrus (19)	-38	-62	-4	4.7	--	--	--	--
Vermis_7	--	--	--	--	2	-74	-22	5.2
c) M.E.: hand-specific effects								
M.E.: Right Hand > Left Hand (Young)								
Hippocampus (20)	-28	-10	-14	4.6*	--	--	--	--
Postcentral gyrus (3)	-34	-30	56	Inf*	--	--	--	--
Cerebellum_4_5	--	--	--	--	16	-52	-24	4.8*
M.E.: Right Hand > Left Hand (Elderly)								
Postcentral gyrus (3)	-38	-28	54	5.7*	--	--	--	--
M.E.: Left Hand > Right Hand (Young)								
SMA (6)	--	--	--	--	12	-18	52	4.3*
Postcentral gyrus (4)	--	--	--	--	38	-24	54	Inf*
Heschl gyrus	--	--	--	--	44	-18	14	5.0*

Postcentral gyrus (3)	--	--	--	--	40	-24	48	7.4*
	--	--	--	--	36	-26	48	7.3*
M.E.: Left Hand > Right Hand (Elderly)								
Postcentral gyrus (3)	-32	-32	66	2.3	--	--	--	--
Hippocampus (20)	-28	-12	-14	2.5	--	--	--	--
Postcentral gyrus (3)	--	--	--	--	40	-30	66	2.2
M.E.: Left hand > Right hand for Elderly>Young								
Sup. temporal gyrus	--	--	--	--	48	-28	8	5.1
Hippocampus (20)	-34	-28	-8	4.1	--	--	--	--
Mid. temporal gyrus (42)	-60	-42	12	3.7	--	--	--	--
Inf. temporal gyrus (37, compatible with EBA).	--	--	--	--	54	-64	-8	4.3
Inf. occipital gyrus (19)	-44	-72	-12	3.2	46	-66	-14	3.4
	-40	-70	-10	3.2	--	--	--	--
	-42	-62	-6	3.2	--	--	--	--
Fusiform gyrus (19)	-26	-82	-16	4.1	--	--	--	--
	-42	-76	-14	3.4	--	--	--	--
Calcarine fissure (17)	-10	-90	2	4.8	2	-82	-2	4.5
	-6	-96	0	2.8	--	--	--	--
Putamen	-28	-8	10	3.1	--	--	--	--
Thalamus	-20	-18	12	3.2	--	--	--	--
Correlation between behavioural and neurofunctional results								
a) Elderly subjects								
Sup. temporal gyrus	52	-26	14	3.2	--	--	--	--
Fusiform gyrus (18)	-24	-82	-16	2.9	--	--	--	--
Lingual gyrus (19)	-28	-84	-14	2.7	--	--	--	--
Calcarine fissure (17)	-6	-96	0	2.8	2	-82	-8	3.0
Cerebellum	-16	-78	-28	4.1	--	--	--	--
b) Young subjects								
Inf. frontal gyrus (opercular part)	-36	4	26	2.7	--	--	--	--
SMA (6)	-12	2	68	4.8	--	--	--	--
Angular gyrus	-40	-70	46	4.1	--	--	--	--
Precuneus (7)	-16	-68	62	5.1	--	--	--	--
Sup. Parietal lobule (7)	-28	-64	64	3.6	16	-74	58	4.1
Thalamus	-6	-18	6	2.9	12	-6	14	3.3

* FWE correct

5. Correlations between functional and behavioural data.

To further explore the implications of the behavioural and functional anatomical observations related to the age groups described above, the difference between the time taken to imagine a movement and the time taken to execute the same action was used as a covariate in linear regression analyses. The analyses were performed for each group separately using the MI minus rest contrast images (see Figure 2.5a).

In the elderly, the behavioural discrepancy index correlated with the BOLD response in the brain regions where the activation had been stronger compared to the younger participants; in particular, the higher the neural activity in these areas, the larger the temporal discrepancy between MI and M.E (see Figure 2.5b).

On the other hand, in the younger subjects, the same analysis showed a correlation with areas that belong to the motor system (e.g., SMA) (see Figure 2.5c).

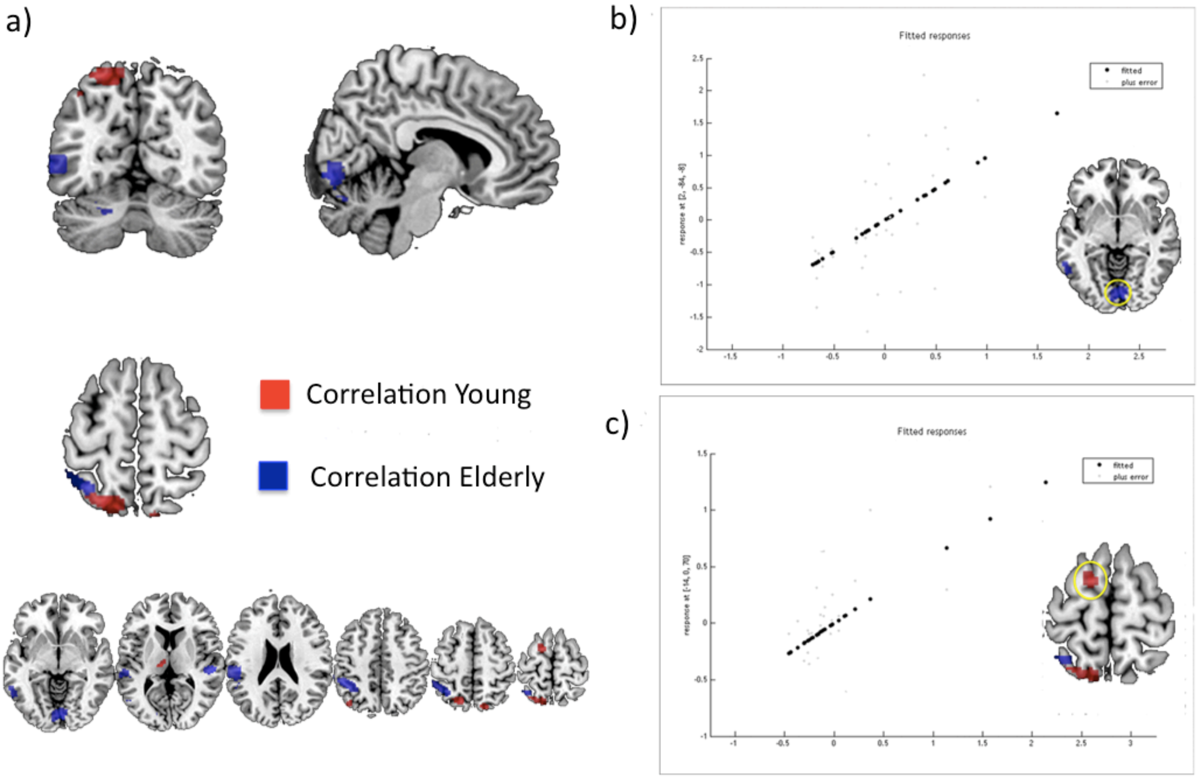

Figure 2.5. Correlation between fMRI and behavioural data.

6. Discussion

This experiment was designed to expand the research on aging in the domain of motor performance and explicit MI. The latter has been the object of intensive investigation, given its potential to unravel residual mental/neural activity in severely brain-damaged patients but also given its potential role in neurological rehabilitation (Ietswaart et al. 2011; Jackson et al. 2004; Johnson-Frey 2004; Liu et al. 2004; Malouin et al. 2004; Page et al. 2001) or in patients with orthopaedic problems (Stenekes et al. 2009).

The results of this study documented for the first time (by the time in which the experiment was published), fMRI patterns illustrating the behavioural changes associated with aging in the domain of explicit MI, suggesting a qualitative difference between elderly and younger participants. It is relevant for my results that fMRI differences were also observed in the actual execution of the motor task, clearly indicating that the execution of simple motor acts, even simple finger movements, less a less automatic (i.e., a more cognitively demanding) activity. In the following pages, I begin by discussing whether motor activity becomes less automatic with aging and continue to discuss the meaning of a more bilaterally distributed response in the primary somatosensory and motor areas. This experiment brings novel evidence to this area of study.

I then continue with a discussion of the core subject of my experiment, namely, explicit MI and aging. In particular, I will discuss whether the fMRI data may provide a functional explanation of the behavioural differences observed between young and elderly participants when they are engaged in a MI task.

Is motor execution more cognitively demanding in elderly subjects?

A progressive decline in motor performance is a hallmark of aging. Another hallmark of aging is a decline in cognitive functions, such as episodic long-term memory (Davis et al. 2008). Motor performance decline, however, can be detected only very late in life. In relatively old subjects (such as those in my sample), the accuracy of motor performance remains similar to that of young subjects (Mattay et al. 2002; Wu and Hallett 2005). Age-related differences in motor performance are detected only in tasks of increasing complexity, such as visually guided hand movements and more demanding tasks performed under time pressure (Kauranen and Vanharanta 1996); these differences become more marked after the age of 60 (Smith et al. 1999). Identical (i.e., not significantly different) motor performance for the relatively simple finger opposition task adopted here was a by-design trait of my findings in the subjects in their early 60s (the oldest subject was 70 years old).

Models of graceful aging predict that the maintenance of juvenile performance comes at the cost of a greater neuronal labour in the elderly, an adaptation labelled as a compensatory process. Compensatory processes have been observed in previous experiments. For example, Mattay et al. (2002) found that older subjects involved in an auditory paced motor task overactivated a number of fronto-parietal regions, as well as the cerebellum, once compared with the younger participants. Interestingly, among the elderly subjects, they found a negative correlation between hyperactivations and the M.E. durations. A similar scenario has been observed by Ward and Frackowiak (2003), who tested the effects of aging using a visually paced power-grip task. In both cases, the findings were interpreted as evidence of “an adaptable motor network able to respond to age-related degenerative changes in order to maintain performance levels” (Ward and Frackowiak 2003).

My results for the motor tasks broadly replicate these previous findings, not only by showing the increased activations for the elderly subjects in motor specific regions, such as the SMA, the paracentral lobule and the cerebellum, but also in regions such as the pre-SMA, which is typically associated with cognitively demanding tasks (Nachev et al. 2008; Deblieck et al. 2003). The pre-SMA is considered a high-level motor planning area, as it is involved in processes such as conflict monitoring and inhibitory control (for a review see Nachev et al. 2008).

Moreover, Lau et al. (2004) proposed that activation of the pre-SMA is a functional correlate of the “intention to move”. Similar considerations may apply for the cerebellum, a structure that is more activated during tasks of greater complexity, as demonstrated by a number of previous studies (e.g., Catalan et al., 1998) and confirmed by the meta-analysis by Chan and colleagues (Chan et al. 2009), who found a complexity effect for the regions of the vermis. In the same vein, as the elderly subjects showed significantly greater activation in the region of the vermis while performing the same task as the younger participants, we hypothesise that task complexity was intrinsically greater for elderly participants because of the effects of aging.

Another age-related topographical difference in the fMRI patterns of M.E. was in the occipital lobes, which showed greater activation in the elderly group. Similar differences were found in a previous study by Heuninckx et al. (2005), in which the authors investigated the age-related BOLD responses during flexion-extension of the right hand and/or the right foot. The complexity of the task was manipulated by asking subjects to perform the same movements (isodirectional task) rather than opposite movements (non-isodirectional task) with the two body segments. Interestingly, there were several additional brain areas activated in the elderly, including the occipital lobe, in association with the more difficult non-isodirectional tasks, a result similar to my study results. Based on the overall fMRI pattern observed in the elderly, I therefore propose that even simple movements are perceived by the elderly as relatively difficult tasks. The additional occipital activation may also suggest that during relatively artificial conditions, such as those of an fMRI experiment, elderly subjects may use a mental visual imagery strategy. The results of Guillot et al. (2009) are in line with this hypothesis, showing a specific activation of the occipital lobes during visual imagery (Guillot et al., 2009); moreover, similar activations were previously associated in relation to movement observation (Bonda et al., 1996; Grezes et al., 1998). The use of a visualization strategy may help elderly subjects in monitoring their motor performance, as already proposed by Heunincx (2005).

The same line of reasoning allows one to predict that **elderly subjects may rely more on visual control when they act compared to younger subjects**. This controversial issue was recently addressed by Coats and Wann (2011). In their study, young and elderly subjects performed a reaching and grasping experiment using an apparatus that eventually obscured the target and the approaching hand, after allowing for initial visual exploration. For the elderly subjects, both reaching and grasping were affected selectively when visualisation of the hand was prevented; they produced additional reaching movements and had longer adjustment times for the grasping phase of the movement. **These findings suggest that elderly subjects are more reliant on visual feedback than the young in tasks that require precise manual control**.

Of course, the finger-opposition task is very different from a reaching and grasping task, and therefore the confirmatory value of this evidence on my interpretation of the fMRI data requires some caution. Further experimental confirmation would strengthen my hypothesis that the visual observation of hand-movements becomes so hardwired in elderly subjects that occipital involvement occurs during these movements, even when subjects keep their eyes shut **(see chapter 5).**

Finally, there is an argument in favour of the hypotheses discussed here, as we found that there was **only a marginal difference in brain activation between MI and M.E. for the elderly subjects**. This was **not the case for the younger participants**, who showed additional activation of a fronto-temporo-parietal network of associative cortices for explicit MI compared to M.E. The age-related difference, qualified by a second order interaction (group x imagery-minus-motor execution), was highly significant. This finding, unique to my experiment, provides further evidence that M.E. becomes less automatic and more cognitively demanding in elderly subjects.

Hand-specific effects and the reduced functional asymmetry in sensorimotor cortices in the elderly.

Another substantial difference between the two groups was a comparatively larger response in both areas S1/M1 in the elderly subjects for the motion of the ipsilateral hand. The bar graphs in figure 2.4b show the size of these effects in the left and right areas S1 in the hand region. The elderly had a comparatively larger response for the ipsilateral moving hand, causing a significant attenuation of the differential response for the two hands in these somatotopically organised regions. In other words, in the elderly subjects, areas S1/M1 displayed a smaller functional difference for the motion of the contralateral hand and the ipsilateral hand. Although these may be loosely interpreted in terms of reduced hemispheric specialisation – or commitment to the contralateral half of the body – for the elderly, technically speaking, these effects are different from those in which the hemispheric lateralisation of brain response is tested with some type of lateralisation index or map (Hutsler and Galuske 2003; Seghier 2008; Strauss et al. 1983). Previous studies have suggested a reduction of hemispheric asymmetry in older adults during cognitive tasks (Cabeza et al. 2002; Grady et al. 1994). For the domain of motor control, Mattay et al. (2002) have shown increased ipsilateral activation in older subjects in a number of fronto-parietal regions involved in M.E. during a paced key-pressing task. While elderly subjects were significantly slower, their accuracy matched that of the younger participants. The authors concluded that their data suggested that compensatory changes in brain activation are present even at the level of simple motor functions.

The topographical cortical distribution of the effects permits some functional speculation about their meaning, while not necessarily advocating to the conceptual umbrella of compensatory processes. The region most involved was area S1, a somatotopically organised somatosensory cortex in the hand region. Rather than suggesting a form of compensation, the comparatively larger response for the ipsilateral hand may represent an indication of a **reduced signal-to-noise ratio in the somatosensory system of the elderly** (in this case, for re-entering somatosensory signals). There is some recent evidence consistent with this general interpretation. According to Kalisch et al. (2009), **2-point discrimination thresholds show a strong decline with age,** despite electrical dipole signs representing an enlarged hand. Further, Lenz et al. (2012) found a reduced paired pulse suppression in the elderly (i.e., an attenuation of the physiological decrease of the event-related response in area S1 for temporally close stimuli). This phenomenon was also associated with decreased tactile two-point discrimination, particularly for the subjects showing markedly enhanced cortical excitability.

Further studies are needed to fully address the functional meaning of the reduced contra-vs.-ipsilateral differential response in area S1/M1 in the elderly.

Motor Imagery Task

Functional imaging studies on MI may face some scepticism given the *private nature* of the mental activity under investigation.[6] However, previous experiments have shown that, as private as mental activity can be, regional patterns of brain activation can be used to make inferences about the quality of on-going mental processes. For example, O'Craven and Kanwisher (2000) demonstrated that visual imagery for faces and places can be anatomically double dissociated in ways that mimic the dissociation for the perception of the same stimuli. Lumer et al. (1998), by exploiting the binocular rivalry phenomenon, demonstrated that it is possible to retrospectively identify the moment when a subject perceives stimuli in the left eye rather than the right eye. I take the same general approach, and I capitalise on the vast knowledge regarding the regional cortical contribution to cognition, accumulated in the last 20 years of functional imaging experiments, to make inferences about the implications of the fMRI patterns, insofar as the aging process is concerned.

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[6] A common objection to the concept of MI and its motoric nature as demonstrated by functional neuroimaging is that experimenters may occasionally miss small muscle contractions or even quasi-movements that their volunteers make during tasks. Similar to Jeannerod and Decety (1995), I conceptualise MI as a form of cognitive motor rehearsal deprived from an explicit motor outflow. For us, the occasional presence of a green light to spinal motor neurons that manifests itself with occasional motor twitches does not detract from the quality of the mental process under investigation. In addition, the exploration of the neurofunctional activations recorded during MI and the direct comparison with the neural activity of the executed motor task reinforces our suggestion. As in previous experiments, I observed commonalities and differences to strongly suggest the following: (1) the likely motoric nature of MI given the activation of motor/premotor cortices; (2) the much larger implementation of *actual* motor acts during M.E. (see the highly significant larger activation of M1/S1 in the M.E. task); and (3) the more cognitive nature of the MI task overall, as revealed by the recruitment of higher order premotor and parietal cortices during imagery, particularly in the younger participants.

My conclusions about the fMRI effects due to aging in MI rest on a solid behavioural observation. Namely, the temporal correspondence between executed and imagined movements is reduced in elderly adults, especially for movements that impose high spatiotemporal or dynamic constraints. This has previously been observed for a variety of tasks, such as pointing (Skoura et al. 2008), lifting one arm (Personnier et al. 2008), or even walking (Skoura et al. 2005). This experiment shows that the aging effect is also present for a finger opposition task. The functional implications of these findings and the underlying mechanisms remain to be established. Personnier et al. (2008) have proposed that elderly subjects may lack the ability to "efficiently make use of internal models of action for the generation of accurate motor predictions". This proposal, based on a behavioural experiment inspired by forward models of motor control, is based on the degraded correlation between the durations of executed and imagined movements, particularly when subjects imagined a limb loaded with a weight. The same experiment, however, cannot answer the question of whether elderly subjects also make significant use of a qualitatively different strategy when dealing with MI tasks. These findings support this possibility: I found significant neurofunctional differences between young and elderly subjects during the MI task; these differences were manifested as the hyperactivation of the brains of older subjects, primarily in the occipito-temporo-parietal areas.

In previous neuroimaging studies, the involvement of the primary visual area and the extrastriate cortices (the inferior occipital gyrus and the calcarine fissure) was associated with visual imagery tasks (Bartolomeo 2008; Ganis et al. 2004; Kosslyn et al. 1995); the focal rTMS inhibition of visual cortices, starting from area V1, hampers visual imagery in normal subjects (Kosslyn et al. 1999)[7].

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[7] My interpretation of the quality of mental imagery in the elderly relies on the distinctive fMRI patterns of the older subjects. I consider these an explicit neural signature because of the topographical distribution in occipital cortices of well-known functional properties. In principle, one could have used introspective descriptions of the MI experience to document departures from kinaesthetic imagery to visual imagery and used these departures to decipher the fMRI patterns. However, one may argue that there is no guarantee that introspective descriptions about the accuracy or style of the imagery procedure would be accurate. More crucially, the combination of introspective online descriptions of the quality of the imagery experience during fMRI would have changed the nature of our experiment quite dramatically by turning it into a meta-cognitive protocol about MI, something very interesting but different from our intended scope. On the other hand, the post-hoc correlation of the introspective descriptions with the fMRI activity would have proved

Hyperactivation also occurred in the superior parietal cortices, regions that have also been associated with the generation of mental images (Ishai et al. 2000), spatial mental imagery, and mental navigation (Mellet et al. 1998), even in subjects in apparent vegetative states (Owen et al. 2006). More specifically, does this experiment offer evidence of a departure from a strict kinaesthetic strategy to a complementary visual strategy in the elderly? This possibility has been already considered using behavioural investigations. Mulder et al. (2007) used a 24-item questionnaire concerning 24 actions in a cohort of 333 subjects. The participants were invited to imagine these actions either from a first-person perspective (kinaesthetic imagery condition) or as if a third actor were performing the movement (visual imagery condition). The results showed that there was a significant difference between elderly and young subjects in the kinaesthetic imagery condition, while no difference emerged in the visual imagery condition. These results suggest that there might be an age-related shift from a motor imagery based on a first-person modality to a motor imagery based on a third-person perspective.

The functional properties of the cortices that showed greater activation during MI in the elderly are consistent with the aforementioned psychological data, based on introspective considerations. The primary visual cortex and early extrastriate cortices are retinotopically organised brain regions (Mendola et al. 1999; Sereno et al. 1994; Zeki et al. 1991). However, the current literature on the contribution of visual strategies to MI also makes the distinction between a first person and third person perspective (see for example Guillot et al. 2009). In the former case, the visual mental imagery can be compared to that of someone who is mentally observing her/his hands according to egocentrically oriented coordinates; in the latter case, the visual imagery activity may imply

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temporally inaccurate and possibly difficult to analyse statistically. On the contrary, in this experiment, the emphasis was on explicitly measurable variables, such as the chronometric measures during M.E. and MI outside the scanner or the fMRI signal collected during standardised procedures and the ensuing correlations between the two sets of variables.

imagining the hand of an actor performing a motor task according to an allocentrically oriented (hence 3rd person) perspective. These data do not allow us to make this subtle distinction. Rather, they may suggest that both of these forms contributed to visual MI in my sample of elderly subjects. In fact, the elderly subjects showed additional activations in cortical regions whose stereotactic coordinates are compatible with those of **the so-called extrastriate body area (**see Hodzic et al. 2009; Saxe et al. 2006); this area has been previously associated specifically with images of body parts presented from an allocentric perspective (Saxe et al. 2006). On the other hand, some of the visual cortical activations of the elderly were in regions similar to those described by Guillot et al. (2009), who showed the specific recruitment of the occipital lobe during a visual imagery task performed from an egocentric perspective by young participants. My interpretation of the changing strategies used by the elderly is also reinforced by the differences in the correlations of the behavioural data with the fMRI data observed for young and elderly subjects.

In the elderly, there was a significant correlation between the time discrepancy (calculated as M.I – M.E.) and the occipito-parietal areas that were more strongly activated compared to the younger participants. This reinforces the connection between the fMRI data and the behavioural data.

However, the same analysis for the younger participants revealed a correlation between the same behavioural parameter and the activity in the supplementary motor cortex. While the overall fMRI patterns do not represent the ideal double anatomical dissociation of classical neuropsychology[8], I interpret this finding as an indication that younger subjects *stick* to a motor strategy when invited to imagine a motor movements, even when this strategy is time-consuming. The longer the MI duration, the greater the neural labour and the greater the BOLD response in the brain regions associated with motor control.

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[8] I cannot claim evidence for a double functional anatomical dissociation, as I did not find significantly greater activations in motor-related structures in the younger subjects. Indeed, while the elderly subjects had greater activations in the occipital cortices, they still relied, in part, on the activity of motor cortices during MI

It is more complex, and most likely out of my reach for the present study, to explain why elderly subjects also rely on a complementary "visual"[9] strategy when they are invited to mentally rehearse motor movements. Here, I can offer some preliminary educated guesses and working hypotheses. I know that the decreased temporal correspondence between imagined and executed movements in the elderly cannot be explained by a generalised deterioration of their motor systems, as we found that the mean duration of real movements did not significantly differ from those of young subjects. Similar findings have been reported for M.E. by others (e.g. Personnier et al. 2008). Having excluded generalised motor decline as an explanation, there are two competing theories. Motor rehearsal in the elderly may decline (a) because sensory information from the periphery is not as efficiently available to the motor system during MI as it is during the actual execution of movements and might prevent the elderly subjects from verifying whether the imagined movements are similar to the actual ones (Skoura et al. 2008; Zwergal et al. 2012) or (b) because feed-forward simulations of motor movements become less effective (Personnier et al. 2008). To the best of my knowledge, while the data collected by Personnier et al. (2008) support the second hypothesis, there is no evidence to discount the importance of the former. It may well be that the decreased efficiency in proprioceptive monitoring may have a domino effect on the fine-tuning of the motor system and its ability to simulate motor acts, even when proprioceptive feedback is not indispensable, such as during MI[10]. Of course, one should expect that normal aging will partially affect either somatosensory feedback or feed-forward motor control, but normal aging is not associated with a generalised inability to respond to incoming somatosensory signals or to make predictions about the state of the motor system.

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[9] It is worth reemphasising that the elderly also showed activation of the premotor cortices during their MI task. Therefore, we suggest that the "visual" mental imagery testified by the occipital additional activation might be a complementary strategy, rather than a completely alternative one.

[10] A similar interpretation was given by Zwergal et al. (2012) in a fMRI study osn MI during imagined locomotion.

Summary of Chapter 2

In this first experimental Chapter, I explored the effect of aging on real motor execution and explicit motor imagery; I found significant differences between the two groups: even if the duration of motor execution and motor imagery did not differ, elderly subjects lost the behavioural temporal correlation between MI and ME; moreover, they over-recruited occipito-temporal areas.

The temporal discrepancy between MI and ME in the elderly subjects correlated with brain regions that showed increased activations. These observations suggest that elderly subjects have qualitatively different explicit MI abilities.

In the next Chapters I will explore whether this finding is generalizable to other forms of motor imagery, with particular attention to implicit motor imagery abilities investigated with tasks of different complexity.

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Chapter 3 - Like the back of the (right) hand? A new fMRI look on the hand laterality task

This chapter presents my initial assessment of functional anatomical foundations of implicit motor imagery. In particular I assessed the impact of perspective on the prototypical implicit motor imagery task, the Hand Laterality Task (HLT). As much as this in-depth assessment of the HLT may seem a de-tour with reference to the main theme of the thesis, i.e. motor imagery across the adult life-span, a large part of the evidence provided in this experiment focused on younger adults was of crucial importance for the interpretation of the observations discussed in chapter 4 and 5.

1. Introduction

In many linguistic idioms, similar to one's own hand means "as familiar as it gets" in many linguistic idioms. However, there is no consensus on which view of the hand should be used to express such familiarity: in English, it is the back of the hand that counts, whereas in many other languages, it is the palm[11]. Are the two views of the hands that equivalent? This question is something that has been addressed in various experimental settings, motor imagery being the one of choice in this Chapter, in which I provide new behavioural and fMRI evidence on the subject.

Methods for the assessment of MI are heterogeneous (Collet et al. 2011) and research designs vary considerably across studies[12]. As already mentioned in Chapter 1, the way in which imagery is elicited is one of the main distinctions between MI tasks (Jeannerod and Frak 1999). In explicit MI

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[11] As far as I was able to document, for the aforementioned idiomatic expression, reference to the back of the hand is made only in English-speaking countries. The palm is the view of choice in French, Greek, Hebrew, Korean, Italian, Portuguese, Rumanian, Spanish, and Turkish. Other cultures adopt different expressions: Finnish, German, and Norwegian favour the pockets (an alternate expression in Italian and Swedish as well); Albanians, Russians and the Swedish favour the tips of their fingers; in Chinese, one refers to the whole hand or foot; in Arabic, one refers to the whole self. Interestingly, Japanese doesn't seem to have any equivalent idiomatic expression.

[12] The preceding paragraphs are admittedly focused on what is considered an explicit form motor imagery, a mental process that we do not consider as fully equivalent of implicit motor imagery, as discussed in the following paragraphs.

tasks, subjects are simply and directly asked to imagine themselves performing the required action (e.g., “Imagine flexing and extending your fingers”; Ehrsson et al. 2003). MI can be performed with a first-person kinaesthetic stance, that is, while concentrating on the bodily sensations associated with the simulated motor act. This approach stems from the understanding that explicit motor imagery may be more akin to visual imagery if subjects visualise the movement as if they were observing themselves performing the movement from an egocentric perspective or from an allocentric perspective. Explicit MI skills are indirectly investigated with self-report questionnaires or mental chronometry paradigms; the linear correlation between reaction times (RTs) for executed and imagined movements is taken as evidence that explicit MI has motoric components.

Conversely, in implicit motor imagery tasks, such as the grip selection task or the hand laterality task (HLT), subjects are involved in “motorically driven perceptual decisions” for visual stimuli or in “prospective action judgements”, which are made, or so it is believed, on the basis of the mental simulation of an action, even if participants are not aware of being involved in a motor imagery process. For these tasks, the performance can perhaps be quantified in perhaps more objective ways (insofar as the measures lack the introspective components): accuracy and RTs are affected by manipulations of task difficulty and, more importantly, by the position of the limb to be used in the task. These effects have been interpreted as evidence that participants are using a motor simulation strategy to carry out the tasks (Parsons 1987). In spite of the time pressure imposed by the task format – viz., that subjects should respond as fast as possible – and its potential detrimental effect on the quality of the mental imagery process, performance during implicit MI tasks has patterns of speed/accuracy trade-offs due to task difficulty that obey to Fitts’ law in the same manner as “real” motor tasks (Sirigu et al. 1996). Brain imaging studies have supported somewhat more directly supported the inference that a motoric process is adopted during implicit MI tasks, by showing the recruitment of brain regions involved in spatial – motor processing (see below). As I shall show in this Chapter, there is a large degree of functional anatomical overlap between the brain regions involved in implicit and explicit motor imagery to support this claim.

The hand laterality task

The hand laterality task (HLT, Parsons 1987) is a classical example of an implicit MI task: in this paradigm, subjects are asked to decide whether a hand portrayed in a picture (rotated at different angles) is a left or a right one. Whereas in classic mental rotation tasks for stimuli such as letters or objects, RTs can be expressed as a linear function of the angle of rotation (indicating that participants are mentally rotating the stimuli to the upward position), in the mental rotation of body parts, there is not such linear relationship: in the HLT, RTs are influenced by the biomechanical properties of the presented stimulus with respect to the current body position, as if the hand belonged to the observer (Parsons 1987). Indeed, the HLT for stimuli in which the hand is rotated away from the body's midline, which represents an awkward position, requires longer RTs than when the stimuli are hands rotated towards the body's midline. This pattern mimics what is observed for the actual execution of equivalent movements, a possible evidence of the recruitment of a motoric strategy during the HLT (Sekiyama 1982).

However, the effect of the biomechanical constraints on the RTs has not been detected in all of the HLT experiments (see for example Lust et al. 2006; Steenbergen et al. 2007).

Ter Horst and colleagues (2010) suggested that the differences observed in the literature might be explained by the characteristics of the experimental stimuli, with particular reference to the number of axes of rotation of the stimuli[13]: they reported that, when the hands stimuli are rotated only with

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[13] The terminology used for the data of Ter Horst et al (2010), is that of the authors: they presented stimuli that cold be rotated in the coronal, longitudinal or antero-posterior direction (see their figure 1). The terminology can be best understood if one starts from the back-view of the hand pointing up: the first axis of rotation is within the coronal plane (6 possible angles around a transvers axis orthogonally crossing the centre of the carpus). Hands could also be rotated over the longitudinal axis, crossing the hand from the wrist to the top of the middle finger. Here, there were only two possible rotations, at 0° for the back-view and at 180°, for the palm-view. These manipulations of the stimuli were the same as in my work. Ter Horst et al (2010) also had a third potential axis of rotation to generate three different varieties of stimuli and manipulate the perspective of depth of the pointing direction of each given hand stimulus. This is generated by a rotation along a third axis that crosses the wrist in a transverse (from left to right) direction. In that

an in-plane rotation (back-views of the hands with different angles of rotation), subjects may use a non-motoric strategy to solve the task, like the visual cues given by the position of the thumb; for stimuli that may vary for both in-plane rotation and view (palm or back), a strategy purely based on visual cues would not be as efficient, favouring the choice of a motoric strategy.

Blasing et al. (2013) further addressed this issue: the authors reported a medial-over-lateral advantage only for palm-view stimuli but not for stimuli viewed from the back. They claimed that subjects used a mixed strategy to solve the task: palmar hand stimuli would be processed using a motoric strategy, whereas back stimuli would be processed using a visual strategy, with a switch of strategy within the same task.

Functional anatomy of the HLT

To date, eight fMRI studies have been conducted on the HLT. Taken together, these studies have confirmed the involvement of the premotor cortices (the lateral premotor and SMA), of posterior parietal cortices (the superior parietal lobule and intraparietal sulcus) and the cerebellum in the task. (Bonda et al., 1995; De Lange et al., 2006; Ferri et al., 2012; Parsons et al., 1995; Seurinick et al., 2004; Vingerhoets et al., 2002; Wraga et al., 2003)[14]. However, of the aforementioned studies, none has addressed the full behavioural pattern of the HLT: some have merely reported the main effect of the mental rotation of hands (Parsons et al., 1995), whereas others have compared implicit MI (mental rotation of hands) with implicit visual imagery (mental rotation of non-corporal stimuli such as letters, tools, or cubes; De Lange et al., 2005; Vingerhoets et al., 2002; Kosslyn et al., 1998) or simply with non-rotated hands stimuli (Seurinck et al., 2004; Wraga et al., 2002; Bonda et al., 1995).

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experiment, the authors started with 12 stimuli in a canonical back-view, then they added stimuli rotated over the longitudinal axis to end-up with the whole set of 72 stimuli. They claimed that the greater the variety of rotations the greater the need for a mental imagery of a motoric nature.

[14] The involvement of the primary motor cortex is definitely more contentious as shown by a recent ALE meta-analysis that investigated the neural networks of motor imagery in both explicit and implicit forms (Hetu et al. 2013).

On the other hand, there is some EEG/ERP evidence (ter Horst et al. 2012) to support a functional difference at least for palm-view stimuli rotated towards or away from the body's midline: only the outward-rotated stimuli presented a pronounced ERP negativity for extreme angles at approximately 400 msec from the stimulus onset[15], an ERP index called by some "rotation related negativity" (RRN; Heil 2002). This signal is present for the rotations of objects or body stimuli (Tao et al. 2009). According to the authors, a greater RRN for the outward-rotated palms should be an indicator of a shift towards a more visual strategy because the stimuli are biomechanically less plausible. However, because the exact source of the parietal signals described in that paper is not identifiable, a functional interpretation of the meaning of the aforementioned differences remained a matter for further investigation[16].

In a second EEG study, the same research group (ter Horst et al. 2013) found a greater and bilateral mu-power desynchronisation, an index of motor cortex involvement that peaks at approximately 900 msec, for palm view stimuli that were rotated towards the midline – a biomechanically more plausible position.

Despite this interesting evidence, there are several aspects of the behavioural patterns observed in HLTs that remain unexplored, particularly with a technique that permits a fine-grained exploration of functional anatomical patterns, such as fMRI.

Aims of the study

The aim of this study was twofold: first, to reassess the behavioural discrepancies observed in the processing of different views of the hand at different angles and, second, to document with fMRI

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[15] The typical RT for this task is approximately one second, which suggests that events with a 400 msec window capture only part of the process that takes place during a HLT.

[16] Given the resolution if ERPs, it is impossible to make firm functional interpretations of the meaning of signals sampled by a parietal electrode. For example, the same ERP signal may originate from very different regions. A parietal signal originating from the human homologue of area (Galletti et al. 1995) would point to a visuo-oculomotor source of an effect hardly differentiable from the integration processes needed for reaching behaviour; on the other hand, a signal captured by the same electrode but originating from the ventral portion of the intra-parietal region would point to a visuo-motor integration process for grasping objects.

the functional anatomical correlates of any behavioural difference related to the aforementioned experimental variables. Are the different temporal patterns for different views of the hands (back or palm) related to more intense neural labour in the same brain network or can one detect a functional anatomical difference that correlates with the behavioural data? Are the view-dependent effects hand-specific? As discussed in the introduction, some of the view-dependent differences in the HLT are considered an indication of a differential engagement of motoric rather than more visual strategies (ter Horst et al. 2013). If such were the case, a specific functional imaging paradigm based on fMRI, and its high spatial resolution, should be able to settle these issues.

To the best of my knowledge, such an experiment has never been done before using fMRI. The general face validity of the present data, with reference to previous experiments with the HLT or to the "motoric nature" of the brain patterns observed in the present study, was assessed by comparison with a new formal meta-analysis of previous fMRI data using the ALE technique (Eickhoff et al. 2012) and by comparison with the data from the experiment described in Chapter 2. In addition, the fMRI data were also investigated while taking into account the event-by-event precise chronometry of subjects' responses: I expected to replicate previous behavioural effects while being able to assess whether view-dependent effects and possibly hand-specific effects can be explained by differences in processing time and by the contribution of specific brain regions.

2. Materials and methods

2.1 Participants and neuropsychological assessment

Thirty-one subjects (mean age 27.5 ± 6.2 years; mean education level 14.9 ± 2.5 years; male/female ratio: 13/18) with no history of neurological or psychiatric illness participated in this study. All were right-handed as assessed by the Edinburgh handedness inventory (Oldfield 1971). The study protocol was approved by the Institutional Review Board (Comitato Etico Azienda Sanitaria Locale Città di Milano), and informed written consent was obtained from all subjects, according to the

Helsinki Declaration (1964). All subjects participated after the nature of the procedure had been fully explained. In order to exclude subjects with cognitive deficits, a brief neuropsychological screening was performed on each participant. The neuropsychological battery included a summary index of cognitive functioning, the Mini-Mental State Examination (Folstein et al. 1975), and a series of more specific neuropsychological tests assessing cognitive functions: Raven's Coloured Progressive Matrices to test abstract reasoning (Raven 1962), short story recall (Novelli et al. 1986), and delayed recall on the Rey-Osterrieth complex figure for long-term verbal and visuo-spatial memory (Carlesimo et al. 2002), as well as the Frontal Assessment Battery (FAB, Dubois et al. 2000). One 34 y.o. woman was excluded from the sample as she did not pass the Mini Mental State Examination nor she did understand the hand rotation task. None of the remaining 30 subjects had a single pathological score at the neuropsychological test battery. These were further examined in the present study.

2.2 Experimental task

The present experiment consisted of a classic hand laterality judgement task, similar to the one proposed, for example, by Parsons (Parsons 1987b).

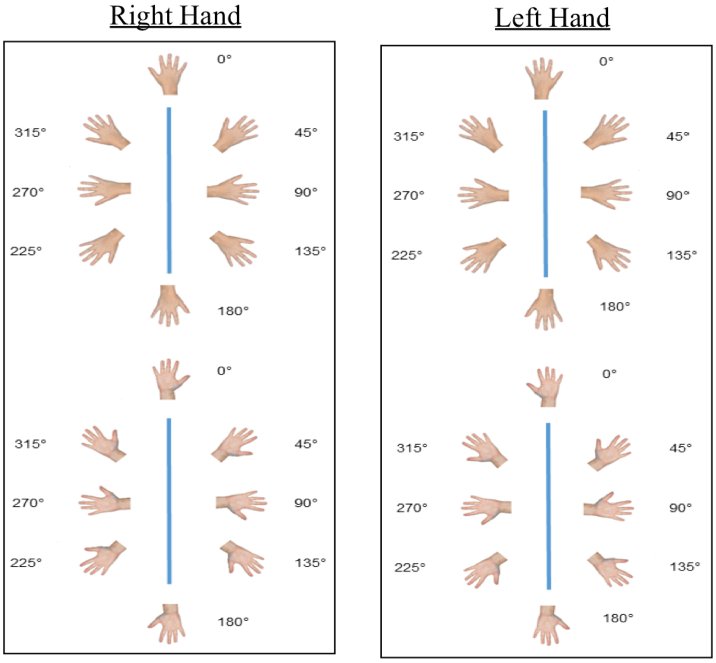
Subjects were shown photos of right or left hands from the front or the reverse side-view (palm up/down), differently rotated from their standard anatomical position (starting at 0° and proceeding by 45° increments: 0°, 45°, 90°, 135°, 180°, 225°, 270°, and 315°). A total of 64 experimental stimuli were presented (2 x 8 angles of rotation x 2 hands x 2 [the palm or back of the hand]).

The baseline stimuli were 64 scrambled pictures derived from the hands' pictures. Each scrambled image had a green or a pink square in the centre. See Figure 3.1.

Procedure

The participants practised the task before beginning the scanning session. For both MI tasks, the subjects were familiarised with the stimuli by performing half of the trials (32 trials). During this training, warning feedback was given in case of an error. After the training, all of the subjects were able to perform the task: incorrect responses amounted to a total of 7.3% (± 4.8%) of the experimental trials. This level of accuracy was in line with similar behavioural studies on this topic (see, for example, de Lange et al. 2006; Ionta et al. 2007). For the fMRI experiment, the stimuli

Experimental Stimuli



Baseline Stimuli

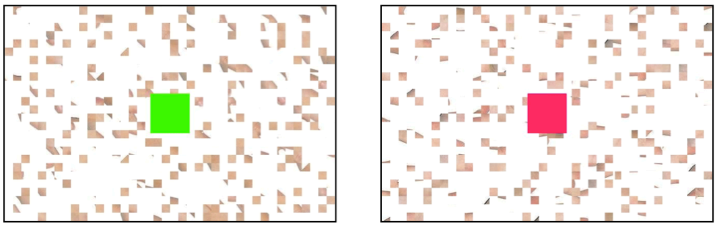


Figure 3.1. Experimental and Baseline stimuli.

were randomly alternated according to an event-related design. Each stimulus remained visible for 4000 ms and was preceded by a fixation point in the centre of the screen, variably lasting from 750 ms to 1250 ms (inter-stimulus interval: ISI). Subjects were asked to report whether they were shown a right or a left hand by pressing a button with their right or left index fingers. When shown the scrambled images, the subjects had to press with the right finger when they saw a green square or with the left finger when the square was pink. Accordingly, the contribution of the laterality of the motor response was controlled for in the analyses of the MI task. The experimenter reminded the participants to be fast and accurate in responding.

The RTs and accuracy were recorded. Visual stimuli were delivered using Visuastim fibre-optic goggles. Responses were given through two response boxes (one for each hand) (Resonance Technology Inc.).

These data were compared with those of the experiment described in Chapter 2. As none of the subjects of the control experiment participated to the hand-laterality experiment, the two data sets were fully independent.

2.3 Statistical analyses of the behavioural data

The RTs recorded during the fMRI session were analysed as follows: RTs of the participants recorded inside the scanner were analysed by means of a repeated-measures 2 x 2 x 8 ANOVA with “Hand” (Right/Left), “View” (Palm/Back) and “Angle of Rotation” (the eight aforementioned angles of rotation) as the factors. Only the RTs of the correct trials were included in the analysis.

In line with previous studies, I categorised the stimuli on the basis of their proximity to the body midline (see for example Bläsing et al. 2013; Parsons 1987a; ter Horst et al. 2010). In particular, I followed Parsons et al. (Parsons 1987a) in classifying the views of the hands as “comfortable” or "awkward" following considerations of the biomechanical constraints of the stimuli[17]. Furthermore, to provide a congruent description of the data for the two hands, the different views were classified as *medial,* that is, pointing towards the body midline or *lateral*, that is, pointing laterally (see Figure 3.2a and Figure 3.2b for illustrations of the data classified in this way).

To analyse these effects I performed a separate ANOVA with "Position" (Awkward/Comfortable), "Hand" (Left/Right) and "View" (Palm/Back) as factors.

A Greenhouse–Geisser correction for non-sphericity was used when needed for both ANOVAs.

Behavioural data were available only for 27 subjects due to equipment failure in three cases.

2.4 fMRI data acquisition and analysis

MRI scans were performed using a 1.5 T Siemens *Avanto* scanner, equipped with gradient-echo echo-planar imaging (flip angle 90°, TE=60 msec, TR=3000 msec, FOV=280 x 210 mm and matrix= 96 x 64).

I collected 225 volumes in a single run. The first 10 volumes of each sequence (corresponding to the task's instructions) were discarded from the analyses.

Preprocessing and Statistical analyses of the fMRI data

I adopted the same strategy described in Chapter 2.

Four contrast images were brought to the second level analysis, one for each condition of interest (Hand: Right/Left; View: Palm/Back) after subtracting out the BOLD response for the time matched events of the baseline condition. The full factorial ANOVA generated F-contrasts for the main effect of view and hand, and for the hand x view interaction effects. Post-hoc analyses to

---

[17] Another possible way to indicate that the mental rotation of one stimulus is compatible with biomechanical constraints is to refer to the direction of its rotation, e.g. "clockwise/counter-clockwise" (see, for example, De Lange at al., 2006).

examine the direction of the aforementioned effects were performed using linear contrasts to generate SPM[t] maps.

I characterised all main effects and the relevant interactions whose relevance was anticipated by the behavioural data.

Each main effect was visualized at the threshold $p<0.001$ (uncorrected) at the voxelwise level. I further considered only cluster significant at $p<0.05$ (uncorrected) for its spatial extent. In the Chapter I describe also the level of correction for multiple comparisons achieved by each peak of these clusters. The vast majority of the peaks/clusters reached at least $p<0.05$ false discovery rate (FDR) correction (Chumbley et al., 2010) if not a 0.05 FWE level (Worsley et al., 1996)

There was one interaction effect whose test was motivated by the behavioural results, namely a hand-by-view interaction. To provide a realistic protection against false positives in these higher-level interaction effect (given the presence of a baseline at the first level, the view by hand interactions are second level interactions) I used a small volume correction constrained by the functional localizer of the main effect of the palm-minus-back view (see Friston et al. 2006): the small volume correction for this interaction effect was calculated using a 10 mm radius sphere centred on two local maxima identified by the functional localizer.

The crucial effects of the HLT experiment were also tested for their motoric nature by overlapping the effect of the control experiment with appropriate SPM images derived from the HLT. For example, to assess to what extent the main effect of view (palm > back) in the HLT involved motoric regions, the ensuing SPM image was directly *overlapped* on the “move/imagine” data of the control experiment using MRIcron. Because the baseline condition of the control experiment was rest, here I adopted by default the 0.05 FWE voxel-wise correction.

Parametric modulations of the hemodynamic responses for the individual conditions

In order to assess to what extent different RTs could explain hand and view dependent fMRI patterns, a parametric modulation analysis was performed to identify areas in which the difference across tasks was somehow proportional to the RTs.

This approach is one of the established methods in literature to account the variability of the BOLD response that can be explained by the RTs (see for example Sakai et al. 2013; Wilson et al. 2009).

I first identified the appropriate polynomial expansion for the modulator in each condition (back/palm), by assessing the distribution of the data using the "curve estimation" function as implemented in the software SPSS Inc., with RTs as dependent variable and the angle of rotation as independent variable, separately for back and palm views. The data were best fitted by a cubic polynomial expansion (palm view: $F=4.6$, $p=0.004$, R-square=0.06; back view: $F=35.6$, $p<0.001$, R-square=0.33). Hence, the RTs parametric modulator used for the correlation with the fMRI data was based on a 3rd order polynomial expansion.

The correlations between the hemodynamic response and the parametric modulators were first calculated as fixed-effects for each subjects. The ensuing individual F-contrast images (one for the palm view, one for the back view), explained how good was the model in fitting the BOLD signal of each voxel: these contrast images were then entered in a second-level analysis for group-level inferences (Sakai et al. 2013).

2.5 Similarities and differences of the present data with previous data: meta-analytical comparisons

The current state of the art for the discussion of functional imaging data implies, when possible, a comparison with the results of a quantitative meta-analytical assessment of the previous literature (e.g., Cattinelli et al. 2013): here, I adhered to this standard and I performed a quantitative meta-analysis on the previous experiments on mental hand rotation. I searched in the PubMed database in June 2013 for articles with titles, abstracts or keywords included the terms "mental hand rotation" or "hand laterality judgement" and any of the following terms: "fMRI", "PET", and “neuroimaging”. In addition, the reference sections of the reviewed articles were carefully inspected to identify additional articles of interest. I identified 20 articles. I excluded papers not reporting neuroimaging methods (n=8) and studies with different experimental paradigms (n=4). Eight studies survived this scrutiny, for a total of 158 foci coming from 110 subjects overall (mean number of participants: 14; sd: 5.4; range: 6-22). The studies are listed in Appendix 1. In all of the selected experiments, the subjects had to decide whether two hands rotated at different angles were the same or not (n=5) or whether the picture presented a right or a left hand (n=3). Seven out of eight studies were based on a block-design, and one was based on an event-related design (left-right discrimination). All of the studies reported data thresholded at least at a 0.001 uncorrected p- value.

It should be noted that none of these studies did report data on the palm view of the hand. Yet, I reasoned that a general consistency with previous evidence would have added further validity to our new evidence on the more detailed aspects of the HLT fMRI patterns.

The meta-analysis was performed using the Activation Likelihood Estimation (ALE) approach, which, in the authors’ words (Eickhoff et al. 2012) “determines the convergence of foci reported from different experiments. ALE analysis involves modelling these foci as probability distributions whose width is based on empirical estimates of the spatial uncertainty due to the between-subject and between-template variability of neuroimaging data. ALE results are assessed against a null-distribution of random spatial association between experiments, resulting in random-effects inference” (Eickhoff et al. 2012).

Once the ALE maps were generated, I assessed their spatial congruency with my results by direct superimposition of the statistical ALE maps with my own maps. A $p<0.05$ pID FDR correction was applied to the ALE maps (Genovese et al. 2002).

3. Behavioural results

These results are presented in Figure 3.2 and in Figure 3.3 and summarised in Table 3.1.

In short, there were faster reaction times for the back view and hand-dependent angle-specific effects (cf. Figure 3.2a and Figure 3.2b). The reaction times were faster overall for the right hand and particularly faster for the back view of the right hand (2x2x8 ANOVA, see Figure 3.3a).

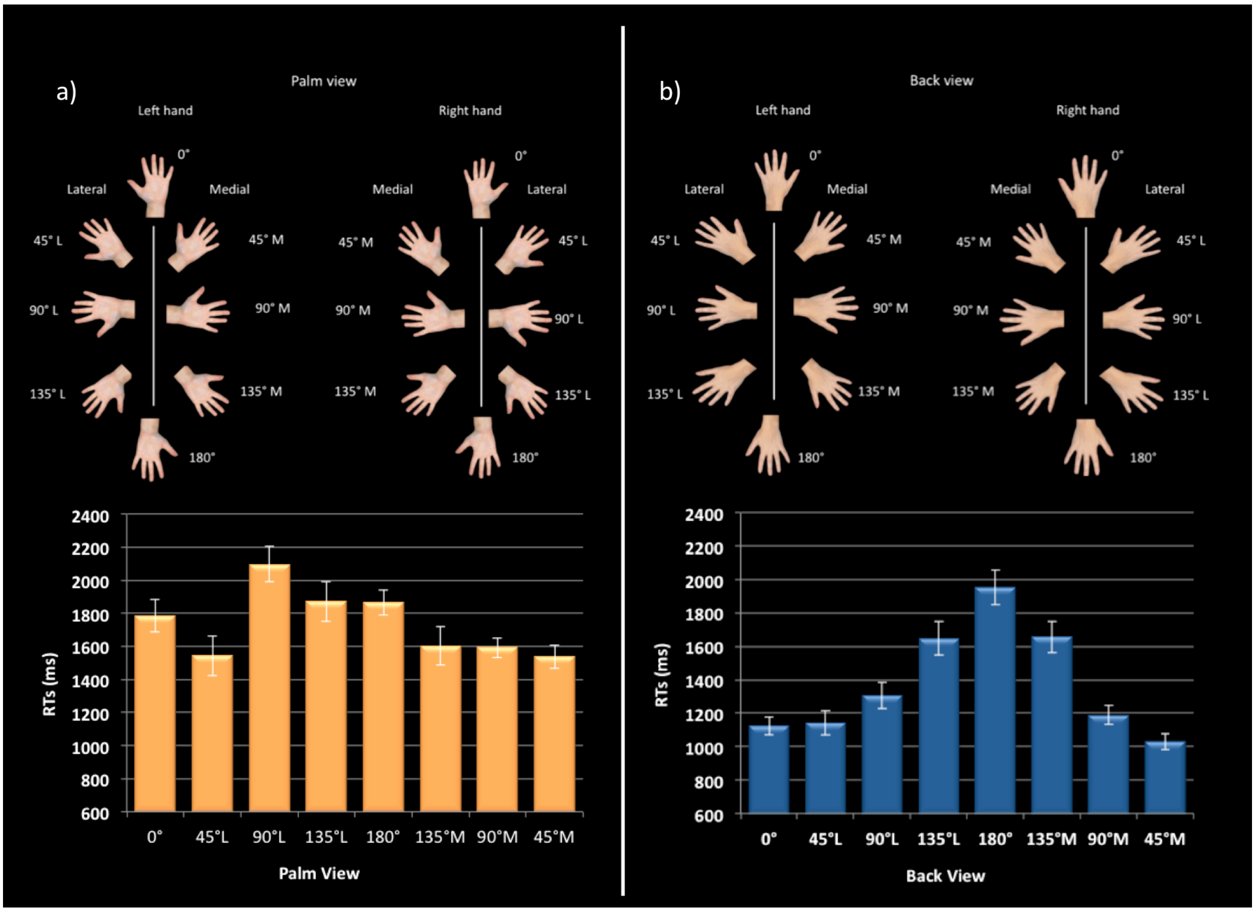


Figure 3.2. Classification of the stimuli presented in the HLT and RT profiles for the different rotation angles for the (a) palm view and (b) back view.

Once the stimuli were lumped into those portraying "comfortable" versus "awkward" positions, there was a clear advantage for the "comfortable" positions, together with the aforementioned disadvantage for the palm view. The "awkward" position effect was significant only for the palm view (see Figure 3.3b).

These results are described more formally below and are also summarised in Table 3.1.

Table 3.1. Summary of the behavioural results (RTs analysis).

Repeated-measures 2 (Hand: Right/Left) x 2 (View: Palm /Back) x 8 (Angles of Rotation) ANOVA			
	F	***p-value***	η^2
Main effects			
Hand	F(1, 26)=10.4	**p=0.003**	$\eta^2=0.29$
View	F(1, 26)=68.1	**p<0.001**	$\eta^2=0.72$
Angle of Rotation	F(4.4, 113.8)=27.9	**p<0.001**	$\eta^2=0.52$
Interactions			
Hand*View	F(1, 26)=4.7	**p=0.04**	$\eta^2=0.15$
Hand*Angle	F(4.2, 109.9)=3.5	**p=0.008**	$\eta^2=0.12$
View*Angle	F(4.5, 117)=16.3;	**p<0.001**	$\eta^2=0.39$
Hand*View*Angle	F(5.1, 133.3)=1.2	p=0.3	$\eta^2=0.041$
Repeated-measures 2 (Awkward Position/Comfortable Position) x 2 (Palm View/Back View) x 2 (Right Hand/Left Hand) ANOVA.			
	F	***p-value***	η^2
Main effects			
Position	F(1, 26)=21.1	**p<0.001**	$\eta^2=0.45$
View	F(1, 26)=94.9	**p<0.001**	$\eta^2=0.78$
Hand	F(1, 26)=0.9	p=0.3	$\eta^2=0.04$
Interactions			
View*Position	F(1,26)=17.6;	**p<0.001**	$\eta^2=0.4$
Hand*View	F(1, 26)=3.8	p=0.06	$\eta^2=0.13$
Hand*Position	F(1,26)=1.4	p=0.2;	$\eta^2=0.05$
Hand*View*Position	F(1,26)=0.5	p=0.5	$\eta^2=0.02$

2 x 2 x 8 ANOVA

The repeated-measures 2 (Hand: Right/Left) x 2 (View: Palm /Back) x 8 (Angles of Rotation) ANOVA on RTs data yielded the following results.

I applied the Greenhouse–Geisser correction when Mauchly's test indicated that the assumption of sphericity had been violated; this was the case for the main effect of the factor "Angle"(χ^2 (27) = 54.5; p=0.001), for the interaction "Hand x Angle" (χ^2 (27) =58.1; p=0.001) and for the interaction "View x Angle" (χ^2 (27) =50.1; p=0.005).

Post-hoc tests were Bonferroni corrected.

Main effects

Hand: F(1, 26)=10.4; p=0.003; η^2=0.29, with faster RTs for the right hand. View: F(1, 26)= 68.1; p<0.001; η^2=0.72, with the longest RTs for the palm view. Angle of rotation F(4.4, 113.8)=27.9; p<0.001; η^2=0.52, with the RTs increasing with respect to increasing angles of rotation (the RTs for the hands being oriented at 180° overall), with the only exception for faster RTs overall being when the stimuli were oriented at 45°M.

Interactions

Hand*View: F(1, 26)=4.7; p=0.04; η^2=0.15, with a significantly larger view-dependent difference for the right hand. The RTs for the back-viewed right hand were significantly faster than for any other condition. Post-hoc analyses in fact showed that, for the back view, the subjects were significantly faster for the right hand; the same difference did not hold true for the palm view [back view: t(27)=3.3; p=0.03; palm view: t(27)=1.5; p=0.15)] (see Figure 3.3).

Hand*Angle: F(4.2, 109.9)=3.5; p=0.008; η^2=0.12, with an angle-specific difference at 135°M (p=0.001, with the RTs for the right hand being faster).

View*Angle: F(4.5, 117)=16.3; p<0.001; η^2=0.39: For the back-of-the-hand views, there was a similar inverted U-shaped response, with the longest RTs at 180° degrees; for the palm views, the longest response time was for the 90°L rotation. As described in Figures 3.2a and 3.2b, these views correspond to the most unnatural or less-frequently observed views of the palms because these can be produced only by a very artificial intra-rotation of a supinated hand with the elbow facing the sternum. Moreover, the RTs were significantly faster for the back view when the stimuli were presented at 0° ($p<0.001$), at 45°L ($p<0.001$), at 90°L ($p<0.001$), at 135°L ($p=0.02$), at 90°M ($p<0.001$) and at 45°M ($p<0.001$). Hand*View*Angle: $F(5.1, 133.3)=1.2$; $p=0.3$; $\eta^2=0.041$.

ANOVA based on a classification of the hand positions as "*awkward*" or "*comfortable*".

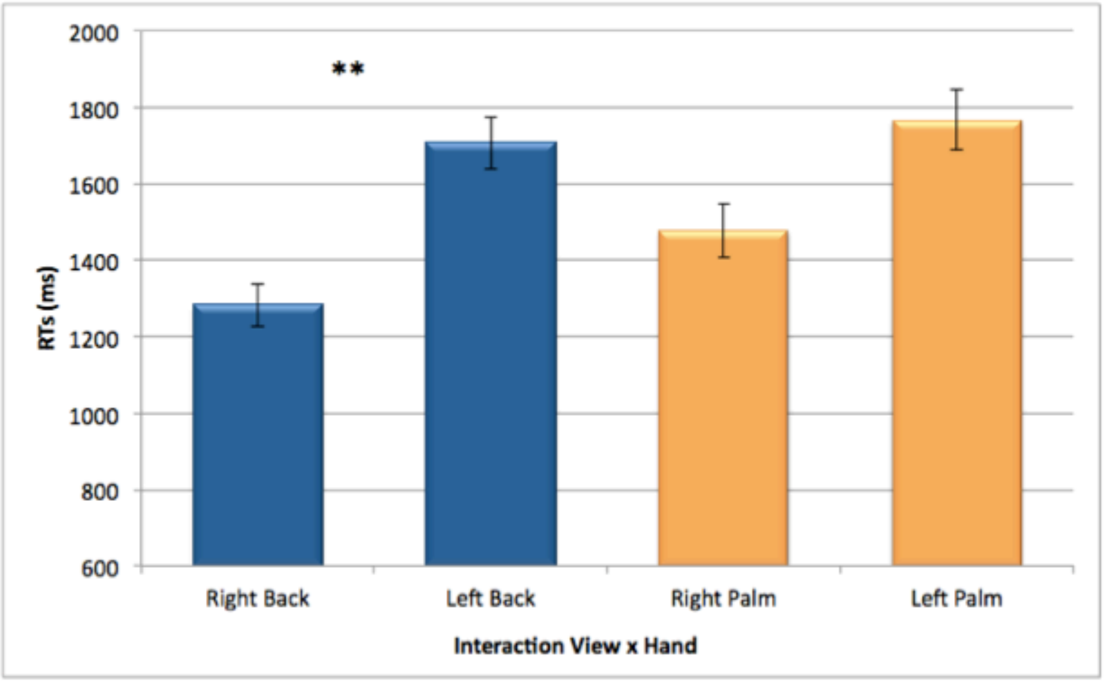
This repeated-measures 2 (Awkward Position/Comfortable Position) x 2 (Palm View/Back View) x 2 (Right Hand/Left Hand) ANOVA on RTs data yielded the following results (see Figure 3.3b).

Main effects

Position: $F(1, 26)=21.1$; $p<0.001$; $\eta^2=0.45$, with slower RTs for awkward positions. View: $F(1, 26)=94.9$; $p<0.001$; $\eta^2=0.78$, with the well-established slower RTs for the palm view. Hand: $F(1, 26)=0.9$; $p=0.3$; $\eta^2=0.04$.

Interactions

View*Position: $F(1,26)=17.6$; $p<0.001$; $\eta^2=0.4$, with a stronger effect of awkward positions for the stimuli presented in the palm view; Hand*View: $F(1, 26)=3.8$; $p=0.06$; $\eta^2=0.13$; Hand*Position: $F(1,26)=1.4$, $p=0.2$; $\eta^2=0.05$; Hand*View*Position: $F(1,26)=0.5$; $p=0.5$; $\eta^2=0.02$.



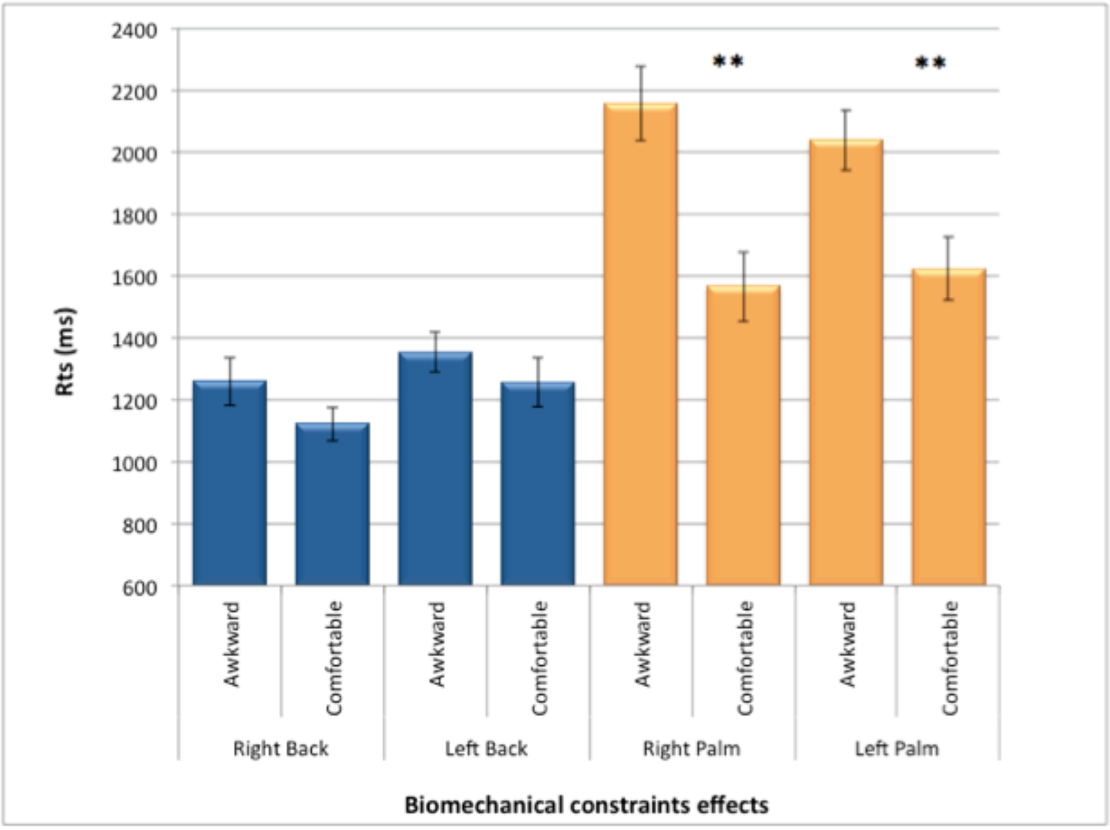


Figure 3.3. Behavioural results: (a) View by Hand interaction; (b) Hand Position by View interaction.

4. fMRI results

Overall, my findings were consistent with previous data on motor imagery and with previous HLT data.

A vast pattern of fronto-parieto-occipital and temporal activations was noted as a main effect of the task in comparison with the baseline (see Figure 3.4a and Table 3.2).

Comparison with the control fMRI experiment: Many of these areas, particularly the fronto-parietal areas, were significantly activated to a similar extent in the explicit and imagined finger opposition tasks. This was assessed via a full conjunction of the four conditions of the control experiment.

In addition, the overall pattern of the HLT was consistent with the results of the meta-analysis performed on the data from the previous literature (see Figure 3.6). It can be noted that the overall pattern found by my experiment was similar to the set of brain areas identified by previous studies, with the noticeable difference that I were the first to compare different views of the hand and the relationship between these and the rotation of the stimuli. There were minor differences in that some early visual areas were emphasised in previous experiments but not in my own; the same applies to some subcortical structures. I imply that my baseline task had a similar level of activity in these regions or that some of the differences were due to the adoption of different baselines for the experimental hand laterality judgement tasks.

Table 3.2. Pattern of brain activation for the Hand Laterality Task.

Brain regions (BA)	***MNI coordinates***							
	x	***y***	***z***	***Z-score***	***x***	***y***	***z***	***Z-score***
	Left hemisphere				***Right hemisphere***			
Mid. frontal gyrus (46)	-36	48	6	5.8 *	--	--	--	--
Mid. frontal gyrus (6)	-28	-2	54	Inf *	34	0	56	Inf*
Inf. frontal op. gyrus (44)	--	--	--	--	48	6	28	6.8 *
Inf. frontal tri. gyrus (45)	-44	28	26	5.4 *	--	--	--	--
Precentral gyrus (44)	-46	4	30	7.5 *	--	--	--	--
Precentral gyrus (6)	-56	6	32	7.6 *	--	--	--	--
SMA (6)	-4	16	48	6.6 *	--	--	--	--
Postcentral gyrus (2)	--	--	--	--	34	-44	58	Inf *
Sup. parietal lobule (5)	-18	-58	58	Inf *	--	--	--	--
Sup. parietal lobule (7)	-26	-54	58	Inf *	16	-62	56	Inf *
	--	--	--	--	26	-54	56	Inf *
Inf. parietal lobule (40)	-36	-42	50	Inf *°	34	-46	54	Inf *
Supramarginal gyrus (40)	--	--	--	--	38	-34	40	Inf *
Precuneus (7)	-12	-74	56	Inf *	--	--	--	--
Sup. occipital gyrus (19)	--	--	--	--	26	-76	38	Inf *
Mid. occipital gyrus (19)	-26	-76	32	Inf *	34	-86	22	Inf *
Inf. occipital gyrus (19)	-48	-76	-2	Inf *	46	-72	-6	Inf *
Cerebellum_Crus2	-4	-76	-28	5.8 *	--	--	--	--
Vermis_7	--	--	--	--	0	-74	-26	6.0 *

* FWE correct

Specific effects on the HLT

The full factorial analysis on the HLT data also showed a main effect of the factor “View”, a main effect of the factor “Hand” and an interaction of “View x Hand” (see Figure 3.4b, 3.4c, 3.4d, 3.5 and Table 3.3).

Larger activations for the palm view

Post-hoc analyses revealed that, for the palm view > the back view comparison, there were two significant clusters (significant at least at $p<0.05$ corrected for multiple comparisons of spatial extent); these were located in the left hemisphere and included the left dorsal premotor cortex (BA 6), the SMA, the postcentral gyrus and the inferior parietal lobule (see Figure 3.4 b and Table 3.3a). Comparison with the control fMRI experiment: Both of these areas were significantly activated for all of the tasks of the control experiment. The post-central signal was also an area of significant right>left difference in the control experiment, which indicated a specificity of this area for the right hand.

Larger activations for the back view

The opposite contrast (back view > palm view) showed a larger recruitment of more posterior regions (left cuneus, precuneus and superior occipital gyrus); further activations were also found in left temporal areas and in the cingulate cortex (see Figure 3.4c and Table 3.3a).

Comparison with the control fMRI experiment: none of these regions belonged to the explicit motor execution or motor imagery patterns noted in the control experiment.

Hand-specific effects

There was a relatively larger BOLD signal in the left early visual areas (i.e., the lingual gyrus and inferior occipital lobe) and in the left cerebellum for the left-hand conditions. No significant difference was present in the opposite comparison (see 3.4d and Table 3.3b).

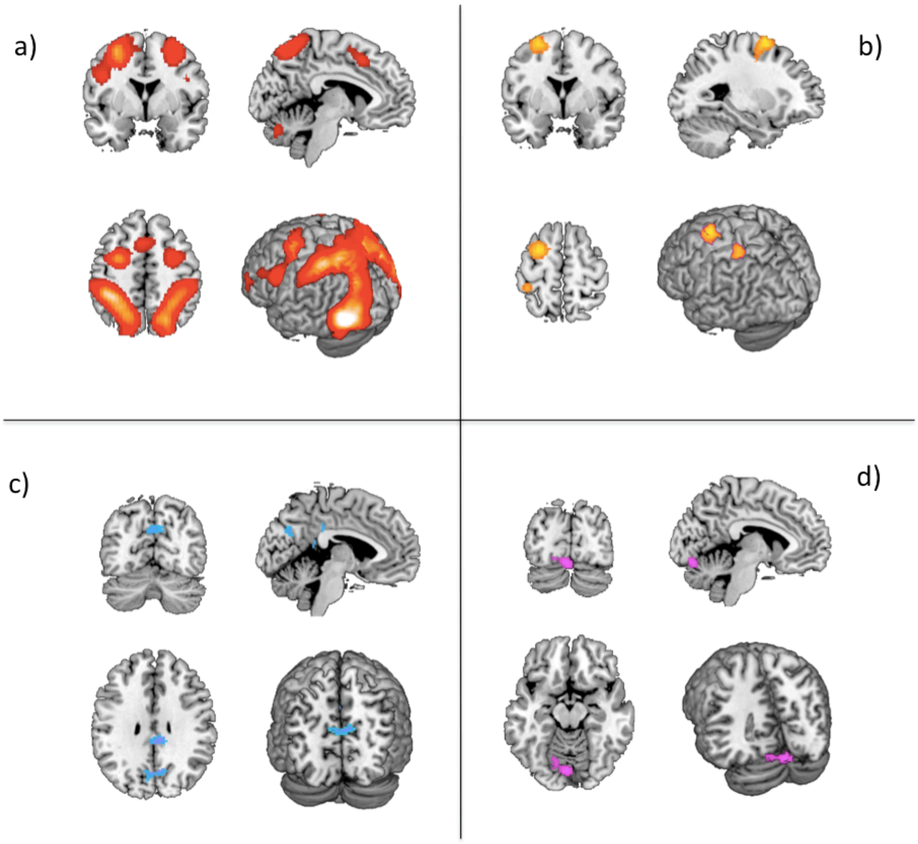


Figure 3.4. fMRI results: Neurofunctional activations for (a) the hand laterality task; (b) view effects – palm view; (c) view effects – palm view; (d) left hand effect.

<u>“Hand x View” interactions</u>

There were interaction effects in the left dorsal parietal cortex (x= -44; y=-38; z=62; Z=score: 3.3; p [uncorrected] <0.001; p [FWE small-volume corrected]: 0.02) with a strong trend in left dorsal premotor cortex (x= -30; y=-4; z=60; Z=score: 2.75; p [uncorrected] <0.003; p [FWE small-volume corrected]: 0.096).

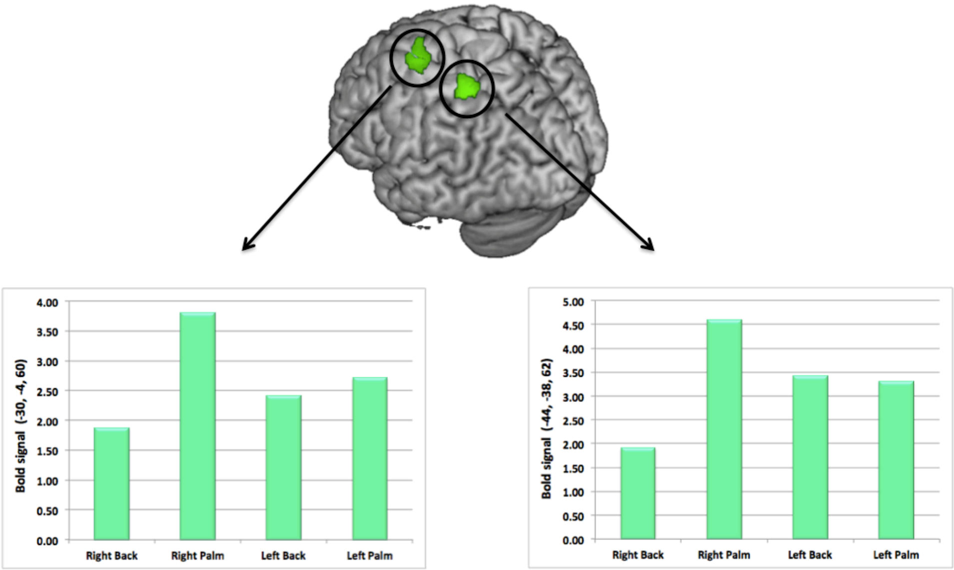


Figure 3.5. Interaction view by hand: plot of the hemodynamic response.

These interaction effects were due to a comparatively smaller BOLD response for the back-view of the right hand. This was confirmed when the BOLD response for the back-view of the right hand was compared with all other conditions pooled together in the left dorsal parietal cortex (x= -38; y= -40; z= 56; Z score: 4.1; p=0.001 uncorrected; p<0.002 FWE small volume corrected) and in the left dorsal premotor cortex (x= -32; y= 2; z= 60; Z score: 3.4; p=0.001 uncorrected; p<0.017 FWE small volume corrected). A plot of the hemodynamic responses in these areas is illustrated in Figure 3.5.

Table 3.3. View specific and Hand specific effects of the HLT.

Brain regions (BA)	MNI coordinates							
	x	y	z	Z-score	x	y	z	Z-score
	Left hemisphere				*Right hemisphere*			
(a) View effects								
Palm View > Back View								
Sup. frontal gyrus (6)	-26	2	66	4.7 *	--	--	--	--
Mid. frontal gyrus (6)	-28	-4	52	3.6	--	--	--	--
SMA (6)	-10	8	56	3.5	--	--	--	--
Precentral gyrus (6)	-28	-6	46	3.4	--	--	--	--
Postcentral gyrus (2)	-36	-40	60	4.1	--	--	--	--
Inf. parietal lobule (40)	-36	-38	44	3.5	--	--	--	--
Back View > Palm View								
Mid. temporal gyrus (21)	-60	-22	-12	4.2	--	--	--	--
Mid. temporal gyrus (20)	-56	-24	-12	3.8	--	--	--	--
Inf. temporal gyrus (20)	-50	-30	-16	3.6	--	--	--	--
Mid. Cingulum (23)	--	--	--	--	6	-34	34	4.4
Post. Cingulum	-2	-44	16	3.6	--	--	--	--
Precuneus	--	--	--	--	4	-66	28	4.1
Cuneus	-2	-68	30	3.8	--	--	--	--
Sup. occipital gyrus (18)	-10	-80	26	3.2	--	--	--	--
(b) Hand effects								
Left Hand > Right Hand								
Lingual gyrus (18)	-16	-76	-12	3.3 *	--	--	--	--
Inf. occipital gyrus (18)	-20	-92	-4	4.0 *	--	--	--	--
Mid. occipital gyrus (18)	-20	-88	-2	4.0 *	--	--	--	--
Cerebellum_Crus1	-2	-80	-16	4.1 *	--	--	--	--
Cerebellum_6	-16	-68	-18	3.5 *	--	--	--	--

* FWE corrected

A comparison with the control experiment based on explicit motor execution and imagery showed that the aforementioned left parietal and left premotor regions region belonged to the explicit motor execution or motor imagery patterns for all conditions.

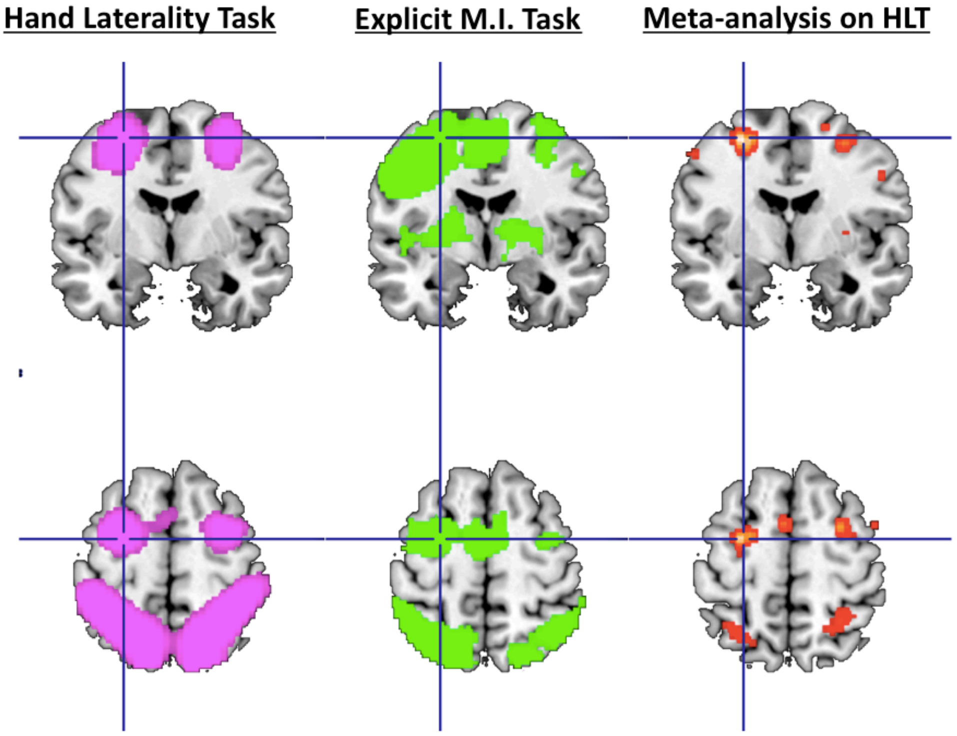


Figure 3.6. fMRI results: Level of congruency between the main effect of the HLT (areas in purple), the neural activations associated with the control explicit MI task (areas in green) and the meta-analysis of similar motor imagery tasks (areas in red).

Table 3.4. Meta-analysis of previous HLT experiments: location and cluster size of significant ALE effects.

Brain regions (BA)	MNI coordinates							
	x	y	z	Volume (mm^3)	x	y	z	Volume (mm^3)
	Left hemisphere				*Right hemisphere*			
Frontal Sub-Gyral (6)	--	--	--	--	29	0	56	3688
Medial Frontal Gyrus (6)	-3	5	59	1248	4	19	44	1672
	-26	-5	57	4408	9	3	51	448
Medial Frontal Gyrus (9)	-22	52	15	1024	--	--	--	--
Middle Frontal Gyrus (11)	-40	47	-22	296	--	--	--	--
Inferior Frontal Gyrus (9)	--	--	--	--	60	9	21	392

Inferior Frontal Gyrus (47)	--	--	--	--	29	20	-33	384
Claustrum	-27	17	-10	288	--	--	--	--
Subcallosal Gyrus (25)	--	--	--	--	4	14	-22	264
Precentral Gyrus (6)	-44	6	30	2488	48	3	32	1344
Precentral Gyrus (4)	-49	-2	48	800	47	3	56	296
Cingulate Gyrus (31)	-9	-36	48	352	--	--	--	--
Paracentral Lobule (4)	-6	-30	66	264	--	--	--	--
Posterior Cingulate (29)	-7	-42	16	352	28	-55	53	6040
Superior Parietal Lobule (7)	-15	-57	67	464	28	-54	73	232
	-35	-65	49	256	--	--	--	--
Inferior Parietal Lobule (40)	-40	-33	45	4616	--	--	--	--
Superior Temporal Gyrus (38)	--	--	--	--	35	3	-46	384
Parahippocampal Gyrus (19)	--	--	--	--	24	-52	-9	896
Middle Temporal Gyrus	-39	-81	30	384	--	--	--	--
Inferior Temporal Gyrus (37)	-45	-72	1	1824	--	--	--	--
Precuneus (7)	-27	-56	57	4720	--	--	--	--
Cuneus (23)	-12	-75	12	352	--	--	--	--
Lingual Gyrus (18)	-12	-90	-6	512	12	-83	3	4224
Middle Occipital Gyrus (19)	-27	-93	12	384	36	-90	14	608
	--	--	--	--	48	-69	6	1856
Inferior Occipital Gyrus (19)	-47	-85	-4	312	--	--	--	--
Cerebellum (Anterior Lobe)	-9	-47	-11	512	26	-48	-31	1224
Cerebellum (Posterior Lobe)	-36	-59	-23	1320	44	-62	-16	1440
	-24	-55	-10	1104	27	-78	-15	400
	--	--	--	--	20	-95	-17	384
	--	--	--	--	44	-77	-19	344
Putamen	--	--	--	--	31	-2	4	352
Insula (13)	-45	7	-1	448	51	12	9	384
	-47	-15	7	256	--	--	--	--

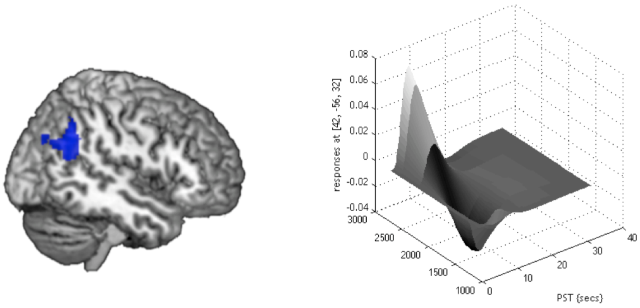
5. Reaction time-dependent fMRI patterns: parametric modulations

The analysis of parametric modulation of the hemodynamic responses revealed view- or hand-related effects that were accounted for by the reaction times in each condition. These were in different regions compared with those identified by the general linear model unmodulated analyses described above.

For the back-view stimuli, RT-specific greater effects, compared with the palm view, were found in the angular gyri and superior temporal gyri bilaterally and in several occipital regions (viz., the right middle occipital gyrus, left lingual gyrus and calcarine fissure; see Figure 3.7a and Table 3.5).

For the palm view, compared with the back view, the same analysis revealed greater RT-dependent activity in the right cerebellum; see Figure 3.7b and Table 3.5). Only a substantial trend for a similar correlation was found in left dorsal pre-motor cortex in a region showing an overall larger activation for the palm views (stereotactic coordinates: x = -28, y = 6, z = 68; p<0.003). It is important to note that these results are complementary rather than in contradiction with the previous unmodulated general linear model assessments of the view and hand-dependent effects. Taken together, the unmodulated analyses and the modulated ones show that there are RTs-independent and RTs-dependent regions that correlate with view and hand-specific effects.

Back View



Palm View

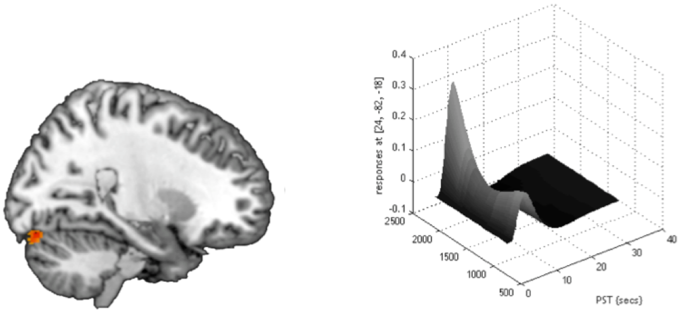


Figure 3.7. Parametric modulation analysis: modulation of the hemodynamic response with reference to the RTs in a representative subject; for the back view stimuli (a) and for the palm view stimuli (b). The BOLD signal response is plotted as a function of the reaction time (horizontal axis with units expressed in msec) and of the delay from stimulus onset (horizontal axis with units expressed in seconds).

Table 3.5. Parametric modulation analysis: fMRI effects parametrically explained by RTs

Brain regions (BA)	MNI coordinates							
	x	y	z	Z-score	x	y	z	Z-score
	Left hemisphere				*Right hemisphere*			
(a) View effect								
Palm View > Back View								
Cerebellum_Crus1	--	--	--		20	-86	-18	4.2+
Back View > Palm View								
Angular gyrus (39)	-46	-64	26	4.3*	46	-56	30	4.2*
Angular gyrus (39)	-40	-54	28	3.4*	40	-54	40	3.2*
Sup. temporal gyrus (22)	--	--	--	--	56	-50	22	3.5*
Mid. temporal gyrus (39)	-50	-66	22	4.2*	48	-58	18	3.8*
Mid. occipital gyrus (19)	--	--	--	--	44	-78	34	3.4*
Lingual gyrus (17)	-10	-56	4	4.1*	--	--	--	--
Calcarine fissure (17)	-12	-56	8	4.2*	--	--	--	--
Calcarine fissure (17)	-20	-66	12	3.5*	--	--	--	--

6. Discussion

With the aim of further exploring the neurofunctional correlates of implicit motor imagery, I focused on the well-known hand laterality task. This class of tasks has considerable potentials for the study of motor representations in normal subjects or brain-damaged patients (Tomasino et al. 2003a; Tomasino et al. 2003b; Tomasino and Rumiati 2004; Jenkinson et al. 2009) as it provides fairly objective measures of motor imagery[18]. I conceptualise implicit MI as a form of action simulation that requires the mental manipulation of body representation, in order to provide a prospective action judgement (Jeannerod 2001). The hand laterality judgement task is a classic example of such an implicit motor imagery task, with a well-defined pattern of performance with reference to manipulations such as the view (palm or back) and the rotation angle. The results of my

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[18] The RTs measured in implicit motor imagery tasks are generally considered more objective measures than RTs for the introspective assessment of the completion of an explicit motor imagery task such as, for example, a finger-tapping task.

study demonstrate, for the first time, that the main behavioural effects observed for the task are also reflected by meaningful data at the neurofunctional level.

I begin the discussion by reviewing my evidence with respect to previous behavioural and fMRI data on mental hand rotation; I then continue by discussing the specific neurofunctional counterparts associated with the behavioural effects recorded in my experiment. In particular, I discuss to what extent the fMRI data may provide a functional explanation of the behavioural differences observed in this MI task.

I finally conclude by discussing the working hypotheses that may be suggested by the discovery that different hand views may entail different levels of motor imagery.

Mental rotation of body parts: behavioural and functional imaging findings

Behaviour

The culturally dominant idiomatic expression for familiarity, which refers to the palm of the hand, was not accompanied by a visual discrimination advantage for that view, rather, in line with previous observations from the Anglo-Saxon cultures, that favour the back of the hand in idiomatic expressions, the view of the back of the hand was associated with faster reaction times (see, for examplle, Ní Choisdealbha et al. 2011). The magnitude of the back-view advantage, of approximately 300 msec, was also consistent with previous reports (see, for example, Wolpert and Ghahramani 2000)[19]. In addition, these findings were also similar to previous ones for the view-by-angle interaction effects (see, for example, Ní Choisdealbha et al. 2011, Figure 2): for the back view, there was a longer RTs for the 180° rotation pointing downward; for the palm view, the longest RTs were for hand rotations that, if imagined on one's own hand, would require an awkward intra-

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[19] We therefore assume that if one physical constraint exists to determine the Italian, French or Spanish idioms, this must be justified by a familiarity with local features, such as palm lines, rather than with the whole hand shape or its spatial configuration.

rotation of the elbow to face the sternum with the hand in a supinated position. More generally, once I classified the different hand rotations into the categories described by Parsons et al. (1987b)[20], I found a significant interaction effect whereby the awkward positions required longer processing times specifically for the palm view.

Finally, the behavioural results suggest that the back of the right hand may have a special status, because this was the condition with the fastest RTs. Indeed, a right-versus-left advantage was present for the back-view stimuli but was absent for the palm-view stimuli.

Taken together, these observations suggest that my subjects, while lying inside an fMRI scanner, were performing the tasks according to expectations based on data collected from subjects who were behaving in more ecological settings. This observation further justifies my inferences from the fMRI data, which I discuss next.

fMRI findings: comparisons with previous data

The comparison of my main task with the baseline revealed a well-known pattern of activation of a large fronto-parieto-occipital network that I now consider typical of motor planning in response to a visual stimulus[21]. The *motoric nature* of the networks involved in the HLT task was also confirmed by a direct comparison with the finger opposition task and explicit MI for the same task described in Chapter 2 (see Figure 3.6's areas in green). Among these regions, the network consisted of the bilateral premotor areas, such as the lateral premotor cortex (BA 6)—both ventral and dorsal—and the supplementary motor area (SMA); all of these are implicated in motor intention and preparation

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[20] The authors classified hand rotations according to the extent to which the resulting hand position was awkward rather than comfortable for someone imagining the position from his or her own perspective.

[21] The use of the wording "motor planning" is not a casual one. After 20 years of fMRI studies, one may look at the involvement of the premotor cortices in tasks such as my own with little surprise. Yet, the demonstration of the activation of such cortices on tasks that in principle could be performed by using purely visual cues and strategies still remains one of the major empirical advances, with conceptual implications, in modern cognitive neuroscience in showing the important contribution of the visuo-motor integration processes that might occur automatically even for such tasks.

for reaching and for eventual object grasping (for a review see Jeannerod 1997; for recent fMRI data, see Cavina-Pratesi et al. 2010). In addition, during the HLT there were robust activations of the cortex of the superior parietal lobules and of the intraparietal sulci; this result is in line with the findings of a number of mental rotation studies (not only for body parts: see Zacks 2008 for a review). This result also converges with neuropsychological data in suggesting an important role for the superior parietal regions in motor transformations based on visuo-spatial stimuli (Ratcliff 1979). The same structures are involved in visually guided reaching movements (see Grefkes and Fink 2005 for a review), whereas the cortex enfolded in the intraparietal sulcus contains a number of specific subregions that integrate neural signals from different sensory modalities for guiding and controlling action in space. These regions are the anterior intraparietal sulcus (AIP), which is involved in object manipulation and grasping movements (Grefkes et al. 2002); the ventral intraparietal area (VIP), which is engaged in the elaboration of multi-sensorial motion information (Bremmer et al. 2001); and the lateral intraparietal area (LIP), which is involved in the attention and control of eye movements (see for example Corbetta et al. 1998). The whole intra-parietal sulcus appeared active during the HLT, as several local maxima survived even stellar thresholds like 0.000001 FWE corrected. Among the IPS areas, by comparison with the stereotactic coordinates described in the literature (Grefkes et al., 2002), there was definitively activation also of the anterior (AIP). The AIP activation recorded in my task is consistent with previous results on mental rotation and might be explained by the role of the AIP in coding the position and the orientation of body parts (see, for example, Bonda et al. 1995).

Finally, the bulk of the activations during the HLT also involved several occipital areas (viz., the superior, middle, and inferior occipital gyri and the right fusiform gyrus). A large number of mental rotation studies have reported activation in the visual areas (see Zacks 2008 for a meta-analytic review); these regions might reflect the visual transformation process engaged in the mental rotation task.

Occipital activations in the HLT task main effect also occurred in cortical regions with stereotactic coordinates that are comparable to those of the so-called extrastriate body area, a region involved in the visual processing of images of the human body (Downing et al. 2001; Hodzic et al. 2009; Saxe et al. 2006). This area has been previously associated specifically with images of body parts presented from an allocentric perspective (Saxe et al. 2006).

A formal comparison of my data with the results of a meta-analysis conducted on previous studies on the HLT (figure 3.6, areas in red/hot scale) showed that all areas from the meta-analysis were included in my pattern with the exception of a few early visual cortices in the occipital lobe in regions close to V1 or in the lingual gyrus. These were present in the meta-analysis but not in the main effects from my results; I imply that those areas were at least equally activated by my baseline. However, a signal in early visual cortices was present for the left-hand stimuli when compared the right-hand ones.

In addition, most of the HLT patterns of activation fell into areas showing a highly significant activation in the previous experiment on explicit motor execution and motor imagery (Chapter 2).

To summarise this section, much as with the behavioural data, the core of my fMRI observations is fully consistent with previous findings on HLTs to support the claim that my additional and novel findings discussed below did not come from a peculiar data set.

This aspect of my results is discussed in the following section.

7.2 Neurofunctional counterparts of behavioural effects

View effect: back view versus palm view

Judgements of the back-view hand stimuli were associated with stronger activation of the occipital regions, which has been observed in visual imagery tasks (Guillot et al. 2009), suggesting at least a partial dissociation between the cognitive strategies used to process hand stimuli from different views.

On the other hand, the palm-view stimuli were associated with a stronger activation at the level of the areas usually associated with motor execution and motoric imagery processes, such as the dorsal premotor cortices (viz., the superior frontal gyrus and pre-SMA) and the somatosensory cortices of the postcentral gyrus (see for example Hanakawa et al. 2003). These results also fit well with the behavioural analysis of the effect of the biomechanical constraints if one takes them, as I do, as an indication of the engagement of a *motoric* strategy: the awkwardness of the position of the stimulus had a significant effect on palm-view stimuli alone (Figure 3.3b). The present data are also perfectly in line with the hypothesis of a recent behavioural study mentioned in the introduction, although my interpretation is not the same as that of Blasing and colleagues (2013). Blasing and colleagues tested the issue of whether subjects engaged with an HLT would adopt purely visual or motoric strategies or a combination of the two; because they found a medial-over-lateral advantage, an indication of the effect of biomechanical constraints only for stimuli in palm view, they concluded that only these stimuli are processed by using a motor strategy, whereas dorsal-view stimuli should be processed by using a visual strategy alone.

However, my functional imaging data show that the anatomical dissociation behind the behavioural effects is not complete and is certainly not one of the double anatomical dissociations typical of neuropsychological studies. There was a large overlap of the systems involved in viewing the back rather than the palm of a hand, the difference between the two being in the topographical extension or the local effect size of the BOLD response in the occipital (for the back) rather than in the premotor/parietal cortex (for the palm)[22].

The hypothesis of a partial dissociation of the neurocognitive strategy for the elaboration of

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[22] To us, the partial dissociations described here are also remarkable because, if anything, the adoption of an event-related design, with a complete randomization of the stimuli, may work against the possibility of finding a dissociation. The subjects, not knowing which kind of stimulus was occurring next, may have had all possible strategies active at the same time: yet, a view effect and a view-by-hand interaction effect were detectable in the fMRI data.

different views of a hand is also in line with data on the influence of the volunteers' hand positions on their RTs during the HLT. Shenton et al. (2004) showed that, when subjects had their hand palms down, RTs were faster for the judgement of back-view hand stimuli; in the opposite situation (palm up), RTs were faster for the palm-up stimuli. This observation offers strong evidence in favour of the recruitment of motoric processes during the HLT. However, it was also reported that the congruence effect of the actual posture of the subjects' hands was larger for the palm-view stimuli, suggesting greater dependence from motoric processes for these stimuli. Finally, the results of Shenton et al. (2004) are also important because they found longer RTs for palm-view stimuli, compared with the back view ones, even in the congruent condition—that is, palm stimuli with the subjects' palm pointing up versus back stimuli with subjects' hands pointing down.

A neurofunctional dissociation between the stimuli in different views was further confirmed by the parametric modulation analysis in which the activation patterns were modelled according to the RTs recorded during the task: the overall pattern was of occipito-temporoparietal areas for the back view and of the right cerebellum for the palm view, with a substantial trend also in the left dorsal pre-motor cortex in a region showing an overall larger activation for the palm views from the unmodulated analyses (stereotactic coordinates: $x = -28$, $y = 6$, $z = 68$; $p<0.003$).

It is important to note that these results are complementary rather than in contradiction with the previous unmodulated general linear model assessments of the view- and hand-dependent effects.

Taken together, my results identify RT-independent and RT-dependent view specific fMRI patterns[23]. The use of partially different strategies in the same *MI* task may partly depend on differences in the familiarity of different hand views: hands might be more commonly observed in the back view, and this familiarity could facilitate the use of visuo-spatial transformation to solve

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[23] By definition, un-modulated and modulated analyses do not necessarily have to give overlapping results (see, for example, Kehoe et al. 2013). On the other hand, the characterization of RT-independent and RT-dependent fMRI patterns makes the functional anatomical assessment more complete.

the task, whereas with the palm-view stimuli, this might be more demanding and depend more extensively from a motoric simulation to address the perceptual problem.

Like the back of the (right) hand: Overall hand effects and hand-by-view effects

I conclude the discussion of my fMRI data by suggesting that the back of the right hand may have a privileged status for the majority of us, certainly for right-handers such as my volunteers.

The behavioural results showed an overall significant advantage for the right hand, particularly for the back view.

The fMRI data mirrored the behavioural data in showing a comparatively overall more intense neural labour for the left hand in occipital cortices and a similar view-dependent difference whereby the response time for the back-view of the right hand was the lowest of all and posterior parietal and premotor cortices. Taken together, this evidence indicates the disadvantage of making laterality judgements for the non-dominant hand. The general interpretation that greater activations are related to task complexity is supported, in the domain of motor imagery, by the data of Kuhtz-Buschbeck and colleagues (Kuhtz-Buschbeck et al. 2003), who found additional activations when comparing the motor imagination of complex movements with the mental rehearsal of simpler actions.

Previous behavioural studies have also shown right-hand advantages in the HLT (for a recent case, see Ní Choisdealbha et al. 2011). This advantage is somehow associated with handedness: right-handers are faster when performing the task in natural conditions, with the advantage for the right hand being exaggerated if the left arm is kept behind the chest and lessened if it is the right hand to be kept in such an unnatural position. A different pattern was found for left-handers—an advantage for the left hand was noted only when the right hand was kept in an unnatural position, but not in the absence of such manipulation[24].

However, there was one additional finding in my data, namely a view-by-hand interaction effect that went *hand-in-hand*, so to speak, with the observation that the RTs for the back-viewed right hand stimuli were the fastest. Exploration of the regional BOLD response *in the left dorsal premotor cortex* and in the dorsal parietal cortex (see the bar graphs in Figure 3.4) clearly shows that the effect was driven by the smaller response for the back-viewed right hand stimuli, whereas the response for the left stimuli was not modulated by the view factor at all.

The suggestion that I are particularly familiar with the back of a right hand is broadly consistent with the behavioural evidence of Ferri et al. (2012): they showed that Italian subjects are faster in discriminating the laterality of the back of their own hand from the back of someone else's hand; however, this was true for the right hand only.

It is also worth noting that all of my right-hand-related effects were evoked by a standard/impersonal hand, rather than by personal pictures of the hands of each participant. This finding suggests that the representation of the right hand, the embodiment evoked by the task, and the ensuing facilitating effects related to the view of the back of the right hand are strongly hardwired to the extent that the observation of one's own hand is not needed for the effects to take place.

It would be tempting to attribute my findings to the factor *handedness*. Because I did not study a sample of left-handers with the same fMRI paradigm, I cannot make firm statements on this matter. In other words, it remains to be seen whether left-handers would show similar neurofunctional patterns: the aforementioned behavioural results (Ní Choisdealbha et al. 2011) suggest that this may not be the case, although the behavioural patterns in previous experiments were not mirror-reversed in comparison with those of the right-handers.

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[24] The lack of an advantage for the dominant hand in left-handers under natural conditions was also previously noted by Takeda et al. (2009).

However, the epidemics of neuropsychological disorders (e.g., apraxia, spatial neglect) related to motor or visual spatial behaviour in left-handers would suggest that left-handers may not be that different from right-handers (Bisiach 1996; De Renzi and Faglioni 1999). Yet, because handedness may be the driving force for the greater familiarity with the back of the dominant hand, this particular domain may represent an exception to the golden rule that the majority of left-handers have neural representations for space and motor behaviour similar to those of right-handers.

Furthermore, the neurofunctional differences in the premotor and parietal cortices for the motorically more demanding HLTs with the palm view were restricted to the left hemisphere, much as it would be suggested by the fact that ideomotor apraxias (see the review in De Renzi and Faglioni 1999) are associated with left-hemispheric damage. Consistent with the view that HLTs rely on left-hemispheric motor simulation strategies is the study of a single case with ideomotor apraxia by Tomasino et al. (2003a), in which substantial impairment in the HLT was observed, whereas the judgement of laterality was preserved for objects[25]. Moreover, the same authors found a double dissociation between the mental rotation of hands and external objects: right-hemisphere-damaged (RHD) patients were impaired in the object rotation task but not hand rotation, whereas left-hemisphere-damaged (LHD) patients were impaired in mental hand-rotation but not object-rotation tasks (Tomasino et al. 2003b). The same authors, in a more recent study (De Simone et al. 2013), expanded these findings and proposed the existence of different mental rotation strategies, regardless of the stimulus type used in the task: they showed that LHD patients were selectively impaired in tasks that required a motor strategy (viewer-based mental rotation), whereas they had normal performance when instructed to adopt a visual strategy centred on the object to solve the task; this was true no matter whether the stimuli were hands or objects (De Simone et al. 2013).

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[25] There is evidence however, that the hemispheric lateralization of similar effects in motor imagery task is driven by the nature of the imagery task itself, the explicit motor imagery task having a less obvious pattern of hemispheric lateralization (see for example Kuhtz-Buschbeck et al. 2003; Sabaté et al. 2004; Michelon et al. 2006; Stinear et al. 2007; Malouin et al. 2012). Furthermore, the HLT may prove less “left-hemispheric” if compared with the more semantically oriented grip selection task, as suggested by the data of Daprati et al. (2010). See below.

A word of caution should be added here while making statements on the hemispheric specialization for the performance of a given task with reference to the neuropsychological literature: particularly when patients' performance in not overtly pathological, the left rather than right hemispheric association may depend on the reference point adopted. Much as the HLT appears more "left hemispheric" when compared with a visual imagery task (e.g. Tommasino et al., 2003), the same task may prove less challenging for LBD patients if compared with a semantically oriented task like a object grip selection motor imagery task (see for example, Daprati's et al. (2010).

To conclude, I wish to make a final comment on the HLT brain patterns in relation with the reaching and grasping fronto-parietal networks. It is worth noting that none of the pictures used in my experiment represent views of an easily graspable hand, and the motor simulation implied by the present HLT would not evoke a grasping-like behaviour. The brain network involved in grasping is strongly dependent on ventral premotor and inferior parietal cortices (Fogassi et al. 2001; Rizzolatti et al. 2002), whereas most of my laterality-specific or view-specific premotor effects were rather in the dorsal parietal and premotor regions. These, according to an influential model (Jeannerod 1997) and recent fMRI data (Cavina-Pratesi et al. 2010), are more concerned with reaching behaviour. It remains to be seen whether the presentation of hands in a graspable view would be associated with similar effects within a grasping oriented brain network that could be differentiated from the one identified here. Further studies are needed to assess this issue.

Summary of Chapter 3

The new look into the HLT provided a number of important new observations and a functional anatomical counterpart to previous behavioural data suggesting that the HLT implies a form of motor simulation and that our ability to visually discriminate a right from a left hand is influenced by perspective. I replicated previous behavioural evidence by showing faster reaction times for the back-view and view-specific interaction effects with the angle of rotation. In addition, the RTs were particularly faster for back views of the right hand. fMRI measurements revealed a stronger BOLD signal increase in left premotor and parietal cortices for stimuli viewed from the palm, whereas back-view stimuli were associated with stronger occipital activations, suggesting a view-specific cognitive strategy: more visually oriented for the back of the hand; more in need of the support of a motoric imagery process for the palms. These differences suggest the existence of brain-encoded, view-dependent representations of body segments.

To what extent the HLT is solved with the same neural machinery in elderly subjects is addressed in Chapter 4.

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Chapter 4 - When I am (almost) 64: the effect of normal ageing on implicit motor imagery in young elderlies.

1. *Introduction*

Explicit Motor Imagery in the life cycle: behavioural and fMRI findings

To date, only few behavioural studies investigated the influence of ageing on implicit MI processes, the focus of my investigation here. Saimpont and colleagues (2009), for example, reported a decline in the ability to implicitly simulate hands movements in elderly subjects, with longer RTs and lower accuracy, especially for the non-dominant hand and for stimuli presented in an awkward position with reference to the biomechanical constraints imposed by the stimuli. Devlin & Wilson (2010) found similar results, showing a decline in elderly's performance in the HLT but also in a whole-body mental rotation task: they speculate that age-related changes in MI could be due to disruption of body schema (Devlin and Wilson, 2010).

A combination of the classical HLT in egocentric reference frame and the same task in an allocentric-reference frame has been used in a recent study by De Simone et al. (De Simone *et al.*, 2013) to compare multisensory, sensory-motor, and visual aspects of implicit MI in elderly and younger people. They showed that elderly participants were less accurate and slower for biomechanically awkward hand postures only when performing the HLT in a egocentric-reference frame; they concluded that ageing is associated with a specific degradation of the sensory-motor mechanisms necessary to perform complex effector-centred mental transformations (De Simone *et al.*, 2013).

It is worth noting that the aforementioned studies are based on elderly subjects in their mid seventies on average. It remains unknown what happens in *younger* elderlies, one and a half decade earlier. Do they have preserved implicit motor imagery skills, and if so, are these subserved by the same functional anatomical patterns as in younger adults?

No study has yet investigated these issues nor it is known whether the eventual preservation of their imagery abilities is based on compensatory mechanisms of some kind. Given the rich literature on neurofunctional compensation processes in ageing, one could expect to observe different pattern of activation in young elderly subjects, which could be considered as a successful compensatory process or as a compensatory attempt, depending on whether the performance reaches a level similar to that of younger subjects (Berlingeri *et al.*, 2010).

Aim of the study

The aim of this study was to investigate the behavioural and fMRI effects of normal ageing on implicit motor processes, by using a classical HLT paradigm (Parsons, 1987b). I did so by comparing behavioural and fMRI patterns of 27 young (mean age 30 years) and 29 *young* elderly (mean age: 61) normal subjects.

In the same study I explored the specificity of any age related change in the HLT behaviour and/or functional anatomical patterns: to do so, the same subjects were also challenged with a Letter Rotation Task (LRT) during which they had to decide whether rotated letters were presented in standard or mirror orientation. On the basis of my previous work on ageing in explicit motor imagery on *young elderlies* of the same age described in Chapter 2, I predicted a shift towards the visual cortices in the HLT for the elderly because of an impoverished ability to do imagery in a motor modality; this prediction would be fulfilled if such shift were greater for the HLT than for the LRT.

2. Materials and methods

2.1 Participants and neuropsychological assessment

27 young subjects (mean age: 31 years, SD: 9 years) and 29 elderly subjects (mean age: 61 years; SD: 7 years) underwent two event-related design fMRI experiments. The socio-economical status

was the middle class from both groups; the educational level was matched (young subjects: 16 years, SD: 2.9; elderly subjects: 15 years, SD: 3.7).

None of the subjects had a history of neurological or psychiatric illness. All were right-handed as assessed by the Edinburgh handedness inventory (Oldfield, 1971). The study was approved by the Local Ethics Committee (Comitato Etico Azienda Sanitaria Locale Città di Milano), and informed written consent was obtained from all subjects, according to the Helsinki Declaration (1964). All subjects participated after the nature of the procedure had been fully explained. A brief neuropsychological assessment was performed on each participant, as already described in Chapter 2. None of the subjects had a single pathological score at the neuropsychological test battery.

2.2 Experimental task

2.2.1 Hand Laterality Task (HLT)

For the first fMRI experiment I used a classic hand laterality judgement task, similar to the one proposed by Parsons (Parsons, 1987b) and already described in Chapter 3.

2.2.2 Letter Rotation Task

In the second fMRI experiment I used a Letter Rotation Task (LRT).

Subjects were shown photos of two different letters (J or F), rotated by different rotation angles (starting at 0° and proceeding by 45° increments: 0°, 45°, 90°, 135°, 180°, 225°, 270°, and 315°). See Figure 4.1.

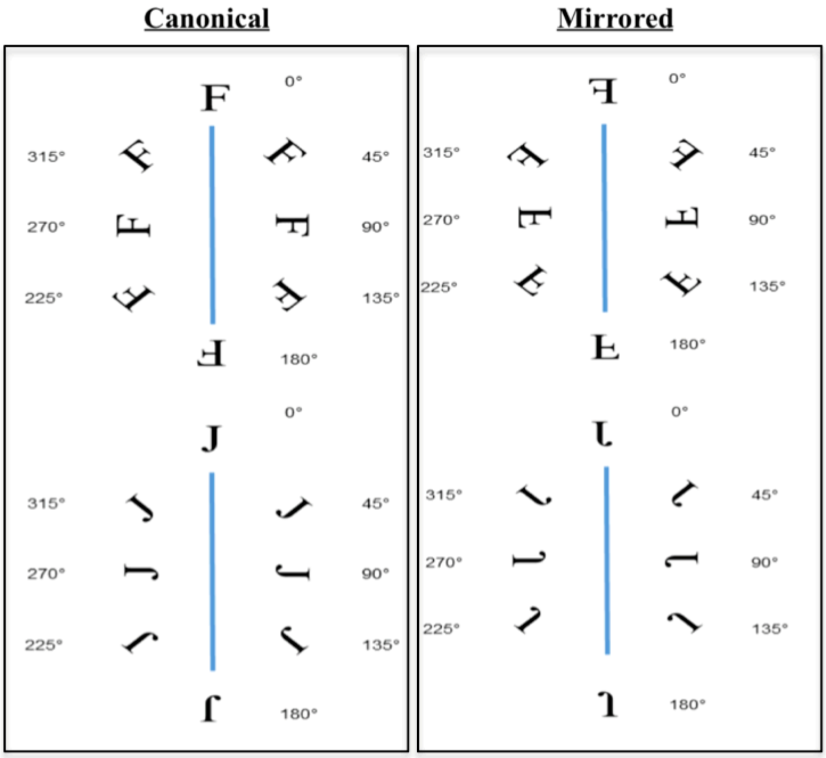
Subjects had to decide whether the letters were presented in standard or mirror orientation.

A total of 64 experimental stimuli were presented (2 x 8 angles of rotation x 2 letters x 2 orientations).

The baseline stimuli were 64 scrambled pictures derived from the letters' pictures.

Each scrambled image had a green or a pink square in the centre.

Experimental Stimuli



Baseline Stimuli

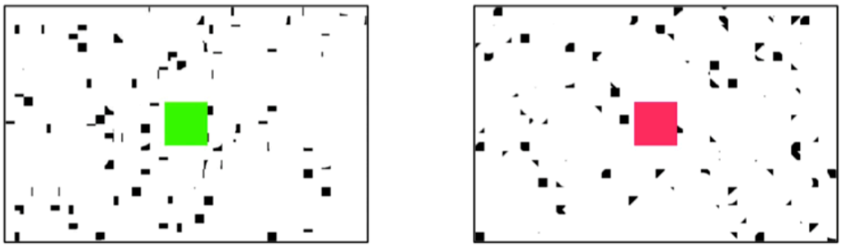


Figure 4.1. Letter Rotation Task: Experimental and Baseline Stimuli

Procedure

The participants practised each task before the scanning session: subjects were familiarised with the stimuli by performing half of the trials (32 trials).

During this training, a warning feedback was given in case of an error.

For the fMRI experiment, the stimuli were randomly alternated according to an event-related design. Each stimulus remained visible for 4000 ms and was preceded by a fixation point in the centre of the screen: the ISI was jitterd and it was randomly varied from 750 ms to 1250 ms (inter-stimulus interval: ISI). Subjects were asked to report whether they were shown a right or a left hand or whether they were shown a standard or mirrored orientated letter by pressing a button with their right or left index fingers. For the scrambled images, subjects had to respond with the right index finger when they saw a green square or with the left index finger when the square was pink. Accordingly, the contribution of the laterality of the motor response was controlled for in the analyses of each task. The experimenter reminded the participants to be fast and accurate in responding.

RTs and accuracy were recorded. Visual stimuli were delivered using the *Visuastim* (Resonance Technology Inc.) fibre-optic goggles. Responses were given through two response boxes (one for each hand).

2.3 Statistical analyses of the behavioural data

Mean accuracy and response time (RT) were calculated for each participant. Accuracy was defined as the proportion of correct responses, while RTs corresponded to the interval between the onset of the stimulus and subjects' button press. Individual performance was considered above chance level when the overall accuracy was greater than 60% (Saimpont *et al.*, 2009). One elderly subject did not reach this criterion for the LRT task and he was excluded from the study.

The accuracy data were analysed by mean of non-parametric test (Kolmogorov-Smirnov test for independent samples).

Outliers (± 2 SD) and incorrect responses were excluded from RTs analyses and fMRI data analyses.

Then, for each subject, I subtracted from RTs of each experimental trial the RTs of the associated baseline trial (simple RTs). This was done to assure that the potential differences between groups were not related to a generalized ageing related decrease of speed in giving motor responses (see for example Nebes, 1978).

The resulting RTs data were analysed as follows:

- HLT: RTs of the participants recorded inside the scanner were analysed by means of a mixed design 2 x 2 x 2 ANOVA with "Group" (Elderly/Young) as between factor and "Hand" (Right/Left) and "View" (Palm/Back) as within group factors.
- LRT: RTs of the participants recorded inside the scanner were analysed by means of a mixed design 2 x 2 x 2 ANOVA with "Group" (Elderly/Young) as between factor "Letter" (F/J) and "Orientation" (Standard/Mirrored) as within group factors.

2.4 fMRI data acquisition and analysis

MRI scans were performed using a 1.5 T Siemens *Avanto* scanner, equipped with gradient-echo echo-planar imaging (flip angle 90°, TE=60 msec, TR=3000 msec, FOV=280 x 210 mm and matrix= 96 x 64).

I collected 225 volumes for each task, in two separate runs. The first 10 volumes of each sequence (corresponding to the task's instructions) did not correspond to any stimulation and were discarded from the analyses.

Preprocessing and Statistical analyses of the fMRI data

I adopted the same strategy described in Chapter 2.

Four contrast images were brought to the second level analysis, one for each condition of interest; for the HLT: Hand (Right or Left); View (Palm or Back); for the LRT: Letter (F or J), Orientation (Standard or Mirror), after subtracting out the BOLD response for the time matched events of the baseline condition. The full factorial ANOVA generated F-contrasts for the main effect of view and hand, and for the hand x view interaction effects and similar effects for the conditions of the LRT. Post-hoc analyses to examine the direction of the aforementioned effects were performed using linear contrasts to generate SPM[t] maps. To minimize the impact of the RTs on the results, these were treated as confounding covariate.

In the following section I describe all the effects whose relevance was anticipated by the behavioural results. The specificity of the between group differences were then assessed by comparison with the LRT data.

1. HLT

1a. Effects shared by young and elderly subjects: regardless of the experimental group, I first evaluated the neurofunctional counterparts of the main behavioural effects like for example the effect of view, of hand or the interactions between these factors.

1b. Between-groups differences: activation pattern differences between the two groups for the HLT.

1c. Correlations between fMRI and behavioural HLT measures: the behavioural measures were used as a predicting covariate of the fMRI patterns;

2. LRT: between group comparison of the LRT.

3. Group by task interaction effects: the magnitude of the between group activation difference for the HLT was compared with that of the same between group difference for the LRT.

Each effect was visualized at the voxelwise threshold of $p<0.001$ (uncorrected). I further considered only cluster significant at $p<0.05$ for its spatial extent. In Chapter I describe also the level of correction for multiple comparisons met by each peak of these clusters. The vast majority of the peaks/clusters reached at least $p<0.05$ false discovery rate (FDR) correction (Chumbley *et al.*, 2010) if not a 0.05 FWE level (Worsley *et al.*, 1996).

3. Behavioural results

3.1.1 Hand Laterality Task

I first determined whether there were behavioural differences between the two groups in terms of accuracy: there were none. The Kolmogorov-Smirnov test for independent samples did not highlight any significant difference in any of the experimental condition (Right back: $p=0.4$, Right palm: $p=0.6$, Left back: $p=0.9$, Left palm: $p=0.6$). The mean accuracy was 89% for the elderly group and 92% for the young group.

Then, we looked at the RTs, by means of a 2 x 2 x 2 repeated-measures ANOVA on RTs with "Group" (Elderly/Young) as between factor and "Hand" (Right/Left) and "View" (Palm/Back) as within factors.

Main effects. While there was no overall between group differences ($F(1, 54) = 1.7$; $p = 0.194$; $\eta^2 = 0.03$); the analyses of the within group effects showed that there were faster RTs for the back view with respect to the palm view ($F(1, 54) = 78.9$; $p < 0.001$; $\eta^2 = 0.59$); moreover, RTs were faster overall for the right hand ($F(1, 54) = 16.9$; $p < 0.001$; $\eta^2= 0.24$).

Within group interactions. A trend of significance was found for the Hand by View interaction: $F(1, 54) = 3.3$; $p = 0.075$; $\eta^2 = 0.06$). Exploratory post hoc analyses showed that the RTs for the back-viewed right hand were significantly faster than for any other condition (Right Back vs Left Back: $t(55)=4.3$; $p < 0.001$; Right Back vs Right Palm: $t(55)=8.3$; $p < 0.001$; Right Back vs Left Palm: $t(55)=8.5$; $p < 0.001$).

Group by task interactions. On the other hand, no group-specific effects emerged: the View by

Group interaction: F(1, 54) = 2.7; p = 0.109; $\eta^2 = 0.05$; the Hand by Group interaction: F(1, 54) = 0.4; p = 0.527; $\eta^2 = 0.01$ and View by Hand by Group interaction: F(1, 54) = 0.87; p = 0.355; $\eta^2 = 0.016$ were all far from significance.

These results are also summarised in Table 4.1a and Figure 4.2.

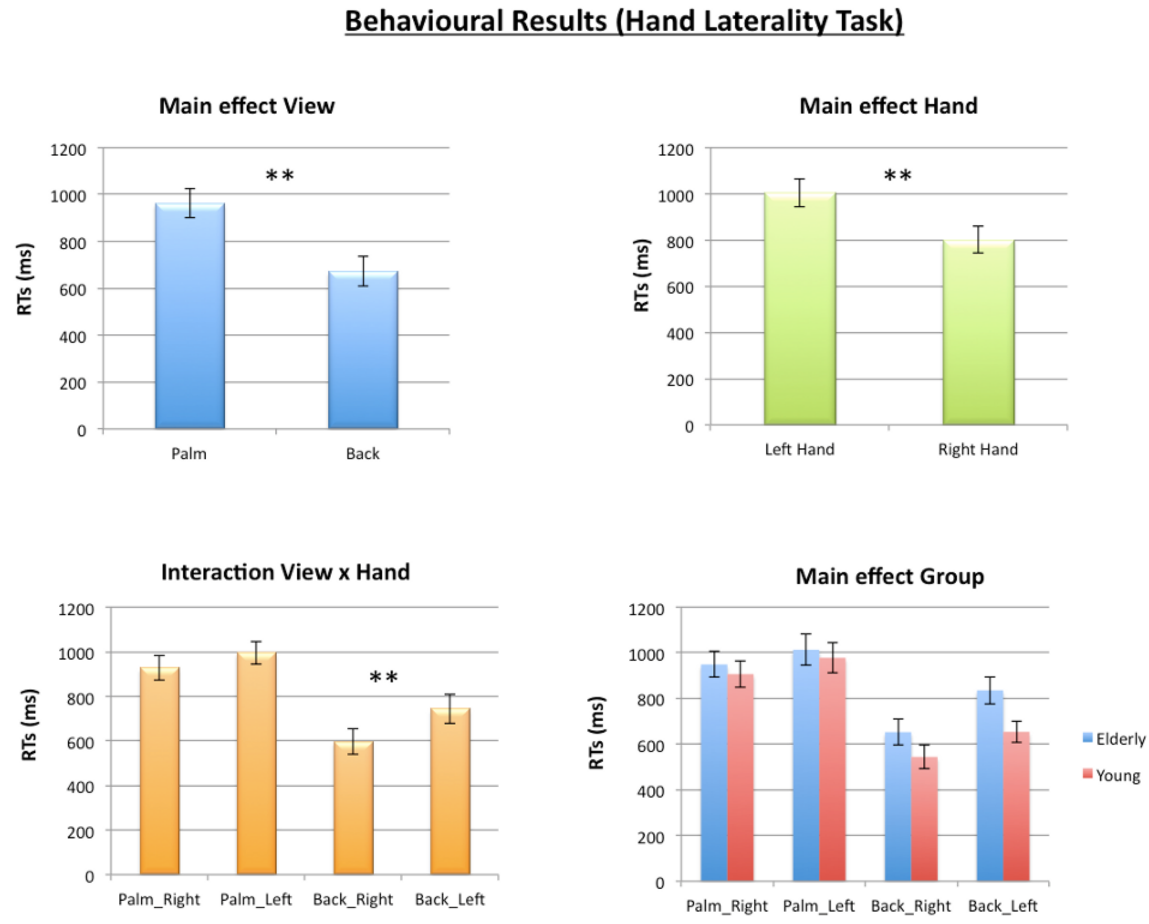


Figure 4.2. Hand Laterality Task: behavioural results.

3.1.2 Letter Rotation Task

The Kolmogorov-Smirnov test for independent samples did not highlight any significant difference between the two groups in terms of accuracy in any of the experimental condition (F Canonical: p= 0.4, F mirror: p=0.2, J Canonical: p=0.9, J mirror: p=0.4). The mean accuracy was 90% for the elderly group and 94% for the young group. See Table 4.1b.

The 2 x 2 x 2 repeated-measures ANOVA on RTs with "Group" (Elderly/Young) as between factor "Letter" (F/J) and "Orientation" (Standard/Mirrored) as within factors revealed the following results.

<u>Main effects</u>: there were no between group differences_(F(1, 53) = 1.7; p= 0.2; $\eta^2 = 0.03$); the within group main effects analysis showed that the RTs were faster for the letter "F" (F(1, 53) = 40.7; $p < 0.001$; $\eta^2 = 0.43$) and for the canonical orientation (F(1, 53) = 66.7; $p < 0.001$; $\eta^2 = 0.56$).

<u>Within group interactions</u>: the interaction Orientation by Letter was not significant (F(1, 53) = 2.1; $p = 0.150$; $\eta^2= 0.04$).

<u>Group by letter name or by letter orientation interactions</u>: the group by letter orientation or by letter name interaction effects were both not significant (Orientation by Group interaction: F(1, 53) = 1.2; $p = 0.279$; $\eta^2 = 0.02$; Letter by Group interaction: F(1, 53) = 0.002; $p = 0.966$; η2 = 0.001.

Table 4.1a. Summary of mean RTs (and standard error) recorded during the HLT task.

		Condition			
		Back_Right	***Back_Left***	***Palm_Right***	***Palm_Left***
Elderly	***Experimental Trials***	1468.4 (65.1)	1653.7 (68.3)	1818.3 (68.2)	1856.4 (73.1)
	Baseline Trials	815.9 (39.2)	818.1 (33.3)	869.4 (31.4)	843.4 (31.2)
	ΔRTs	652.5 (57.2)	835.6 (67.3)	948.8 (56.3)	1013.1 (59.6)
Young	***Experimental Trials***	1276.1 (78.1)	1387 (77.7)	1658.9 (98.2)	1708.7 (98.6)
	Baseline Trials	732 (37.9)	734.2 (31)	752.2 (31.3)	730.7 (33.1)
	ΔRTs	544.1 (57.9)	653.7 (66.8)	906.7 (52.2)	978.0 (46.1)

Table 4.1b. Summary of mean RTs (and standard error) recorded during the LRT task

		Condition			
		F canonical	***F mirror***	***J canonical***	***J mirror***
Elderly	***Experimental Trials***	1245.2 (41.8)	1369.2 (49.6)	1412.4 (64.1)	1645 (77.9)
	Baseline Trials	835.6 (37.3)	831.4 (33.5)	830.3 (37.9)	856.4 (35.7)
	ΔRTs	409.6 (26.9)	564.8 (48.9)	582.1 (46.9)	788.6 (69)
Young	***Experimental Trials***	1061.9 (40.5)	1230.9 (36.9)	1187.7 (55.8)	1491.8 (59.1)
	Baseline Trials	734.2 (41.5)	730.1 (49.3)	722.8 (26.4)	727.2 (31.8)
	ΔRTs	327.7 (46.7)	500.7 (46.9)	464.8 (49.8)	764.6 (55.6)

4. fMRI results

4.1 Hand Laterality Task

Across groups effects

The effects shared by both young and elderly subjects were in line with my previous findings and supported the behavioural effects described also in Chapter 3.

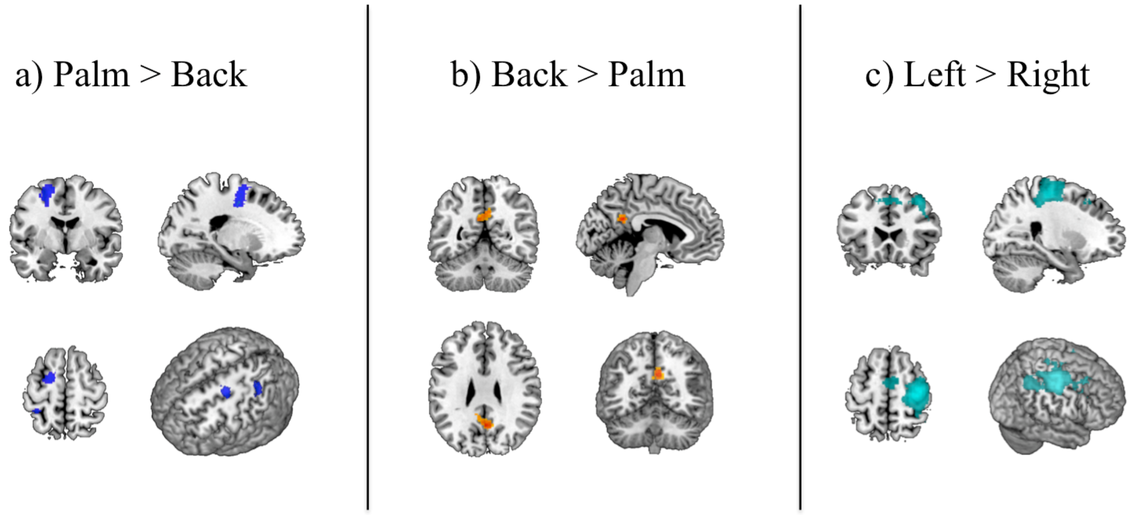


Figure 4.3. fMRI results: Across group effects (Hand Laterality Task).

The factor “VIEW” was highly significant: post hoc analyses (by means of linear t-contrasts) revealed that these were all due to greater activation for the palm view stimuli with stronger activity at the level of the left superior and middle frontal gyri, the left SMA, and the left inferior and superior parietal lobule; on the other hand, the back-view stimuli were associated with specific recruitment of the lingual gyrus bilaterally and the right precuneus. See Figures 4.3a and 4.3b and Tables 4.2a and 4.2b.

The factor “HAND” was also highly significant, with larger BOLD signal for stimuli depicting left hands in bilateral anterior regions (middle frontal gyrus, precentral gyrus), in right mid cingulum, postcentral gyrus. See Figure 4.3c. As subjects responded with the left hand during the baseline as many times as during the experimental task, this effect cannot be explained by the mere implementation of the motor response. Further left hand larger activations were also found in posterior regions including fusiform gyrus, lingual gyrus and cerebellum in the left hemisphere. See Figure 4.2c and Table 4.2c.

These results confirm my previous observations on the greater neural labour needed to process hand stimuli in palm view and depicting left hands.

The “View by Hand” interaction was also significant with specific effects in bilateral SMA, due to a comparatively smaller BOLD response for both elderly and young subjects for the back view of the right hand. See Figure 4.4 and Table 4.2d. A plot of the hemodynamic responses is illustrated in Figure 4.4.

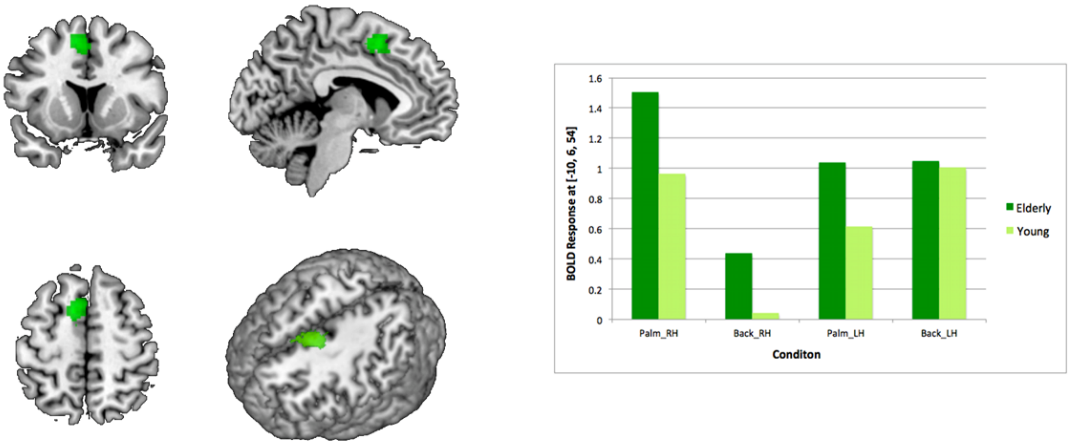


Figure 4.4. fMRI results: Interaction View by Hand (Hand Laterality Task)

Table 4.2. fMRI across-group results (Hand Laterality Task)

Brain regions (BA)	MNI coordinates							
	Left hemisphere				Right hemisphere			
	x	y	z	Z-score	x	y	z	Z-score
a. Palm > Back								
Superior Frontal gyrus (6)	-22	-8	44	4.7*	--	--	--	--
Superior Frontal gyrus (6)	-20	-6	56	4.0	--	--	--	--
Middle Frontal gyrus (6)	-24	-4	52	4.0	--	--	--	--
SMA (6)	-12	4	62	3.2	--	--	--	--
Superior Parietal Lobule (2)	-32	-42	60	3.6	--	--	--	--
Inferior Parietal Lobule (40)	-36	-42	54	3.6	--	--	--	--
b. Back > Palm								
Lingual gyrus (18)	-6	-50	26	3.4	12	-58	26	2.7
Precuneus	--	--	--	--	6	-60	32	3.3
c. Left Hand > Right Hand								
Middle Frontal gyrus (9)	-30	10	48	3.5	38	20	50	4.9*
	-44	16	50	3.1	--	--	--	--
Middle Frontal gyrus (8)	-28	14	50	3.6	--	--	--	--

	-28	18	48	3.5	--	--	--	--
	-26	20	54	3.3	--	--	--	--
	-24	14	44	3.2	--	--	--	--
Precentral gyrus (6)	-38	8	34	4.7*	34	-14	58	6.1*
Precentral gyrus (6)	-44	4	38	4.5*	44	-14	52	5.6*
Precentral gyrus (6)	-48	6	38	4.2	42	-14	56	5.5*
SMA (6)	--	--	--	--	16	-8	68	4.6*
Mid. cingulum (24)	--	--	--	--	6	-16	46	4.7*
	--	--	--	--	6	-12	48	4.7*
	--	--	--	--	8	0	42	4.7*
	--	--	--	--	12	6	40	4.7*
	--	--	--	--	8	-4	46	4.6*
Precentral gyrus (4)	--	--	--	--	34	-20	52	6.1*
	--	--	--	--	34	-24	54	6.1*
	--	--	--	--	32	-20	56	6.1*
	--	--	--	--	48	-16	44	6.0*
Postcentral gyrus (3)	--	--	--	--	46	-20	48	5.9*
	--	--	--	--	38	-20	48	5.8*
Lingual gyrus (18)	-14	-88	-10	3.9	--	--	--	--
	-10	-84	-12	3.8	--	--	--	--
	-16	-86	-14	3.8	--	--	--	--
	-20	-80	-16	3.6	--	--	--	--
Fusiform gyrus (18)	-24	-72	-14	3.3	--	--	--	--
Fusiform gyrus (19)	-30	-68	-16	3.2	--	--	--	--
Cerebellum (18)	-20	-74	-16	3.4	--	--	--	--
d. Interaction View x Hand								
SMA (6)	-10	6	54	4.5	--	--	--	--
SMA(32)	0	14	48	3.9	--	--	--	--
	-8	-4	56	3.3	--	--	--	--

* FWE corrected

Importantly, there were also between-group differences: the elderly subjects showed larger activations in the bilateral inferior frontal gyrus (opercular part), the superior parietal lobule, the angular gyrus. Further hyperactivations were found in the precentral gyrus, the inferior parietal lobule in the left hemisphere. Additional recruitments were also observed in the occipital lobe (superior and middle occipital gyri, lingual gyrus), in the calcarine fissure and in the fusiform gyrus bilaterally. See Figure 4.5a and Table 4.3a. On the other hand, the comparison Young > Elderly yielded no significant increase in BOLD signal in any brain region.

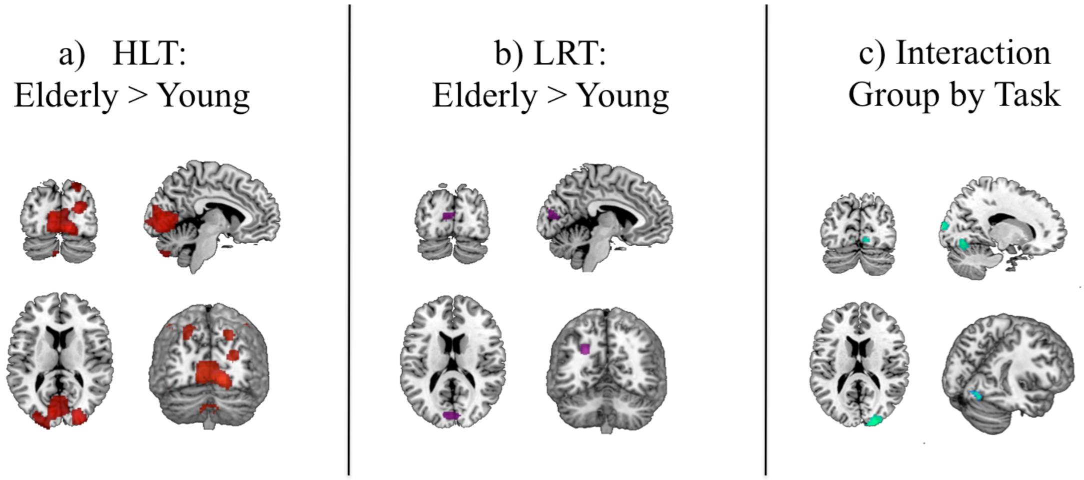


Figure 4.5. fMRI results: between group effects (Hand Laterality Task and Letter Rotation Task).

To further explore the functional meaning of the regions of hyperactivation in the elderly subjects, their fMRI data were correlated with the RTs during the HLT in a linear regression analysis. The analysis was restricted to the regions of significant hyperactivtion in the elderly. A $p<0.005$ significant, negative correlation, was found in the left lingual gyrus whereby the higher the neural activity the better was the behavioural performance. See Figure 4.6.

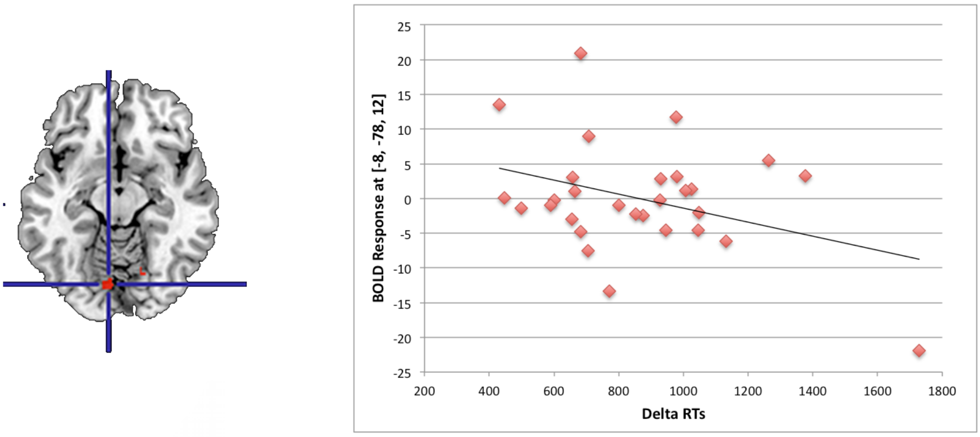


Figure 4.6. Negative correlation between older subjects' hyperactivations in the occipital lobe and RTs.

4.2 Letter Rotation Task

I found an over-recruitment in the elderly group at the level of the left middle occipital gyrus, the left calcarine fissure and the left superior parietal lobule in elderlies compared with youngers, whereas the opposite contrast (Young > Elderly) did not reveal any significant hyperactivation in the young group. See Figure 4.5b and Table 4.3b.

The other comparisons (letter F vs letter J or canonical view vs mirror view) yielded not significant increased BOLD signal in any brain region.

4.3 Group by task second order interaction effect.

I found a significant second order interaction effect, with the group of elderlies having increased hyperactivations for the HLT task that were significantly greater than for the LRT. These effects were in the right lingual gyrus and in the right superior occipital gyrus. See Figure 4.5c and Table 4.3c.

Table 4.3. fMRI between-group results.

Brain regions (BA)	**MNI coordinates**							
	Left hemisphere				**Right hemisphere**			
	x	**y**	**z**	**Z-score**	**x**	**y**	**z**	**Z-score**
a. Elderly > Young (HLT)								
Inferior Frontal op. gyrus (44)	-38	10	28	4.0	38	8	26	4.2*
Precentral gyrus (44)	-38	8	32	4.3*	--	--	--	--
Precentral gyrus (6)	-44	6	50	4.6*	--	--	--	--
Superior Parietal lobule (7)	-24	-72	48	4.0	24	-74	46	4.3*
Inferior Parietal lobule (39)	-44	-58	54	3.4	--	--	--	--
	-42	-56	48	3.3	--	--	--	--
Inferior Parietal lobule (40)	-42	-52	40	3.5	--	--	--	--
	-40	-48	48	3.5	--	--	--	--
	-40	-50	44	3.5	--	--	--	--
	-44	-50	54	3.5	--	--	--	--
	-48	-50	58	3.4	--	--	--	--
Angular gyrus (39)	-44	-52	36	3.4	46	-52	38	4.0
Fusiform gyrus (19)	--	--	--	--	24	-60	-14	4.8*
Fusiform gyrus (37)	-44	-56	-14	4.0	--	--	--	--
Superior Occipital gyrus (19)	-20	-98	16	4.2*	28	-66	28	4.2*
Middle Occipital gyrus (18)	-28	-90	10	4.0	26	-88	18	5.3*
	-28	-64	30	4.3*	--	--	--	--
Lingual gyrus (17)	-6	-72	6	4.5*	--	--	--	--
	-4	-72	2	4.4*	6	-70	6	4.1
Lingual gyrus (18)	-10	-80	-4	4.7*	14	-76	-6	5.6*
Calcarine fissure (17)	-8	-84	10	4.9*	--	--	--	--
	-8	-80	8	4.9*	--	--	--	--
Calcarine fissure (18)	-8	-84	-4	4.7*	--	--	--	--
b. Elderly > Young (LRT)								
Inferior Frontal op. gyrus (44)	-34	10	28	4.3	--	--	--	--
Superior parietal lobule (7)	-26	-72	52	3.5	--	--	--	--
Cuneus	-6	-92	22	3.1	--	--	--	--
Middle occipital gyrus (19)	-26	-62	34	4.8*	--	--	--	--
Calcarine fissure (17)	-6	-86	12	4.2	--	--	--	--
c. Elderly > Young (HLT > LRT)								
Lingual gyrus (18)	--	--	--	--	16	-72	-10	3.8
Superior Occipital gyrus (18)	--	--	--	--	22	-96	16	4.0

* FWE corrected

5. Discussion

The aim of the present study was to investigate the influence of normal ageing in its early stages on implicit motor imagery processes. To do so, I used the classic Hand Laterality Task. The specificity of any ageing related finding in the HLT was tested by comparison with another visual mental imagery task, the letter rotation task, wich was delivered both in a behavioural setting and during fMRI. The presence of the LRT control task and the relatively large sample of subjects (58 overall) makes my inference on aging effects in implicit motor imagery specific and solid grounded.

HLT is considered an implicit motor imagery task: it is widely believed that during the task subjects rely on a mental rotation of their own hand to match the position of the one presented on the screen (Parsons, 1987a). This task has been largely used for studying motor representations in both normal subjects or brain-damaged patients (McAvinue and Robertson, 2008), as it provides measureable indexes of motor imagery processes in the forms of RTs and accuracies and, importantly, their dependencies from biomechanical constraints (Parsons, 1987a; Parsons, 1987b).

The results of my study demonstrate for the first time the existence of significant neurofunctional effects of early ageing on the neural substrates of these implicit motor mechanisms.

I start this section by discussing my behavioural findings, considering both across- and between-group effects: the behavioural component of the study was important to interpret the fMRI patterns, because it allowed us to tell whether any hyper- or hypo-activation in ageing was a sign of successful compensation or an unsuccessful compensatory attempt (for discussion and illustration of multiple behaviour-fMRI scenarios, see Berlingeri *et al.*, 2010).

I then address the meaning of the neurofunctional differences associated with ageing, that were mainly located in occipital regions, brain areas whose hyperactivations were already associated with successful compensation in other studies on ageing (Berlingeri *et al.*, 2010).

Finally, I will discuss the relevance of my findings for the more general understanding of the effect of ageing on motor control.

Behavioural findings

For both young and elderly subjects, I observed faster RTs associated with hand stimuli presented in the back-view, particularly for the the right hand.

Interestingly, a robust right hand advantage is found particularly for the back view stimuli confirming the "special status" of this set of stimuli, having this condition the fastest of all RTs in both groups. Taken together, these observations suggest that both groups were performing the task according to expectations based on data collected from different subjects in previous experiments who were behaving in more ecological settings than an fMRI scanning session 3(Parsons, 1987a).

Exploration of the between-group effects revealed that the elderly group was comparable to group of younger subjects, both in terms of accuracy and normalized RTs; these findings may seem in contrast with previous studies that explored the same issue (Saimpont *et al.*, 2009, b; Devlin and Wilson, 2010; De Simone *et al.*, 2013).

Saimpont and colleagues (2009), for example, found that elderly subjects were overall nearly as accurate as younger subjects while performing the HLT (90 % overall accuracy in elderlies vs 96% in youngers); however, they had longer RTs and a closer look to the accuracy data revealed that the older subjects were less precise particularly for stimuli corresponding to biomechanically awkward positions, like the palm of the hand at 90° or the back of the hand at 180° (see for example ter Horst *et al.*, 2010) The authors concluded that elderly subjects suffer of a specific impairment in visuo-perceptual processing in ways that are constrained by biomechanical motoric factors (ter Horst *et al.*, 2010; ter Horst *et al.*, 2012; Bläsing *et al.*, 2013; ter Horst *et al.*, 2013).

In line with Saimpont et al. (2009) findings, De Simone & colleagues (2013) also showed that elderlies were less accurate and slower while preforming HLT in an egocentric-reference frame (De Simone *et al.*, 2013). On the other hand, Devlin & Wilson (2010) found that elderly people are slower but not less accurate (Devlin and Wilson, 2010).

However, the discrepancy between my findings with the aforementioned studies may be explained by two main factors: first, the different mean age of the elderly participants in the studies: 61 years in my study versus 78 in Saimpont's study (2009), 72 in De Simone et al. (2013) and 74 in Devlin et al. (2010); it is well documented that a decline of motor performance in healthy ageing can be detected only in fairly old subjects while in *young* elderly subjects, as the ones of my sample, performance may remains similar to that of young subjects (see for example Mattay *et al.*, 2002; Wu and Hallett, 2005). This does not deny the possibility that the equivalent behaviour could be generated by a re-organized brain, as I will discuss below.

Second, in aforementioned studies, only absolute RTs values were considered; to avoid the confound of a global lengthening of RTs for the elderlies (see for example Nebes, 1978), I rather analysed "ΔRTs" (RTs associated with experimental trials *minus* RTs for baseline trials). I adopted this approach because I observed longer absolute RTs in the elderly group that were mirrored by longer RTs also in the baseline conditions, suggesting a general lengthening of motor responses rather than a specific decline in mental motor representations[26].

Taken together, my results suggest that in normal early ageing behavioural performance in implicit motor tasks may stay close to a juvenile-like level; the fMRI experiment allowed us to further explore this finding, investigating whether the two groups show also similar neural patterns (suggesting that early ageing does not affect the domain of implicit motor representation) or different fMRI patterns, a finding that would be explainable in terms of successful compensation.

Neurofunctional counterparts of the behavioural data

Across groups effects

I identified view-specific fMRI patterns in motor mental imagery of hands. As revealed by the direct comparison Palm view > Back view, visuo-perceptual judgments for hands displayed in palm

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[26] In addition, as we will argue, ΔRTs were the appropriate covariate measures for the fMRI analysis as the fMRI dependent variables were differential responses for the HLT and its baseline.

view were associated with increased BOLD response at level of left premotor cortices (superior frontal gyrus and SMA) and left somatosensory cortices (postcentral gyrus) as if responses for this class of stimuli were more “motorically driven” (Jeannerod & Frak, 1999) or in need of motoric strategies. Indeed, the involvement of these areas in both motor execution and MI tasks has been extensively proved (for a meta-analysis, see Hétu *et al.*, 2013).

On the other hand, the contrast Back view > Palm view yielded specific activations in occipital cortices, which have been observed in visual imagery tasks (Guillot *et al.*, 2009), suggesting at least a partial dissociation between the cognitive strategies used to process hand stimuli from different views, as already pointed out by previous literature on young subjects (ter Horst *et al.*, 2010; Bläsing *et al.*, 2013).

It is important to highlight that the stronger premotor recruitment seen for the palm view could not be explained by longer RTs associated with this condition since the impact of the ΔRTs on the BOLD response was covaried-out in my fMRI analyses.

This finding was further explored by looking at the Interaction effect “Hand by View”: both groups showed a significant interaction at the level of left SMA, with the lowest neural recruitment of this area for the right hand presented in back view, suggesting a minor engagement of kinaesthetic and motoric strategies in both young and elderly participant for a stimulus viewed from this perspective (see Figure 3).

My findings therefore confirm the behavioural hypothesis of a “privileged status” for the back of the right hand, as already seen in young people, also in elderly right-handers healthy subjects.

Implicit motor imagery in healthy ageing: between group differences

Investigation of neurofunctional changes across the adult lifespan has been the aim of many fMRI studies (for a review, see Goh, 2011).

Modifications of fMRI patterns in the elderly have been interpreted as evidence of compensatory processes by a number of studies (Grady *et al.*, 1994; Cabeza, 2002; Cabeza *et al.*, 2002; Buckner, 2004; Davis *et al.*, 2008). When the performance remains comparable with the younger counterparts, compensatory processes manifest themselves in the recruitment of additional brain regions or by a stronger activation of some of the constituent components (e.g., the present study). These patterns have been documented in several cognitive domains (e.g., working memory, episodic memory retrieval, perception, inhibitory control, etc.). This phenomenon was initially observed in the prefrontal cortex and inspired the so called HAROLD model (Cabeza, 2002), but more recent evidence has shown that the compensatory hyperactivations of the elderly may involve brain regions also outside the frontal lobe, in a task dependent manner (Berlingeri *et al.*, 2010; Berlingeri *et al.*, 2013).

fMRI compensatory processes have been previously described also in the domain of motor function, using a variety of motor tasks, ranging from simple to complex (Mattay *et al.*, 2002; Ward and Frackowiak, 2003; Heuninckx *et al.*, 2005). These studies showed age-related differences, especially in non-motor brain regions associated with more cognitively demanding tasks, like pre-SMA, which may reflect increased cognitive monitoring of performance (see Nachev *et al.*, 2008 for a review); these differences are usually greater when complex tasks are used (Heuninckx *et al.*, 2005). These findings are interpreted as a sign of ‘‘*an adaptable motor network able to respond to age-related degenerative changes in order to maintain performance levels*’’ (Ward and Frackowiak, 2003).

Given the vast functional equivalence between motor execution and motor imagery at the cortical level, one would expect a similar scenario also for the motor imagery domain. Only few studies investigated this issue with evidence available only for explicit motor imagery processes: these previous studies showed stronger activation of area M1 (posterior portion, Sharma and Baron, 2014), SMA and prefrontal regions (Allali *et al.*, 2014), and occipital lobes (Zwergal *et al.*, 2012; Wang *et al.*, 2014).

My current findings on implicit processes are partially in line with this literature, reporting additional recruitment occipital regions (superior occipital and lingual gyri) in elderly people. These regions have been associated with visual imagery of body part movements, which shares common occipital substrates with visual perception (Guillot *et al.*, 2009). I thus confirm the elderly's need of an additional strategy or their greater reliance on visual areas to deal with the task, even in implicit motor imagery processes. The linear regression analysis on the elderly subjects' RTs data confirmed this hypothesis: the greater the recruitment of these additional regions, the better was the behavioural performance (i.e. the shorter were the RTs).

It is important to recall that the fMRI differences are specifically related to the domain of motor representation and could not be explained as a general difficulty to mentally manipulate visual stimuli, given the fact that they were significantly greater in the hand laterality task than in the letter rotation task (see Figure 4c).

As already discussed above, the elderly's hyperactivations in my task are not mirrored by substantial behavioural differences, something different from what found in my previous study on explicit MI in a different but age-matched sample of subjects (mean age: 60 years).

It is possible that this discrepancy could be due the different nature of the tasks. As already pointed out by De Lange et al. (2008), explicit and implicit motor imagery tasks present a **differential load on self-monitoring of actions,** which is increased when subjects are explicitly asked to imagine their hands moving. In their study, the authors showed how manipulating the degree of action monitoring in patients with conversion paralysis influences the imagery process and the ensuing cortical response: their basic finding was a reduced premotor activation for the hysterically paralyzed hand during implicit motor imagery. However, this effect was abolished when subjects were challenged with an explicit motor imagery task (de Lange *et al.*, 2008).

Other evidence supporting this hypothesis comes from the studies on explicit and implicit motor imagery in schizophrenic patients (Danckert *et al.*, 2002): in explicit motor imagery tasks they showed a poor relationship between imagined and real movement duration, as if they were unable to generate accurate internal images of their own actions; on the contrary de Vignemont et al. (2006), investigating the same issue using implicit MI paradigm, found that implicit MI was preserved in schizophrenic patients (de Vignemont *et al.*, 2006).

My results suggest that in the early phase of ageing compensatory processes in the domain of motor representations could be successful primarily in MI tasks with a low degree of explicit action monitoring, like HLT, in which the "desired state" of the system is visually available; this results in a normal behavioural performance. That is not true for explicit motor imagery processes, where I found "unsuccessful" compensatory neural mechanism with the loss of temporal congruency between real and imagined movements. In the advanced stage of ageing (after the age of 70) the compensatory process would not be sufficient, resulting in a behavioural decline for both explicit and implicit tasks as previously described (Saimpont et *al.*, 2009, De Simone et *al.*, 2013 and Devlin and Wilson, 2010).

The group of elderly subjects studied here, the "when I am (almost) 64" subjects, belong to an age that could be called of *young elderly*, as they belong to the age range when retirement normally begins. They reveal a pattern of graceful aging whereby cognitive performance remains within more than acceptable levels thanks to some compensatory brain processes. It remains to be seen what it would be the behavioural and fMRI pattern in implicit motor imagery one decade later. Previous studies (Saimpont et *al.*, 2009, De Simone et *al.*, 2013 and Devlin and Wilson, 2010) demonstrated significant changes in terms of behavioural proficiency one decade later. Also, as my group of *young elderlies* was taken from a relatively privileged social and educational endeavour, it would be interesting to expand the study to less favoured groups, in terms of education and occupation, whose aging process may follow different trajectories.

Summary of Chapter 4

In this experiment I have shown that implicit MI in normal early ageing is not substantially modified at behavioural level, even if it is characterised by a stronger recruitment of visual cortices and the neurofunctional level.

My study leaves a number of outstanding issues: it will be important, for example, to investigate whether, as already seen in the domain of the real motor execution, the effect of early ageing could be detected by using more complex implicit MI tasks (e.g. the grip selection task).

The grip selection task involves more complex visuo-motor transformations, possibly with less degrees of freedom as far as the alternative compensatory strategies that one may use to solve the task beyond the motoric ones. It remained to be seen whether under these task constraints one could observe behavioural and/or functional anatomical patterns similar to those already seen in explicit motor imagery or in implicit motor imagery as challenged by the HLT. This is what I discuss with the experiment presented in Chapter 5.

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Chapter 5 – Grasping minds: the effect of aging on implicitly simulated reaching movements.

1. Introduction

Grip Selection Task and movement representations

The studies on implicit MI described in literature mainly focused on mental rotation of body parts (e.g. Parsons, 1987a; Parsons, 1987b); as already mentioned in Chapter 1, another implicit MI task is the Grip Selection Task (GST), where subjects are shown pictures of different tools, preceded by an indication of which hand to use to mentally grasp the depicted object. Subjects are then asked to indicate whether they would grasp the object with an under-grip or an over-grip.

These "prospective action judgements" involve the mental simulation of grasping movements, as shown by behavioural and fMRI studies.

Johnson (2000b) for example investigated for the first time the behavioural mechanisms by which prospective action judgements are computed, by using a series of tasks that involved either the actual grasping (M.E. conditions) or the imagined grasping (MI conditions) of a dowel presented in different orientations (Johnson, 2000b).

Johnson's results showed similar responses in both M.E. and MI conditions: when allowed to select the most natural grip (overhand versus underhand) or hand (left versus right) for grasping the dowel, subjects preferred identical responses in the two tasks; moreover, the time required to make a grip selection decision was predicted by the angular distance between the effector's position and the end state of the simulated grip, following a biomechanically plausible pattern. Finally, RTs were longer and the accuracy was lower for awkward hand postures both in M.E. and MI tasks.

The involvement of motor simulation in GST is confirmed by a study on neurological patients: in another study Johnson (2000a) studied 12 hemiparetic/hemiplegic patients after a cerebro-vascular accident with the GST. The results showed that the performance was compromised in cases with right posterior parietal or left frontal regions; these findings are in line with the idea that imagined grasping involves a fronto-parietal network, like actual prehension (Johnson, 2000a).

Neurofunctional correlates of GST

The same authors (Johnson *et al.*, 2002) formally tested this hypothesis in what remains to date the only neurofunctional study available in the literature: they used the same experimental approach described in their previous behavioural study (Johnson, 2000b) and they demonstrated that imagined grip selection specifically activates a fronto-parietal circuit, that includes the premotor cortex bilaterally, the intraparietal sulcus and the right superior parietal lobule, regardless of the hand involved in the task.

The areas identified by this task are similar to the parieto-frontal network described in monkeys with electrophysiological recordings during planning and reaching movements (Cohen and Andersen, 2002).

These findings support the idea that GST activates action-specific motor representations, computed in parieto-frontal circuits. In the light of these data, the authors proposed a cognitive model of reach simulation (the Prospective Action Model, see Figure 5.1): they postulated that movement simulations are used to evaluate the different possible responses before movement selection and then used to select the most efficient alternative from a biomechanical point of view. The model also predicts the neural correlates of the different components described, on the basis of their fMRI results (see figure 5.1): (1) the spatial properties of the object and the arm position represent the input to the model; (2) this information is then integrated by the premotor cortex in order to form the two alternative pre-movement plans for reaching (under or over-hand grip). These plans are sent to the superior parietal lobule (3), where the so-called effective reach simulation takes place to be then projected back (4) to the premotor system for response selection (Johnson *et al.*, 2002).

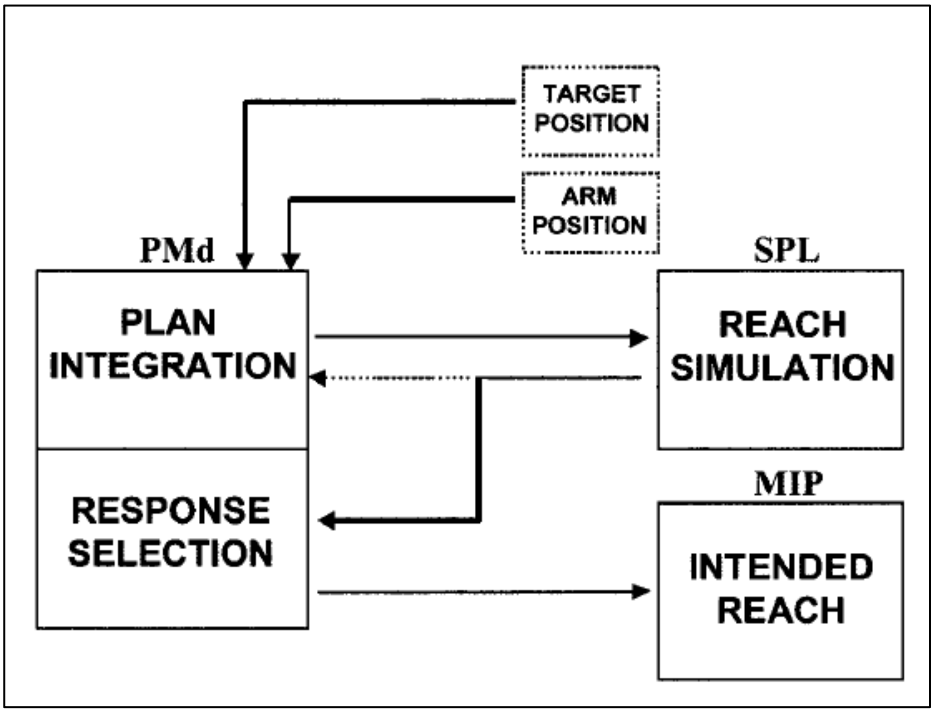

Figure 5.1. Prospective Action Model proposed by Johnson et al. (2002).

Grip Selection Task: something different from the Hand Laterality Task

Daprati and colleagues (2010) further investigated this issue studying stroke patients with varying motor impairment and lesion side: they used different implicit MI tasks, the same HLT described in Chapters 3 and 4, and the GST, focus of my attention here. They showed that RTs were positively correlated with the severity of motor impairment. Moreover, the accuracy in the different tasks varied on the basis of the lesion side: left brain damaged patients were more impaired in GST, while the performance of right brain damaged patients was more compromised in HLT. Interestingly, when judgment involved the interaction with an object (GST), patients with severe motor impairment had a worse performance, while this pattern was reversed for the HLT, with mildly impaired patients going worse than the ones with severe motor impairment. This surprising pattern of results was explained by postulating that HLT and GST might depend on different cognitive strategies (and different neural substrates): in HLT patients with severe motor impairment could have adopted an alternative non-motor strategy (e.g. location of the thumb and of the pinkie), rather than mentally simulate a movement known to be impossible in the real life. The use of such visuo-spatial transformations could rely more on the right hemisphere competence, explaining why patients with lesions in this hemisphere had a worse performance in HLT. Such alternative strategies are not applicable to the GST, given the motoric nature of the task (Daprati *et al.*, 2010).

Aim of the study

Given all the above, the GST seemed an ideal extension for my quest on motor imagery and its changes across the life span. The grip selection task involves more complex visuo-motor transformations than the HLT, possibly with less degrees of freedom as far as the alternative compensatory strategies that one may use to solve the task beyond the motoric ones. It remained to be seen whether under these task constraints one could observe behavioural and/or functional anatomical patterns similar to those already seen in explicit motor imagery or in implicit motor imagery as challenged by the HLT. On the basis of Daprati et al. data, one would rather expect a different pattern of behavioural and fMRI results. Of course, the scenario anticipated on the basis of Daprati et al. (2010) data, that is, less degrees of freedom for compensatory strategies in a demanding motor imagery task and less room for compensation, needed explicit empirical testing, something that is provided in the final experiment described below.

2. Materials and Methods

2.1 Participants and neuropsychological assessment

24 young subjects (mean age: 28.8 years, SD: 7 years) and 24 elderly subjects (mean age: 60 years; SD: 7.4 years) of the previous sample (see Chapter 4) underwent this event-related design fMRI experiment. The socio-economical status was the middle class from both groups; the educational level was matched (young subjects: 16 years, SD: 2.3; elderly subjects: 15 years, SD: 3.3).

None of the subjects had a history of neurological or psychiatric illness. All were right-handed as assessed by the Edinburgh handedness inventory (Oldfield, 1971). The study was approved by the Local Ethics Committee (Comitato Etico Azienda Sanitaria Locale Città di Milano), and informed written consent was obtained from all subjects, according to the Helsinki Declaration (1964). All subjects participated after the nature of the procedure had been fully explained. A brief neuropsychological assessment was performed on each participant, as described in Chapter 2. None of the subjects had a single pathological score at the neuropsychological test battery.

2.2 Experimental task

For the fMRI experiment we used a Grip Selection task, similar to the one proposed by Daprati (Daprati, 2010).

Subjects were shown photos of different tools, all with a handle horizontally oriented appearing on the right or left side of the image, preceded by an indication of which hand they should have used to imagine the movement of grasping (see below for a detailed description of the experimental task).

A total of 64 experimental stimuli were presented (2 x 8 objects x 2 hands x 2 handle orientations).

The baseline stimuli were 64 scrambled pictures derived from the tools' pictures. Each scrambled image had a green or a pink square in the centre. See Figure 5.2.

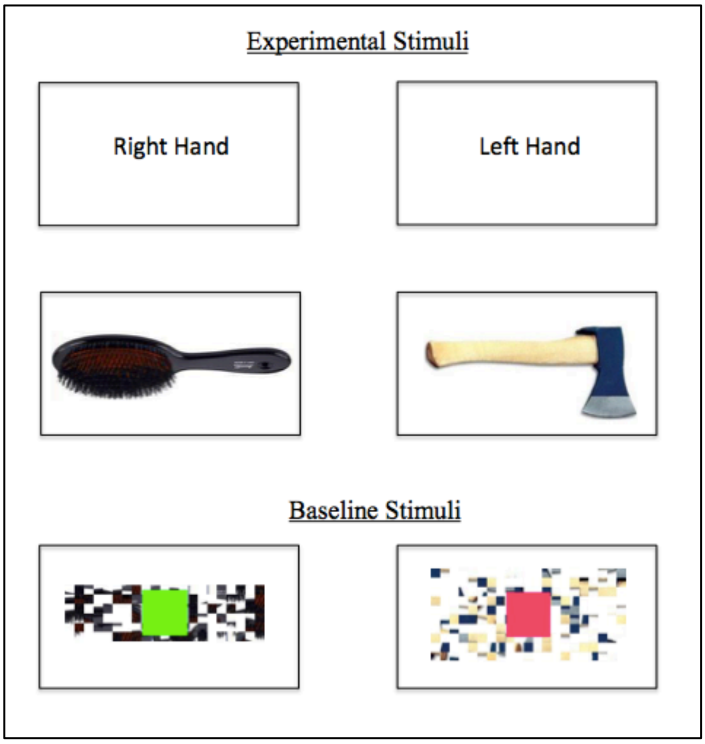

Figure 5.2 Example of GTS experimental and baseline stimuli.

Procedure

Participants practised each task before the scanning session: subjects were familiarised with the stimuli by performing half of the trials (32 experimental trials).

During this training, a warning feedback was given in case of an error.

For the fMRI experiment, the stimuli were randomly alternated according to an event-related design. Each stimulus remained visible for 4000 ms and was preceded by the indication of the hand to use to imagine the movement in the centre of the screen: the ISI was jitterd and it was randomly varied from 750 ms to 1250 ms (inter-stimulus interval: ISI). Subjects were asked to report whether they would have gripped the object to use it properly with an overhand or an underhand grip by pressing a button with their right or left index fingers. For the scrambled images, subjects had to respond with the right index finger when they saw a green square or with the left index finger when the square was pink. Accordingly, the contribution of the laterality of the motor response was controlled for in the analyses of each task. The experimenter reminded the participants to be fast and accurate in responding.

RTs and accuracy were recorded. Visual stimuli were delivered using the *Visuastim* (Resonance Technology Inc.) fibre-optic goggles. Responses were given through two response boxes (one for each hand).

2.3 Statistical analyses of the behavioural data

Mean accuracy and response time (RTs) were calculated for each participant. Accuracy was defined as the proportion of correct responses, while RTs corresponded to the interval between the onset of the stimulus and subjects' button press. Individual performance was considered above chance level when the overall accuracy was greater than 60%.

The accuracy data were analysed by mean of non-parametric tests.

For each subject, we subtracted from RTs of each experimental trial the RTs of the associated baseline trial (simple RTs). This was done to assure that the potential differences between groups were not related to a generalized ageing related decrease of speed in giving motor responses (see for example, Nebes, 1978).

The resulting RTs data were analysed as follows: RTs of the participants recorded inside the scanner were analysed by means of a mixed design 2 x 2 x 2 ANOVA with "Group" (Elderly/Young) as between factor and "Hand" (Right/Left) and "Handle orientation" (Congruent/Incongruent with the hand to be used for the movement) as within group factors.

2.4 fMRI data acquisition and analysis

MRI scans were performed using a 1.5 T Siemens *Avanto* scanner, equipped with gradient-echo echo-planar imaging (flip angle 90°, TE=60 msec, TR=3000 msec, FOV=280 x 210 mm and matrix= 96 x 64).

We collected 225 volumes. The first 10 volumes (corresponding to the task's instructions) did not correspond to any stimulation and were discarded from the analyses.

Preprocessing and Statistical analyses of the fMRI data

I adopted the same strategy described in Chapter 2.

Four contrast images were brought to the second level analysis, one for each condition of interest: Hand (Right or Left), Handle Orientation (Congruent or Incongruent), after subtracting out the BOLD response for the time matched events of the baseline condition. Post-hoc analyses to examine the direction of the aforementioned effects were performed using linear contrasts to generate SPM[t] maps. To minimize the impact of the RTs on the results, these were treated as confounding covariate.

The main pattern of activation for the GST and across group effects are described in Table 5.1a,b,c and in Figure 5.5a, while specific group effects are described in Table 5.1d and 5.1e and Figure 5.5b and 5.5c.

Each effect was visualized at the voxelwise threshold of $p<0.001$ (uncorrected) and at the cluster threshold of $p<0.05$ (uncorrected).

3. Behavioural Results

I first determined whether there were behavioural differences between the two groups in terms of accuracy. The Mann-Whitney test for independent samples did not highlight any significant difference in the right-hand experimental condition (Right Congruent: $p=0.94$, Right Incongruent:

p=0.7), but a significant difference was found in the left-hand experimental conditions (Left Congruent: p=0.04, Left Incongruent: p=0.03). The mean accuracy was 85% for the elderly group and 91% for the young group. See Figure 5.3.

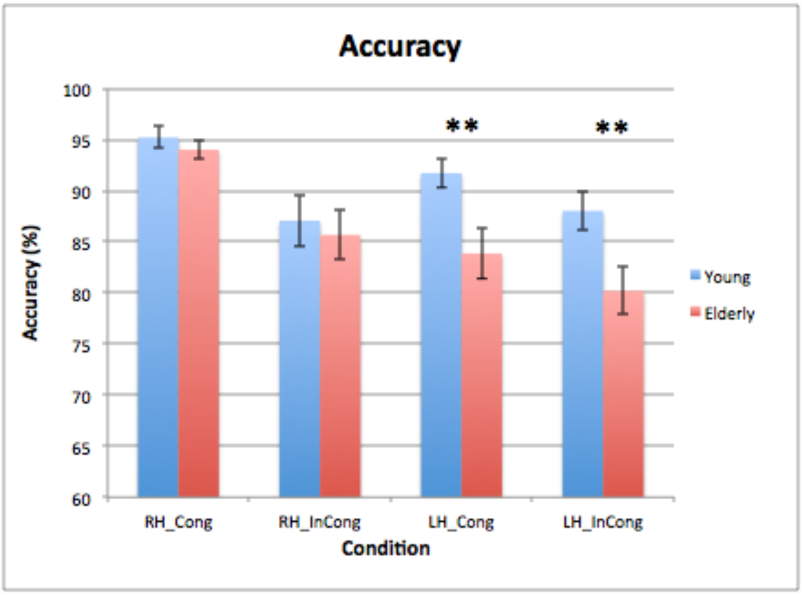

Figure 5.3. Behavioural Results (Accuracy)

I looked then at the RTs, by means of a 2 x 2 x 2 repeated-measures ANOVA on RTs with “Group” (Elderly/Young) as between factor and “Hand” (Right/Left) and “Handle Orientation” (Congruent/Incongruent) as within factors.

<u>Main effects</u>. There wasn’t an overall <u>between group difference</u> (F(1, 46) = 3.7; *p* = 0.059; η^2 = 0.075); the analyses of the <u>within group effects</u> showed RTs were faste for the right hand with respect to the left one (F(1, 46) = 88.3; ***p* < 0.001**; η^2 = 0.597); moreover, RTs were faster overall for the handle congruent orientation (F(1, 46) = 97.9; ***p* < 0.001**; η^2= 0.659).

<u>Within group interactions.</u> The Hand by Handle Orientation interaction was significant: F(1, 46) = 29.8; ***p* < 0.001**; η^2 = 0.358): there was a significant advantage in terms of speed for the right hand in congruent conditions.

Group by task interactions. Group-specific effects emerged: the Hand by Group interaction: F(1, 46) = 13.6; p = 0.001; η^2 = 0.092; the Handle Orientation by Group interaction: F(1, 46) = 4.7; p = 0.035; η^2 = 0.032 and Hand by Handle Orientation by Group interaction: F(1, 46) = 7.4; p = 0.009; η^2 = 0.089 were all significant. In summary, elderly subjects were slower in simulating grasping movements with the left hand and in non-congruent conditions.

These results are summarised in Figure 5.4.

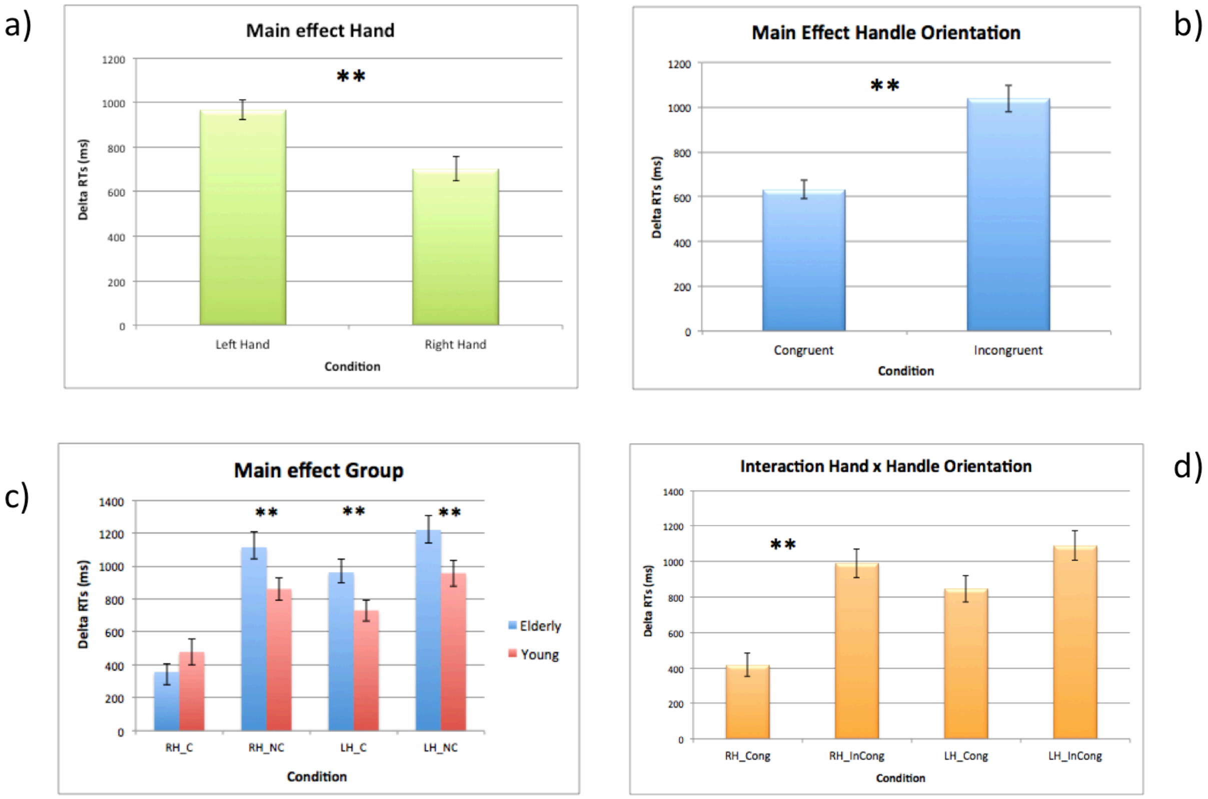

Figure 5.4. Behavioural Results (Delta RTs)

4. fMRI Results

Across groups effects

A vast pattern of fronto-parieto-occipital and temporal activations was reported as a **main effect of**

task in comparison with the baseline: neural activity was found bilaterally at the level of the inferior frontal (triangular subdivision) gyrus, the inferior frontal operculum, the insula, the superior parietal lobule, the inferior parietal lobule, the fusiform gyrus, the calcarine fissure, the pallidum, the cerebellum, the left superior frontal gyrus, the left middle frontal orbital gyrus, the left inferior frontal triangular gyrus, the left precentral gyrus, the left lingual gyrus, the left middle occipital gyrus, the left inferior occipital gyrus, the left cerebellum, the right inferior frontal opercular gyrus, the right SMA, the right middle frontal gyrus, the right inferior temporal gyrus, the right lingual gyrus, the right superior occipital gyrus and the right inferior occipital gyrus. See Figure 5.5a and Table 5.1a.

Moreover, we found a significant main effect of the Factor "Hand", we greater activations for the right hand in the contralateral motor system (precentral and postecentral gyrus). See Table 5.1b. Finally a significant interaction "Hand by Congruency" was recorded at the level of the left precentral gyrus and bilaterally in occipital regions; post hoc analyses by means of simple t-contrasts revealed that left precentral and postcentral gyri were mainly activated by the imagination of the right hand when the handle was presented in congruent orientation, while the interaction recorded in occipital lobes represented a de-activation of the visual areas that mapped the hemi-space not containing the relevant information to solve the task (e.g. in which the handle was not presented). See Table 5.1c.

Group effects

The conjunction analysis showed shared activations between the two groups bilaterally in the inferior frontal triangular gyrus, the inferior frontal opercular gyrus, the precentral gyrus, the inferior parietal lobule, the superior occipital gyrus, the inferior occipital gyrus, in the left superior frontal gyrus, the middle frontal gyrus, the insula, the precuneus, the superior parietal lobule, the inferior occipital gyrus, the right middle frontal gyrus, the SMA, the superior parietal lobule, the inferior temporal gyrus and the calcarine fissure. See Figure 5.5b and Table 5.1d.

Importantly, there were also **<u>between-group differences</u>**: elderly subjects showed reduced activations in the bilateral superior parietal lobule. See Figure 5.5c and Table 5.1e.

No significant differences were found in the opposite contrast (Elderly > Young).

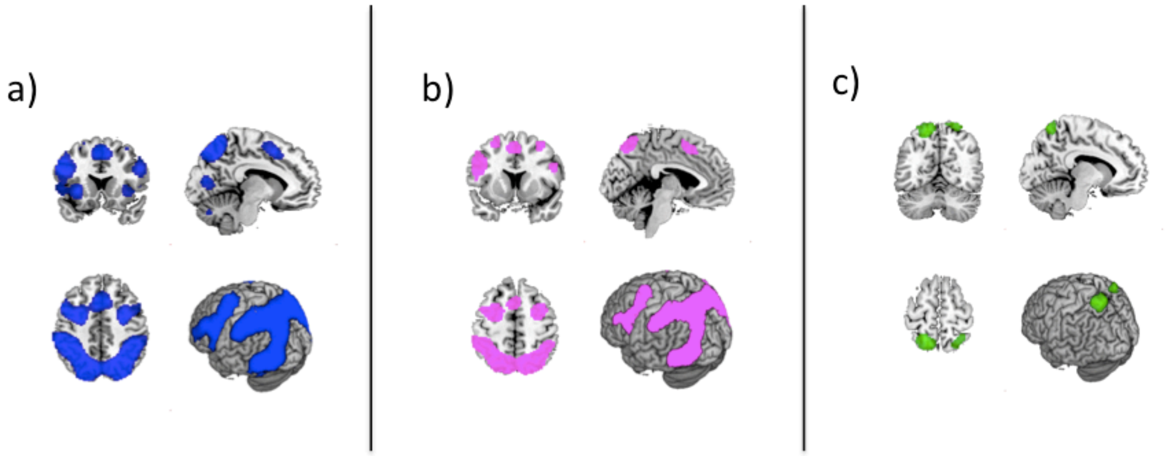

Figure 5.5. fMRI Results

Table 5.1. Grip Selection Task: fMRI Results

Brain regions (BA)	MNI coordinates							
	Left hemisphere				Right hemisphere			
	x	y	z	Z-score	x	y	z	Z-score
a. Main effect Task								
Sup. frontal gyrus (6)	-22	-2	52	Inf *	--	--	--	--
Mid. frontal orb. gyrus (47)	-42	46	0	6.2 *	--	--	--	--
Inf. frontal tri. gyrus (45)	-44	28	26	Inf *	48	32	28	7.3 *
Inf. frontal tri. gyrus (44)	-48	22	30	Inf *	--	--	--	--
Inf. frontal op. gyrus (44)	-52	12	6	6.7 *	48	10	30	Inf *
Insula	-30	20	-4	Inf *	34	24	-4	Inf *
Precentral gyrus (44)	-46	8	34	Inf *	--	--	--	--
Precentral gyrus (6)	-38	0	52	Inf *	--	--	--	--
SMA (32)	--	--	--	--	0	14	50	Inf *
Mid. frontal gyrus (6)	--	--	--	--	32	0	56	Inf *
Sup. parietal lobule (7)	-18	-64	56	Inf *	16	-68	54	Inf *
Inf. parietal lobule (40)	-38	-44	50	Inf *	42	-42	48	Inf *
	--	--	--	--	36	-50	52	Inf *
Fusiform gyrus (37)	-34	-54	-18	Inf *	36	-56	-20	Inf *

Inf. temporal gyrus (19)	--	--	--	--	44	-68	-10	Inf *
Lingual gyrus (18)	--	--	--	--	10	-78	-30	5.7 *
Sup. occipital gyrus (19)	--	--	--	--	28	-76	38	Inf
Mid. occipital gyrus (19)	-40	-80	16	Inf	--	--	--	--
Calcarine fissure (17)	-10	-78	12	7.1	12	-76	10	7.7
Inf. occipital gyrus (19)	-48	-68	-4	Inf	44	-84	-6	Inf
Cerebellum_6	--	--	--	--	36	-44	-26	Inf
Cerebellum_Crus2	-8	-76	-28	5.6	--	--	--	--
Pallidum	-16	8	0	4.9	14	10	-2	5.0
b. Main effect Hand								
Precentral gyrus (6)	-32	-26	64	4.8 *	--	--	--	--
Precentral gyrus (4)	-32	-30	66	4.7 *	--	--	--	--
Postcentral gyrus (3)	-26	-38	56	5.2 *	--	--	--	--
c. Interaction Hand x Congruency								
Precentral gyrus (4)	-40	-16	60	4.1	--	--	--	--
Postcentral gyrus (3)	-34	-22	46	4.1	--	--	--	--
Fusiform gyrus (19)	--	--	--	--	26	-62	-8	5.0
Sup. occipital gyrus (17)	-18	-98	14	3.8	20	-94	18	6.5
Lingual gyrus (18)	--	--	--	--	18	-76	-10	4.2
d. Conjunction								
Sup. frontal gyrus (6)	-26	-4	56	Inf	--	--	--	--
Mid. frontal gyrus (6)	--	--	--	--	34	0	56	Inf
Inf. frontal tri. gyrus (45)	-42	36	14	4.8	46	34	28	5.2
	-44	28	26	6.4	50	32	30	5.1
Inf. frontal tri. gyrus	-48	24	26	6.2	--	--	--	--
Inf. frontal op. gyrus	-50	12	6	4.7	34	22	-2	6.1
Inf. frontal op. gyrus (44)	--	--	--	--	52	10	28	5.4
Precentral gyrus (44)	-48	8	32	Inf	--	--	--	--
Precentral gyrus (6)	--	--	--	--	46	4	38	4.8
Insula (47)	-28	22	-4	5.9	--	--	--	--
SMA (32)	--	--	--	--	0	14	50	7.3
Sup. parietal lobule (7)	--	--	--	--	16	-68	54	Inf
Inf. parietal lobule (2)	-54	-30	40	7.6	--	--	--	--
Inf. parietal lobule (40)	-38	-44	50	Inf	44	-44	50	7.7
Inf. parietal lobule (7)	-30	-52	52	Inf	--	--	--	--
Inf. temporal gyrus (37)	--	--	--	--	44	-60	-10	Inf
Precuneus (7)	-12	-68	54	Inf	--	--	--	--
Sup. occipital gyrus (19)	-26	-78	32	Inf	28	-78	36	Inf
Calcarine fissure (17)	--	--	--	--	10	-74	10	5.3
Inf. occipital gyrus (37)	-48	-68	-4	Inf	42	-68	-10	Inf
	--	--	--	--	42	-86	-4	7.3
e. Young > Elderly								
Sup. parietal lobule (5)	-20	-54	64	4.5	--	--	--	--

Sup. parietal lobule (7)	--	--	--	--	32	-56	66	3.4
	--	--	--	--	22	-64	70	4.0

* FWE corrected

5. Discussion

In the previous chapter I provided evidence that the early stages of senescence are associated with brain compensatory processes that make implicit motor imagery, challenged by the Hand Laterality Task (HLT), still possible at a quasi-juvenile level. The aim of the present study was to investigate whether such observations could be generalized to another implicit motor imagery task, the Grip Selection Task. To date, there are no studies (behavioural or neurofunctional) that explored this issue. If compared with the HLT, the GST involves more complex visuo-motor transformations and the (mental) interaction with an external object, daily life tools in our study.

The involvement of MI in GST is confirmed by a number of experiments showing how subjects were slower and less accurate (i.e. less “similar”[27] to actual movements) in decisions that involved adopting awkward postures (as already seen in other MI tasks, see for example Parsons et al., 1987b). Moreover, the time required for these judgements increased as a function of the distance between the location of the subjects' hands and the orientation of the chosen posture, through the biomechanically defined trajectory.

All these findings suggest that GST involves *“on-line, analogue, simulations of movements”* (Johnson, 2000b).

The results of the present study demonstrate the existence of significant behavioural and neurofunctional effects of early ageing on implicit motor mechanisms involved in simulated grasping, that are clearly different from what obesrved with other kind of MI tasks described in Chapters 2 and 4.

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[27] Similar here means less correlated to the actual execution as far as the reaction times are concerned.

I start this last section of Chapter 5 by discussing the behavioural findings, considering both across- and between-group effects and their relative interactions. I then address the neurofunctional differences associated with ageing: the differences between younger and elderly in this case were mainly represented by hypoactivations in older subjects' group in the superior parietal lobules.

Behavioural results

Across group effects

The across group results showed faster RTs for movement simulation with the right hand. These results are in line with behavioural results of both Chapters 3 and 4 on HLT. In addition, there was a special advantage for congruent stimuli to be mentally grasped by the right hand. This visuo-motor priming effect could be explained by hand preference of our subjects, as they were all right-hand dominant at the Oldfield handedness test. Conversely, these findings are different from what observed in previous behavioural studies on GST: for example Johnson (2000b) described a similar performance for both right and left hand, hypothesizing that subjects mentally simulate movements with both the hands before giving a response (Johnson, 2000b). However, in this study they used a standard dowel, an object not commonly manipulated in "real life" and deprived of any semantic. On the contrary, in my study I used pictures of real tools as experimental stimuli; it is possible that right-handers subjects, as the ones included in my sample, have a sort of facilitation in mentally simulating movements with their dominant hand to interact with an ecological object.

The Handle Position factor was also significant: when the handle was located on the same side as the hand on which participants responded RTs were faster than when it was located on the opposite side; this could be explained by the physical distance between the imagined hand's position and the handle location: in non-congruent conditions, this distance is greater and results in longer RTs, in line with previous literature (Johnson, 2000b).

Between group effects

The comparison between groups showed significant effects, both for accuracy and RTs.

First, elderly subjects were less accurate for the imagination of movements with the non-dominant hand. For what concerns the latencies, there wasn't an overall group effect; however, significant interactions between group and hand and group and handle orientation suggest how older subjects were slower in conditions involving the non-dominant hand and when the handle orientation was incongruent with the hand's position. The existence of lower accuracy and slower RTs in *young elderlies* is something different with respect to what found with other MI tasks; it is important to observe that differences are present in conditions involving the non-dominant hand or when the distance between the hand and the tool's handle is increased, suggesting an increased cognitive load needed to solve the task because the movement to imagine is more difficult.

Neurofunctional findings

Across group effects

A vast pattern of fronto-parieto-occipital and temporal activations was reported as main effect of the task in comparison with the baseline, largely similar to the one involved in other implicit MI tasks (see Chapters 3-4 and Parsons *et al.*, 1995; Vingerhoets *et al.*, 2002; Seurinck *et al.*, 2004; de Lange *et al.*, 2005; de Lange *et al.*, 2006; Helmich *et al.*, 2007). There were also some task-specific differences (i.e. overall larger activations in the GST when compared with the HLT and vice-versa that I omit here for brevity).

In line with the only fMRI study on GST, there was a large activation of the regions involved in reaching and grasping movements observed in monkeys, as the frontal and the precentral gyrus, the inferior and superior parietal lobules and also occipital areas (Johnson *et al.*, 2002).

There were also specific effects associated with the imagined effector: the mental simulation of movements with the right hand determined a greater activation in the contralateral motor system; I did not record the same effect for the left hand. Probably the presence of daily life tools determined a greater recruitment of motor representations when the hand to use for the task is the same that usually subjects used to manipulate them. This greater recruitment for the right hand is more evident in congruent conditions, when the handle is presented on the same portion of space of the effector.

Between group effects

Even if the network activated by the task resulted mostly shared between the two groups, I found also significant neurofunctional differences between the two groups, represented by decreased activations in older subjects at the level of the superior parietal lobule, bilaterally.

This region is known to be specifically involved in the real execution of grasping/reaching movements and in the interaction with external objects. The first evidence comes from studies on monkeys: nonhuman primate experiments suggested that populations of neurons in the posterior parietal cortex may represent high-level aspects of action planning; the posterior parietal cortex for example is involved in combining visual information of the external object with motor information about the acting effector (e.g. the limb position, see for example Cohen and Andersen, 2002).

The involvement of the posterior parietal cortex in visuo-motor integration is also confirmed by studies on neurological populations, with various impairments resulting from lesions in different regions of the posterior parietal cortex (for a review, see Battaglia-Mayer and Caminiti, 2002). Finally, direct evidence from fMRI studies on humans confirmed all these findings: for example, Hermsdörfer et al. (2007) found a posterior parietal activations associated both with planning and execution of pantomimed and actual tool use in healthy subjects, using a variety of familiar tools and objects that were tested on both the left and right hand (Hermsdörfer *et al.*, 2007).

The seminal demonstration of the specificity of this region also in mental representations reaching and grasping comes from a single case study on a tetraplegic patient (Aflalo *et al.*, 2015): in this experiment the authors recorded neural population activity with microelectrodes implanted in the posterior parietal cortex (in the same region hypoactivated in our elderly group [x=-17, y=-65, z=56, Talairach coordinates converted to MNI space]) and they observed how MI of reaching and grasping could be decoded from these neural populations, including imagined goals, trajectories, and types of movement. These findings indicate that this portion of parietal cortex represents high-level, cognitive aspects of action and that it can be a source for neural prosthetics that assist paralyzed patients (Aflalo *et al.*, 2015).

It is interesting to note that the recordings made by Aflalo et al. (2015) covered two subdivisions of the intra-parietal sulcus: the AIP and the MIP. These were both activated in the main task effect, with the data of the young and elderly averaged. The between group difference emerged in the more dorsal component of the region in an area that also encompasses the MIP but definitively does not include the AIP.

These two regions and the most dorsal regions of the superior parietal cortex have distinct roles in reaching and grasping, the more dorsal ones being involved more in reaching and the AIP more in grasping.

The selective hypoactivation of the superior parietal cortex rather than the AIP provides a strong clue about the specific components that might become less efficient in implicit motor imagery for the elderlies, namely the reaching component.

The same superior parietal regions were more active for the incongruent conditions. It is useful to recall that these imply to mentally cross the body midline to reach from below the tools whose handle is pointing to the opposite side of the mentally moving limb.

This finding is compatible with the idea that elderly subjects may generally rely more on visual control when they act compared to younger subjects. As discussed in Chapter 2, this issue was addressed by Coats and Wann (2011). In their study, young and elderly subjects performed a reaching and grasping experiment using an apparatus that eventually obscured the target and the approaching hand, after allowing for initial visual exploration. For the elderly subjects, both reaching and grasping were affected selectively when visualisation of the hand was prevented; they produced additional reaching movements and had longer adjustment times for the grasping phase of the movement. These findings suggest that elderly subjects may need more direct visual feedback than the young in tasks that require precise manual control (Coats and Wann, 2011). The present GST data indicate that the reaching behaviour may be more vulnerable if compared with the grasping one.

Of course, the GST in the format adopted in this experiment was not sufficiently specific to permit a subtle distinction between the reaching and grasping phases of the mental behaviour and their dynamic interactions.

Nevertheless, I consider the specific superior parietal finding as a neural signature of the greater age-related vulnerability of the neural substrates of the reaching component of the task rather than the semantically driven grasping component. This latter, was, in fact, only moderately challenged as the graspable component of the tools was similar for all the objects to induce a stereotyped mentally simulated grasp (see, by comparison, experiments on action observation and the mirror system in which the grasping behaviour was changed depending on the context with goal-specific behaviours; Iacoboni *et al.*, 1999)

To summarize, my results thus suggest a specific behavioural and neurofunctional decline in mental representations of reaching and grasping movements associated with early aging.

This is something different from what observed in other MI tasks described in previous Chapters, that engaged simpler movements and that did not involve any kind of mental interaction with external objects. One possible explanation of this difference is, as already mentioned in the introduction, that during the GST subjects cannot revert to other strategies to deal with the task, giving prominence to visual features of the stimulus (as in HLT) or relying more on visual imagery (as in explicit MI). This is like to say that in other motor imagery tasks there are more degrees of freedom as far as the strategy of choice that one subject may rely on than for the GST.

It remains to be seen whether other components of the functional information processing flow are impaired in elderlies. For example, it is well known that simple observation of an object automatically activates motor representations (something similar to the "visuo-motor priming", described by Craighero *et al.*, 1996). Whether access to these is fully preserved in ageing people remains to be demonstrated.

The present results have another important methodological implication because, contrary to what observed in the previous experiments – preserved performance and compensatory hyperactivations – here I saw a reduced performance that was accompanied by a reduced activation of specific brain areas. This is reinsuring in the context of the current understanding of the ageing brain (Reuter-Lorenz and Cappell, 2008; Berlingeri *et al.*, 2010).

Summary of Chapter 5

In this experiment I have shown that a significant decline in the domain of implicit mental motor representations due to aging, even in its early stages, can be detected by using an implicit motor imagery task that involves more complex visuo-motor transformations; I suggest that this task may have less degrees of freedom with respect to the ones discussed in previous Chapters, not allowing the use of alternative compensatory strategies to solve the task beyond the motoric ones. This decline is associated with reduced activations at the level of the posterior parietal lobule, in a sub-region specifically associated with reaching behaviour, suggesting a specific age-related vulnerability of the neural substrates of the reaching component of the task rather than the semantically driven grasping component.

Taken together with the results of previous Chapters, this study permits a more general discussion about neurocognitive models of aging in the domain of motor imagery.

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Chapter 6 – General discussion

Neurophysiological changes associated with aging are currently the focus of much research.

Brain imaging represented a new important method for the study of the aging effect on cognitive functions: brain-based measures, that can be linked to cognitive processes, expand the range of questions that can be addressed about the aging mind; this is something impossible with the behavioural methods or the association brain lesion-symptom typically used by the clinical neuropsychology. The emerging neurofunctional data have inspired new ways to think about the normal aging process and about functional brain organization across the lifespan.

Interpretation of my data in the light of neurocognitive models of aging

Typically, modifications of fMRI patterns in the elderly have been interpreted as evidence of compensatory processes of graceful aging by a number of authors (Buckner 2004; Cabeza et al. 2002; Grady et al. 1994). If performance remains unaffected, compensatory processes manifest themselves in the recruitment of additional brain regions. These patterns have been documented in several cognitive domains (e.g., working memory, episodic memory retrieval, perception, inhibitory control, etc.). This phenomenon was initially observed in the prefrontal cortex; moreover, compensatory processes have been described as reduced inter-hemispheric asymmetries for tasks that are associated with strongly lateralised fMRI patterns in younger participants (Cabeza 2002).

In this thesis, the issue about compensatory processes has been further explored by evaluating age-related neurofunctional differences between elderly and young participants in the domain of mental motor representations, with the empirical evidence of neurofunctional and behavioural outcomes.

First, I showed that the compensatory hyperactivations of the elderly may involve brain regions well outside the frontal lobe, depending on the task (as already hypothesized by Berlingeri et al.

2010); moreover, I did not observe bilateral increased activation in older adults across task domains, suggesting that the model proposed by Cabeza et al. (2002) might represent only a specific manifestation of aging that is not generalizable across all cognitive functions or experimental tasks.

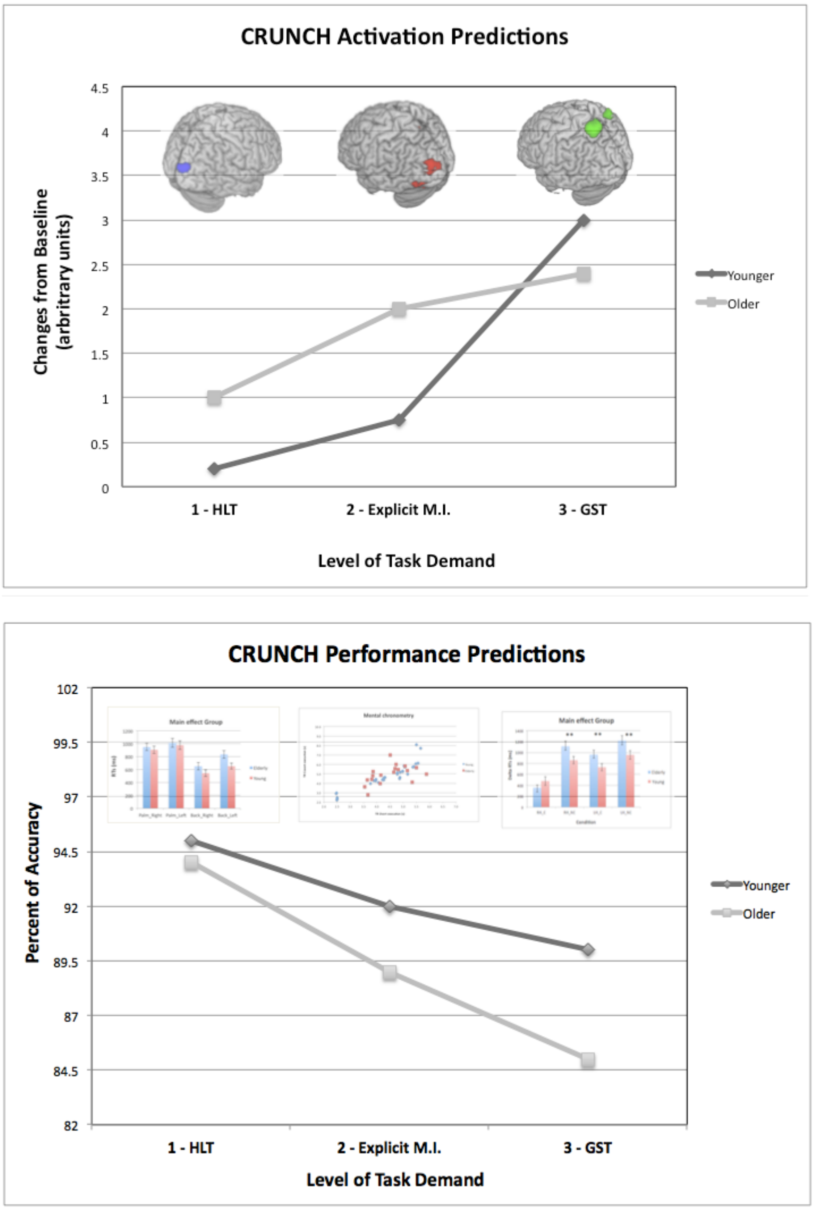

Figure 6.1. CRUNCH hypothesis adapted to my data.

Similarly, my data cannot support another popular model of the ageing brain, the PASA (posterior-to-anterior-shift in ageing) pattern model: the model predicates that with ageing frontal cortex becomes generally more prominent in conjunction with reduced importance of the posterior cortices. This was inconsistent with what I observed, the increased posterior activations found in my elderlies subjects while performing at a juvenile-like level. On the contrary, it seems that a more general model as the one proposed in the CRUNCH hypothesis could better explain my data, as shown in Figure 6.1., adapted from (Reuter-Lorenz and Cappell, 2008).

Consistently with the model, my results showed that at lower levels of task demands, region-specific hyperactivations in older subjects are associated with good performance. With the increase of the cognitive load, the attempt of compensations become less successful and then, beyond a certain level of task demand, the elderly brain does not show sufficient activation levels, and performance declines relative to the younger group.

The first task might be represented by the HLT task (Chapter 4), where older subjects have a behavioural performance comparable with the younger in terms of accuracy and normalized RTs, mirrored by over-activations in the occipital cortices, whose response was positively correlated with the behaviour.

My results suggest that in the early phase of ageing compensatory processes in the domain of motor representations could be successful in MI tasks with a low degree of explicit action monitoring, like HLT, in which the “desired state” of the system is visually available; this results in a normal behavioural performance.

That was not true for explicit motor imagery processes, where I found an “partially successful” compensatory neural mechanism represented by the occipital hyperactivations associated with the loss of temporal congruency between real and imagined movements, even if MI duration was comparable in the two groups. This finding suggests an initial decrease in MI abilities.

This decline becomes evident with the GST, where the nature of the task does not allow any compensatory attempt, something confirmed on one hand by the behavioural decline and on the other one by the lack of hyperactivations and the presence of reduced activity in a key region for mental representations of reaching movements.

Implications for clinical practice and rehabilitation

Besides the theoretical implications, the present data provide additional information also for the domain of motor rehabilitation, indicating that motor imagery is a more complex phenomenon than previously understood, to which separate cognitive operations can contribute and that decrease in different ways with aging.

My findings add some important hints to this issue. First, they may help to identify the best age-range that could take advantage from MI, used as a complementary technique in motor re-learning with patients affected by neurological or orthopaedic diseases. On the basis of my results it remains questionable and open to explicit testing whether young elderly subjects may still benefit of implicit motor imagery techniques, in spite of their qualitative shift in terms of brain activation patterns.

Indeed, my results suggest that patients (who have usually the same age of my subjects or are older) may not exclusively use mental motor simulation when dealing with motor imagery tasks (maybe partially explaining the mixed results obtained following mental practice). It is possible that when spatial strategies or visual imagery are used, the effects of mental practice are reduced. At the same time, tasks devised in order to actively prompt a motor simulation, like GTS, should be more efficient.

Outstanding issues

There are very many outstanding issues in the domain of motor imagery, ageing and the ensuing brain bases. I will mention here just a few.

- First and foremost, are the functional and anatomical changes documented reversible with training?

- Could neuromodulatory techniques (e.g. tDCS or TMS) increase the size and duration of the effects of such training?
- If so, could one observe the transfer of in effect on real life motor performance?
- Can mental training with motor images have a positive impact in pathological situations affecting the central or the peripheral nervous system or indeed the most peripheral conditions, those connected with osteo-articular disorders?
- What happens in later age-ranges of senescence? Admittedly I tested relatively young elderlies. It remains to be seen what happens
- Could one use motor imagery task –and which one is the best- to guide the implant of electrophysiological cortical devices that guide prosthetic limbs in paralyzed patients with spinal cord damage? Preliminary evidence exists in the work of Richard Andersen's group (Aflalo et al., 2015).

There are more cognitively oriented outstanding issues as well.

It might be interesting to look at the aging effects on cortical motor representations when these one are evoked in a more indirect way such as action observation, using, for example, the paradigm of automatic imitation; it would be interesting to study whether the presence of congruency between the observed actions and the movements to produce has a stronger/weaker effect in elderly people. These effects might be then investigated with neuroimaging methods as well.

To the best of my knowledge, all these issues are unexplored for the time being.

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