Parieto-frontal circuitry in visuomotor control

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“Alone, when I felt like crying I cried, and I never felt more likely it than when I removed from the envelope the series of pictures of his brain. [..] simply because it was his brain, my father’s brain, what prompted him to think the blunt way he thought, speaking the emphatic way he spoke, to reason the emotional way he reasoned, decide the impulsive way he decided. This was the tissue that had manufactured his set of endless worries and sustained for more than eight decades his stubborn self-discipline. The source of everything that had frustrated me as his adolescent son, […]

Maybe the impact wasn’t quite what it would have been had I been holding that brain in the palm of my hands, but it was along those lines. God’s will erupted out of a burning bush and, no less miraculously, Herman Roth’s had issued forth all these years from this bulbous organ. I had seen my father’s brain, and everything and nothing was revealed. A mystery scarcely short of divine, the brain, even in the case of a retired insurance man with an eighth-grade education from Newark’s Thirteenth Avenue school.”

Philip Roth – Patrimony (1991)

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Chapter 1

INTRODUCTION

1.1 How does sensory information influence the motor system?

A fundamental question in neuroscience is how sensory information influences the motor system (Toni and Passingham, 1999; Passingham et al., 1998). This thesis is concerned with finding an answer to this question. It is well established that different circuits in the brain allow visual information to reach the motor system. Information propagates through the brain dependent on the kind of processing required by the circumstances we are in. For example, two main pathways through the brain that diverge from the visual cortex have been identified to process visual information for different purposes. The dorsal visual stream terminates in the superior parietal cortex and is involved in the visual guidance of action, while a ventral stream, propagating in the direction of the temporal cortex, processes visual information for perception (Ungerleider and Mishkin, 1982; Goodale and Milner, 1992). In turn, these pathways can be subdivided in other parallel streams and numerous interconnections have been identified between them. In general, the employment of any pathway from visual to motor cortex will depend on the visual information that comes to us and how we choose to respond to this information.

For responding to the sensory information we receive, the motor system has provided us with a number of different actions to choose from. We can move directly towards the location of a stimulus, like grasping for the knob of a door when we want to open it. Alternatively, a big red button next to the door might instruct us to press it in order to have the door opening itself automatically. Those actions, guided spatially or through symbolic instruction, are instances of actions that are under voluntary control. Voluntary actions are defined as learned actions based on context, chosen among alternatives on the basis of expected outcome (Passingham, 1993). We are able to learn to decide what movements to perform in which circumstances and at which moments in time. Other actions have been genetically encoded in our motor system over generations in the form of innate motor programs and reflexes, helping us to protect, feed and defend ourselves (Shadmehr and Wise, 2005). When we press the red button and the automatic door swings towards us at a higher speed than expected, we reflexively step backwards before we walk through. If we are used to pressing the red button everyday and the system breaks down one morning, we might very well bump into the closed door before noticing that it is not working. Those reflexes and habits are beyond our voluntary control. We also have the ability to acquire new motor skills and adapt them to new circumstances. For example, if you know how to pedal when riding a tricycle, you will still have to adapt your cycling skills to maintain balance when riding a regular bike. Both skill acquisition and motor adaptation are important in maintaining stability and control in our limbs (Shadmehr and Wise, 2005). In this thesis I will not address the latter two categories, but focus on different kinds of voluntary actions, which are outlined below.

Voluntary actions can be divided according to whether they are guided spatially or by arbitrary rules. When the location of a stimulus, like the doorknob from the example above, or a cup of coffee on the table, guides the movement directly, this is called *standard sensorimotor mapping.* When the stimulus-response relation is more flexible and the movement is not directly driven by spatial information, this is called *nonstandard sensorimotor mapping* (Wise et al., 1996a). An indirect cue instructing the movement can

contain spatial information that requires a transformational mapping, for example when you have to move a joystick in relation to a visible target under an angle of 90 degrees. If the cue is entirely arbitrary, that is, there is no spatial link between the stimulus and the response, it is called *arbitrary sensorimotor mapping* (Wise and Murray, 2000). This is an instance of non-standard sensorimotor mapping and is also known as conditional learning or arbitrary visuomotor associative behavior.

There is substantial overlap between the networks involved in different types of action. Standard sensorimotor mapping or spatially-guided action seems, for example, to be controlled by a dedicated parieto-frontal circuit (Milner and Goodale, 1995). This circuit can be subdivided into two anatomically segregated pathways that are thought to be concerned with either grasping or reaching. This topic will be introduced in paragraph 1.2.2. Arbitrary mappings, in contrast, are assumed to be controlled by a distributed fronto-striatal circuit (Wise and Murray, 2000; Toni et al, 2001a). This topic will be introduced in paragraph 1.2.3. At all levels of these networks interconnections can be identified that could mediate communication between these circuits.

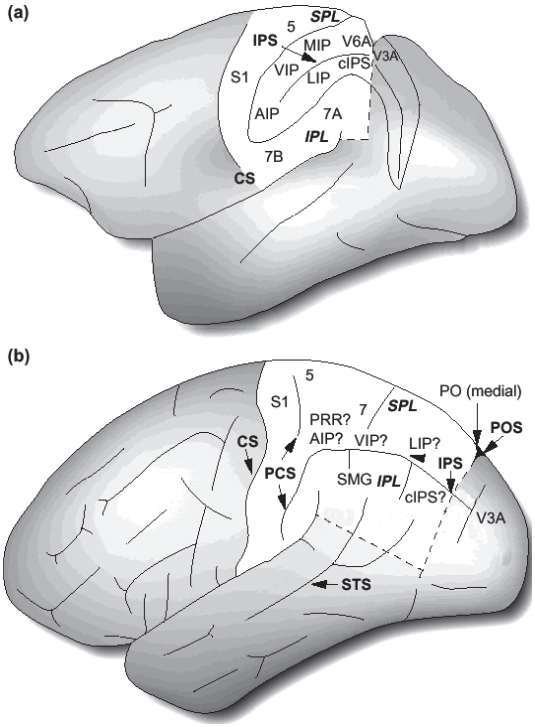
In this thesis the question is asked how functionally segregated the circuits that were identified to underlie standard and non-standard visuomotor mapping are, and what they represent. One of the main questions is whether the routes by which visual information reaches the motor cortex can change under the influence of learning. If we would have as much lifetime training in non-standard sensorimotor mapping as we have in standard sensorimotor mapping, would both still activate different circuitry? It is also explored whether reaching and grasping are distinct processes represented along anatomically segregated pathways. Each of these questions will be introduced in more detail in the next paragraphs.

The posterior parietal cortex (PPC) is an area that is known to play a role in different kinds of sensorimotor mapping (Culham et al., 2006a). Here a short overview of parietal cortex function and the neural bases of both standard and nonstandard sensorimotor mapping is given. Although this thesis will focus on the role of areas in the PPC in the questions raised above, our real interest lies in the interactions *between* the areas within parietofrontal circuits. Several theories about motor control have been framed in terms of networks and circuits. But due to a lack of methodological and analytical tools several questions originating from this system-level perspective could not be answered experimentally. Analyses of effective connectivity allow us to explore the functional coupling between brain regions within dedicated networks and allow us to test novel hypotheses about the function of specific circuits experimentally. In this thesis, not only cerebral activity in parietal areas is measured, but the effective connectivity in dedicated parietofrontal circuits is assessed as well. Because effective connectivity analyses are an important tool in investigating these networks, these analyses and their technical details will be introduced in paragraph 1.3.

1.2 The role of the posterior parietal cortex (PPC)

1.2.1 Anatomy and organization of the parietal cortex

The parietal lobe is part of the dorsal visual stream. It can be divided into the anterior (Brodmann areas 1, 2, and 3) and the posterior parietal cortices. In the anterior part of the parietal lobe, adjoining the central sulcus (CS) and bordering on the posterior side the postcentral sulcus (PCS), the primary (S1) and secondary somatosensory areas are located. The posterior parietal cortex (PPC) (figure 1) is situated between these sensorimotor areas anteriorly and the visual areas behind the occipitoparietal sulcus posteriorly. The intraparietal sulcus (IPS) divides the PPC into two parts: the superior parietal lobule (SPL) and the inferior parietal lobule (IPL). In macaques (Figure 1a), SPL is made up of areas 5a and 5b, while IPL contains areas 7a and 7b. In humans (Figure 1b), SPL contains areas 5 and 7 and IPL areas 39 and 40. The superior and inferior parietal lobes divide the dorsal stream into upper and lower substreams, which connect to the frontal lobe.



The areas around the IPS are arranged in a modular fashion (Grefkes and Fink, 2005). They are heavily interconnected to each other and to visual areas in the occipital cortex (Rizzolatti et al., 1998) and motor areas in the frontal cortex. Together, they form a series of parieto-frontal circuits with different connectivity patterns. Due to its anatomical position and interconnections with frontal and occipital cortices, PPC receives both visual and somatosensory input and sends output to premotor and motor areas in frontal cortex. Accordingly, the posterior parts of the IPS are predominantly concerned with visual information processing whereas anterior parts are mostly dedicated to sensorimotor processing.

Figure 1.
Comparison of monkey and human parietal lobes.
Adapted from Culham and Kanwisher (2001).
Lateral view of (a) macaque monkey and (b) human brain, showing parietal lobes in white. Bold text indicates major sulci, italicized text indicates lobules, and plain text indicates functional or anatomical areas. Abbreviations crucial to this introduction are explained in the text. For more detials I refer to Culham and Kanwisher (2001).

Electrophysiologic studies in macaques have identified a mosaic of distinct cortical areas around the IPS, that seem to have different functional properties as each of them processes different kinds of information. These areas were named after their topographical position. Each of them seems to control specific body parts (Fig. 1a): the anterior intraparietal area (area AIP) is suggested to be concerned with hand movements, the ventral intraparietal area (area VIP) with movements of the head or face (encoding the space and motion around the head) and the lateral intraparietal area (LIP) seems to represent eye movements, like saccade planning. The parietal reach region (PRR) is known to be crucially involved in reaching (Snyder et al., 2000; Andersen and Buneo, 2002, Buneo et al., 2002) and was thought to consist of the medial intraparietal area (area MIP) and area V6A (Batista et al., 1999). However, more recent findings suggest that PRR is only located in MIP (Calton et al., 2002; Gail and Andersen, 2006). In macaques, V6A and V6 form what is called the V6-complex (also known as the parieto-occipital areas (PO)) and are considered part of the visual cortex (Colby et al, 1988).

The human IPS resembles the IPS of the macaque, but is larger and more expanded (Fig. 1b) (Grefkes and Fink, 2005). As invasive measures, like electrophysiology, can not readily be used in human subjects, it is hard to determine the homologies between human and non-human-primates. To a certain extent, neuroimaging techniques allow us to explore the possible functional equivalences between macaque and human PPC and suggest that a similar mosaic of specialized sensorimotor areas exists around the human IPS. A number of neuroimaging studies have shown the involvement of the human posterior parietal cortex in visually-guided action and attention (Culham & Kanwisher, 2001). Clinical studies of patients with lesions in the parietal cortex (Geschwind and Damasio, 1985; Goodale and Milner, 1992; Perenin and Vighetto, 1988) have confirmed the role of human PPC in high-level sensorimotor integration (Andersen and Buneo, 2002).

Also, from macaque studies it is known that many areas in the PPC are strongly interconnected with frontal areas. Each motor area receives projections from a set of parietal areas, while at the same time each part of the posterior parietal cortex projects to several frontal areas. The inputs into a motor area can be strong ('predominant') or weak. At the same time, parietal areas have privileged afferents into one specific motor region. These predominant connections link parietal and frontal areas with comparable functional properties, forming different parallel parietofrontal circuits. These parietofrontal circuits have been identified to accommodate different kinds of visuomotor transformations (for details see Rizzolatti et al., 1998; Matelli and Luppino, 2001).

For example, area 5 (PE) informs M1 (F1) about the location of the limbs and other body parts for the control of movement. Within the premotor areas each part receives specific projections from one parietal area. The dorsal premotor cortex consists of three parts: F2 (dimple), F2vr (where visually responsive neurons are located) and F7. Accordingly, three predominant parietofrontal circuits can be identified: F2 dimple is a target of areas PEc and PEip (higher order somatosensory areas), F2vr receives its major projections from MIP and V6A, and F7 receives minor parietal afferents originating from area PGm, that is connected with PG and with extrastriate visual areas. It has been suggested, on basis of these connections, that the F7 circuit is concerned with coding object locations in space for the control of arm–body movements (Matelli and Luppino, 2001).

The ventral premotor cortex (PMv) is formed by areas F4 and F5. A loop that consists of VIP and F4 is suggested to be involved in the transformation of object locations into

appropriate movements towards these objects in a body-part centered frame of reference (Matelli and Luppino, 2001). The most investigated loop is the connection between AIP and F5. In the next paragraph I will focus on the latter circuit and the circuit consisting of V6A and PMd/F2, that have both been identified to be involved in standard sensorimotor mapping, in particular in grasping and reaching movements. In paragraph 1.2.2 it is discussed why it is interesting to investigate the role of PPC in non-standard sensorimotor mapping as well.

1.2.2 PPC in standard sensorimotor mapping

The functional anatomy of spatially-guided movements has been extensively studied in both macaques and humans, showing clear involvement of a frontoparietal network in spatially guided action planning (Rushworth et al., 2003; Kalaska et al., 1997; Passingham, 1993; Kakei et al., 2001; Passingham et al., 1998).

Within this frontoparietal network two parallel substreams have been identified, the dorsomedial and dorsolateral pathways, that are thought to be involved in the reaching (Burnod et al., 1999; Caminiti et al., 1999) and grasping (Jeannerod et al., 1995) components of prehension, respectively. This theory, called the two-visuomotor-channel hypothesis (Jeannerod, 1995), stems from the notion that for accurately grasping an object visuospatial information of the extrinsic features (spatial location) and intrinsic features (size, shape, orientation) of the object is required. It was based on the functional division of manual prehension (made in psychophysics) into a reach component, transporting the hand towards the object on the basis of its extrinsic features, and a grasp component, pre-shaping the fingers around the centre of mass of the object on the basis of its intrinsic features (Jeannerod et al., 1988). Although this functional organization appears to have a physiological counterpart in the two dorsolateral and dorsomedial circuits mentioned above, the question remains how integrated control mechanisms of reaching and grasping can be implemented in two anatomically segregated circuits. Crucially, in human neuroimaging the focus of research has been on the cerebral activity in segregated areas of these pathways and not on the functional integration within these parietofrontal circuits. In chapter 5 the effective connectivity during prehension will be investigated, to contribute to the ongoing debate on the parietofrontal circuitry underlying different aspects of visually-guided reaching-grasping movements. Here, an overview is given of the posterior parietal areas identified to be involved in reaching and grasping. This summary is based on the excellent reviews of Culham et al (2006a,b) and Grefkes and Fink (2005).

Reaching is defined as the stretching of the arm to touch a distant target. Electrophysiologic studies in macaque monkeys have shown that various PPC areas contain cells that respond to reaching movements, for example the medial intraparietal area (MIP) (Johnson et al, 1996) and area V6A (Fattori et al, 2001; Galletti et al.,1997). Area V6A in macaques contains visuomotor neurons coding object position in space (Galletti et al., 1999) and disruption or lesions of this area lead to misreaching (optic ataxia) (Battaglini et al., 2002; Karnath and Perenin, 2005).

The different tasks employed in reaching and grasping experiments are very diverse (Culham et al, 2006c), due to several technical problems accompanying the study of arm movements in human neuroimaging. In chapter 4 of this thesis the problems and solutions associated with studying visually guided reach to grasp movements in a fMRI experimental

setup are discussed in detail. Because of the problems with extending the arm in the fMRI-scanner, several studies have instead investigated pointing movements, in which the index finger is directed towards the target without extension of the arm, reach-to-point movements or reaching movements in which the object is touched with the knuckles (Culham et al., 2003). Pointing without extending the arm evokes activity in the medial IPS (mIPS) and the precuneus, a putative homologue of macaque PRR (Connolly et al, 2003).

Support for the involvement of certain regions in reaching can also be found when looking at the anatomical connectivity of an area. That is, whether this area is projecting to regions involved in reaching. Area V6A directly projects to premotor regions, in particular the caudal dorsal premotor cortex (PMd, area F2) (Matelli et al, 1998; Galletti et al, 2003), important for planning arm movements (Wise et al, 1997). This is an additional argument for V6A being involved in prehension movements. V6A and PMd together form the parietofrontal circuit called the dorso-medial pathway.

For *grasping* an object we need more than a reaching movement of the arm to bring the hand to the target: the hand has to preshape according to the intrinsic visual features of the object as well. A grasping action consists of both transport and preshaping movements and is therefore often called a reach-to-grasp action. The area that is suggested to play a central role in the preshaping of the hand in order to grasp an object is the anterior intraparietal sulcus (AIP). Electrophysiological studies in macaques show that neurons in AIP fire during the manipulation of a particular object, with different neurons tuned to different objects (Murata et al., 2000). This is independent of the position of the object (Taira et al., 1990). Three categories of neurons can be distinguished in AIP, dependent on whether they fire during object manipulation in the light or the dark. Visual dominant neurons need light to be activated, while motor neurons fire during object manipulation independent of light conditions (Sakata et al., 1995). In addition, intermediate “visual-and-motor” neurons exist, illustrating the capability of AIP to transform information in different modalities, like translating intrinsic features of 3D objects into accurate hand shapes. Lesions or disruptions of AIP lead to severe impairments in the preshaping of the hand during grasping (Perenin and Vighetto, 1988, Gallese et al., 1994; Tunik et al., 2005; Rice et al., 2006). Patients with lesions in the anterior intraparietal sulcus are more impaired at grasping than reaching (Binkofski et al., 1998).

Neuroimaging data suggest that the *human* homologue of macaque AIP is located at the junction between the anterior intraparietal sulcus and the inferior postcentral sulcus (Binkofski et al., 1998; Culham et al, 2003; Faillenot et al, 1997; Frey et al, 2005). This area has, as is true for the macaque AIP, both visual and motor properties and is active during visually-guided grasping (Binkofski et al., 1998; Culham et al., 2003; Frey et al., 2005; Grezes et al, 2003). A nearby area in the postcentral sulcus shows higher activity for grasping objects than for object-related arbitrary hand gestures (Toni et al, 2001a).

Anatomically, AIP is connected to the rostral part of the ventral premotor cortex (area F5) (Matelli et al., 1986; Luppino et al., 1999) and together they form the subdivision of the dorsal stream that we call the dorsolateral or dorsoventral pathway. Area F5 is also involved in planning and executing grasping movements (Fogassi et al., 2001; Davare et al., 2006). It contains neurons that respond to both specific hand-object manipulations and visual and tactile stimuli (Murata et al., 1997, Graziano and Gross, 1998). Area AIP and area F5 together have been suggested to support visually guided grasping movements by transforming 3D object features into accurate finger and hand formations (Rizzolatti et al., 1998; Murata et al., 2000).

Together, these findings have led to the belief that a functional dichotomy exists between reaching and grasping along respectively the dorsomedial pathway, that consists of area V6A and the caudal dorsal premotor cortex (area F2) (Tanne-Gariepy et al., 2002; Galletti et al., 2003) and the dorsolateral pathway, consisting of AIP connected to the rostral part of the ventral premotor cortex (area F5). But so far, no double dissociation between reaching and grasping deficits in neuropsychological studies has been described (Pisella et al., 2006). In addition, it was recently suggested that macaque area V6A is not only involved in reaching, but in grasping as well (Galletti, et al, 2003). Some V6A cells are specifically modulated during the grasping of visual objects (Fattori et al., 2004). Patients with occipito-parietal lesions show severe impairments in both reaching and grasping (Jeannerod et al.,1994; Milner et al., 2003). Similarly, controlled lesions of V6A in monkeys provoked deficits in reaching, wrist orientation, and grasping (Battaglini et al., 2002). Neurons in area F2 were shown to be selective for both the type of prehension and the wrist orientation required for grasping an object, showing that F2 might be involved in grasping as well (Raos et al, 2004). Accordingly, some authors have moved beyond the two visuomotor channel hypothesis (Hoff and Arbib, 1993), proposing more integrated control mechanisms of prehension (Smeets and Brenner, 1999; Ulloa and Bullock, 2003; Zaal et al., 1998; Haggard and Wing, 1995).

How these integrated control mechanisms can be represented by the two anatomically segregated parieto-frontal circuits has still to be explained. In order to investigate the integrated activity of the areas within and between these pathways, we have to move beyond the standard fMRI analyses measuring cerebral activity in segregated areas and explore how the areas within these circuits mutually interact. In Chapter 5 Dynamic Causal Modelling (Friston et al, 2003), an effective connectivity analysis, is applied to fMRI-data acquired during an experiment on visually-guided grasping. In this experiment it was attempted to make the grasping conditions as natural as possible. In chapter 4 the methods and tools for studying natural grasping movements in the fMRI-scanner are discussed extensively. Methods and concepts of connectivity, in particular Dynamic Causal Modelling, will be discussed in more detail later in this introduction and in chapter 5. Assessing the parieto-frontal connectivity during prehension movements provides us with knowledge that is constructive to the ongoing two-visuomotor-channel debate.

1.2.3 PPC in arbitrary sensorimotor mapping

In paragraph 1.2.2 we have seen that the posterior parietal cortex plays an important role in standard sensorimotor mapping. It was discussed how the PPC accommodates the information flow from visual to motor cortex, when there is a spatial congruence between the visual cue and the movement. The shape and location of a 3D object directly guide the trajectory of the hand movement and the formation of an accurate grip and the PPC aids in the transformation from these object properties into grip formation. However, to what extent the PPC is involved in *arbitrary* sensorimotor mapping is still undecided.

Humans have a lifetime of experience with spatially-guided movements, but limited practice with the arbitrary visuomotor associations used in previous imaging studies (Boettiger and D'Esposito, 2005; Deiber et al., 1997; Grafton et al., 1998; Toni et al., 2001b; Toni and Passingham, 1999; Weeks et al., 2001). This raises the question whether the distinction between standard and non-standard sensorimotor mapping reflects intrinsic neuro-computational differences, or occurrences of the same time-varying phenomenon. For instance, it has been suggested that the motor plan automatically afforded by an object or by a location might require a learning process that abstracts relevant stimuli features (Oztop et al., 2004). Even apparently direct spatial correspondences between stimuli and responses might be the result of sensorimotor associations learned by trial and error, in which the relevant mapping was initially arbitrary. Analogously, arbitrary visuomotor associations can be trained to a degree of automaticity that makes them insensitive to reward devaluation and thus akin to habits (Shadmehr and Wise, 2005; Packard and Knowlton, 2002; White and McDonald, 2002; Graybiel, 1995;). Do spatially-guided and arbitrarily instructed movements remain neurally distinct categories of sensori-motor transformations even when the latter class of movements has become automatic? Or will information start to flow through the dorsal stream and accordingly, will PPC become involved in arbitrary visuomotor mapping when the associations are overlearned? In chapter 2 and 3 this hypothesis is tested. Here, I will shortly summarize some of the neuroimaging work that led to this specific question. The content described in this paragraph goes back to a large extent to the work of Toni et al. (1999, 2001a, 2001b, 2002a).

As already mentioned, the primate brain possesses the ability to map any discriminable sensory stimulus into any element of the animal's motor repertoire (Passingham, 1993). Both human and non-human primates are able to learn to combine cues and movements that have no systematic spatial relationship to each other. Colours and shapes, like the big red button that instructed the automatic opening of a door, road panels in the street, written or spoken words: all of these can guide our actions without spatially relating to those actions. This mapping ability may have been of crucial importance in the evolution of human language, as a predecessor of the ability to learn arbitrary names (Wise and Murray, 2000). It has not been fully clarified yet how these symbolic instructions influence the motor system.

Substantial evidence points to the involvement of a fronto-striatal system in the acquisition of arbitrary visuomotor associations (Passingham, 1993; Toni and Passingham, 1999; for a review see Wise and Murray, 2000;). Ablations of the dorsal premotor cortex (Petrides, 1982) and dorsolateral prefrontal cortex (Gaffan and Harrison, 1988/1989) as well as bilateral hippocampal lesions (Murray and Wise, 1996) in macaques caused

impairments in learning arbitrary visuomotor mappings. Disconnecting inferior temporal cortex (Gaffan and Harrison, 1988/1989) or the basal ganglia (Canavan et al., 1989) from prefrontal cortex disrupts this behavior as well. Neuroimaging data indicated that the premotor cortex increased its activity during arbitrary visuomotor mapping (Deiber et al., 1997). When contrasting spatially-guided grasping with movements instructed by arbitrary rules, in which subjects had to decide between different hand actions in response to non-spatial tokens, cerebral activity was observed in ventral prefrontal, anterior striatal and dorsal precentral areas (Toni et al, 2001a).

When arbitrary visual stimuli such as two-dimensional patterns or colours instruct the movements, these patterns must be correctly identified before one is able to decide on the accurate response to make. It is known that the ventral visual system is heavily involved in such object recognition (Mishkin et al., 1983; Milner and Goodale, 1995). Accordingly, ventral stream areas have been found to be activated during arbitrary visuomotor learning. The emphasis here is on learning, because when cues and responses are associated on basis of arbitrary rules, these rules always have to be *learned*. Studying the temporal dynamics of cerebral activity during visuomotor associative learning allows to identify more subtle differences between the areas involved in this process. A positron emission tomography (PET) study investigating changes in cerebral activity over four different stages of learning a visuomotor conditional task (Toni and Passingham, 1999), showed increasing activity over learning stages in the right lingual gyrus. This result was accompanied by learning-related changes in left parahippocampal cortex, right inferior frontal sulcus, caudate nucleus, and the left rostral cingulate motor area. These results confirm the involvement of frontostriatal areas in visuomotor associative learning and suggest that it activates a distributed network in the ventral extrastriate and prefrontal cortex combined with the basal ganglia and the parahippocampal gyrus (Toni and Passingham, 1999). A follow-up fMRI study (Toni et al, 2001b) further confirmed the involvement of ventral stream areas in visuomotor associative learning, as learning-related activity was found in a temporo-prefrontal circuit, in particular in the inferior temporal cortex. Early in learning the hippocampal/parahippocampal complex was activated, while later in learning the basal ganglia system started to convey information to the premotor cortex. Structural equation modelling (SEM, described in paragraph 1.3) applied to these data showed increases in effective connectivity as a function of learning in temporo-striatal and fronto-striatal circuits (Toni et al, 2002a). In summary, these studies suggest that both frontostriatal and frontotemporal circuits are crucial in visuomotor associative learning (figure 2, in yellow) .

From the inferotemporal cortex visual information can not directly reach the premotor cortices, as the inferotemporal cortex does not directly project to the premotor cortex (Seltzer and Pandya 1989; Distler et al. 1993; Boussaoud et al. 1995). This is not surprising: the neural representation of the two-dimensional visual patterns in the inferior temporal cortex are incompatible with the codes representing movement kinematics in premotor cortex. However, several pathways interconnect the dorsal and ventral stream. For example, prestriate and inferotemporal cortex project to the inferior parietal cortex (Morel and Bullier 1990; Baizer et al. 1991) that in its turn connects to the premotor cortices. On the basis of these connectional patterns, it can be argued that after the stimulus is identified the information is transferred to the premotor cortex through the dorsal stream (figure 2, in red), which is able to do the necessary sensorimotor transformations to guide the movement.

Despite the existence of these interconnections, none of the studies so far have revealed clear parietal contributions to the learning of visuomotor associations or any alterations in parietofrontal connectivity during conditional learning (Toni et al, 2002a). Still, evidence exists that activity in the parietal cortex is evoked by visual conditional tasks. This is shown by several studies in human (Toni and Passingham, 1999; Deiber et al., 1996, 1997; Grafton et al., 1998) and non-human primates (Crammond and Kalaska, 1994; Kalaska, 1996). Large PPC lesions in humans can impair movement selection on the basis of arbitrary cues (Buxbaum et al., 2003; Haaland et al., 2000). Furthermore, we know that after extensive training, intraparietal cells can encode non-spatial features of instructions that are relevant to the task (Sereno and Maunsell, 1998; Toth and Assad, 2002). PPC seems to be able to dissociate between different courses of action defined by the visual stimuli specifying the arbitrary movements, regardless of whether the visual stimuli were followed by an actual movement (Thoenissen et al., 2002). Even more interesting, although no apparent learning-related changes in PPC were found, in one of the experiments described above, a reduction of activity in a parietal region was observed (Toni et al, 2001b) that was consistent with a reduction in the variability of responses.

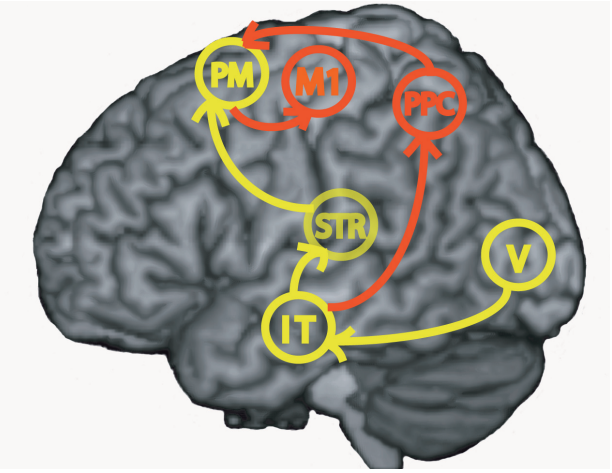


Figure 2
Frontostriatal and frontotemporal circuits are crucial in visuomotor associative learning (in yellow). However, several interconnections between the dorsal and ventral stream exist. For example, inferotemporal cortex (IT) projects to the parietal cortex (PPC) that in its turn connects to the premotor cortices (PM). It could be argued that after stimulus identification the information is transferred to the premotor cortex through the dorsal stream (in red). M1 = primary motor cortex; STR = striatum.

Could the route visual information takes to reach the motor cortex in arbitrary visuomotor mapping change under the influence of learning? Could it be the case that we fail to find parietal involvement in arbitrary visuomotor associative behavior, because the difference in the degree of automaticity between spatially and arbitrarily instructed movements is too large? Or would standard and non-standard visuomotor mapping still activate different circuitry when we would have as much lifetime training in the latter as we have in the former? In chapter 2 the role of PPC in arbitrary visuomotor mapping is investigated.

In chapter 3 the nature of the movement representation of overlearned arbitrary visuomotor associations is explored. If the PPC becomes involved in visuomotor associative behavior when the associations are sufficiently trained, it would suggest that overlearned arbitrary visuomotor associations could come to rely on a spatial framework, similarly to spatially-guided movements. Alternatively, it is possible that the PPC contribution to overlearned visuomotor associations is non-spatial in nature, as suggested by the finding

that after extensive training this region can encode non-spatial features of instructions that are relevant to the task (Sereno and Maunsell, 1998; Toth and Assad, 2002). These two possibilities are contrasted, assessing how performance of extensively trained arbitrary visuomotor associations depends on the effector used to provide the response.

1.3 On structure and function: connectivity analyses

In paragraph 1.2.2 it was questioned how two integrated control mechanisms of prehension can be represented by the two anatomically segregated parieto-frontal circuits. In order to investigate the integrated activity of the areas within and between these pathways, we have to move beyond the standard fMRI analyses measuring cerebral activity in segregated areas. A way to investigate how the areas within these circuits mutually interact is by exploring the changes in connectivity between these areas during prehension movements. In this paragraph it will be explained what additional value connectivity analyses have with respect to the standard analyses used in neuroimaging and why it is important to take not only functional, but also structural information into account. Next, an overview will be given of the connectivity analyses currently available. The ideas and concepts discussed in this section draw strongly from the work of Horwitz, McIntosh and Friston and are excellently discussed by Stephan (2004; for another review see Ramnani et al, 2004). Because fMRI is the method used in this thesis I will focus on connectivity analyses that have been applied to fMRI data, ignoring a large body of connectivity (also called coherence) research done in EEG and MEG.

From single cells to cortical columns to large cortical areas: we have extensive knowledge about the structural and functional organization of the brain at different scales. But despite this knowledge it is not entirely clear yet how the structural properties of neural units at each level of brain organization relate to the functions larger cortical areas are associated with. Neuroimaging has linked the cerebral activity recorded in these large areas directly to discrete functional or cognitive processes. But how do the structural properties lead to this observed cerebral activity? (Stephan, 2004).

In paragraph 1.2.2 the functional dichotomy was discussed that is believed to exist between reaching and grasping along respectively the dorsomedial pathway, consisting of area V6A and the caudal dorsal premotor cortex (area F2) and the dorsolateral pathway, that consists of AIP connected to the rostral part of the ventral premotor cortex (area F5). This theory is based on several findings: the direct projections between the areas in both pathways have been established by tracer studies in non-human primates and electrophysiology has observed specific behavior of single cells within these areas. With neuroimaging in humans cerebral activity during visually-guided grasping has been observed in several areas that could be putative homologies to the areas activated in macaques. There is no way yet to simultaneously take these different kinds of information into account. Furthermore, it would not be easy to decide what level of detail to include in our investigations. Nevertheless, neuroimaging might greatly benefit from incorporating more of its knowledge on brain structure into its research practice.

Functional integration, the belief that neural units causally interact instead of only hosting localized functions (Friston, 2002), was already an important matter under discussion more than 100 years ago (e.g. Goltz, 1834-1902). It is well established that at all levels of brain organization the brain is composed of *interconnected* neural elements. These neural elements continuously influence other neural units, either in their vicinity or over large distances, causing changes in each other's activities. The connectional properties of different neuronal populations have been investigated extensively.

But despite the well-established existence of the interactions between brain regions, neuroimaging methods have mostly linked the activity recorded in the brain directly to discrete functional or cognitive processes. This approach, based on the notion of *functional specialization,* defining function as being organized in specialized neural units concerned with certain aspects of information processing (Horwitz, 2003; Marshal and Fink, 2003), has become the dominating approach in cognitive neuroscience and has provided us with at least one functional label for each cortical area. Yet, when looking at brain activity in general it can been easily observed that more than one area is active during even a simple cognitive task. Grasping an object evokes a wide-spread pattern of activation in the brain, activating several areas associated with for example visual perception, planning, selecting or executing movements. At the same time, one single area can be involved in different cognitive functions. Additionally, the response of an area is dependent on context and can change over time or during learning.

It is now well established that functional integration and specialization seem to be complementary principles of brain organization (Friston, 2002). Nowadays more or less general agreement exists in the neuroimaging community on the belief that the brain has to be regarded as a dynamical system consisting of strongly interconnected more or less specialized modules. Surprisingly, neuroimaging experiments still mainly focus on the direct linkage of the responses in brain areas to a cognitive task. The amount of connectivity studies is marginal in comparison to the bulk of neuroimaging literature available.

The basic idea of connectivity originates from the premise that two areas in space that are functionally interacting with each other will show correlated patterns of activity in time. This notion came from electrophysiology where Aertsen and Preissl (1991) were among the first to cross-correlate spike trains of neurons to measure their temporal coherence. Within the connectivity analyses on neuroimaging time series we can differentiate between functional and effective connectivity. *Functional connectivity* has been defined as the *temporal correlations* between spatially segregated neurophysiologic processes (Friston, 1995). *Effective connectivity* is defined as the direct (causal) influences of one neural element onto another (Friston, 1995). Effective connectivity might be a concept that can appropriately characterize how the anatomical connectivity leads to the cerebral activity observed. It is important to understand that the anatomical connectivity between two areas is necessary, but not sufficient for determining the causal interactions between those areas. The same anatomical structure can underlie different functions. The anatomical connectivity has to be seen as the skeleton that defines the space in which functional interactions can take place, invariant of the dynamics (Strogatz, 2001; Stephan, 2004).

The currently available imaging techniques have provided us with an extensive amount of functional information on the level of cortical areas. The patterns of cerebral activity observed under a variety of tasks have contributed greatly to our understanding and changed our view on brain function. Yet, to obtain genuine insight on how structure meets function

we need to move beyond these analyses and explore the causal interactions between the areas we are interested in. In the next paragraphs I give an overview of the connectivity analyses available, of which the objectives range from exploring the correlational patterns in the data to modelling the brain as a biologically plausible dynamical system.

1.3.1 Analyses of functional connectivity

In neuroimaging, interregional "seed voxel" correlation analysis (SVCA) was one of the first methods used to examine functional connectivity in PET-experiments (Horwitz et al, 1998). In SVCA the correlation of all voxels or regions-of-interest (ROI) in the brain unto one chosen reference region or voxel is computed to determine which brain regions are functionally linked to the region of interest. Another early approach was to decompose fMRI-data with principal component analysis (PCA) into a set of spatially and temporally uncorrelated modes that were ordered according to the amount of variance they explained. From the comparison of the most prevalent modes to the experimental task emerged a pattern of functional connectivity associated with the task at hand (Friston et al, 1993). When two groups (e.g. patient vs. controls) are compared, the principal component can be identified that is maximally expressed in one group and minimally in another (generalized eigenimage analysis; Friston et al, 1997) in order to identify in what respect the functional connectivity patterns of these groups differ. More recent studies use independent component analysis (ICA) to decompose fMRI data into independent modes in the spatial and temporal domain. To investigate coherent signals over subjects and sessions, tensor probabilistic ICA (TICA, Beckmann and Smith, 2005) is employed. The extracted components allow to distinguish meaningful coherent networks from signal modulations induced by confounds, like head movement or cardiac pulsation.

In general, the meaning of a functional connection is hard to interpret. A functional connection between A and B does not mean that there must be a direct causal interaction between them. Time series A and B could be correlated because A influences B, B influences A, or because they mutually influence each other. A and B could be equally strongly influenced by a third site resulting in similar activity changes in both regions. Although patterns of functional connectivity are difficult to interpret, they might constitute meaningful functional networks, both during rest and tasks. The study of functional connectivity during rest generated a set of dedicated connectivity patterns that seem to be very consistent over subjects and sessions (Damoiseaux et al, 2006). Recently, it has been suggested that the background activity present in the brain at rest is highly organized and might, in still unknown ways, contribute to information processing (Greicius et al., 2003; Beckmann et al., 2006). To test the functional relevance of these resting-state patterns, the activity in the networks that are identified have to be related to physiological and neuropsychological measures.

As no assumptions about the underlying connectional structure between the regions are made, the functional connectivity methods are purely data-driven. The exploratory character makes this class of methods specifically suitable when no additional knowledge is available on the anatomical connectivity or the regions involved in the task or group under study. Practical applications of functional connectivity analyses in rest are predominantly found in clinical studies where it is either hard to design appropriate tasks because there is no hypothesis about the differences between the groups under study or because

patients are too severely disabled to accurately perform tasks.

If we have no hypotheses about the regions involved in our experiment and the connections between them, functional connectivity methods are a good choice. However, if knowledge about the regions and their connectional structure is available to us and if something is known about how their activity changes in different contexts, we want to incorporate this knowledge into our models.

1.3.2 Analyses of effective connectivity

Effective connectivity is defined as the direct (causal) influences of one neural element onto another (Friston, 1995). Different approaches have been developed for measuring effective connectivity. What all methods have in common is that they infer directionality between the regions. Most of them are model-driven instead of data-driven.

Structural Equation Modelling

Structural Equation Modelling (SEM) originating from econometrics and extensively applied in the social sciences, was first applied to neuroimaging data in 1994 by McIntosh and Gonzalez-Lima. SEM is a multivariate technique used to test hypotheses about the causal relations between defined variables (McIntosh et al., 1994; Büchel and Friston, 1997). As in other effective connectivity approaches a SEM can be divided into two parts: an anatomical model and a measurement model. The former defines the a priori assumptions on the connectional structure that is presumed to underlie the process under investigation and is graphically depicted in the form of a path model. This path model describes which areas are thought to be involved and how these areas are interconnected. Within this path model the effective connectivity between interacting areas can be described as a system of linear equations modelling the hemodynamic change in one area in the model as a function of other areas. The strength of the connections, the path coefficients, represent to what extent a unit change in a source region causes a unit change in a target region. Crucial to all model-driven approaches is the choice of a plausible model, which can be complicated given the lack of human connectional data. A clear disadvantage of SEM related to this, is the fact that only a limited number of connections can be included in the model, because of problems of identifiability. As most biological systems have a large number of reciprocal connections, this limits the scope of this method to a large extent. The path coefficients are estimated by minimizing the difference between the observed and modelled variance-covariance matrix. The covariance matrix can be constructed over subjects (PET) or over time (fMRI). However, even when correlations are calculated over time, no temporal information is taken into account. In principle, the time indexes of the data could be randomly shuffled and still the analysis would give identical results. As the amount of neural activity at a certain point in time is always dependent on the activity that occurred earlier in time, this is a another clear limitation.

Multivariate AutoRegressive models

FMRI measurements provide not only spatial information about the brain areas involved in a cognitive task, but also contain valuable information about the process that generated it, because of the temporal precedence of measurements in a time series. A way to exploit this information is by an autoregressive process that models the current value of a time

series as a weighted linear sum of previous values. Multivariate AutoRegressive models (MAR models) extend this approach to multiple time series such that the vector of current values of all variables is modelled as a linear sum of previous activities (Harrison et al., 2003). In Granger Causality Mapping (GCM), based on the same vector autoregressive modelling, the temporal precedence is used to identify the direction of causality from information in the data. A time series X is said to Granger-cause Y if it is shown that incorporating past values of x improves the prediction of the current value of y (Goebel at al, 2003; Roebroeck et al, 2005). Granger Causality maps (GCMs) can identify voxels that are sources or targets of directed influence for any chosen seed region. GCM is unique in that it is the only method measuring effective connectivity that is exploratory in nature, because it is not required to define a network model a priori. The predefined anatomical models as used in the other effective connectivity methods can easily be misspecified. Granger Causality can also complement these methods in aiding in the selection of effectively interconnected regions and the directionality of these connections (Goebel at al, 2003; Roebroeck et al, 2005).

PsychoPhysiological Interactions

Most biological systems are dependent on nonlinear processes for their characteristic behavior. Interconnected areas interact dynamically with each other in different contexts. Their connection strengths can increase or decrease when they are modulated by a certain condition, like attention, or can gradually change over time, as during learning. Describing responses as a linear combination of independent and additive inputs, is therefore insufficient. Nonlinear terms have to be incorporated in our models to allow us to test for contextual changes. To model the modulating effect a certain condition or context has on the value of a connection, we have to expand our model with a nonlinear term describing how the context changes the influence of region A on region B. With structural equation modelling, Toni et al (2002a) showed how learning novel arbitrary visuomotor associations changes the functional couplings within a striato-frontal circuit by allowing learning effects over time to adjust the path coefficients in the SEM. In a block design, like used in the latter study, the data can easily be partitioned and the path coefficients can be compared between conditions. Because of the transient nature of evoked responses this is problematic in event-related designs (as is the use of bilinear modulation terms) (Stephan, 2004, Gitelman et al, 2003).

The simplest bilinear method computing how an experimental context can change the connection between two regions is the PsychoPhysiological Interactions method (PPI) (Friston et al., 1997). When regressing the activity in an area A onto another area B under different conditions, a PPI reflects the difference in regression slope between one condition and next. A well known example of a PPI is the increased modulation by attention to motion on the connection from V1 to V5 in a visual motion task (Büchel and Friston, 1997). The contextual modulation of attention is described by a bilinear term representing the interaction between the physiological activity (the time series of e.g. area A) and the psychological context C. PPI computes the effective connectivity from one seed voxel to all other voxels in the brain and is thereby more exploratory in nature, like Granger Causality Mapping. Unlike correlation analyses, PPIs are directional. Regressing the interaction of area A with context C onto time series B is not the same as regressing B x C onto the time series of area A (Stephan, 2004). One disadvantage of PPI is that it is a very simple

model that can only test for functional interactions between pairs of areas. And it ignores the time series properties of the data, as in SEM.

Dynamic Causal Modelling

Both PPI, MAR models and SEM operate at the level of the measured BOLD-signals, that result from a haemodynamic convolution of the underlying neural activity. Instead, we would like to identify the causal architecture of the system we are interested in at the level of neuronal dynamics (which is not directly accessible for fMRI). To enable inferences about connectivity between neural units we need models that combine: (i) a biologically and anatomically plausible model of interacting cortical regions at the neuronal level and (ii) a biophysically plausible forward model that translates the neural activity into the measured BOLD-signal (Stephan, 2004).

Recently, a novel method was introduced that solves some of the problems associated with the methods described above. The aim of Dynamic Causal Modelling (DCM) is to estimate parameters at the neuronal level (computed separately for each area) such that the modelled BOLD signals are maximally similar to the experimentally measured BOLD signals. Furthermore, DCM, like PPI, is a bilinear model. It aims to estimate and make inferences about the causal influences or coupling among brain regions, but more importantly, it asks the question how this coupling is modulated by the experimental manipulation at hand (Friston et al., 2003). Here I briefly summarize the main concept of DCM, but for a more detailed description of the methods and applications I refer to the papers of Friston (2002, 2003) and Stephan (2004, 2007). Because in this thesis only fMRI data are considered, I summarize the implementation of DCM for fMRI, but it has been implemented for EEG and MEG as well (David et al., 2006).

Dynamic Causal Modelling (DCM) is a method that regards the brain as a dynamical system that is driven by experimentally controlled external inputs and produces outputs. A system is formally defined as a set of elements which interact in a spatially and temporally specific fashion. The changes in the neural states of a system in time (i.e. the first derivative of the state vector z with regard to time t) are a function of the current states of the system z, the external inputs u to the system and a set of parameters θn (n denoting 'neural') describing the functional architecture and interactions among brain regions at a neuronal level:

$$\begin{bmatrix} \frac{dz_1}{dt} \\ \vdots \\ \frac{dz_n}{dt} \end{bmatrix} = \frac{dz}{dt} = F(z, u, \theta^n). \qquad (1)$$

The neural states of the regions do not represent neurophysiological measurements on the level of individual neurons. They rather represent a summary index of the dynamics of large neural populations. Concerning the specific definition of function F, the neural state equation in DCM uses a bilinear form:

$$\frac{dz}{dt} = Az + \sum_{j=1}^{m} u_j B^j z + Cu \qquad (2)$$

Here, z is the state vector (with each state variable representing the population activity of one region in the model), t is continuous time, and u_j is the j-th input to the modelled system (i.e. some experimentally controlled manipulation). In this state equation, the A matrix contains the "intrinsic" or "fixed" connection strengths between the modelled regions. The external inputs can enter the model in two different ways: they can directly perturb the system by influencing specific regions, like when visual stimulation evokes activity in visual areas. The C matrix represents the strengths of these direct ("driving") inputs to the modelled system. The external inputs can also elicit responses through the modulation of the coupling between regions (e.g. during learning or attention or in our case, during the different kinds of prehension movements). Accordingly, the $B^{(1)}...B^{(m)}$ matrices represent the context-dependent modulation of these connections as an additive change. Note that the inputs u correspond to designed causes (e.g., boxcar or delta stimulus functions), like those used to form design matrices in conventional fMRI analyses. The outputs correspond to the observed BOLD time series of the selected volumes of interest (VOI). Being based on first order differential equations, the parameters in a DCM denote the speed or rate of change of neuronal activity (Hz) in one area as induced by an input or by the output from another area, respectively. The focus of DCM is typically on the B parameters, the modulatory effects.

In DCM, the neuronal model described above is supplemented with a haemodynamic forward model of how neuronal activity is transformed into a measured BOLD response. This "Balloon model" (Buxton et al, 1998; Friston et al, 2000) consists of a set of differential equations that describe the relations between four haemodynamic state variables, using five parameters (θ^h). The mean and variance of the five hemodynamic parameters were computed over a large amount of voxels from another experiment. Changes in neural activity elicit a vasodilatory signal that leads to increases in blood flow and subsequently to changes in blood volume and deoxyhemoglobin content. The latter two lead in turn to the predicted BOLD signal (Friston et al., 2000; Stephan et al, 2004).

The neural and hemodynamic parameters are $\theta = \{\theta^n, \theta^h\}$ are simultaneously estimated from the measured BOLD data such that the modelled BOLD signals are maximally similar to the experimentally measured BOLD signals. For the estimation a fully Bayesian approach is employed, with empirical priors (based on experimental data) for the haemodynamic parameters and conservative shrinkage priors (with a mean of zero) for the coupling parameters. With priors we are expressing the a priori knowledge we have about the parameters of the model. The estimation is done by Bayesian inversion using an Expectation Maximization algorithm and a Laplace approximation to the posterior density (see Friston et al., 2003 for details). The posterior distributions of the resulting parameter estimates can be used to test hypotheses about connection strengths. DCMs are constructed for each single subject separately. To test whether the modelled processes are expressed consistently across subjects, the subject-specific intrinsic couplings and modulatory effects can be entered into separate classical one-t-tests.

Like SEM, DCM is a model-driven approach. It is therefore extremely important to specify a clear a priori hypothesis and ensure that the model used is suitable to test this hypothesis. Often there is uncertainty about the connectional structure of the system under investigation. Or different competing hypotheses exist that we want to represented in different DCMs. To test whether a model is superior to possible alternative models, one can apply Bayesian inference to the models themselves (Penny et al, 2004; Stephan et al,

2006). Bayes factors, i.e. ratios of model evidences, are used to compare different models. The model with the highest evidence is a model that is optimally balanced with regard to model fit (accuracy) and model complexity. In the context of DCM, suitable approximations to the model evidence are given by the Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC). In chapter 5 DCM is used to investigate the parieto-frontal connectivity during prehension movements.

1.4 Outline of this thesis

In summary, one of the fundamental questions in neuroscience is the question how sensory cues influence the motor system (Toni and Passingham, 1999, Passingham et al. 1998) and this thesis is concerned with this general question. Different circuits underlying standard and non-standard visuomotor mapping were introduced. In this thesis is investigated how segregated these circuits really are and in what circumstances they are employed.

Chapter 2 starts by asking whether learning arbitrary visuomotor mappings changes the routes by which visual information reaches the motor cortex and whether the PPC might become activated when arbitrary mappings become automatic. If we would have as much lifetime training in non-standard sensorimotor mapping as we have in standard sensorimotor mapping would both processes still rely on different circuitry? In chapter 3 this matter is further investigated by examining the movement representation of these overlearned mappings, testing whether the brain learns to represent arbitrary visuomotor mappings in a spatial framework.

In chapters 4 and 5 of this thesis novel acquisition and analysis techniques are employed that contribute to an ongoing debate about the parietofrontal circuitry underlying different aspects of visually-guided reaching-grasping movements. Are reaching and grasping distinct processes represented along anatomically segregated pathways? Investigating reach-to-grasp movements in the specific environment of an fMRI scanner asks for creative solutions to a number of technical difficulties. In chapter 4 of this thesis a new protocol is described to study visually guided reach-to-grasp movements in a fMRI experimental setup that allows subjects to perform the movements in a natural way, with full sight of their hands and objects to be manipulated. In chapter 5 Dynamic Causal Modelling, an effective connectivity analysis, is used to assess the parieto-frontal connectivity during prehension movements.

Chapter 2

CEREBRAL CHANGES DURING PERFORMANCE OF OVERLEARNED ARBITRARY VISUOMOTOR ASSOCIATIONS

Grol, M.J., de Lange, F.P., Verstraten, F.A.J., Passingham, R.E., Toni, I. (2006). Journal of Neuroscience, 26: 117-25.

The posterior parietal cortex (PPC) is known to be involved in the control of automatic movements that are spatially guided, such as grasping an apple. We considered whether the PPC might also contribute to the performance of visuomotor associations in which stimuli and responses are linked arbitrarily, such as producing a certain sound for a typographical character when reading aloud or pressing pedals according to the colour of a traffic light when driving a motor vehicle. The PPC does not appear to be necessary for learning new arbitrary visuomotor associations, but with extensive training, the PPC can encode nonspatial sensory features of task-relevant cues. Accordingly, we have tested whether the contributions of the PPC might become apparent once arbitrary sensorimotor mappings are overlearned. We have used functional magnetic resonance imaging to measure cerebral activity while subjects were learning novel arbitrary visuomotor associations, overlearning known mappings, or attempting to learn frequently changing novel mappings. To capture the dynamic features of cerebral activity related to the learning process, we have compared time-varying modulations of activity between conditions rather than average (steady-state) responses.

Frontal, striatal, and intraparietal regions showed decreasing or stable activity when subjects learned or attempted to learn novel associations, respectively. Importantly, the same frontal, striatal, and intraparietal regions showed time-dependent increases in activity over time as the mappings become overlearned, i.e., despite time-invariant behavioral responses. The automaticity of these mappings predicted the degree of intraparietal changes, indicating that the contribution of the PPC might be related to a particular stage of the overlearning process. We suggest that, as the visuomotor mappings become robust to interference, the PPC may convey relevant sensory information toward the motor cortex. More generally, our findings illustrate how rich cerebral dynamics can underlie stable behavior.

Introduction

Distinctions have been drawn between spatially guided responses and arbitrarily instructed movements. Spatially guided movements rely on information available online for immediate performance (Goodale et al., 1994), possibly through the automatic implementation of the motor plan afforded by an object or location (Grezes et al., 2003); they are controlled by a dedicated parietofrontal circuit (Milner and Goodale, 1995). In contrast, movements instructed by visual cues according to arbitrary rules are learned voluntary actions, selected among alternatives according to an expected outcome (Passingham, 1993), and they are indifferent to the temporal relationship between stimuli and responses (Brasted and Wise, 2005); they are controlled by a distributed frontostriatal circuit (Wise and Murray, 2000).

Humans, however, have a lifetime of experience with spatially guided movements but limited practice with the arbitrary visuomotor associations that have been used in previous imaging studies (Deiber et al., 1997; Grafton et al., 1998; Toni and Passingham, 1999; Toni et al., 2001a; Weeks et al., 2001; Boettiger and D'Esposito, 2005). This raises the issue of whether the distinctions detailed above reflect intrinsic neurocomputational differences or training effects. Do spatially guided and arbitrarily instructed movements remain neurally distinct categories of sensorimotor transformations even when the latter class of movements has become automatic?

Here we address this issue by testing whether and where changes in cerebral activity are generated during overlearning of arbitrary visuomotor mappings as compared with initial learning of novel mappings. It has been shown that premotor–striatal circuits are necessary for the retention and retrieval of learned visuomotor mappings (Passingham, 1985; Nixon et al., 2004b), whereas other portions of the striatum, the hippocampal system, and the ventral prefrontal cortex appear to be concerned mainly with the rapid acquisition of novel mappings (Bussey et al., 2001; Brasted et al., 2005; Pasupathy and Miller, 2005). In contrast, evidence of the contributions of the posterior parietal cortex (PPC) to the automatic performance of arbitrary visuomotor mappings remains inconclusive. Partial lesions of the PPC in macaques do not influence visuomotor conditional learning (Rushworth et al., 1997). On the other hand, large PPC lesions in humans can impair movement selection on the basis of arbitrary cues, such as the verbal commands or the "token" objects used to instruct pantomimes during neuropsychological tests of ideomotor apraxia (Haaland et al., 2000; Buxbaum et al., 2003). Token here refers to the fact that, in these tests, objects are used to instruct movements rather than being the target of the action. Furthermore, although the PPC is known for controlling visually guided hand movements (Sakata et al., 1995), intraparietal cells can be trained to encode both the identity of task-relevant cues (Sereno and Maunsell, 1998; Toth and Assad, 2002) and the motor relevance of visual stimuli specifying arbitrary movements (Thoenissen et al., 2002).

To test the hypothesis detailed above, we used fMRI to measure cerebral activity while subjects were performing arbitrary visuomotor mappings at three different levels of task proficiency: namely, learning novel mappings, overlearning known mappings, or attempting to learn frequently changing mappings between visual patterns and finger movements. Given the intrinsically dynamic nature of learning, these three conditions were compared in terms of differential time-varying modulation of cerebral activity rather than in terms of average (time-invariant) responses. Our rationale was that overlearned performance, although behaviorally invariant, might still display a rich neural dynamic (Hasselmo and McClelland, 1999).

Subjects.

We studied 24 right-handed [Edinburgh Handedness Inventory (Oldfield, 1971); 85±13%; mean±SD] male volunteers (22±3 years) with normal or corrected-to-normal vision. Participants gave informed consent according to institutional guidelines of the local ethics committee (Commissie Mensgebonden Onderzoek Region Arnhem-Nijmegen, The Netherlands), and they were paid €35 for their participation. Data from six subjects were discarded for the following reasons: failure to overlearn visuomotor associations (one subject), anatomical distortions (two subjects), head-movement artefacts (one subject), and scanner artefacts (two subjects).

Task.

Subjects were asked to learn (by trial and error) arbitrary associations between visual stimuli (line patterns derived from Asian characters, which were unfamiliar to the subjects) (Fig. 1A) and motor responses (finger presses). After presentation of the visual stimulus (0.15 s; stimulus onset asynchrony, 4.6 s; range, 3.4 –5.8 s; uniform distribution), the subjects had to flex one of four fingers of the right hand to press a button on a four-button keypad. After the motor response, visual feedback stimuli (green–red– blue squares) indicated whether the movement was correct, incorrect, or exceeded a reaction time (RT) cutoff (Fig. 1A). Subjects were instructed to try to avoid exceeding the RT cutoff. The RT cutoff was 1.5 s during both the training and scanning sessions.

Procedure.

The experiment consisted of a series of training sessions that took place on 3 consecutive days, followed by a scanning session. On day 1, the subjects had to learn, by trial and error, the correct associations between a set of four visual patterns and four different movements; they performed a total of 1200 trials (Fig. 1B, set 1). On days 2 and 3, the subjects practiced the same set of associations learned on day 1 and performed a total of 1350 additional training trials. During the training sessions on days 2 and 3, overlearned trials were pseudorandomly intermixed with trials requiring novel visuomotor associations (Fig. 1B, set 2); i.e., on these trials, novel visual patterns were presented that needed to be associated with one of the four fingers of the right hand. This procedure allowed the subject to become accustomed to learning more than one set of mappings at a time. During the training sessions, the visual stimuli (visual angle, ~6°) were presented on a computer screen in front of the subject. Motor responses were recorded via a four-button keypad that was positioned on the right armrest of the subjects' chair. Subjects positioned their index, middle, ring, and little fingers on a corresponding button of the keypad.

Before starting the scanning session (on day 3), we assessed the degree of automaticity in the performance of the overlearned associations. Automaticity was tested by means of a dual-task procedure, a standard method to assess whether a given task could be

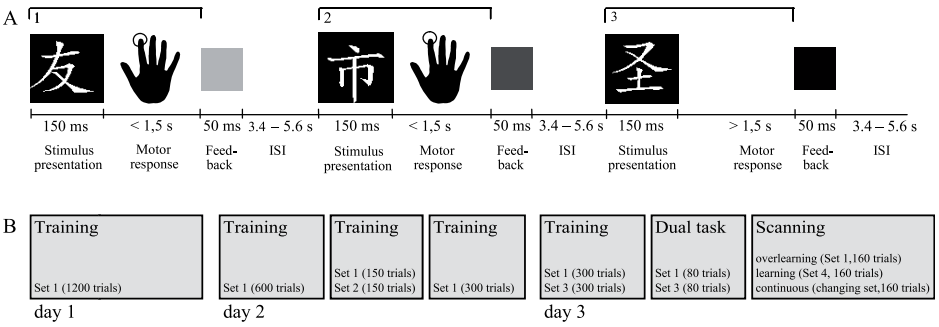


Figure 1. Experimental setup.

A) Task setup. Subjects were asked to associate visual stimuli (white line patterns on black background) with motor responses (flexion of one of four fingers of the right hand to press a button on a four-button keypad). Following presentation of a visual stimulus, the subjects had to flex one of four fingers of the right hand. Following the motor response, visual feedback stimuli indicated whether the movement was incorrect (red square, example #1), correct (green square, example #2), or too late (blue square, example #3).
B) Experimental setup. During fMRI scanning, trials from three different conditions were pseudorandomly intermixed. In the visuomotor overlearned condition (overlearning), subjects retrieved a set of visuomotor associations learned before scanning (set 1, in total 2630 trials over three days). In the visuomotor learning condition (learning, set 4), subjects learned novel visuomotor associations between four new visual patterns and the four finger movements. In the continuous learning task (continuous), subjects attempted to learn novel visuomotor associations. In this latter condition, novel visual patterns (unseen during the training) were constantly introduced and removed from the stimulus set. To assess the degree of automaticity achieved during overlearning, we compared performance during a dual-task procedure involving overlearning trials (set 1) and a set of learned trials (set 3 - see Fig. 3). ISI, interstimulus interval.

performed with minimal interference at the same time as another task (Passingham, 1996; Oliveira et al., 1998). Our goal was to show that performance of the overlearned associations suffered less interference from a concurrent task as compared with performance of newly learned associations. Accordingly, we asked subjects to simultaneously execute the visuomotor associative task and an overt verbal fluency task on every trial and to give priority to the verbal fluency task. During the visuomotor associative task, subjects were asked to retrieve either the previously learned visuomotor associations (overlearning: already practiced over 2550 trials) (Fig. 1B, set 1) or newly learned visuomotor associations (learned: practiced for 300 trials before the start of the dual-task procedure) (Fig. 1B, set 3). Note that during overlearning and learned conditions, accuracy was indistinguishable when tested under single-task conditions; that is, subjects produced virtually error-free performances in both conditions. During the verbal fluency task, subjects were asked to either repeat an auditorily presented noun (repeat) or generate a verb semantically congruent with the noun (generate). The auditory presentation of the noun was synchronous with the visual presentation of the pattern instructing the finger movement. The auditory stimuli were presented by speakers placed in front of the subjects at both the left and right sides. The auditory stimuli and the subjects' vocal responses were recorded via a

microphone on a digital audio tape. This dual-task procedure involved the presence of two concurrent sensory inputs (auditory nouns and visual patterns) and two concurrent motor responses (vocal utterances and finger presses), and the subjects were given explicit instructions to give priority to the verbal fluency task. Accordingly, here we have operationalized "overlearned performance" in terms of differential interference effects evoked by the verbal fluency task on visuomotor associations that were practiced extensively or just learned. This can be contrasted with other uses of dual-task techniques, as when one wants to show that the performance of a given primary task is not affected by a secondary task (Poldrack et al., 2005).

On day 3, after the dual-task procedure, subjects participated in the scanning session in which trials from three different conditions were pseudorandomly intermixed. In the visuomotor overlearned condition (overlearning) (Fig. 1B, set 1), subjects retrieved the visuomotor associations learned before scanning. In the visuomotor learning condition (learning) (Fig. 1B, set 4), subjects learned novel visuomotor associations between four new characters (not present during the training) and the four finger movements. In the continuous learning task (continuous), subjects attempted to learn novel visuomotor associations. In this latter condition, novel visual patterns (unseen during the training) were introduced and removed from the stimulus set after a pseudorandom and stepwise algorithm devised to keep subjects' performance in a state of initial learning over the whole scanning session. During the scanning session, subjects performed a total of 160 trials for each of the three conditions. Before the start of image acquisition, subjects practiced the task in the scanner for 50 trials using a different set of stimuli for the learning and continuous conditions and the same overlearned set for the overlearning condition. During the scanning session, subjects lay supine in the scanner. Head movements were minimized by a padded, adjustable head holder. Subjects viewed the visual stimuli (visual angle, ~6°), which were projected onto a screen behind the subjects' heads, via a mirror attached to the head coil. Motor responses were recorded via an MR-compatible keypad (MRI Devices, Waukesha, WI) that was positioned on the right side of the subject's abdomen with the four fingers of the right hand on the four buttons. During the entire experiment, stimulus presentation and response collection were controlled by a PC running Presentation 0.51 (Neurobehavioral Systems, San Francisco, CA).

Behavioral analysis.

Mean RTs and error rates (ERs) measured during the scanning session were analyzed separately and considered as independent variables of a 3 x 8 repeated measures ANOVA with main effects of task (three levels: overlearning, learning, and continuous) and time (eight levels: blocks 1–8, arising from the subdivision of the RT time series and the ER of each participant into eight equal-length blocks, after removal of missed trials). Subjects were considered as a random factor. Simple main effects were tested with a least square difference *post hoc* test. The α level was set at $p = 0.05$, using a multivariate approach (Pillai's trace corrected). For the dual task, RTs and ERs measured during performance of the visuomotor associative task were analyzed in a 2 x 2 repeated measures ANOVA with main effects of training (two levels: overlearning and learned) and verbal fluency task (two levels: repeat and generate).

Image acquisition.

Images were acquired with a 3T Trio scanner (17 subjects) and a 1.5T Sonata scanner (1 subject) (Siemens, Erlangen, Germany). Blood oxygen level-dependent (BOLD) sensitive functional images were acquired with a single shot gradient echo planar imaging sequence (repetition time, 2.56 s; echo time, 40 ms; 32 transverse slices; interleaved acquisition; voxel size 3.5 x 3.5 x 3.5 mm). At the end of the scanning session, structural images were acquired with a magnetization-prepared rapid gradient-echo sequence (repetition time, 1960 ms; echo time 5.59 ms; longitudinal relaxation time, 1100 ms; voxel size, 1 x 1 x 1 mm).

Image analysis.

Functional data were preprocessed and analyzed with Statistical Parametric Mapping (SPM2) (www.fil.ion.ucl.ac.uk/spm). The first five volumes of each participant's data set were discarded to allow for longitudinal relaxation time equilibration. The image time series were spatially realigned with a sinc interpolation algorithm that estimates rigid body transformations (translations and rotations) by minimizing head movements between each image and the reference image (Friston et al., 1994). The time series for each voxel were realigned temporally to acquisition of the middle slice. Subsequently, images were normalized onto a custom Montreal Neurological Institute (MNI)- aligned EPI template (based on 24 male brains acquired on the Siemens Trio at the F. C. Donders Centre) with both linear and 16 nonlinear transformations and resampled at an isotropic voxel size of 2 mm. Finally, the normalized images were spatially smoothed with an isotropic 10 mm full-width-half-maximum Gaussian kernel. Each participant's structural image was spatially coregistered to the mean of the functional images (Ashburner and Friston, 1997) and spatially normalized by using the same transformation matrix applied to the functional images.

The fMRI time series were analyzed with an event-related approach in the context of the general linear model. Analysis of the imaging data considered main effects of task and outcome [seven levels: overlearning correct, overlearning incorrect (where applicable), learning correct, learning incorrect, continuous correct, continuous incorrect, and trials with responses exceeding the RT cutoff] and task x time interactions, i.e., differential changes in activity over time between conditions. Each effect was modelled on a trial-by-trial basis as a concatenation of square-wave functions, with onsets time-locked to the presentation of the relevant visual patterns and offsets time-locked to the corresponding motor response. Each of these seven square-wave functions was then convolved with a canonical hemodynamic response function and its temporal derivative and down sampled at each scan to generate 14 regressors modelling the main effects described above (Friston et al., 1994). This approach intrinsically accounted for trial-by-trial differences in trial duration and allowed us to assess differences in intensity of the BOLD signal between conditions over and above differences in BOLD signal caused by differences in trial duration.

Time-dependent modulations of task-related activity (task x time interactions) were modelled as first- and second-order parametric effects of (scanning) time on the regressors describing the main effects of task and outcome. Separate covariates including the first derivatives of the head-related movements (as estimated by the spatial realignment procedure) and a constant term over scans were also considered in the model. Data were

high-pass filtered (cutoff, 128 s) to remove low-frequency confounds such as scanner drifts. Temporal autocorrelation was modelled as an autoregressive process.

Statistical inference.

The statistical significance of the estimated evoked hemodynamic responses was assessed with T statistics in the context of a multiple regression analysis. Contrasts of the parameter estimates for the main effects and task x time interactions were calculated and entered into a one-way, repeated measures ANOVA with subjects as a random variable (Friston et al., 1999). Specifically, we were interested in assessing differential modulation of time-related signal changes during performance of overlearning and learning. Linear time-dependent changes in activity during overlearning (correct trials only) were compared with the corresponding effect during learning (correct trials only). For this purpose, SPMs of the T statistic for these two linear time effects were created, with the degrees of freedom corrected for nonsphericity at each voxel.

We report the results of a random effects analysis, with inferences drawn at the cluster level, corrected for multiple comparisons with family-wise error correction ($p < 0.05$) (Friston et al., 1996). In addition to the procedure described above, in three particular instances we have constrained our inferences on the basis of independent anatomical information by using a volume of interest (VOI) approach. We relied on published stereotactical coordinates of areas that showed learning-related changes during an equivalent task (Toni et al., 2001b) to position VOIs along the PPC (-36, -50, 44), the striatum (-18, 18, 4), and the middle temporal gyrus (60, -6, -18), and we used the full-width-half-maximum of our statistical images to define the radius of the VOIs (12 mm). Finally, on the basis of the results obtained from the main analysis described above (differential modulation of time-related signal changes during performance of overlearning and learning), we performed post hoc comparisons on differential time-related effects between overlearning and continuous and between learning and continuous (correct trials only).

For some areas displaying significant learning-related effects, we plotted the BOLD signal time course during the scanning session for each condition separately. In particular, we calculated the intersubject average and SE of the peak BOLD response for each of eight consecutive blocks of trials equally spaced along the whole scanning session.

Anatomical inference.

Anatomical details of significant signal changes were obtained by superimposing the SPMs on the structural images of each subject in MNI coordinates. The atlas of Duvernoy et al. (1991) was used to identify relevant anatomical landmarks. When applicable, Brodmann areas were assigned on the basis of the SPM anatomy toolbox (Eickhoff et al., 2005); i.e., the anatomical position of our significant clusters and local maxima was formally tested against published three-dimensional probabilistic cytoarchitectonic maps.

Brain-behavior correlations.

We assessed correlations between changes in BOLD signal and degree of automaticity during overlearning trials. Cerebral effects were indexed by the subjects' rate of change

of BOLD signal evoked in the PPC during the overlearning trials. This corresponds to the standardized parameter estimates (SE units) of the linear time-dependent changes in activity during overlearning (correct trials only). Behavioral effects were indexed by subjects' performance during the dual-task test. This corresponds to the difference in error rates evoked during overlearning and learned trials when a word is generated as compared with simply being repeated (training x task interaction) (see Fig. 3). Note that rather than using group-averaged indexes, this analysis exploited the intersubject variability in behavioral and cerebral performance. The purpose of this analysis was to test whether the cerebral increases reported below (see Results) might saturate when performance is highly automatic. A simple linear or quadratic function would not be adequate to capture a possible transient increase in cerebral activity related to a particular stage of automaticity followed by a state during which cerebral activity does not change as automaticity increases. Therefore, we fit the data of the cerebral– behavioral scatterplot (see Fig. 5) to a fourth-order polynomial function.

Results

Behavioral performance

Figure 2 illustrates the mean RT and ER as a function of time during the three experimental conditions. The data indicate that our design was successful in manipulating the degree of learning achieved by the participants during the scanning session. Subjects were faster and made fewer errors in the overlearning than in the learning and continuous conditions [main effect of task (RT: $F_{(2,34)} = 169.8$; $p < 0.01$; ER: $F_{(2,34)} = 121.2$; $p < 0.01$)]. RT and ER decreased over time during both learning and continuous, but not during overlearning [task x time interaction (RT: $F_{(14,238)} = 7.4$; $p < 0.01$; ER: $F_{(14,238)} = 13.6$; $p < 0.01$)]. Post hoc comparisons indicated that during learning the error rate decreased faster over time than during continuous ($p < 0.007$).

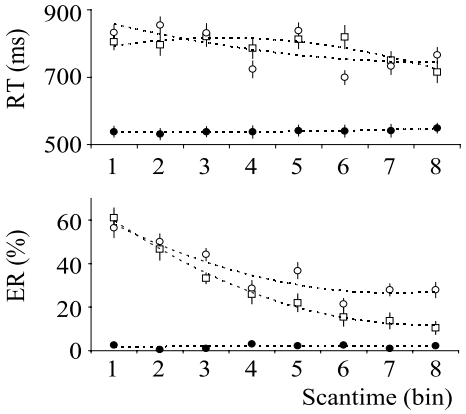


Figure 2. Behavioral performance. Average error rate (ER) and reaction times (RT) over scanning time (binned in blocks of 20 trials, inter-subjects mean ± SEM) for overlearning (black dots), learning (white squares) and continuous (white circles). During overlearning trials, performance was stable and virtually error-free. During learning error rates dropped from chance-level to 10%. During continuous, subjects' learning rate was significantly reduced as compared to learning.

Figure 3 illustrates the mean RT and ER during the dual-task procedure. The data indicate that the extensive training induced a high degree of automaticity in the performance of extensively trained associations (overlearning condition). Subjects were faster and made fewer errors during the overlearning condition than during the learned condition (RT: $F_{(1,17)} = 69.8$; $p < 0.01$; ER: $F_{(1,17)} = 17.7$; $p < 0.01$). Subjects were faster and made fewer errors during word repetition than during word generation (RT: $F_{(1,17)} = 49.9$; $p < 0.01$; ER: $F_{(1,17)} = 44.6$; $p < 0.01$). The increase in RT and ER during word generation in comparison with word repetition was significantly larger during the learned condition than during the overlearning condition [training x task interaction (RT: $F_{(1,17)} = 6.6$; $p < 0.02$; ER: $F_{(1,17)} = 3.8$; $p = 0.068$)].

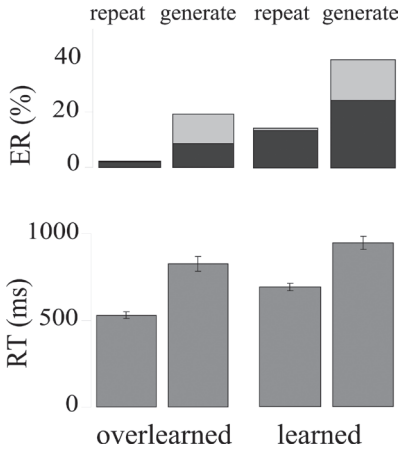


Figure 3. Dual task performance.
Before starting the fMRI measurements, we used a dual-task procedure to assess the degree of automaticity of overlearning performance. This test required concurrent performance of the visuomotor associative task and of a verbal fluency task (see Methods). The figure shows the average error rate (ER, inter-subjects mean ± SEM) (light grey: incorrect responses, black: missed responses) and reaction times (RT, inter-subjects mean ± SEM) of the visuomotor associative task, for both overlearned associations (left) and newly learned associations (right), during concurrent performance of a noun repetition task (Repeat) and a verb generation task (Generate). During overlearning trials, subjects were faster and made fewer errors as compared to the learned condition. Note that on each trial of the dual task procedure there were two concurrent sensory inputs (auditory nouns, visual patterns), and two concurrent motor responses (vocal utterances, finger presses). Furthermore, the subjects received the explicit instruction of putting priority on the verbal fluency task. Accordingly, our goal here was to demonstrate that performance of the overlearned associations suffered less interference from a concurrent task as compared to performance of newly learned associations. This can be contrasted with other uses of dual task techniques, as when one wants to demonstrate that performance of a given primary task is not affected by a secondary task (Poldrack et al., 2005).

Imaging data

We isolated BOLD signals showing differential learning effects during the overlearning and learning conditions by testing, over the whole brain, for time-dependent increases and time-dependent decreases in activity during correct performance of overlearning and learning trials, respectively. By looking specifically at the differences in temporal modulation of the effects evoked in these two tightly matched conditions, we were able to isolate genuine learning-related changes rather than mere timerelated effects such as fatigue, habituation, or sensitization.

A small volume correction analysis on the posterior parietal VOI revealed a cluster along the intraparietal sulcus (-36, -48, 46; $p < 0.049$; cluster-level corrected) that increased its activity during the overlearning condition and modestly decreased its activity during learning, as illustrated in Figure 4A. The intraparietal activity is caudal to the 10% probabilistic boundary of cytoarchitectonically defined Brodmann area (BA) 2 (Eickhoff et al., 2005). There was no change in activity over time during the continuous condition, a further indication that the changes observed during learning and overlearning are related to learning rather than nonspecific effects of time.

We found significant task x time interactions (overlearning vs learning; correct responses only) in two clusters along the left superior frontal gyrus and in the left inferior frontal gyrus (Table 1). The superior frontal cluster consisted of maxima in the dorsal precentral sulcus, in the mesial aspects of the superior frontal gyrus, and in the paracingulate sulcus. The dorsal precentral activity (Fig. 4B) is located within the 60% probabilistic boundary of cytoarchitectonically defined BA 6 (Eickhoff et al., 2005) and rostral to the anterior border of BA 4. The inferior frontal cluster consisted of maxima in the left inferior frontal gyrus, stretching toward the inferior frontal sulcus, the frontal operculum, and the insula. The inferior frontal activity (Fig. 4C) is located within the 20 and 40% probabilistic border of cytoarchitectonically defined BA 45 and BA 44, respectively, and rostral to BA 6 (Eickhoff et al., 2005).

Figure 4B illustrates the portion of the dorsal precentral sulcus (-20, 2, 62) that increased its activity over time during the overlearning condition, and decreased during the learning condition (correct trials only, Z-score = 3.54). Figure 4C shows a similar pattern of activity along the inferior frontal sulcus (-40, 28, 28), although the learning increase levels out in the second half of the scanning session (Z-score = 3.66).

A SVC analysis on the striatal VOI (Fig. 4D) showed activity (bilaterally) around the head of the caudate nucleus ($p < 0.016$, FWE-corrected). This region increased its activity during overlearning and quickly decreased its activity during the first half of the learning condition converging onto the timecourse of overlearning.

We also assessed time-dependent increases and time-dependent decreases in activity during correct performance of learning and overlearning trials, respectively (Table 2). A cluster spanning the right fusiform gyrus and the parahippocampal gyrus increased its activity over time during learning but not during continuous, whereas overlearning activity decreased over time. Activity in the lingual gyrus and in the middle temporal gyrus was somewhat increasing during learning and continuous, with a strong decrease during the overlearning condition.

Table 1.
Differential signal changes over time between overlearning and learning (correct trials only).

Anatomical region	Cluster-size (voxels)	Z-score	Stereotactic-coordinates
Left superior precentral sulcus	556	3.54	-20 2 62
Left superior frontal gyrus		3.78	-4 8 60
Left paracingulate sulcus		3.51	-2 20 44
Left inferior frontal sulcus	816	3.66	-40 28 28
		3.36	-44 6 26
Left intraparietal sulcus*	601	3.07	-36 -48 46
Left caudate nucleus (head)*	(76)	3.80	-10 12 -2

List of significant local maxima ($p < 0.05$, corrected for multiple-comparisons) showing time-related increases during overlearning and decreases during learning.
* Corrected for multiple comparisons within a predefined search volume (see Methods).

Table 2.
Differential signal changes over time between learning and overlearning (correct trials only).

Anatomical region	Cluster-size (voxels)	Z-score	Stereotactic-coordinates
Left inferior occipital gyrus	1071	4.35	-24 -90 -8
Right fusiform gyrus	4075	4.34	28 -70 -14
Right parahippocampal gyrus		4.01	28 -56 -12
Right middle temporal gyrus	280	3.62	56 4 -22

List of significant local maxima ($p < 0.05$, corrected for multiple-comparisons) showing time-related increases during learning and decreases during overlearning.

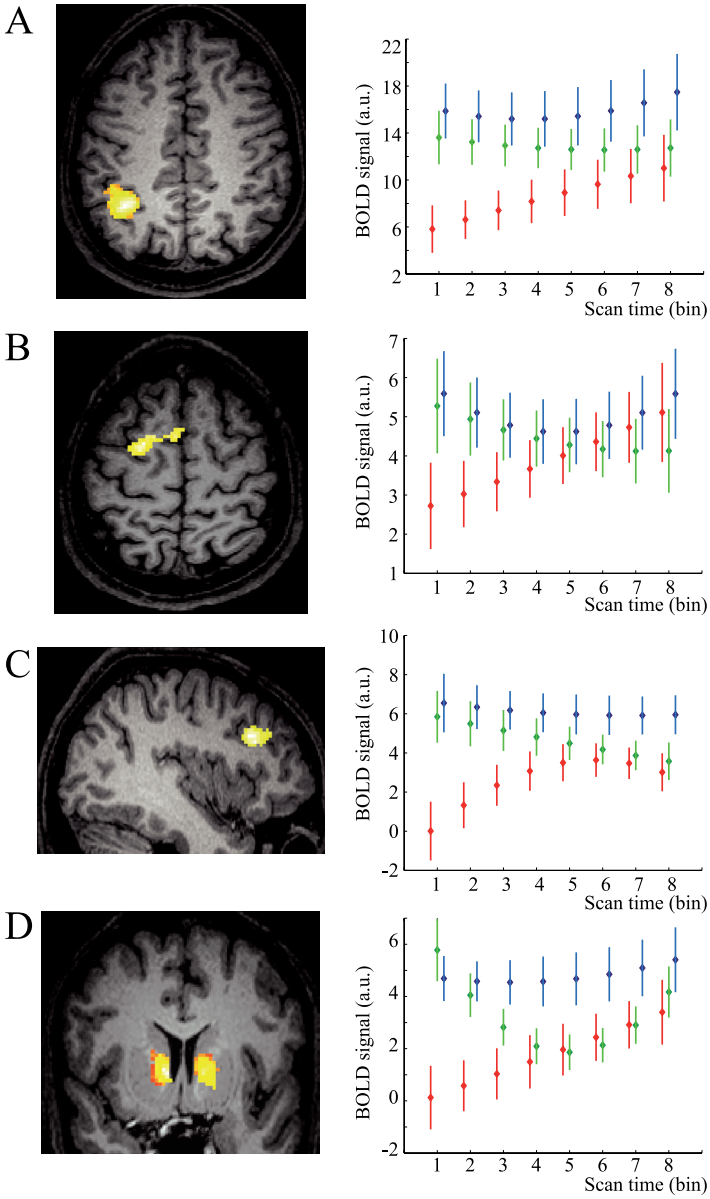


Figure 4. Imaging results.
Differential time-related changes of cerebral activity across conditions, relative to the contrast between time-dependent increases and time-dependent decreases in activity during correct performance of overlearning and learning trials. Right column: peak BOLD signal change over scanning time (binned in blocks of 20 trials, inter-subjects mean±SEM) for overlearning (red), learning (green) and continuous (blue). Left column: SPM{t} of the relevant contrast superimposed on anatomical sections of a representative subject. A) left intraparietal sulcus (-36 -48 46); B) left superior precentral sulcus (-20 2 62); C) left inferior frontal sulcus (-40 28 28); and D) left caudate nucleus (-10 12 -2);

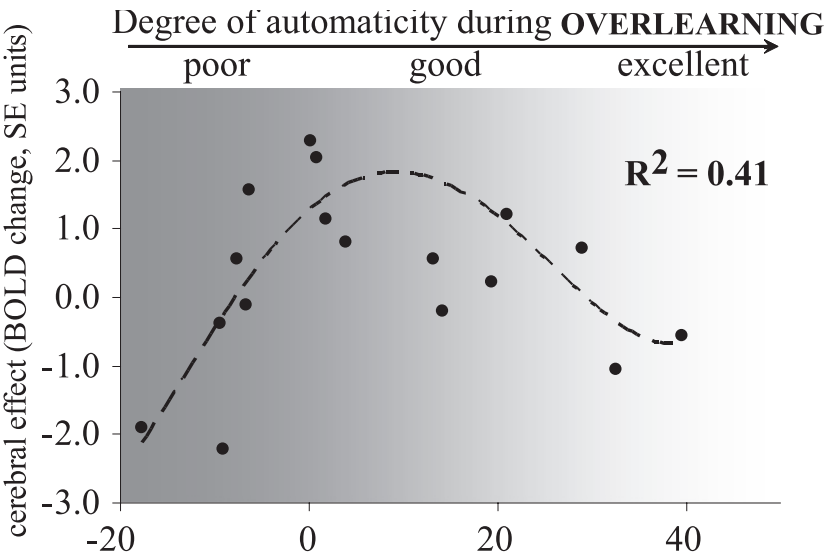


Figure 5. Relation between behavioral and cerebral effects.
Relation between the time-related change in cerebral activity observed during overlearning trials and the degree of automaticity of the visuomotor transformation evoked in that condition. The cerebral effect (y-axis) denotes the variation in signal over time for each subject, as indexed by the standardized (SE units) parameter estimate of the linear change over time in BOLD signal. The behavioral effect (x-axis) denotes the amount of interference generated by the dual task procedure for each subject, as indexed by the difference in error rates evoked during overlearning and learned trials when generating a word as compared to simply repeating it. The figure illustrates a significant non-linear relationship between dual-task performance and parietal increase in BOLD signal (black circles). Parietal activity decreased over time (negative cerebral effect) for those subjects with a poor degree of automaticity during overlearning (negative behavioral effect - this indicates that the verb generation task hampered performance of the learned trials less than performance of the overlearning trials). Conversely, parietal activity increased over time (positive cerebral effect) for those subjects with a good degree of automaticity during overlearning (moderately positive behavioral effects). Crucially, parietal activity remained constant over time (zero cerebral effect) for those subjects with an *excellent* degree of automaticity during overlearning (extremely positive behavioral effects). The dashed line indicates the least square fit of a fourth order polynomial ($R^2 = 0.41$).

Relation between behavioral and cerebral effects

We have used a post hoc correlational analysis to test whether the increase in parietal activity observed during overlearning might eventually saturate. We found that the degree of automaticity achieved in the overlearning condition across subjects explained a considerable portion of the intersubject variance in the rate of change in parietal activity (R^2 = 0.41) (Fig. 5). It can be seen that parietal activity decreased over time (negative cerebral effect) for those subjects with a poor degree of automaticity during overlearning (negative behavioral effect; this indicates that the verb generation task hampered performance of the learned trials less than performance of the overlearning trials). Conversely, parietal activity increased over time (positive cerebral effect) for those subjects with a good degree of automaticity during overlearning (moderately positive behavioral effects). Importantly, parietal activity remained constant over time (zero cerebral effect) for those subjects with an excellent degree of automaticity during overlearning (Fig. 5) (extremely positive behavioral effects).

Finally, this nonlinear relationship between changes in BOLD signal and automaticity of the visuomotor transformation might be regionally specific, insofar as this characteristic was not observed in the other regions showing time-related increases during the overlearning trials. The inferior frontal sulcus and the dorsal precentral sulcus revealed lower R^2 values (0.20 and 0.18, respectively). The R^2 value observed for the striatum was higher (R^2 = 0.31), but it was driven by one outlier, and the brain– behavior relationship was not comparable with the one observed in the PPC.

Overall, these results suggest that the increase in parietal activity reported in this study might be transitory and could reflect a particular stage of the overlearning process, which is critically dependent on the degree of automaticity achieved during the training procedure.

Discussion

We have assessed the neural consequences of overlearning arbitrary visuomotor associations, testing whether and where changes in cerebral activity support the automatization of performance as compared with initial learning of new associations (learning). Rather than comparing the average strength of the neurovascular signal evoked during these two conditions, we have isolated differential time-dependent modulations to define cerebral activity associated with the dynamic process of learning and overlearning arbitrary visuomotor associations.

Frontal, striatal, and intraparietal regions revealed consistent timedependent increases in activity while subjects were performing overlearned associations. Learning or attempting to learn novel associations (Fig. 2) resulted in decreased or stable activity in these same areas, together with increases in ventral occipital and temporal regions. These results suggest that different but not completely segregated circuits support visuomotor mappings at different stages of task proficiency. Importantly, the dynamics of parietal activity indicate that, once the mappings are becoming automatic, this region might join frontostriatal circuits and contribute to the performance of arbitrary visuomotor associations.

Behavioral performance

During scanning, subjects performed arbitrary visuomotor mappings at three different levels of proficiency (Fig. 2). During overlearning trials, performance was stable, virtually error free, and more resistant to interference (Fig. 3). During learning trials, performance improved from chance level to occasional errors. During continuous trials, subjects attempted to learn novel mappings, but the rapid stimulus turnover significantly reduced their average learning rate.

PPC

Previous studies have reported learning-related increases in the PPC during tasks in which the visual cue guides the movement through an appropriate spatial transformation (Grafton et al., 2001; Eliassen et al., 2003); however, here the location of the stimuli was not related to the motor response, and PPC activity showed a learning-related decrease during initial learning (Fig. 4A), confirming previous reports (Deiber et al., 1997; Toni et al., 2001b). Importantly, this same PPC cluster increased its activity during overlearned performance. These changes in activity cannot be attributed to variations in behavior, because performance did not change during overlearning (Fig. 2). Variations in reward rate cannot explain overlearning changes, because we distinguished correct from incorrect trials. The instruction cues were presented briefly and intermixed pseudorandomly; therefore, overlearning changes cannot be caused by time-dependent alterations of saccadic behavior or preparatory activity. Changes in activity during overlearning cannot be a by-product of novelty effects, because during continuous, the subjects were exposed to a larger number of novel patterns than during learning or overlearning, yet the BOLD signal during continuous did not change. Finally, the overlearning-related increase in parietal

activity (as indexed by the rate of change in BOLD signal) is unlikely to be a by-product of changes in task difficulty or stimulus familiarity (as indexed by the decrease in error rate during learning trials), because these two parameters were not correlated across subjects ($R^2 = 0.01$; $p = 0.55$).

It might be argued that the learning-related changes that we observed are an instance of consolidation of procedural memories, known to induce state-dependent increases in neurovascular activity during learning of motor skills (Shadmehr and Holcomb, 1997); however, when considering the average activity measured during overlearning as compared with new learning, the parietal signal decreases. In fact, here we have focused on the changes in trial-by-trial activity between learning stages. By this measure, cerebral activity in the PPC increases during the performance of overlearned visuomotor associations. This result confirms that, in some circumstances, imaging can provide more sensitive measures of cognitive changes than behavior (Wilkinson and Halligan, 2004). Because there were no obvious time-dependent behavioral adjustments during the overlearning trials, however, one might wonder whether the changes in cerebral activity observed during those trials are specifically related to learning. Although learning-related neural adjustments can continue after behavioral signs of learning have disappeared (Chen and Wise, 1996; Wise et al., 1998; Hadj-Bouziane and Boussaoud, 2003), it is implausible that neural activity could steadily increase over a prolonged period of stable behavior. Accordingly, we have tested whether the increase in parietal activity reported in this study is transitory in nature. Figure 5 suggests that the group-related changes in parietal activity during overlearning might depend on the degree of automaticity achieved during the training procedure; i.e., these changes might reflect a particular stage of the overlearning process. Additional experiments are necessary to confirm the learning-related nature of the cerebral changes reported here.

The contrasting patterns of change observed during overlearning and learning might reflect a transition in the sensorimotor mapping encoded in this region. During learning, the PPC might have attempted to find an appropriate spatial transformation for mapping stimuli to responses. Because the location of the visual patterns was not related to the motor response, this procedure was not reinforced, leading to decreased PPC activity over time. During overlearned performance, the stimulus–response statistics would have become stable, allowing slow Hebbian plasticity to emerge (Houk and Wise, 1995). In this scenario, BOLD signal could increase by virtue of the increases in synchronous firing associated with Hebbian learning (Paulsen and Sejnowski, 2000; Singh et al., 2002; Niessing et al., 2005), generating the dynamic changes in PPC activity observed during overlearning. Although speculative, this account suggests that once visuomotor associations become robust to interference, a portion of the PPC might start to convey relevant sensory information toward the motor cortex. It remains to be seen whether this information relates to the identity of the visual cue or to the selection of the motor response, and whether this activity is necessary for overlearned performance of arbitrary visuomotor mappings.

Premotor cortex

There has been a surprising consistency in the failure of previous imaging studies to find significant learning-related changes of neurovascular activity in the dorsal precentral

region (Deiber et al., 1997; Toni and Passingham, 1999; Toni et al., 2001b; Boettiger and D'Esposito, 2005), yet we know that the firing rate of precentral neurons changes during the learning of novel arbitrary visuomotor associations (Mitz et al., 1991; Chen and Wise, 1995; Wallis and Miller, 2003) and that precentral tissue is necessary for relearning previously acquired associations (Passingham, 1985). Our findings suggest that previous negative reports might have resulted from merging different learning epochs into a single experimental unit. Figure 4B illustrates the opposite dynamics generated in dorsal premotor cortex during different learning stages, confirming that this region contributes to both initial learning and retention of arbitrary visuomotor associations (Halsband and Freund, 1990; Kurata and Hoffman, 1994; Petrides, 1997).

Striatum

Electrophysiological studies of striatal and precentral activity during learning of arbitrary visuomotor associations have shown persistent changes in neural activity even during stable behavioral performance (Hadj-Bouziane and Boussaoud, 2003; Brasted and Wise, 2004) but also rapid changes during initial learning of the same associations (Hadj-Bouziane and Boussaoud, 2003; Pasupathy and Miller, 2005). Our results provide independent evidence supporting both early and late changes in striatal responses (Fig. 4D), confirming the role of the striatum during overlearned performance of arbitrary visuomotor associations (Nixon et al., 2004b). Furthermore, our study reveals that, in contrast with the linear pattern of changes observed in other cortical structures, during initial learning the striatum displays a rapid decrease followed by an increase in BOLD signal. It has been suggested that reward-prediction signals processed in the striatum (Seymour et al., 2004; Tobler et al., 2005) might support the generation of rapid stimulus–response associations during the early stages of learning (Pasupathy and Miller, 2005). In this potential scenario, it is conceivable that as learning of novel associations progresses, the temporal difference signal carried by dopamine afferents to the striatum is extinguished (Suri, 2002), and the local synaptic activity indexed by BOLD could decrease (Lauritzen, 2005). This might explain the rapid signal decrease that we observed in the striatum; however, we also know that this region increases its coupling with frontal areas during learning of novel arbitrary mappings (Toni et al., 2002a), and this increased (or more effective) afferent activity might possibly lead, in turn, to the increasing BOLD signal observed once performance becomes less dependent on error feedback (Fig. 4D).

Inferior frontal gyrus

In macaques, disconnection of ventrolateral and orbital prefrontal cortex [i.e., areas 46/9v, 47/12, and 45/44 of Petrides and Pandya (2002)] from inferior temporal regions severely impairs both the acquisition and retention of novel visuomotor associations (Bussey et al., 2002). Figure 4C illustrates a clear and specific time-dependent decrease in BOLD signal during learning, localized within the probabilistic borders of BA 44/45 (Eickhoff et al., 2005), followed by an increase during the first blocks of automatic performance. Our findings confirm and localize the contribution of this region to both the initial learning and the longterm retention of arbitrary visuomotor associations. Given that this region has been linked with a particular class of arbitrary visuomotor transformations, i.e., orthographic-to-

phonologic transformations (Indefrey and Levelt, 2004; Nixon et al., 2004a), the pattern of activity that we observed could reflect the labeling of the visual cues with verbal tags; however, this account does not explain why the increase in signal seen during overlearning trials disappeared during the second half of the scanning session (Fig. 4C). An alternative interpretation is suggested by the contributions of this region to rule-based and prospective behavior (Rainer et al., 1999; White and Wise, 1999; Bunge et al., 2003; Wallis and Miller, 2003); i.e., it is conceivable that this region might abstract cue-finger pairs, not only in terms of stimulus– response mappings but also in terms of response–stimulus mappings. Accordingly, establishing novel stimulus–response mappings would imply the updating of the existing response– stimulus mappings, because novel stimuli map into a constant number of fingers. By this account, improvements in learning performance are meant to induce the updating of response–stimuli pairs during overlearning while they reduce the amount of possible mappings during learning. The concurrent flattening of both learning error rate and overlearning BOLD changes (Fig. 4C) is consistent with this interpretation.

Conclusions

Our results indicate that overlearned performance of arbitrary visuomotor associations involves not only striatofrontal circuits but also parietal regions. We suggest that once visuomotor associations become robust to interference, PPC might start to convey relevant sensory information toward the motor cortex.

Chapter 3

SPATIAL REPRESENTATION OF OVERLEARNED ARBITRARY VISUOMOTOR ASSOCIATIONS

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Manuscript submitted.

Our movements can be guided directly by spatial information, but also more flexibly through arbitrary rules. We have recently shown that as arbitrary visuomotor mappings became overlearned, they come to rely not only on fronto-striatal circuits, but also on the posterior parietal cortex (PPC). This finding suggests that overlearned visuomotor associations could come to rely on a spatial framework, similarly to spatially-guided movements. Alternatively, PPC contribution to overlearned visuomotor associations could be non-spatial in nature. In this study we investigate the characteristics of the movement representations supporting arbitrary visuomotor mappings by assessing how performance of extensively trained arbitrary visuomotor associations depends on the effector used to provide the response.

After extensive training on a set of arbitrary visuomotor associations, subjects were asked to perform the same task in one of two novel settings that varied either the spatial or the motor relationship between visual instructions and finger movements. We found that the change in spatial configuration resulted in a larger amount of interference on the performance of the original mappings than the configuration change in motor coordinates. This result suggests that the visual stimuli became arbitrarily coupled to locations in space and not directly to the finger movements. We infer that overlearned arbitrary visuomotor associations are represented in spatial coordinates, in an effector-independent framework. Accordingly, the previously reported involvement of the posterior parietal cortex in overlearned visuomotor behavior might reflect the transition of an arbitrary visuomotor mapping into a spatially-based stimulus-location-response mapping.

Introduction

We are in constant interaction with our environment. Sensory input often guides our movements by providing spatial information like the location and size of an object we would like to pick up. These are spatially guided visuomotor transformations (Wise et al., 1996, Jeannerod et al, 1995). However, we can also use sensory information in more flexible ways, as when we steer a boat according to the color of a buoy. These are arbitrarily instructed movements (Wise and Murray, 2000).

Several distinctions can be drawn between these two categories of sensorimotor transformations. For instance, arbitrarily instructed and spatially guided movements are supported by largely different parieto-frontal and fronto-striatal circuits (Milner and Goodale, 1995, Toni et al, 2001a) and these two types of sensorimotor processes appear to be driven either by object affordances or by learned stimulus-response-outcome mappings (Grezes et al, 2003, Passingham, 1993). However, it remains unclear whether these are structural distinctions, or different occurrences of the same time-varying phenomenon. For instance, it has been suggested that the motor plan automatically afforded by an object or by a location might require a learning process that abstracts relevant stimuli features (Oztop et al., 2004). This observation emphasizes that even apparently direct spatial correspondences between stimuli and responses might be the result of sensorimotor associations learned by trial and errors and in which the relevant mapping is initially arbitrary. Analogously, arbitrary visuomotor associations can be trained to a degree of automaticity that makes them un-sensitive to reward devaluation and thus akin to habits (Shadmehr and Wise, 2005; Packard and Knowlton, 2002; White and McDonald, 2002; Graybiel, 1995;). These considerations raise the issue of whether these two categories of sensorimotor transformations are computationally distinct, or whether training effects might account for some of the differences mentioned above.

We have recently shown that as arbitrary visuomotor mappings became overlearned, they come to rely not only on fronto-striatal circuits (Nixon et al., 2004) but also on the posterior parietal cortex (PPC) (Grol et al., 2006), an area well known for controlling spatially-guided hand movements (Faillenot et al., 1997; Sakata et al., 1995). This finding suggests that overlearned visuomotor associations could come to rely on a spatial framework, similarly to spatially-guided movements. Alternatively, it is possible that the PPC contribution to overlearned visuomotor associations is non-spatial in nature, as suggested by the finding that after extensive training this region can encode non-spatial features of instructions that are relevant to the task (Sereno and Maunsell, 1998; Toth and Assad, 2002). In this study we contrast these two possibilities.

To address this issue, we exploit experimental procedures developed in the context of motor skill learning (Keele et al., 1995; Hikosaka et al, 1995; Bapi et al, 2000). These procedures have been previously used to test whether the knowledge of learned sequences of movements is bound to the particular effector used for learning (effector-dependent), or whether sensorimotor regularities can be generalized across different movements (effector-independent). Accordingly, here we used these procedures to assess whether the performance of extensively trained arbitrary visuomotor associations depends either on the particular finger used to provide the response, or on the particular spatial location

of the response. Furthermore, to increase the sensitivity of our test, we have used an interference protocol. This allowed us to assess differential interference effects induced by performing visuomotor associations in two novel settings. After extensive training on a set of arbitrary visuomotor associations, subjects were asked to perform the same task in one of two novel settings that varied either the spatial or the motor relationship between visual instructions and finger movements. The rationale of this approach is that if the overlearned arbitrary associations have come to rely on a spatial mapping, then altering the spatial relationship between instructions and finger movements (while keeping the instruction-to-finger mapping constant) would produce stronger interference effects than altering the relationship between instructions and finger movements (while keeping the spatial layout of the instruction-to-movement mapping invariant).

Methods

Participants

We studied 25 right-handed volunteers (9 male, 16 female) with normal or corrected-to-normal vision. The participants' age ranged from 18 to 27 years (mean 22). Subjects gave informed consent according to the guidelines of the institutional ethics committee and were paid for their participation.

Task and experimental setup

Subjects learned, by trial and error, the correct associations between a set of four visual patterns (black and white line drawings) and four different motor responses (finger presses). Following the presentation of a visual pattern on a computer monitor, the subjects had to flex a finger of the right hand to press a button on a four-button keypad (fig. 1). Subjects positioned their index, middle, ring and little fingers on each of four corresponding buttons of the keypad. The hand was positioned either above or below the keypad. We label these two hand configurations as "top" (fig. 1. upper row, PRETEST) and "bottom" (fig.1. Bottom row, PRETEST), respectively. Subjects switched between these two configurations by rotating the subjects' right hand and forearm by 180˚ degrees along its sagittal axis, i.e. with a pronation or a supination movement around the elbow. The forearm was supported by an armrest attached to the chair on which the subject sat. The upper arm was kept in the same position in both hand-forearm configurations. In the top configuration, a cardboard prevented the vision of the hand to the subject. When the subject's hand was in the bottom configuration, the table holding the keypad prevented vision of the hand. In other words, the same amount of visual information was available irrespectively of the hand configuration.

Crucially, we manipulated the spatial relation between the keypad and the fingers. There were two different experimental conditions ("MOTOR" and "SPATIAL"). In one condition, the mapping between the stimuli and the finger movements was the same irrespectively of the hand configuration. For instance, a car would instruct a middle finger flexion in both the PRETEST (fig.1 upper row, left) and the TEST (Fig.1. upper row, left, $TEST_{SPATIAL}$).

This implies that the body-centered spatial position of the button associated with the car would change as a function of the hand configuration. Figure 1 illustrates that, in the top configuration (fig. 1 upper row, left, PRETEST), the second button from the left is associated with the car drawing, whereas in the spatial TEST (fig.1 upper row, left, $TEST_{SPATIAL}$) the third button from the left is associated with the car drawing. In the other condition, the mapping between the stimuli and the buttons was the same irrespectively of the hand configuration. For instance, a car would instruct to press the second button from the left on the keypad irrespectively of the hand configuration ($TEST_{MOTOR}$). This implies that the finger associated with the car would change as a function of the hand configuration. Figure 1 (upper row, right) illustrates that, in the PRETEST the middle finger is associated with the car drawing, whereas in the motor TEST (fig.1 upper row, right, $TEST_{MOTOR}$) the ring finger is associated with the car drawing.

The visual stimuli were four black and white drawings of vehicles. The fingers were randomly assigned to the visual patterns for the different subjects. After the subjects' response, a red, green, or blue square indicated whether the movement was correct, incorrect, or exceeded a reaction-time (RT) cutoff. The patterns were presented for 0.2 s every 2.2 s (range: 1.8 – 2.4 s; uniform distribution), with a RT cutoff of 1.5 s. A fixation cross was presented during the inter-stimulus intervals. Subjects were instructed to respond as fast and accurately as possible. The feedback following an incorrect response was accompanied by an auditory stimulus (duration: 50 ms). Viewing distance was 80 cm resulting in a visual angle of about 6°. Stimulus control and recording of subject responses was performed with Presentation® software (Version 9.70).

Procedure

The experiment consisted of one training session and of one interference session, on two separate days. On day 1 the subjects had to learn and practice the visuomotor associations in 5 blocks of 300 trials. Each block was followed by a break of 2 minutes. Half of the subjects performed the training sessions starting in the top configuration (fig. 1 upper row), the other half in the bottom configuration (fig. 1 lower row). Subjects that failed to perform the final block of the training session with less than 95% correct responses were dismissed.

The interference session took place on day 2, and it was structured in three blocks. First, the subjects performed the visuomotor mappings learned on day 1 (fig. 1, PRETEST, 600 trials) in the same configuration used during the training sessions. Second, the subjects performed the visuomotor mappings learned on day 1 (TEST, 600 trials) in either one of the two experimental conditions (Fig. 1, $TEST_{MOTOR}$, $TEST_{SPATIAL}$). Third, the subjects performed again the visuomotor mappings learned on day 1 (fig. 1, POST-TEST, 200 trials) in the same configuration used during the training sessions.

In summary, the subjects performed 2100 trials in the same configuration, before the interference session. This number of trials was chosen on the basis of an earlier experiment (Grol et al, 2006). More precisely, in that experiment we found that after 2550 trials the subjects had acquired a high degree of automaticity in the performance of the visuomotor associations, as indexed by a dual task procedure. In the current experiment we used considerably simpler visual patterns in order to further facilitate the overtraining of the visuomotor associations.

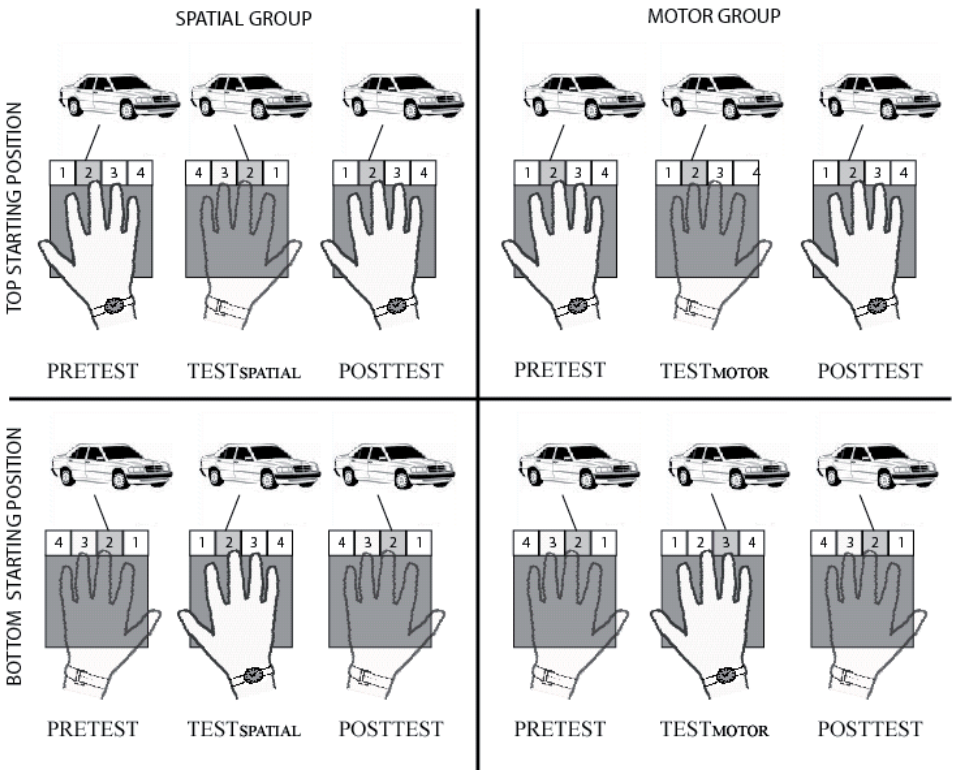

Figure 1:
Following the presentation of a visual pattern on a computer monitor, the subjects had to flex a finger of the right hand to press a button on a four-button keypad. The hand was positioned either above or below the keypad (top and bottom configuration, respectively).
The subjects were divided in four groups. Half of the subjects performed the training sessions (day 1) in the top configuration (upper row), the other half in the bottom configuration (bottom row). First, during PRE-TEST, the subjects performed the visuomotor mappings learned on day 1 in the same configuration used during the training sessions. Second, during TEST, the subjects performed the visuomotor mappings learned on day 1 in either one of the two experimental conditions ($TEST_{SPATIAL,}$ (left), $TEST_{MOTOR}$ (right)). In the SPATIAL condition, the mapping between the stimuli and the finger movements was the same irrespectively of the hand configuration. For instance, a car instructed a flexion of the middle finger towards the second button from the left in the top configuration (upper row, left, PRE-TEST) and a flexion of the same finger towards the third button from the left in the $TEST_{SPATIAL}$. This implies that the body-centered spatial position of the button associated with the car would change as a function of the hand configuration. In the MOTOR condition, the mapping between the stimuli and the buttons was the same irrespectively of the hand configuration. The car here instructs to press the second button from the left on the keypad irrespectively of the hand configuration (upper row, right, $TEST_{MOTOR}$). This implies that the finger associated with the car would change as a function of the hand configuration. In the PRE-TEST, the middle finger is associated with the car drawing, whereas in the $TEST_{MOTOR}$ the ring finger is associated with the car drawing. Third, the subjects performed again the visuomotor mappings learned on day 1 (POST-TEST) in the same configuration used during the training sessions.

Data analysis

Statistical analyses were performed within the framework of the general linear model (GLM, SPSS Version 14.0). Average reaction times (RT, the time from the onset of the visual stimulus until the button press) of correct responses and error rates (ER; the percentage of incorrect responses and responses after the reaction time cut-off) were analyzed together in a repeated measures MANOVA with a within-subject main effect of Block (3 levels: PRE-TEST, TEST, POST-TEST) and the between-subject factors of Condition (SPATIAL, MOTOR) and Configuration (TOP, BOTTOM). Simple main effects between groups were tested with Least Square Difference post-hoc tests (Table 1). Subjects were considered a random factor. Alpha-level was set at $p = 0.05$, multivariate approach, Pillai's Trace corrected. Simple main effects between sessions were tested using post-hoc paired T-tests (Table 1).

Table 1: Posthoc tests
Mean difference and standard error of the mean for RT and ER of separate groups and sessions. Simple main effects between groups were tested with Least Square Difference post-hoc tests. Simple main effects between sessions were tested using post-hoc paired T-tests. Non-significant comparisons are printed in grey.

	RT: Mean difference	RT: standard error of the mean	ER: mean difference	ER: standard error of the mean
LSD pairwise comparisons				
PRE-TEST vs $TEST_{SPATIAL}$	-94	22	-4.9%	1.3%
PRE-TEST vs $TEST_{MOTOR}$	-74	13	-1.7%	0.4%
PRE-TEST vs $POST\text{-}TEST_{SPATIAL}$	-37	16	-3.1%	0.7%
PRE-TEST vs $POST\text{-}TEST_{MOTOR}$	-30	13	-1.5%	0.6%
Posthoc paired t-tests				
$PRE\text{-}TEST_{SPATIAL}$ vs $PRE\text{-}TEST_{MOTOR}$	27	23	0.5%	0.6%
$TEST_{SPATIAL}$ vs $TEST_{MOTOR}$	48	38	3.7%	1.6%
POSTTEST spatial vs POSTTEST motor	34	35	2.0%	1.2%

Results

We analyzed the interference-session performance of 22 subjects that were able to overlearn the visuomotor associations during the training session. Figure 2 illustrates the mean RT and ER as a function of Block and Condition, pooled across Configurations. It can be seen that, although subjects never practised the task in the configuration used during the TEST block, their performance was far above chance level. This finding indicates that, overall, the overlearned visuomotor associations were largely generalized to a novel spatial or motor configuration. Nevertheless, performing the task in a novel configuration had obvious effects on performance. There were significant differences between the PRE-TEST and the subsequent blocks (TEST, POST-TEST; main effect of Block: RT: $F_{(2,36)} = 41.882$; $P < 0.001$; ER: $F_{(2,36)} = 19.275$; $P < 0.001$). Subjects were slower and less accurate during the interference test for both conditions (Table 1: PRE-TEST vs $TEST_{SPATIAL}$ and PRE-TEST vs $TEST_{MOTOR}$;). This finding indicates that the interference test was effective in altering the performance of the visuomotor associative task. This interference was not limited to the trials of the TEST block: although the mappings during the POST-TEST were identical to those of the PRE-TEST, subjects performance was detrimentally influenced by the interference test for both conditions (Table 1: PRE-TEST vs $POST\text{-}TEST_{SPATIAL}$ and PRE-TEST vs $POST\text{-}TEST_{MOTOR}$;). This finding shows that following performance of the same associations in different motor or spatial coordinates, the subjects needed to re-learn the associations in the original coordinates. Taken together, these data indicate that our experimental manipulation was succesful at inducing interference effects.

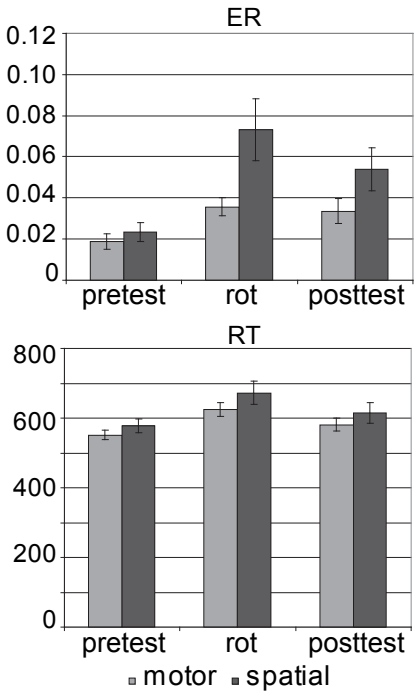

Figure 2
Mean Reaction Time and Error Rate over Sessions for the SPATIAL and the MOTOR group of subjects.

The main point of this study was to test whether overlearned arbitrary visuomotor associations are represented in a spatial (effector-independent) or in a motor (effector-dependent) framework. The former hypothesis would predict a stronger interference effect during the $TEST_{SPATIAL}$ than during the $TEST_{MOTOR}$ condition. This is what we found. Subjects in the SPATIAL condition made significantly more errors during the TEST and POST-TEST blocks, as compared to the PRE-TEST block, than subjects in the MOTOR condition (interaction Block x Condition: ER: $F_{(2,36)} = 4.702$; $P<0.015$). This effect was strongly driven by accuracy differences during the TEST block (Table 1: $TEST_{SPATIAL}$ vs $TEST_{MOTOR}$;), and this was not a speed-accuracy trade-off, since there was no effect on RT (interaction Block x Condition: RT: $F_{(2,36)} = 1.07$; $P< 0.35$). In addition, there was a significant difference in the POSTTEST between subjects in the spatial group and subjects in the motor group in ER (Table 1: POSTTEST spatial vs POSTTEST motor;). Again, no effect was found in RT.

We performed further controls to verify the specificity of these effects. First, we assessed whether the initial hand position (i.e. the factor Configuration) influenced the subsequent interference effects, and there was no significant influence on performance (interaction Block x Condition x Configuration: ER: $F_{(2,36)} = 0.97$; $P<0.39$; RT: $F_{(2,36)} = 1.53$; $P<0.23$). This finding indicates that the interference effects were comparable across the two groups with different initial hand positions. Second, the hand configuration had an influence of the speed of overall task performance (interaction Block x Configuration: RT: $F_{(2,36)} = 8.03$; $P< .001$), a likely reflection of the greater familiarity subjects have with keyboards laying under rather than above their hands. However, this effect did not influence task accuracy (interaction Block x Configuration: ER: $F_{(2,36)} = .23$; $P<.799$). Third, the between-conditions difference observed at TEST was not a by-product of between-groups chance variations in the PRE-TEST data, i.e. there were no significant performance differences at PRE-TEST as a function of the subsequent subdivision of the subjects pool in the SPATIAL and MOTOR sub-groups (Table 1: $PRE\text{-}TEST_{SPATIAL}$ vs $PRE\text{-}TEST_{MOTOR}$;), confirming that both groups did not differ in overall performance before the interference manipulation started.

Discussion

The aim of this experiment was to investigate whether overlearned arbitrary visuomotor associations are represented in a motor or in a spatial framework. After an initial extensive training on performance of these associations, subjects were asked to perform the same task in a novel setting that interfered with either the spatial or the motor coordinates of their performance. Following this manipulation, we also tested whether performing the visuomotor associations in the original training setting was influenced by the type of interference experienced by the subjects. We found that performance was influenced by this experimental manipulation, with stronger interference effects following spatial alterations in the relationship between visual instructions and finger movements that preserved the instruction-to-finger mapping. This result suggests that extensively trained arbitrary visuomotor associations are retrieved using a spatial framework. These data are compatible with the notion that overtrained arbitrary mappings come to rely on a spatial framework linking visual instructions with locations in space (the buttons of the keypad). It can also be inferred that these arbitrary mappings become independent from direct couplings between stimuli and finger movements, i.e. they come to rely on an effector-independent representation.

A vast body of work has addressed the issue of effector-independent representations in the context of learning and automatization of motor skills (Wright, 1990; Morton et al., 2001;). For instance, finger tapping and motor sequence learning are thought to be largely independent from the effector used to produce the motor responses (Laszlo et al., 1970; Japikse et al., 2003; Taylor and Heilman, 1980). Several studies have shown positive interlimb skill transfer, for example in writing from dominant to non-dominant hand (Wright, 1990), ball catching (Morton et al., 2001), finger tapping (Laszlo et al., 1970), and sequential finger movements (Japikse et al., 2003, Taylor and Heilman, 1980). However, other authors have argued that overlearning might generate effector-dependent representations (Jordan, 1995) . For instance, Thut (1996) found that having learned to draw with the left hand negatively interfered with contralateral performance. It has also been suggested that both effector-depedent and effector-independent representations play a role in learning motor skills, with a relative contribution that varies as a function of the learning stage (Nakahara et al., 2000, Bapi et al., 2000, Hikosaka et al., 1999): Early in learning, changes in performance mostly consist of fast improvements in accuracy, and these changes could rely on effector-independent representations; Late in learning, changes in performance mostly consist of slow improvements in speed, and these changes could rely on effector-dependent representations. This explanatory framework is supported by a functional separation in the neural correlates of these two processes (Sakai et al., 1998. Accordingly, it could be argued that our observation window was biased towards fast (effector-independent) changes, rather than towards slow (effector-dependent) changes. However, it should be emphasized that the effects we report are not about learning a novel motor task, but rather about the relative degree of interference evoked by two different manipulations upon extensively trained visuomotor associations.

Furthermore, it should be emphasized that motor skills and arbitrary mappings differ in a number of important aspects, and that explanatory frameworks for the former might not hold for the latter. For instance, motor skills have been studied by means of sequence learning experiments, with performance parametrized through error rates and reaction times describing the sum of uncorrect sequences and the total amount of time before a complete sequence was correctly performed. These performance measures are different from those used in our experiment. In addition, motor sequences are inherently spatial, whereas in our experiment the relation between the stimuli and movements is entirely arbitrary. Motor sequences, after sufficient learning, can be performed irrespectively of visual instructions, whereas in arbitrary visuomotor mapping each instruction remains necessary for selecting the correct response. Accordingly, the present findings support the observation that overlearned visuomotor associations might rely not only on the fronto-striatal circuit known to be involved in arbitrary visuomotor learning (Toni and Passingham, 1999; Wise and Murray, 2000; Nixon et al., 2004;), but also on portions of the posterior parietal cortex (Grol et al, 2006) known to be involved in spatially guided behavior (Sakata et al., 1995). We suggest that once the coupling between a stimulus and the spatial location of the associated motor response has become automatic, the movement of the finger towards this location might start to resemble a spatially-guided movement. We know intraparietal cells can be trained to encode the motor relevance of visual stimuli specifying arbitrary movements and can transform spatial information directly between different reference frames (Andersen and Buneo, 2002). We could therefore speculate that the cortico-cortical connections between parietal areas and premotor cortex subserve the spatial-to-motor mapping from keypad location to finger movement by translating head-centered information into a hand-centered reference frame.

Conclusions

This experiment provides empirical evidence suggesting that overlearned arbitrary visuomotor associations are represented in an effector-independent framework in spatial coordinates. Following extensive training, it appears that visual stimuli became arbitrarily coupled to locations in space and not directly to the finger movements. We speculate that during learning the increased coupling of the stimulus to its location in space might change the arbitrary mapping into a more spatially-guided movement, calling for involvement of the posterior parietal cortex in overlearned visuomotor behavior.

Chapter 4

ECOLOGICALLY VALID VISUALLY-GUIDED GRASPING IN THE MR-ENVIRONMENT

PRACTICAL SOLUTIONS AND APPLICATIONS

Based on:
Verhagen, L., Grol, M.J., Dijkerman, H.C., Toni, I. Studying visually-guided reach to grasp movements in an MR-environment. *Manuscript submitted.*

Majdandžić, J., Grol, M.J., van Schie, H.T., Verhagen, L., Toni, I., Bekkering, H. (2007) The role of immediate and final goals in action planning: An fMRI study. Neuroimage, 37:589-98

Verhagen, L., Dijkerman, H.C., Grol, M.J., Toni, I. Perceptuo-motor interactions during prehension movements. *Manuscript in preparation.*

Introduction

The MR scanner is not an ideal environment to study the performance of natural reaching and grasping movements. The limited space available in the bore of a whole body magnet and the supine position of the subject do not easily allow subjects to make natural arm and hand movements towards targets in their direct line of sight. Furthermore, investigating prehension is complicated by the fact that arm motion in itself can cause serious artifacts. Any motion or disturbance of the magnetic field has a detrimental effect on the MR measurement. Not only can movements of the arm translate into head movements, the movement of a conductive body, like the human arm and hand, in the static magnetic field can lead to disturbances of the MR image that have a global effect on the signal measured (Diedrichsen et al. 2005; Raj et al. 2001).

These reasons have prevented researchers from investigating visually-guided movement with fMRI to the same extent as other topics in the field of motor control. This is a pity, as this field could greatly benefit from using fMRI to supplement the large body of kinematic studies available. In this chapter several solutions are presented to solve the problems associated with studying visually-guided grasping movements in an MR environment. The proposed protocol combines mechanical devices, experimental design, a diagnostic tool for artefacts related to head motion, and a novel way to account for changes in global signal in the analysis of fMRI timeseries. It allows subjects to reach and grasp with free gaze while using only the standard MR equipment.

This protocol was developed and tested in the context of a small fMRI experiment (Verhagen et al, submitted) that was a precursor to another study investigating dorsal and ventral stream contributions to visuomotor transformations (Verhagen et al, in preparation). It was further applied to another grasping experiment investigating the role of immediate and final goals in action planning (Majdandžić et al, 2007). A subset of the data of this latter experiment were used in a novel analysis exploring the parietofrontal connectivity during visually-guided grasping that is described in chapter 5. The current chapter is therefore mainly meant as a prelude to the material discussed in chapter 5. In the following methods and results sections we will elaborate on the methodological solutions to the problems that come up when investigating reach-to-grasp movements in the fMRI scanner. We will focus on the methodology as tested in the context of the first exploratory study of Verhagen et al. (in preparation), from now on called Experiment 1A. To illustrate what kind of experiments might benefit from the solutions proposed here, we will shortly describe the main questions and results of Verhagen et al (in preparation), called experiment 1B, and of the study of Majdandžić et al. (2007), called Experiment 2. It is outside the scope of this chapter to describe both these studies in detail. For a detailed discussion I refer to the original papers.

Experiment 1B investigates how the integration of perceptual and motoric abilities during visuomotor transformations is implemented in the brain. Visual processing is organized along two functionally and anatomically segregated circuits (Milner and Goodale, 1995; Jeannerod and Rossetti, 1993; Felleman and Van Essen, 1991), the ventral and dorsal visual stream, that are respectively thought to be involved in object recognition and action guidance. The question can be asked how these pathways functionally integrate, for

example when you have to adjust the strength of your grip according to colour information telling you about the ripeness of the fruit you are grasping. To manipulate the differential involvement of ventral and dorsal stream in visually-guided grasping, the dependency of the dorsal stream on binocular input (Sakata et al., 1995; Taira et al., 2000) is employed. In visual agnosic patients, visuomotor performance is severely disturbed during monocular view of a target object (Dijkerman et al., 1996; Marotta et al., 1997). This suggests that when binocular vision is not available, dorsal stream processing is insufficient for adequate visuomotor performance, and that pictorial cues of depth become crucial for the guidance of the prehension movement. These monocular depth cues, such as texture, illumination gradients, and perspective are processed along the ventral visual stream (Huxlin et al., 2000; Kovacs et al., 2003; Mon-Williams et al, 2001). Viewing conditions (monocular vs binocular) were altered during reach-to-grasp movements towards a prism oriented in different angles in the depth plane. The rationale behind this approach is that the ventral stream has to increase its relative functional integration with the dorsal stream when pictorial cues become more important, i.e. under monocular vision. The analysis was focussed on the one hand on the anterior intraparietal area (AIP) and the rostroventral premotor region (area F5), crucially involved in goal-directed action (Sakata et al, 1995, Fogassi et al., 2001; Davare et al., 2006), and the lateral occipital complex (LOC) involved in object recognition (Amedi et al., 2002; Moore and Engel, 2001), at the other side.

Experiment 2 explored the cerebral activity related to different levels of planning a visually-guided action. The actions we perform in daily life are usually driven by a desired outcome or action goal, rather than being stereotyped responses to different actions. The definition of the intended end-state of an action (the goal) allows us both to have top-down control over the execution of the movement and select the movement details to achieve that goal beforehand. Accordingly, a single goal can be the result of a combination of different action means. Action goals and individual movements are considered to be planned at different levels within a hierarchical system. The highest levels of the hierarchy are concerned with generating commands to achieve an action goal, while lower-level mechanisms translate the commands into a movement. Most studies have focused on single goals like reaching-to-grasp a certain target. However, in daily life grasping is a component of a broader action in which the grasped object is used to achieve a subsequent goal.

It remains unclear how portions of the fronto-parietal network underlying spatially guided action planning (Rushworth et al., 2003; Kalaska et al., 1997; Passingham, 1993; Kakei et al., 2001; Passingham et al., 1998) contribute to action planning from increasingly remote outcome levels. To manipulate these levels, the task in experiment 2 was designed in a way that allowed subjects to perform object manipulations that were either cued by the end-state to be accomplished (the *final goal*), or by the initial grip on the object (the *immediate goal*). fMRI during visually-guided grasping was used to explore how areas within the fronto-parietal network are involved in planning these tasks. The design allowed to compare cerebral activity evoked by actions that involved similar movements, but were planned differently.

For both studies it was of utmost importance to allow the subjects to reach and grasp in a natural way. Therefore these studies are used as an illustration of the protocol proposed for studying reach-to-grasp movements in the MR environment. In the next part of this chapter the different steps of the protocol will be mainly discussed in the context of the experimental setup of experiment 1A. The methodology used in Experiment 2 will

be explained only when it is different from the method section of chapter 5. The protocol consists of solutions regarding the experimental set-up and solutions that aid in the analysis of visually-guided grasping data. We will respectively discuss: the configuration of the subject in the scanner in a way that allows the subject to reach to the target with direct and free gaze, the experimental setup specifying the design of mechanic manipulanda that can be used in the scanner and that allow for recording the timing of different phases in the movement. This will be followed by methods aiding the statistical analysis of the images: a diagnostic tool to identify head-motion related artifacts and a novel method to correct for global signal changes due to the direct effects of arm-hand movements on the static magnetic field.

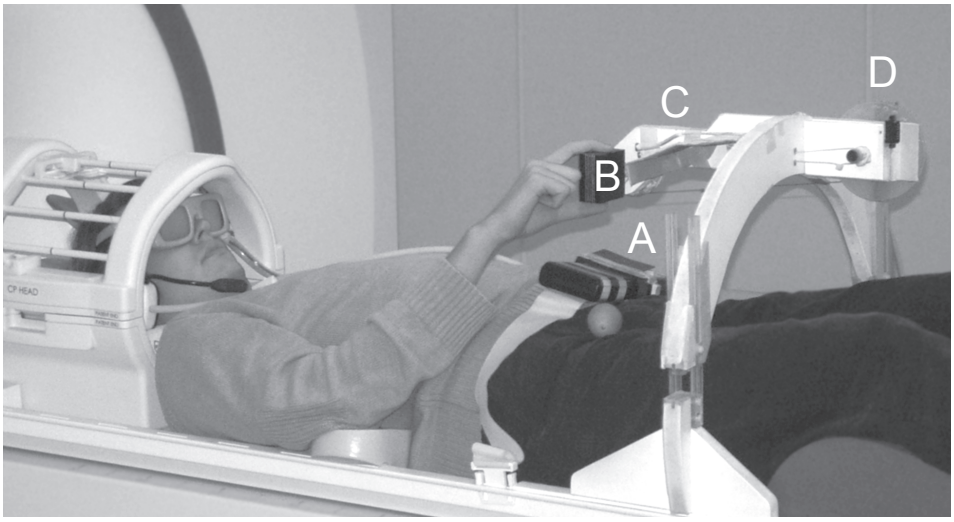

Fig. 1. Subject configuration and experimental setup.
The subject's head was tilted forward by about 30 degrees along the subject's sagittal plane such that the target object was in direct line of sight. The subject could comfortably move from the home-key placed on the left side of the abdomen (A) to the object (B) by rotating his forearm around the elbow and their hand around the wrist. After a cue the subject used a precision grip (finger and thumb) to grasp the object. The experimenter could vary the orientation of the object (from 0 to 90 degrees from the vertical plane, in 7 steps of 15 degrees) by turning a wheel (D). During scanning the target object was located inside the MR-bore, and the turning wheel was outside the bore. A white curtain (not shown) provided a stable and homogeneous visual background for the subject and blocked sight of the experimenter. Vision was controlled by MR-compatible LCD shutter goggles (E). During the rest phase two LED (C) placed behind and besides the object provided an anchor for subject's eye movements when the object was not visible.

Experimental set-up and design

Subject configuration

In both experiments subjects lay supine on the MR scanner bed. The standard mattress of the scanner bed was removed, allowing the subjects to lay considerably lower within the bore of the scanner. Two possible configurations allowed the subject to have direct gaze at the object. In experiment 1A their head was fitted inside a standard circular polarized transmitter-receiver head coil, and tilted forward inside the head coil by about 30 degrees along the subject's sagittal plane (fig. 1). In experiment 1B and 2 the subject's head was fitted inside a phased-array receiver head coil. In this experiment not the head, but the head-coil itself was tilted forward by 30° along the subject's sagittal plane (see chapter 5, Fig. 1A). The rest of the subject configuration details of experiment 2 can be found in the methods section of chapter 5.

In experiment 1A a standard CP head coil was specifically used instead of a phased-array coil, even though this type of head coil gives more freedom in positioning and tilting the head, in order to show that the proposed protocol makes it feasible to study visually-guided reach to grasp movements using only standard MR equipment and accessories. The subject's head was kept in place by using a MR-compatible vacuum bag and foam wedges. The vacuum bag followed the anatomy of the subjects' neck and head, while providing support and comfort. Tight mechanical constraints were avoided, as these proved to generate painful pressures over time. As a consequence, tightly constrained subjects tended to produce large, stochastic head movements when trying to find a less painful position. The subject's right arm was raised using foam wedges, such that the forearm could lie horizontally on the subject's abdomen and press a large home-key (MRI Devices, Waukesha, WI, U.S.A.) – see Figure 1A.

Experimental setup- mechanical devices

Both experiments made use of a mechanical, scannerproof arc-shaped device that could be placed above the subject's hips inside the MR scanner and could hold different kinds of target objects for the subject to grasp. These devices allowed the subject to have a direct line of sight of the object to be grasped, and to comfortably move their hand towards the object by rotating their forearm around the elbow and their hand around the wrist.

In experiment 1 subjects were asked to grasp a black plastic rectangular prism (6 x 4 x 2 cm) mounted on a white wooden frame (Fig. 1B). The configuration of this device could be adjusted along several dimensions. First, the device could be positioned above the subject's abdomen, resting on the scanner bed. Second, its height could be adjusted to allow the subject to comfortably grasp the object. The object could be oriented at different angles by rotating along a transverse axis. In this setup, the object was manually rotated by means of a pulley system controlled by an experimenter standing in the scanner room, out of sight from the subject. Subjects wore MR-compatible liquid crystal shutter goggles (Translucent Technologies, Toronto, Ontario, Canada) to control the type and timing of visual information available (monocular or binocular) (Fig. 1E). The goggles were attached

to the head-coil and their position could be adjusted according to the subject's anatomy to ensure a consistent visual field of view. The main restricting factor for positioning the goggles was to keep the object at least 5 degrees of angle above the lower border of the field of view. Depending on the position of the goggles, the binocular field of view varied between 30 and 60 degrees for different subjects, but this was more than sufficient to enable every subject to see the whole object comfortably with binocular vision. The status of the liquid crystal shutters was individually controlled for the left and right eye by a PC running Presentation software version 0.7 (http://nbs.neuro-bs.com). A high performance custom-made filter prevented current leakages and electrical noise from reaching the scanner room and the head coil.

In both experiments subjects were allowed to move their eyes. In other experimental settings (Culham et al. 2003; James et al. 2003), subjects were required to maintain fixation during the performance of a series of task. This is a dual task procedure that can introduce unknown differential interactions between the fixation task and any of the main tasks. Although in experiment 1 goggles were used to manipulate the amount of visual information, a relatively stable eye position was achieved during the whole scanning session by exploiting two phenomena. First, when vision of the target object was allowed (liquid crystal goggles transparent), subjects fixated the target object, as it occurs naturally in preparation of a grasping movement. Second, when vision of the target object was blocked (liquid crystal goggles opaque), a pair of LEDs were switched on (Fig. 1C). These LEDs generated two bright spots on the opaque glasses of the goggles immediately to the left and to the right of the object's position. These spots provided an anchor for subject's eye movements when the object was not visible. More importantly, the spots ensured that the subject's gaze remained along the same axis during the whole experimental session. This in turn minimized the size and number of saccades generated during those periods in which the object was not visible, reducing the co-contractions of neck muscles (and thus head movements) associated with the saccades (Corneil et al. 2004).

In experiment 2 the subjects were instructed to grasp and manipulate an object consisting of a large red cube and a small green cube, attached to a supporting rail positioned in front of them. The object was positioned next to a rectangular box containing two cubic slots of different size and color. The subject could comfortably perform visually guided reaching–grasping movements towards the object, extract the object from the supporting rail, insert the object into one of the slots, and finally re-position the object in the supporting rail. Crucially, the object and the slots were designed such that the object could be placed in the large slot only when it was grasped at the small cube. Analogously, the object could be placed in the small slot only when it was grasped at the large cube (Chapter 5, Fig. 1B and C). The side of the box that was not visible for the subject contained two cubic slots as well, but the combination of size and color was reversed: while on one side of the box, the yellow slot (located above the blue slot) was large, the yellow slot on the other side of the box was small, still located above the blue slot. Which two slots were visible for the subject could be varied by rotating the box by means of a pneumatic mechanism. An LED was installed in the middle of each of the two sides of the box (Chapter 5, Fig. 1B (3)). The LED could light up in red, green, blue, and yellow. The color of the LED instructed the subject on the movement required to solve the task (see below). MR-compatible switches located at various positions on the device recorded the time at which the object was removed from the supporting rail, the time at which the object was inserted into one of the slots, and the

time at which the object was put back into the supporting rail. The fact that the subjects had to click the object back into the rail ensured that the starting position of the larger cube did not vary over trials. More details on the experimental setup of experiment 2 can be found in the methods section of chapter 5. Important to note is that the sensors and switches built into both mechanical devices allow for identification of the timing of different phases of the movement. For optimization of the experimental design these phases are taken into account beforehand, as is described in the following paragraph.

Experimental design

The experimental design was constrained by the need to minimize correlations between regressors describing possible sources of artifacts and regressors describing cerebral correlates of the visually-guided grasping movements. Before the actual scanning, a series of experimental designs was simulated in order to optimize the order and timing of stimulus presentation, object orientations, and inter-trial intervals. The results of these simulations informed the choice of instructed delays between execution of the grasping movement and return to the home-key, as well as the choice of the shortest inter-trial intervals adequate to distinguish successive trials in time.

Figure 2 provides a schematic view of the time course of a trial in experiment 1A. A trial started with the liquid crystal shutter goggles closed and the subject's right hand laying in the resting position on the home-key. At the beginning of a trial, the LEDs were turned on, generating two visible spots on the opaque goggles. After a further interval (1000 - 4000 ms, uniform distribution, steps of 1 ms), the shutter goggles opened, allowing vision of the target object, such that the subject could view the target and prepare an appropriate grasping movement. After one second from the time the goggles opened, an auditory cue (1000 Hz, 100 ms) instructed the subject to execute the grasping movement. When the subject left the home-key, the goggles closed. Contact between the subject's fingers and the target object was recorded by a change in capacitance of a wire surrounding the target object. Following a further variable delay (4000 – 6000 ms, uniform distribution, steps of 1 ms), a second auditory cue (500 Hz, 100 ms) instructed the subject to return to the home-key. When the subject pressed the home-key, the experimenter in the scanner room rotated the target object in a pseudo-randomized sequence, according to auditory instructions (object orientations: from 0 to 90 degrees from the vertical plane, in 7 steps of 15 degrees).

During the task of experiment 2, in each trial subjects had to grasp the object in a certain way, either at the large or the small part, remove the object from the rail to put it into one of the two slots, and re-position the object in the supporting rail. The timecourse of trial of experiment 2 is shown in figure 1D of chapter 5. These object manipulations could be cued by providing either the required end position of the object (the slot) or the part of the object that had to be grasped. A Final Goal cue typically referred to one of the two slots; it instructed the subject to put the object into either the blue or the yellow slot. Accordingly, subjects had to grasp the object in a way that allowed them to achieve this outcome. An Immediate Goal cue referred to the part of the object that had to be grasped; this could be either the red (large) part or the green (small) part. Subjects then had to transport the object to the slot that could be filled up using this grip. In this way, each action could be cued by either its Immediate or its Final Goal, allowing us to compare otherwise similar movements that differed in only this respect. The cues were signaled using a four-

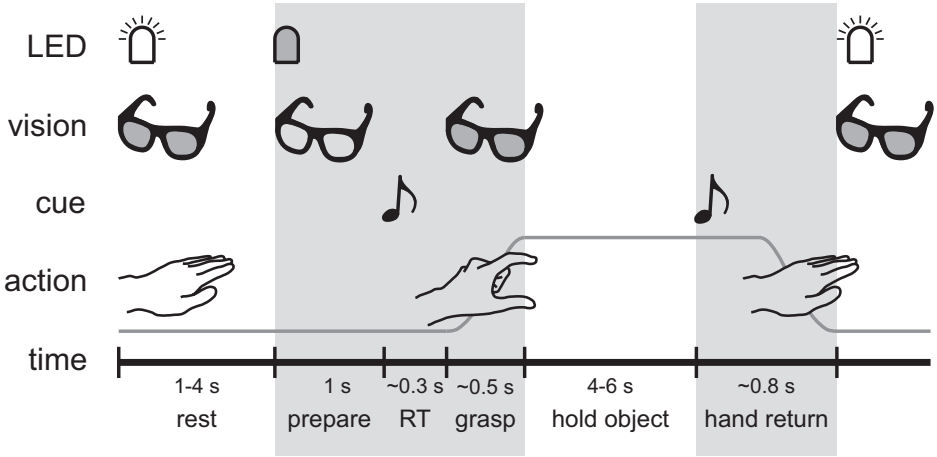

Fig. 2. Trial time course in experiment 1A.
Each trial started with a rest period of variable duration (1-4 sec). During this period the subject's hand was resting on the home-key on the subject's abdomen and the experimenter could rotate the object in the instructed orientation for the upcoming trial. Vision was blocked by opaque liquid crystal goggles, but two LEDs provided an anchor for eye movements. A tone indicated the subject to grasp the object. During the reaction phase the goggles kept allowing the same visual input as during the preparation phase. Only when the subject's hand left the home-key the shutters closed. A change in capacitance in a wire surrounding the target object indicated the moment of first contact between the subject's fingers and the target object. Following a further variable delay (4-6 sec), a second auditory cue (500 Hz) instructed the subject to return to the home-key. In our event-related analysis of the fMRI time series we used the preparation, response and movement phases of the trial (indicated by the first grey block) for the main effect of grasp, and the portion of the trials during which the subject received the second auditory cue and the hand moved from the object to the home-key for main effect of hand return (as indicated by the second grey block).

colored LED. When the LED turned blue or yellow, it referred to the Final Goal, and the object had to be inserted into the blue or yellow slot, respectively. Conversely, a red or green LED referred to the Immediate Goal, and the object had to be grasped at the red (large) or green (small) part. Crucially, the device was rotated from time to time to ensure that color and location of the Final Goal slot were unrelated to the part of the object to be grasped, as signaled by the Immediate Goal cue. This prevented subjects from using any association between Immediate and Final Goal cues as a strategy. Due to the alternating rotation, the small cube was on top of the large cube (orientation 1) in 50% of the trials, and below the large cube (orientation 2) in the other 50% of the trials, which was balanced over the main conditions (Final Goal, Immediate Goal). When the LED switched on, subjects had to leave the home key as soon as possible, make the appropriate object manipulation, and return to the home key.

In fMRI of human subjects, motion can never be completely eliminated and it is usually accounted for by modelling its effects on the images (Andersson et al. 2001; Grootoonk et al. 2000; Lund et al. 2005). Here this general approach is followed. Two sources of motion-related artifact were considered. One source is the effect of changes of head-position in the field of view of the MR scan. A second source, more specific to grasping experiments, is related to the effects of moving a conductive body (i.e. the subject's arm-hand) in the scanner bore during image acquisition.

Motion correction by spatial realignment

Image acquisition and image analysis details of the experiments can be found in Appendix A. To correct for head movement, the image time series were spatially realigned using a sinc interpolation algorithm that estimates rigid body transformations (translations, rotations) by minimizing head-movements between each image and the reference image (Friston et al. 1995a). Since the movement of a conductive body through the magnetic field can cause artifacts in the image, it is conceivable that the spatial realignment procedure might generate a timeseries of estimated head movements that consists of real head movements and artifacts related to the motion of the conductive body. To investigate the extent of this effect, we scanned a structured phantom while an experimenter stood besides the scanner-bed and moved his arm in a similar fashion as subjects did during the real experiment. Applying the spatial realignment procedure generated a timeseries of estimated movements of the phantom that was correlated with the motion of the conductive body. However, the size of this effect was small. First, the variance of this effect did not exceed the variance of the estimated motion of the phantom when no conductive body was moving through the magnetic field. Second, the maximum translation (0,06 mm) and rotation (0,0004 rad) of this effect constitute a small fraction of the movements occurring during scanning of a human subject. On the basis of these considerations, we decided to use the spatial realignment procedure to estimate head movements during scanning, and we considered the timeseries of these estimated head movements as nuisance variables. Furthermore, we considered both original and squared values of the time series of head movements and of the first order derivatives of the head movements (Lund et al. 2005). Data was high-pass filtered (cut-off 128 s) to remove low frequency confounds, such as scanner drifts.

Task- related head motion – a diagnostic tool

It is known that task-related head motion can be a particularly detrimental confound. To assess the extent of this confound for each subject, we developed a simple diagnostic tool. This tool compared the frequency power spectra of the head motion time series (as estimated by the realignment procedure of SPM) and of the experimental design (i.e. the time series of task events) (Fig. 3). Not only the frequency composition but also the phase of the time series is important for dissociating true BOLD activation from head motion (Birn et al. 1999). The phase of the head motion can be compared to the phase of the task events in a similar fashion as the frequency composition. It should be emphasized that this tool does not provide objective criteria to exclude subjects from statistical analysis.

However, this tool provides relevant information on the relationship between the timing of task events and head motion. This information can be useful for refining the experimental design and for the diagnosis of image artifacts related to head-motion.

The second source of motion-related artifacts, i.e. the direct effects of arm-hand movements on the static magnetic field, was indexed in the model by means of global signal changes (see below).

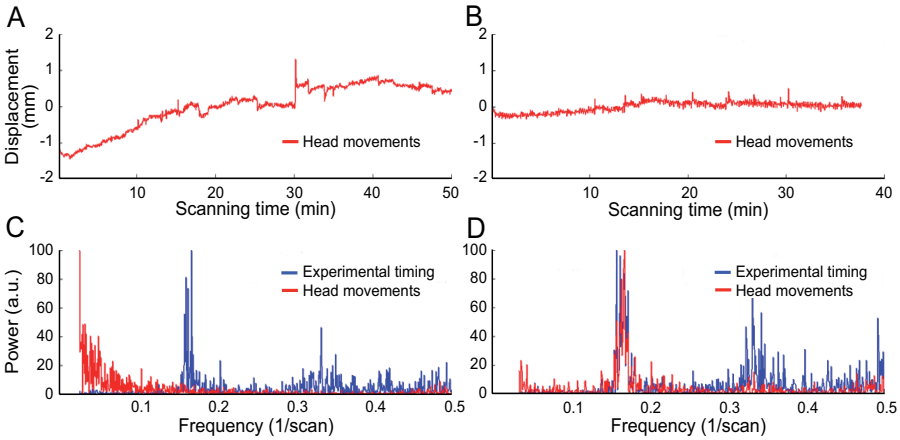

Figure 3.
Relationship between head movements and grasping movements during MR-scanning.
Top row: head movements from two different subjects. It can be seen that the subject on the left (A) moved more than the subject on the right (B). Bottom row: Frequency distribution of head movements and timing of grasping events. In (C), it can be seen that the movements of subject (A) occurred mainly with a low frequency, remaining uncorrelated with the dominant experimental frequency. This pattern allows for an effective removal of BOLD signal linearly and non-linearly related to head-movement during the statistical analysis. Conversely, the minute movements of subject (B) (<1 mm) were time-locked to his grasping movements (D). This pattern does not allow to disambiguate head-motion and grasping-related BOLD activity.

Correcting for global signal changes

In our analysis we also aimed at considering the direct effects of arm movements on the static magnetic field in our model. A disturbance of the magnetic field generated by the reaching-grasping movement has a global effect on the signal measured throughout the field of view. Crucially, this global effect is correlated with the experimental paradigm, and adds to the local BOLD changes. A meaningful imaging experiment of reaching-grasping movements ought to be able to dissociate global disturbances and local BOLD correlates of the movements. To achieve this, it is necessary to characterize the global disturbances by means of indexes that are not informed by the experimental paradigm, otherwise the inclusion of global signal covariates in the analysis alters the interpretation of local BOLD responses (Aguirre et al. 1998). Here, the MR signal sampled from white matter and cerebral-spinal fluid were considered as such indexes. These signals were obtained as follows. First, the mean of the spatially realigned fMRI time series was segmented into four images: grey matter (GM), white matter (WM), cerebral spinal fluid (CSF), and a residual

compartment (RC). Voxels with a compartment probability of less than 25% (as provided by the SPM compartement probability masks after segmentation) were excluded to prevent accidental misclassifications or overlap of signal from one compartment to the other. For the residual compartment a fixed set of voxels (outside the brain and skull) was chosen, in order to avoid sampling from regions with ghosting effects. Second, these four images were applied as spatial masks onto the spatially realigned fMRI time series to extract four separate time series, one for each image compartment, describing the global changes occurring in each compartment during the scanning session. Third, the WM and CSF time series were included in the multiple regression analysis as an additional covariate. Finally, we considered a Volterra expansion of these covariates (Lund et al. 2005). Addition of the RC time series did not explain further sources of variance over and above the WM and CSF covariate. Therefore, this component was not considered further.

Statistical inference

The statistical significance of the estimated evoked haemodynamic responses was assessed using t-statistics in the context of a multiple regression analysis. In this chapter, we describe only the fixed-effects group analysis of experiment 1. The statistical analysis of the fMRI data adopted a mass univariate approach, and the inferences pertain to the voxel level, with an arbitrarily chosen error rate of 5% (p-threshold < 0.05; Z-threshold < 4.8). The Family Wise Error approach was used to correct for performing multiple tests over the whole brain (Friston et al., 1996).

Results

Behavioral performance – validity of experimental setup and design

In experiment 1, we could verify during scanning that participants performed the grasping task on each and every trial, measuring several indexes of the reach to grasp movements (i.e. release of the home-key, time of first contact with the object, and time of home-key press). This can be contrasted with previous studies that relied on subjects' verbal reports to verify task performance (Simon et al. 2002). In the current setting, the behavioral measurements performed during scanning allowed us to account for trial-by-trial variations in task performance that would have otherwise inflated the residual error variance.

More generally, we validated the reliability of our setting by comparing subjects' performance with previous psychophysical data. To this purpose, we performed additional kinematic measurements on three subjects. The experimental settings were identical to those used in the fMRI experiment, but the measurements were performed outside the scanner in order to be able to sample the position and orientation of the index finger and thumb during task performance [Minibird tracking system (Ascension Technology Ltd)]. These measurements were compared with the published results of a psychophysical experiment in which the subjects were sitting upright in a chair and were asked to

grasp a rectangular object under similar viewing conditions (Dijkerman and Milner, 1998). Figure 4A illustrates the close match between the orientation of the grasped object and the orientation of the opposition space generated between the thumb and the index finger immediately before touching the object. These results closely match the behavior described previously in this task (Dijkerman and Milner, 1998). Figure 4B illustrates the time course of the grip aperture measured in a representative subject. It can be seen that the grip aperture reached its maximum well before the target object was touched, at around 70% of the movement time. These results conform with previous psychophysical results (Jeannerod, 1984) and they indicate that the present experimental settings allow for an ecologically relevant grasping movement.

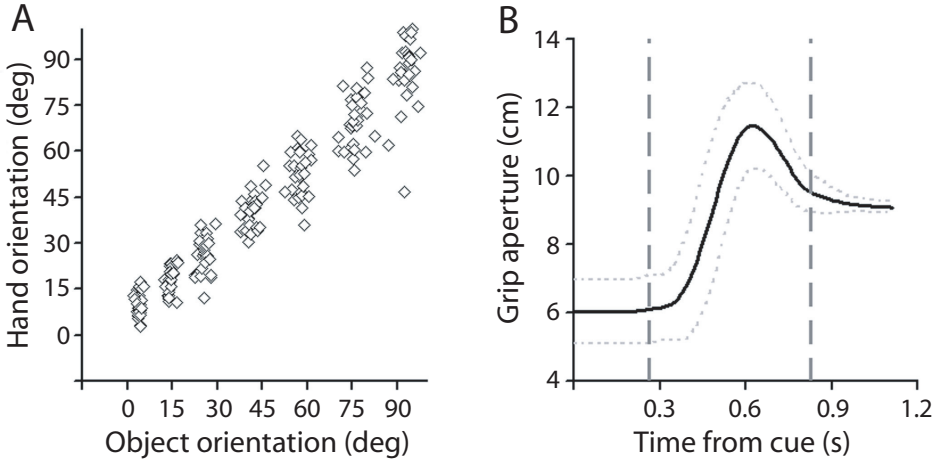

Figure 4. Behavioral results.
A) Orientation (in the vertical plane) of the axis passing between the index finger and the thumb, as a function of the orientation of the grasped object, 10 ms before the fingers touched the object. Data from a representative subject. It can be seen that the hand orientation closely matched the object orientation, analogously to the behavior described previously in similar circumstances (Dijkerman & Milner, 1998). B) Grip aperture (distance between the index finger and the thumb) as a function of time (from visual presentation of the object to be grasped). The magnetic measurement points were attached on the nails of the index finger and thumb, therefore the grip aperture measured includes a constant overestimation of ~3 cm. Black solid line: inter-trial average of grip aperture time courses (temporally normalized). Black dotted lines: standard deviation. Grey dashed lines: on the left, average reaction time (home-key release); on the right, average time of first contact with the object. It can be seen that the maximum grip aperture was reached well before the target object was touched. These results indicate that, in our experimental setting, subjects prepared the grasping movement before execution.

Finding confounds – head movements

We directly compared the frequency power spectra of the head motion time series (as estimated by the realignment procedure of SPM) and of the experimental design (i.e. the time series of task events - Figure 3). Obviously, the spectrum of the task events has the highest power around the frequency corresponding to the average trial length and its harmonics. Figure 3C illustrates how the head motion time series of one representative subject mainly consists of a low frequency component, indicating a slow drift in head position. In other words, despite an overall drift of about one voxel, head motion is not correlated with task performance. Figure 3D illustrates the same relationship for a different subject. It can be seen that, despite minimal head motion (< 1 mm), this subject reveals a substantial correlation between occurrence of the head movements and occurrence of the task events. We also found that the phase of head motion of the subject described in Figure 3D was more strongly correlated with the experimental design than for the subject in Figure 3C. Note that such a relation in both the phase and frequency composition is not obvious from visual inspection of the absolute amount of head motion (Fig. 3B). This same subject revealed typical motion-related artifacts in the fMRI time series (Fig. 5). This result emphasizes how even minute head movements can have a profound influence on the imaging signal when these movements are correlated with the experimental design. Aided by this diagnostic tool, images from three subjects could be excluded from further analysis.

Modelling confounds – correcting for motion-related global signal changes

It is known that body motion (as opposed to head motion) can substantially influence image acquisition, by affecting the static magnetic field (Diedrichsen et al. 2005; Raj et al. 2001). Therefore, we accounted for these confounds by including two further covariates in the design matrix. These covariates were obtained by averaging the signal measured from the white matter (WM) and cerebrospinal fluid (CSF) compartments of each echo-planar image of the fMRI time series. The rationale of this procedure is that these compartments should provide an index of global signal un-affected by cerebral activity (as measured with BOLD), and thus account for the global signal disturbances generated by motion of the subject's arm-hand during image acquisition. Figure 6 illustrate that these covariates explain a significant portion of the overall cerebral variance. As a result, the inclusion of these covariates in the design matrix considerably enhances the sensitivity of the image analysis.

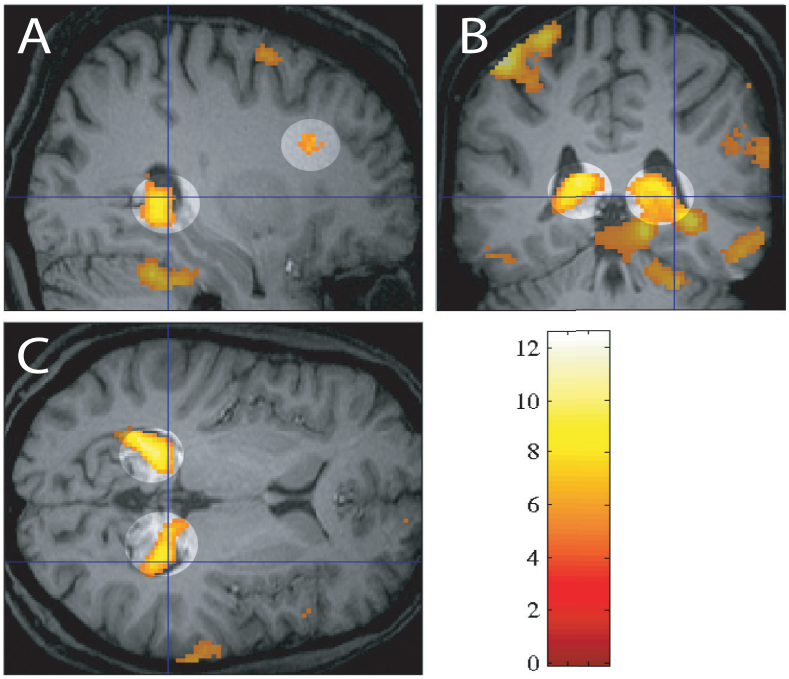

Fig. 5. Imaging results – motion artifacts in an excluded subject.
Anatomical localization in a single subject of the BOLD signal corresponding to the hand return movement contrasted with BOLD signal corresponding to the grasping movement (A: sagittal plane (x = 28), B: coronal plane (y = -38), C: transversal plane (z = 0)) Motion related artifacts appear most clearly as activation in the white matter and ventricles (highlighted areas). This subject was excluded from further analyses.

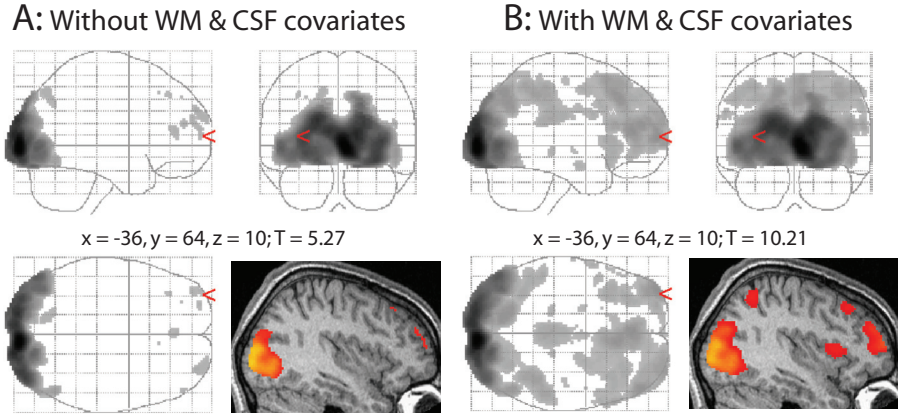

Fig. 6. Imaging results – modeling confounds.
SPM{t}s (threshold p < 0.05 FWE-corrected) generated without (A) and with (B) white matter (WM) and cerebro-spinal fluid (CSF) covariates corresponding to the effects of grasp versus hand return. The sagittal slice at x = -38 is shown for both models. Occipital activity can be seen in both SPM{t}s. However, the model that included the WM and CSF covariates shows additional responses in the parietal and frontal cortices.

Discussion

Behavioral performance – validity of experimental setup and design

In order to investigate visuo-motor behavior using fMRI techniques several subject configurations have been employed (Culham et al., 2006a). For instance, some researchers positioned the participants in the configuration commonly used in visual fMRI studies, i.e. lying supine in the scanner, facing the upper portion of the bore of the magnet (Frey et al., 2005). In these studies the performance of the visually-guided movements was achieved by delivering visual information about the target object through a mirror positioned above the subject's head. This approach is elegantly simple, but it introduces a mismatch between visual input about the target of the movement and proprioceptive information related to the moving arm. It has been shown that portions of posterior parietal cortex are involved in re-calibrating this type of sensory mismatches (Clower et al., 1996). Therefore, this approach raises the issue of whether part of the grasping-related activity could actually be related to this re-calibration procedure, and whether the presence of a visuo-proprioceptive mismatch would alter the cerebral circuit controlling the actions under normal circumstances (Culham, et al. 2003).

Other authors have tilted the head of the participant within the MR head-coil (Binkofski, et al. 1998; Culham, et al. 2003; James, et al. 2003). In this setup, the participants were required to fixate an LED mounted on the head coil, at a visual angle of approximately 10 degrees above the target location. This approach removes any visuo-proprioceptive discrepancy, but it raises the issue of whether it is ecologically relevant to study grasping movements in which the target object is not foveated. It is conceivable that the human brain might react to such an artificial demand by using different cerebral circuits than those dedicated to controlling visually-guided grasping movements with free gaze (Prado et al., 2005).

In the set-up proposed in this chapter subjects were allowed to reach and grasp the target object directly and with free gaze. Our results showed that subjects were able to perform the task, and their performance matched previous psychophysical studies (Dijkerman and Milner, 1998). The current experimental design effectively distinguished between cerebral variance induced by the grasping movement from activity evoked by the stereotypical return movement of the hand to the home-key.

Statistical analysis –modelling movement-related confounds

The effects of arm motion on head movements are of particular concern for reach to grasp tasks, both in terms of the amount of head-motion induced by these tasks and in terms of their temporal relationship with the haemodynamic response. Usually, head movements are assessed by visual inspection of the fMRI time series or the estimated motion (i.e. the realignment parameters). Several studies dealing with reaching-grasping movements adopted this procedure, and they did not consider this source of variance in their statistical model (Chapman, et al. 2002; Culham, et al. 2003; Frey, et al. 2005). Yet, there are ways to take into account the disruptive effects of head movements on MR

images (Friston, et al. 1995b; Grootoonk, et al. 2000), although even these methods are ineffectual when head-motion and task occurrence are highly correlated. Our results emphasize how even minute head movements can have a profound influence on the imaging signal when these movements are correlated with the experimental design. The diagnostic tool proposed in this chapter provided insight in the temporal relationship between task events and head motion and thereby allows to asses confounds that could be ignored when relying on visual inspection.

Finally, the disturbances caused by movements of the hand, finger or even diaphragm in the static magnetic field have not been explicitly addressed during fMRI studies of reaching-grasping movements. The introduction of spatially informed covariates indexing changes in global signal was able to capture additional variance induced by the direct and indirect effects of moving the hand in the MR-environment. The inclusion of these covariates in the design matrix considerably enhances the sensitivity of the image analysis. This solution could also be applicable to other paradigms involving movement of conductive masses within the MR scanner bore.

Applications

With this protocol we were able to acquire visually-guided grasping data for the two experiments (1B and 2) introduced earlier in this chapter. Methodological details of experiment 1B slightly differed from the methodology used in experiment 1A that was meant to test the solutions proposed in this protocol. For details on 1B I refer to the original paper.

In experiment 1B viewing conditions (monocular vs binocular) were altered during reach-to-grasp movements towards a prism oriented in different angles in the depth plane. Reaching and grasping a rectangular prism with the right hand evoked widespread cerebral activity in occipito-temporal (bilaterally) and parieto-frontal regions (mainly in the left hemisphere). More specifically, activity in the medial occipito-parietal fissure (putative area V6A) and in the superior precentral gyrus (putative area PMd) increased proportionally to the deviation of the target object from the vertical plane, irrespectively of viewing conditions. This result fits with the general notion that V6A and PMd, two crucial nodes of the dorsomedial visuomotor stream (Tanne-Gariepy et al., 2002; Galletti et al., 2003), are involved in processing visuospatial information for visual control of arm-reaching movements (Fattori et al., 2001; Fattori et al., 2005). These findings provide further support to the hypothesis that the dorsomedial visuomotor stream is involved in the specification of spatial parameters for prehension movements on the basis of visual information acquired before response onset, irrespectively of target characteristics (Grol et al, 2007; Pisella et al, 2000).

When only monocular visual information is available, pictorial cues of depth information become more relevant for planning an appropriate prehension movement as the object deviates from the vertical plane. Under these circumstances, regions of the dorsolateral visuomotor stream (Jeannerod et al., 1995), the anterior intraparietal region (AIP) and ventral premotor cortex (PMv), and a part of the ventral stream, the lateral occipital complex, more specifically LOtv, increased their activity.

Additionally, PMv and LOtv increased their effective connectivity with AIP during monocular trials as the deviation of the target object from the vertical increased. The authors suggest that when movement-related visual information is absent *and* perceptual informa-

tion is necessary for planning a correct movement (i.e., monocular trials), the dorsolateral stream is involved in the visuomotor process, operating on the basis of perceptual visual information provided by LOtv. In contrast, when the prehension act can be fully specified before movement onset on the basis of visuomotor processes implemented in the dorsomedial stream and irrespectively of perceptual information (i.e., binocular trials), the dorsolateral stream reduces its contributions to the visuomotor process and its functional coupling to LOtv.

The behavioral and imaging results from experiment 2 indicate that actions can be planned at different levels. The data suggest that the cognitive distinction that can be drawn between action immediate and final goals in movement planning is reflected in differential brain activity. Behavioral data suggest that Immediate and Final Goal trials were not equally sensitive to the different spatial accuracy requirements of the small and large objects. This indicates that movements planned on the basis of their immediate or final goal were prepared differently.

Comparing preparatory brain activity during Final Goal trials and Immediate Goal trials showed that Final Goal-cued action planning involves the superior frontal gyrus (bilaterally) and left inferior parietal cortex (supramarginal gyrus). These areas have been previously associated with covertly preparing movements and planning complex motor sequences (Rushworth et al., 2004; Shima and Tanji, 2000; Rowe et al., 2001; Rushworth et al., 2001). This is in line with the notion that action planning based on the desired end-state requires the selection of a course of action at a more abstract level. Conversely, Immediate Goal-cued planning involves the right occipito-parietal sulcus (putative human V6A) and the left occipito-temporal sulcus (LOtv). These areas have been associated with early visuomotor transformations and object perception (Battaglia-Mayer et al., 2001; Amedi et al., 2002; Grill-Spector et al., 1999). Here, the action plan is generated on the basis of spatial object properties and involves selecting a movement spatially compatible with these properties.

Together, these findings show that different fronto-parietal circuits plan the same action, by a relative emphasis on either selecting a sequence of movements to achieve a desired end-state, or selecting movements spatially compatible with given object properties.

Conclusions

The combination of dedicated mechanical devices, experimental design, and image analysis allowed us to use fMRI during the performance of visually-guided reach to grasp movements with free gaze and direct sight on the hand. Meaningful BOLD activity related to the experimental task can be dissociated from other sources of variance including the direct and indirect effects of moving the hand in the MR-environment. We have shown the benefits of modelling both the head movements (as estimated by the spatial realignment procedure) and the global signal disturbances generated by arm and hand motion during image acquisition. The protocol was successfully applied in two experiments investigating visually-guided grasping at different levels of action planning and under different visual conditions.

Chapter 5

PARIETO-FRONTAL CONNECTIVITY DURING VISUALLY-GUIDED GRASPING

Grol, M.J., Majdandžić, J., Stephan, K.E., Verstraten, F.A.J., Toni, I. (2007).
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Grasping an object requires processing visuospatial information about the extrinsic features (spatial location) and intrinsic features (size, shape, orientation) of the object. Accordingly, manual prehension has been subdivided into a reach component, guiding the hand towards the object on the basis of its extrinsic features, and a grasp component, pre-shaping the fingers around the center of mass of the object on the basis of its intrinsic features. In neural terms, this distinction has been linked to a dedicated dorsomedial 'reaching' circuit and a dorsolateral 'grasping' circuit that process extrinsic and intrinsic features, linking occipital areas via parietal regions with the dorsal and ventral premotor cortex, respectively. We have tested an alternative possibility, namely that the relative contribution of the two circuits is related to the degree of online control required by the prehension movement.

We used Dynamic Causal Modelling of fMRI-timeseries to assess how parieto-frontal connectivity is modulated by planning and executing prehension movements towards objects of different size and width. This experimental manipulation evoked different movements, with different planning and execution phases for the different objects. Crucially, grasping large objects increased inter-regional couplings within the dorsomedial circuit, whereas grasping small objects increased the effective connectivity of a mainly dorsolateral circuit, with a degree of overlap between these circuits. These results argue against the presence of dedicated cerebral circuits for reaching and grasping, suggesting that the contributions of the dorsolateral and the dorsomedial circuits are a function of the degree of on-line control required by the movement.

Introduction

It has been suggested that, when we grasp an object, the brain needs to extract visuospatial information about the spatial location of the object relative to the subject (extrinsic features), as well as about its size, shape, and orientation (intrinsic features) (Arbib 1981). Kinematic data show that varying object size affects the maximum hand aperture, while varying object distance affects the kinematic profile of the reaching limb (Jeannerod, 1984). These findings have led to the suggestion that manual prehension is controlled through two visuomotor channels: a reach component, transporting the hand toward the object, and a grasp component, pre-shaping the fingers according to the size and the center of mass of the object (Jeannerod, 1988). This functional organization appears to have a physiological counterpart in two anatomically segregated parieto-frontal circuits: a dorsolateral circuit, consisting of an anterior intraparietal (AIP) area connected to the rostral part of the ventral premotor cortex (area F5); And a dorsomedial circuit, consisting of the anterior portion of the occipito-parietal sulcus (area V6A) and the caudal dorsal premotor cortex (area F2) (Tanne-Gariepy et al., 2002; Galletti et al., 2003). The dorsolateral circuit has been linked to the grasping component of prehension (Jeannerod et al., 1995). AIP contains neurons that are selectively activated during specific grasping movements and respond to 3D shape, size and orientation of objects, while remaining insensitive to the position of an object relative to the animal (Murata et al., 2000). Disruption of AIP leads to severe impairments in the preshaping of the hand during grasping (Gallese et al., 1994; Tunik et al., 2005). Area F5 is crucially involved in planning and executing grasping movements (Fogassi et al., 2001; Davare et al., 2006). In contrast, the dorsomedial circuit has been linked to the reaching component (Burnod et al., 1999). Area V6A in macaques contains reaching cells (Fattori et al., 2001; Fattori et al., 2005) and visuomotor neurons coding object position in space (Galletti et al., 1999). Disruption of V6A leads to errors in reaching (Battaglini et al., 2002; Karnath and Perenin, 2005), and area F2 is important for planning arm movements (Wise et al., 1997).

These findings could suggest a functional dichotomy between reaching and grasping organized along dorsolateral and dorsomedial pathways; yet, no double dissociation between reaching and grasping deficits in neuropsychological studies has been found (Pisella et al., 2006). Accordingly, some authors have proposed more integrated control mechanisms of prehension (Smeets and Brenner, 1999; Ulloa and Bullock, 2003; Zaal et al., 1998; Haggard and Wing, 1995), but it remains unclear how to implement these mechanisms within the segregated dorsomedial and dorsolateral parieto-frontal circuits.

Here, we explore a neglected feature of the cerebral activity supporting reaching-grasping movements, both in human and macaque studies. We used Dynamic Causal Modelling (Friston et al., 2003) on fMRI timeseries acquired during planning and execution of visually-guided reaching-to-grasp movements towards objects of different size to explore the inter-regional couplings between regions of the dorsolateral (AIP and PMv) and the dorsomedial (V6A and PMd) circuits. By assessing how different hand-object interactions modulate the effective connectivity within this network, we tested the hypothesis that the involvement of the dorsolateral and dorsomedial parieto-frontal circuits is related to the degree of online control required by the prehension movement.

Methods

Subjects

Twenty healthy right-handed male volunteers (25±4 years) were recruited to participate in the study. They all had normal or corrected-to-normal vision, and gave informed consent according to the institutional guidelines of the local ethics committee (Commissie Mensgebonden Onderzoek region Arnhem-Nijmegen, Netherlands). Data from three subjects were discarded because of head-movement artefacts during the MR scanning.

Six further right-handed volunteers were recruited to participate in a behavioral control experiment, to measure kinematics parameters of the reaching-to-grasp movements, and to compare these with the kinematics of reaching-to-point movements (see Supplementary Material).

Experimental set-up

Subjects had to perform reaching-to-grasp and place movements while lying supine in the MR scanner. The standard mattress of the scanner bed was removed, allowing the subjects to lie considerably lower within the bore of the scanner to enable them to comfortably bend their head. Their head was fitted inside a phased-array receiver head coil. The head-coil was tilted forward by 30° along the subject's sagittal plane (see Fig. 1A). This set-up allowed the subjects to have a direct line of sight of the objects to be grasped and to visually control their movements. The subjects were not asked to fixate their eyes, so that they could freely explore the visual scene. An optical response button box (MRI Devices, Waukesha, WI), positioned on the upper leg (Fig.1A, nr. 4), served as a home key on which subjects had to keep their hand in between trials. This device allowed us to record subjects' reaction times and total movement times.

We ensured that subjects performed the task by moving their right forearm only. This was achieved by fitting a plastic splint around the elbow, and by firmly but comfortably strapping the arm to the scanner table. The splint constrained the rotations around the elbow to the plane between the home key and the target object, minimizing the movements around the shoulder. The subject's head was kept in place using foam wedges.

The subjects were instructed to grasp and manipulate an object consisting of a large red cube and a small green cube, attached to a supporting rail positioned in front of them. The object was held in place through an arc-shaped device positioned over the subject's hips inside the MR scanner (see Fig. 1A). The object (Fig.1B, nr. 1), was positioned next to a rectangular box (Fig.1B, nr. 2), containing two cubic slots. The subject could comfortably perform visually guided reaching-grasping movements towards the object, extract the object from the supporting rail, insert the object into one of the slots, and finally re-position the object in the supporting rail. The subjects had to insert the object back into the rail to ensure that the starting position of the larger cube did not vary over trials. Whether the small or large object was on top could be varied by means of a computer-controlled pneumatic mechanism.

An LED was installed in the middle of each of the two sides of the box (Fig.1B, nr. 3). The color of the LED instructed the subject on the movement to perform. MR-compatible switches located at various positions on the device recorded the time at which the object was removed from the supporting rail, the time at which the object was inserted into one of the slots, and the time at which the object was put back into the supporting rail. Control of the pneumatic rotation mechanism and recording of the movement-related responses was carried out using a PC running Presentation 0.81 (Neurobehavioral Systems, San Francisco, CA).

Experimental time course and procedures

During the task, in each trial subjects had to grasp the object at either the large (LARGE) or the small (SMALL) part (Fig. 1C), remove the object from the rail to put it into one of the two slots, and finally re-position the object in the supporting rail. When the LED switched on, subjects had to leave the home key as soon as possible, make the appropriate object manipulation, and return to the home key. After 6 seconds, the LED switched off, and a baseline of variable length (1.5–6 seconds) followed. Subjects were instructed to complete their action before the LED switched off. At the beginning of each block, the box was rotated, followed by a variable amount of time (2-7 sec), so that the subject could not predict cue onset. The time course of a trial is shown in figure 1D. Each block contained a randomized number of 3 to 9 trials. Subjects first had a 15 minutes training session outside the scanner, until error-free and sufficiently fast performance was reached. After the subject had been positioned into the scanner, another short practice session followed. The experiment consisted of a total of 252 pseudo-randomized trials, subdivided into 42 blocks. Total scanning time was 45 minutes.

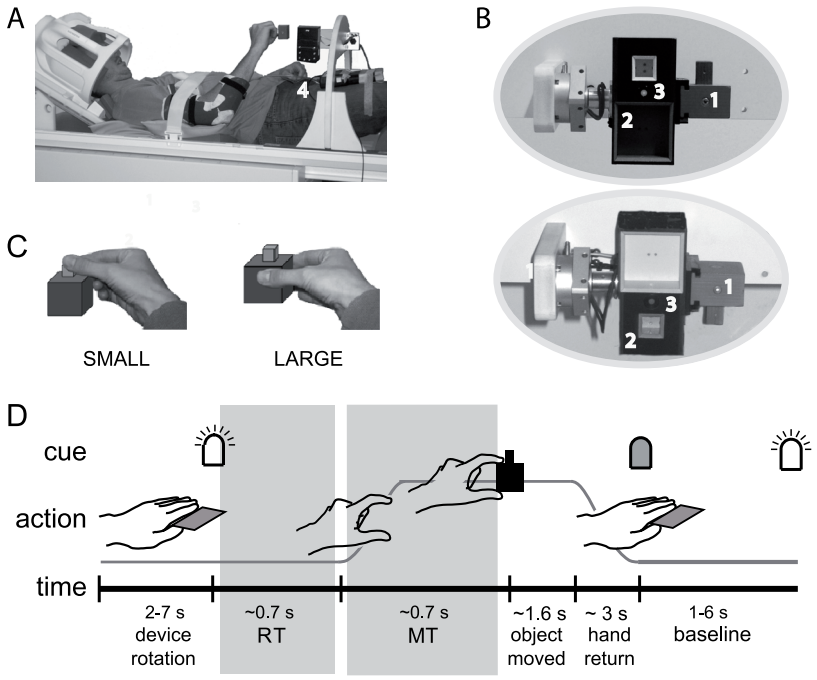

Figure 1. Experimental design

A. Experimental setup. Subjects had to perform visually-guided grasping movements and object manipulations while lying supine in the MR scanner. Their head was fitted inside a phased-array receiver head-coil. The head-coil was tilted forward by 30° along the subject's sagittal plane. This set-up allowed the subjects to have a direct line of sight of the objects to be grasped and to visually control their movements. An optical response button box, positioned on the upper leg (4), served as a home key on which subjects had to keep their hand in between trials. This device recorded subjects' reaction and movement times.

B. Grasping device. The subjects were instructed to grasp and manipulate an object (1) consisting of a large red cube and a small green cube, attached to a supporting rail positioned in front of them. The object (1), was positioned next to a rectangular box (2), containing two cubic slots. The object was held in place through an arc-shaped device positioned over the subject's hips inside the MR scanner. The subject could comfortably perform visually guided reaching-grasping movements towards the object. An LED (3) instructed the subject on the movement to perform. Whether the small or large object was on top could be varied by means of a pneumatic mechanism. The two ellipses show the subject's direct line of sight in both orientations of the object.

C. Task. During the task, subjects grasped the object either at the large (red) or the small (green) part of the object.

D. Experimental Timecourse. During the task, in each trial subjects had to grasp the object either at the large (LARGE) or the small (SMALL) part, remove the object from the rail to put it into one of the two slots, and re-position the object in the supporting rail. When the LED switched on, subjects had to leave the home key as soon as possible, make the appropriate object manipulation, and return to the home key. After 6 seconds, the LED switched off, and a baseline of variable length (1.5–6 seconds) followed. Subjects were instructed to complete their action before the LED switched off. At the beginning of each block the box rotated, followed by a variable amount of time (2-7 sec), so that the subject could not predict cue onset. The grey areas refer to the movement planning (RT) and movement execution (MT) phases considered in the DCM.

Behavioral analysis

For each trial, the Reaction Time (RT; the time interval from the cue onset to the release of the home key) was measured. Given that the subject could see the object during the entire trial, but did not know which part to grasp until the LED was switched on, we consider the reaction time as an index of movement planning time (Fig. 1D). We also considered the following behavioral measures: Movement execution Time (MT, the time interval from the release of home key to the removal of the object from its support), Transport Time (TrT, the time interval from the removal of the object to the insertion of the object into the slot), and Return time (the time interval from the insertion of the object into the slot to the return of the hand on the home key). In addition, we recorded whether the object manipulation was correctly performed. Effects of Object size [LARGE, SMALL] on RTs and MTs measured during the scanning session were assessed using a paired T-test.

The behavioral analysis of the kinematic control experiment is described in the Supplementary Material.

Image acquisition

Images were acquired using a Siemens 3T Trio MRI system (Siemens, Erlangen, Germany), using the body coil for radio frequency transmission, and an 8-channel phased array surface head coil for signal reception. BOLD sensitive functional images were acquired using a single shot gradient EPI sequence (TR/TE 2.3s/40 ms, 31 transversal slices, voxel size 3.5 × 3.5 × 3.5 mm). At the end of the scanning session, anatomical images were acquired using an MPRAGE sequence (TE/TR 3.93/2300 ms, 192 sagittal slices, voxel size 1.0 x 1.0 x 1.0 mm, FoV 256 mm).

Imaging data analysis

Preprocessing

Functional data were spatially pre-processed with SPM2 and statistically analyzed with SPM5 (Statistical Parametric Mapping, www.fil.ion.ucl.ac.uk/spm). The first five volumes of each participant's data set were discarded to allow for T1 equilibration. The image time series were spatially realigned using rigid body transformations and a sinc interpolation algorithm (Friston et al., 1995a).

The timeseries for each voxel was realigned temporally to acquisition of the middle slice. Subsequently, images were normalized onto a custom MNI aligned EPI template (based on 24 male brains acquired on the Siemens Trio at the F.C. Donders Centre) using both linear and nonlinear transformations.

Finally, the normalized images were spatially smoothed using an isotropic 10 mm full-width-at-half-maximum Gaussian kernel. Each participant's structural image was spatially coregistered to the mean of the functional images (Ashburner and Friston, 1997) and spatially normalized using the same transformation matrix as applied to the functional images.

Dynamic Causal Modelling

Effective connectivity is defined as the influence that one neural system exerts over another (Friston, 1995). Dynamic Causal Modelling aims to estimate and make inferences about the causal influences or coupling among brain regions and how this coupling is modulated by the experimental manipulation (Friston et al., 2003).

The first step is to construct a biologically and anatomically plausible model of interacting cortical regions at the neuronal level (not accessible by fMRI). The dynamic causal model here is an input-state-output system, modelled by bilinear differential equations (Friston et al., 2003), in which changes in the states (the neuronal population activities) are modelled on the basis of the known inputs and measured outputs:

$$\frac{dz}{dt} = \left(A + \sum_{j=1}^{m} u_j B^{(j)} \right) z + Cu \qquad (1)$$

Here, z is the state vector (with each state variable representing the population activity of one region in the model), t is continuous time, and u_j is the j-th input to the modelled system (i.e. some experimentally controlled manipulation). In this state equation, the A matrix contains the "intrinsic" or "fixed" connection strengths between the modelled regions, and the $B^{(1)}...B^{(m)}$ matrices represent the context-dependent modulation of these connections, e.g. by task, as an additive change. The C matrix represents the strengths of direct ("driving") inputs to the modelled system (e.g. sensory stimuli). Note that the inputs u correspond to designed causes (e.g., boxcar or delta stimulus functions), like those used to form design matrices in conventional fMRI analyses. The outputs correspond to the observed BOLD timeseries of the selected volumes of interest (VOI). Being based on first order differential equations, the parameters in a DCM denote the speed or rate of change of neuronal activity (Hz) in one area as induced by an input or by the output from another area, respectively. The focus of DCM is typically on the B parameters, the modulatory effects. Estimating these parameters and making statistical inference about them enables us to investigate whether grasping objects of different size is associated with changes in coupling among the brain areas in the parieto-frontal circuits under study.

In DCM, the neuronal model described above is supplemented with a haemodynamic forward model of how neuronal activity is transformed into a measured BOLD response. Neuronal and haemodynamic parameters are estimated by Bayesian inversion using an Expectation Maximization algorithm and a Laplace approximation to the posterior density (see Friston et al., 2003 for details). In brief, the E-step estimates the posterior mean by a gradient ascent on the log posterior whereas the M-step computes the hyperparameters by minimising the variational free energy.

We used DCM as implemented in SPM5 (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm). DCMs were constructed for each single subject separately.

The aim of our DCM analysis was to investigate the changes in inter-regional couplings associated with grasping either SMALL or LARGE objects. Accordingly, for each single subject we isolated cortical regions that were activated during prehension movements directed to both SMALL and LARGE objects. We implemented this constraint by considering the movement execution period of correctly performed prehension movements (from

movement onset to displacement of either SMALL or LARGE objects), distinguishing these two effects from the planning phase of the movement (from cue presentation to movement onset - INPUT); from the movements occurring after the first object displacement; and from the few incorrect trials. The grey areas in figure 1D show the movement planning (RT) and movement execution (MT) phases considered in the model.

General Linear Model

The relevant timeseries for the Volumes of Interest (VOI) were extracted from the fMRI data of each individual subject on the basis of event-related analyses in the context of the General Linear Model. Single subject models consisted of regressors separately describing the movement planning phase (RT) for all visual stimuli [INPUT] and the movement execution phase (MT) for Object (split into distinct regressors for grasping movements directed towards the large [LARGE] and the small [SMALL] part of the object). Trial durations were defined on the basis of the behavioral measurements during the experiment. In addition, we separately modelled the remaining part of the movement (the sum of the Transport Time (TrT) and the Return time), the rotation of the device, and the error trials.

Each effect was modelled on a trial-by-trial basis as a concatenation of square-wave functions: for the RT with onsets time-locked to the onset of the LED cue, and offsets time-locked to the release of the hand from the home key; for both MT regressors with the onsets time-locked to the release of the hand from the home key and the offsets time-locked to taking-off the object from the rail. For the remaining part of the movement the onsets were time-locked to the taking-off of the object; and the offsets were time-locked to the return of the hand on the home key. The rotation of the device was modelled as an event with zero duration. The error trials had a standard length of 6 seconds. Each of the 6 square-wave functions were then convolved with a canonical haemodynamic response function, and downsampled at each scan in order to generate 6 regressors modelling the main effects described above (Friston et al., 1995b).

Head movement effects were accounted for as described by Friston et al. (1996) by including a Volterra expansion of the 6 rigid-body motion parameters as nuisance covariates, which consisted of linear and quadratic effects of the 6 realignment parameters belonging to each volume and also included spin-history effects as linear and quadratic effects of motion parameters in the previous volume, giving a total of 24 regressors (Lund et al., 2005). Three further regressors, describing intensities in white matter (WM), cerebrospinal fluid (CSF), and residual compartment (section outside the brain and skull, RC) were added. This was done to account for image intensity shifts due to movement of the hand within the main magnetic field of the scanner (Culham et al., 2003; Verhagen et al., 2006).

For the selection of Volumes of Interest (VOI) for the DCM, we used a conjunction analysis (Nichols et al., 2005) in each single subject to isolate *commonalities* in cerebral activity evoked during the execution phase of grasping both SMALL and LARGE objects, and we masked this effect by the activity evoked during the presentation of the INPUT (for the details of VOI selection see below).

To assess these commonalities in cerebral activity at the group level, we ran a random effects analysis (RFX) which served as a guideline in the VOI selection. For this analysis, contrasts of the parameter estimates for SMALL and LARGE were calculated for each single subject, and entered into a one-sample T, respectively. Subsequently, Statistical

Parametric Maps (SPMs) of the T statistic for the effects of SMALL and LARGE (Nichols et al, 2005) masked by the visual cues (INPUT) were created, with the degrees of freedom corrected for nonsphericity at each voxel. Inferences were drawn at the voxel level, corrected for multiple comparisons using family-wise error (FWE) correction ($p < 0.05$) across the whole brain. Part of these data have been previously used to address a different issue (Majdandžić et al, 2007).

Anatomical inference

Anatomical details of significant signal changes were obtained by superimposing the SPMs on the structural images of each subject in MNI coordinates. The atlas of Duvernoy et al. (1991) was used to identify relevant anatomical landmarks. When applicable, Brodmann areas were assigned on the basis of the SPM anatomy toolbox (Eickhoff et al., 2005); i.e., the anatomical position of our significant clusters and local maxima was tested post hoc against published three-dimensional probabilistic cytoarchitectonic maps. When the literature used for VOI selection reported the stereotaxical coordinates in Talairach space, these coordinates were converted to coordinates in MNI space by a non-linear transform of Talairach to MNI (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach).

Selection of Volumes of interest - general procedures

For each single subject, we selected Volumes of Interest (VOI) corresponding to the putative human equivalents of area V3A, area V6A, the anterior intraparietal area (AIP), ventral premotor cortex (PMv) and dorsal premotor cortex (PMd). Despite the difficulties of defining homologies between macaque and human brain areas (Culham et al., 2006a), we chose to use these specific functional labels derived from monkey electrophysiological studies in order to facilitate the comparison of results across species. However, given that we cannot reliably distinguish hand and arm fields within PMv (i.e., F5 and F4, respectively), or caudal/rostral portions of PMd (i.e. F2 and F7, respectively) (Geyer et al., 2000), we have chosen to use generic functional labels like PMv and PMd (Wise, 1997).

Given that our right-handed subjects performed the task with their dominant arm, and given the left-hemispheric dominance of several aspects of motor control (de Lange et al., 2006), we restricted our analysis to the left-hemisphere.

The subject-specific location of the VOIs was guided both anatomically and functionally: anatomically by the stereotaxical coordinates reported in the literature and known anatomical landmarks (see below for details), and functionally by the group maxima obtained from the random effects conjunction analysis, if applicable. For each subject-specific VOI, we considered the first eigenvariate of all supra-threshold voxels (uncorrected, $p < 0.05$) within a 6 mm radius around the selected subject-specific maximum. These timeseries were adjusted for the rotation of the device, error trials, head movement artifacts, and intensity shifts in the magnetic field due to arm movement. The timeseries were also adjusted for the remaining part of the movement to ensure that we only considered the coupling changes during the preparation and execution phase of the movement (see Fig. 1D). Therefore, each VOI timeseries solely reflects the activity evoked during the

period starting with the presentation of the instruction cue and ending with the removal of the object from its slot.

For the parietal and frontal VOIs, the subject-specific VOIs were extracted from the conjunction analyses of the effects evoked by both LARGE and SMALL movements, masked by the activity evoked by the INPUT. For area V3A, which served as the area in our models where the visual inputs entered, each subject-specific VOI was selected on basis of the activity evoked by the visual INPUT alone.

Selection of Volumes of interest – anatomical details

The VOI labelled as V3A was selected using the stereotaxical coordinates reported by (Tootell et al., 1997) as a guideline. However, given the absence of individual retinotopic maps, the V3A VOI should be considered as a general area of major visual input, rather than a precise delineation of V3A.

Area V6 and V6A together form what is called the V6-complex. Pitzalis et al. (2006) reported human V6 to be located in or near the posterior branch of the dorsal end of the parieto-occipital sulcus (POS), centered at -11,-77, 46. On the basis of macaque anatomy, it seems reasonable to assume that area V6A would lie more dorsally than V6 along the anterior bank of the POS. Given that V6A is a well-established cerebral area, defined on the basis of electrophysiological, anatomical, and hodological criteria (Luppino et al., 2005; Galletti et al., 1999; Matelli et al., 1998;), we prefer to refer to this general region as V6A rather than as the Parietal Reach Region (PRR). PRR is known to be crucially involved in reaching (Snyder et al., 2000; Andersen and Buneo, 2002, Buneo et al., 2002), and V6A was suggested to represent a portion of it (Batista et al., 1999), but more recent findings suggest that PRR is located in the medial intraparietal cortex (MIP) (Calton et al., 2002; Gail and Andersen, 2006). The anterior intraparietal (AIP) VOI was selected on the basis of the SPM Anatomy Toolbox (Eickhoff et al., 2005). Additionally, the junction between the postcentral and the intraparietal sulci was used as a landmark on a subject-by-subject basis (Culham et al., 2006a).

The ventral premotor (PMv) VOI was selected on the basis of stereotaxical coordinates from neuroimaging studies dealing with precision grasping tasks (Kuhtz-Buschbeck et al., 2001; Ehrsson et al., 2000).

The dorsal premotor (PMd) VOI was selected on the basis of stereotaxical coordinates from neuroimaging studies dealing with grasping tasks (Ehrsson et al., 2000). Similar coordinates for both PMv and PMd were used in a TMS study (Davare et al., 2006) that confirmed the involvement of these particular precentral regions in visuomotor transformations during the performance of grasping movements.

DCM analysis and inference

We considered the anatomical model consisting of the VOI as described above with reciprocal connections between them (fig. 4, Original model). Table 1 provides the anatomical background for each connection of the model.

The instruction cues (INPUT) that triggered the preparation of the appropriate motor program were fed into V3A. The resulting perturbation was then allowed to propagate throughout the model via interconnections from V3A to V6A, terminating in the dorsal

premotor cortex; and from V3A to AIP, terminating in ventral premotor cortex. Object size (SMALL, LARGE) served as a modulatory influence on the connections, but affected the forward connections only.

The central question was whether the forward connections in the model were differentially modulated by object size, especially whether they were more strongly modulated by grasping a small object (SMALL) compared to a large object (LARGE) during the execution of the movement.

To test whether the modelled processes were expressed consistently across subjects, the subject-specific intrinsic couplings and modulatory effects were entered into separate one-sample t-tests (two-sided, statistical threshold $p<0.05$). Second, and most importantly, we tested our hypothesis that grasping a small object changed the coupling between the regions more than grasping a large object, by entering the modulatory parameters of each connection into one-sided paired t-tests, testing at the group level whether the modulatory effect of SMALL was larger than the effect of LARGE. The null hypotheses were rejected at a significance level of $p<0.05$.

Table 1:
Anatomical connectivity – summary of the available evidence on the basis of tracer studies in macaque monkeys.

Connection	References
V3A -> V6A	(Galletti et al., 2001; Shipp et al., 1998) [1]
V6A -> V3A	(Galletti et al., 2001; Shipp et al., 1998) [1]
V6A -> PMd	(Shipp et al., 1998; Marconi et al., 2001; Caminiti et al., 1999; Matelli et al., 1998)
PMd -> V6A	(Marconi et al., 2001; Caminiti et al., 1999; Tanne et al., 1995; Luppino et al., 2005)
V3A -> AIP	(Nakamura et al., 2001) [2]
AIP -> V3A	(Nakamura et al., 2001) [2]
AIP -> PMv	(Matelli et al., 1986)
PMv -> AIP	(Matelli et al., 1986)

[1] Regions connected via V6.
[2] Regions connected via LIP (lateral intraparietal sulcus)

Model selection

For any given research question, several alternative hypotheses (with associated models) usually exist. A model selection approach can be used to compare competing models. To test whether our original model was superior to possible alternative models (fig. 4), we applied Bayesian inference to the models themselves (Penny et al, 2004). Bayes factors, i.e. ratios of model evidences, were used to compare different models. Following the classification by Raftery (1995), a decision amongst models is made if the Bayes factor is at least 3 ("positive evidence"). The model with the highest evidence is a model that is optimally balanced with regard to model fit (accuracy) and model complexity. In the context of DCM, suitable approximations to the model evidence are given by the Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC; see Penny et al. 2004 for details). Because BIC is biased towards simpler models and AIC towards more complex models, a model is selected only when AIC and BIC concur. The more conservative Bayes factor of the two criteria is then used for the final model selection.

The optimal model may vary across subjects. To decide about the optimal model at the group level, we computed the Group Bayes Factor (GBF) for each model comparison. Because Bayes factors are independent probability ratios, the GBF can be computed by multiplying the individual Bayes factors of the same model comparison across subjects. However, in case of outliers, GBFs can be delusive (see Stephan et al., 2007 for an example). Therefore, we additionally computed the positive evidence ratio (PER), i.e. the number of subjects where there is positive (or stronger) evidence for model A divided by the number of subjects with positive (or stronger) evidence for model B (Stephan and Penny, 2007).

Behavioral performance

During scanning, the subjects performed the task accurately (average error rate: 1.9±0.5%). Reaction times (RTs) were shorter when subjects were instructed to grasp the large part of the object (main effect of Object: RT: $T_{1,16} = 3.595$; $p = 0.002$; Small: 764 ± 48 ms (mean ± standard error of the mean); Large: 729 ± 45 ms (mean ± standard error of the mean)). The movement execution times (MT) were shorter as well when subjects were instructed to grasp the large part of the object (main effect of Object - MT: $T_{1,16} = 8.002$; $p < 0.001$; Small: 665 ± 23 ms (mean ± standard error of the mean); Large: 560 ± 17 ms (mean ± standard error of the mean)).

During the kinematic control experiment, subjects' performance was comparable to that measured during the fMRI scanning session. Figure 2 illustrates the movement parameters for the reaching-to-grasp and reaching-to-point trials towards small and large objects. Subjects' RTs (Figure 2A) and MTs (Figure 2B) were shorter when they were instructed to grasp the large part of the object than when they grasped the small part of the object [RT: main effect of Object Size: $F_{1,5} = 9.38$; $p = 0.028$; MT: main effect of Object Size: $F_{1,5} = 43.75$; $p < 0.001$]. This is a replication of the behavioral findings obtained in the fMRI study. Furthermore, in the control experiment, subjects' RTs were longer when they had to make a reaching-to-point movement than when they had to make a reaching-to-grasp movement [RT: main effect of Movement type: $F_{1,5} = 15.63$; $p = 0.011$]. This finding indicates that, in this experimental setting, reaching-to-grasp the large object was not equivalent to reaching-to-point. Accordingly, post-hoc analysis revealed longer RTs preceding reaching-to-point than reaching-to-grasp movements towards the large object. We obtained similar results when considering early kinematic parameters like peak velocity of the hand (HPV: Figure 2C): HPV also differed between movement types, with faster movements during reaching-to-point trials [HPV: main effect of Movement type: $F_{1,5} = 94.53$; $p < 0.001$]. Furthermore, subjects' MTs were sensitive to the size of the object to be grasped, but not to the size of the object to be pointed at [MT: interaction between Object size and Movement type: $F_{1,5} = 18.78$; $p = 0.007$]. In addition, although the MTs of the reaching-to-grasp and reaching-to-point trials were quite similar on average [MT: main effect of Movement type: $F_{1,5} = 5.56$; $p = 0.065$], the hand trajectory (HT; Figure 2D) was substantially longer when subjects were reaching-to-grasp [HT: main effect of Movement type: $F_{1,5} = 54.05$; $p < 0.001$]. As seen for the movement time, the hand trajectory was also influenced by the size of the object to be grasped, but not by the size of the object to be pointed at [HT: interaction between Object size and Movement type: $F_{1,5} = 18.42$; $p = 0.008$].

There were also obvious and trivial differences between the finger movements evoked by the reaching-to-grasp condition: the maximal grip aperture between thumb and index finger (MGA) was sensitive to the size of the object to be grasped, with the difference in the opening of the fingers scaled to the difference in the size of the small and large parts of the object. Finally, a posthoc paired T test between reaching-to-grasp the large and reaching-to-grasp the small object showed a significant difference in MGA [MGA: effect of Object Size: $T_{1,5} = -17.97$; $p < 0.001$; Reaching-to-grasp Small: 6.4 ± 0.2 cm (mean ±

standard error of the mean); Reaching-to-grasp Large: 9.8 ± 0.2 cm (mean ± standard error of the mean)]. Taken together, these results clearly indicate that, in this experiment, the act of grasping the large object does not reduce to a pointing movement.

Figure 2E illustrates the end-point variability for the thumb, index finger, and middle finger measured during the reaching-to-grasp movement towards the small and the large object. This variability index was sensitive, being able to discriminate between the larger end-point variability of the index finger and the variability of the other fingers involved in the grasping movement [main effect of Finger type: $F_{2,10} = 5.139$; $p = 0.029$]. In contrast, the size of the object to be grasped did not influence the end-point variability of the grasping movement [main effect of Object Size: $F_{1,5} = 2.788$; $p = 0.156$]. Therefore, we infer that, in this experimental setting, there are no significant differences in the spatial accuracy demands evoked by reaching-to-grasp movements towards objects of different size.

Imaging data - Volumes of interest

The random effects conjunction analysis for the effects of SMALL and LARGE (Nichols et al, 2005) masked by the visual cues (INPUT) showed extensive common cerebral activity over occipital, parietal, and frontal regions (FWE-corrected, $p < 0.05$). Figure 3A shows the common cerebral activity within the Volumes of Interest used by the DCM on a three-dimensional rendered brain.

On the basis of a priori anatomical information on the putative location of the nodes in our network, we determined subject-specific VOIs as described in the Methods section. For the input region V3A, regions in the left middle occipital gyrus were selected that responded strongly to the visual INPUT. The average group coordinate (-26 -86 18) was slightly superior to the upper border of V3A as defined by (Tootell et al., 1997), and close (< 10 mm) to the stereotaxic coordinates reported by (Pitzalis et al., 2006). The average group coordinates for V6A (-22 -64 54) fell more anteriorly, laterally, and dorsally than the average coordinates for V6, as reported by Pitzalis et al. (2006). This spatial relationship is consistent with the relative position of V6A and V6 in the macaque brain (Galletti et al., 1999).

The AIP activity obtained in the random effects analysis (-40 -52 48) was located within the standard 40% probabilistic boundary (see Eickhoff et al. 2005) of cytoarchitectonically defined hIP2 in the lower bank of the anterior intraparietal sulcus, an anatomical region suggested to correspond to AIP in the macaque (Choi et al., 2006). The single subject coordinates for AIP (average coordinates over subjects: -44 -42 46) varied between y=-32 [similar to the coordinates reported by (Simon et al., 2002)] and y=-50 [closer to the coordinates reported by Culham et al., 2003)].

The average group coordinates for PMv (-46 8 30) were located within the 50% probabilistic boundary of cytoarchitectonically defined Brodmann area (BA) 44 (Eickhoff et al, 2005) and close (< 10 mm) to the coordinates reported by (Kuhtz-Buschbeck et al., 2001; Ehrsson et al., 2000) during performance of grasping tasks. The average group coordinates for PMd (-22 -4 58) were located within the 30% probabilistic boundary of cytoarchitectonically defined BA6 and slightly medial to the coordinates of the premotor hand area as reported by (Ehrsson et al., 2000). Figure 3B shows the average group coordinates of the VOIs (*) in the y- and z- directions and the between-subject variability in 95% confidence interval ellipsoids.

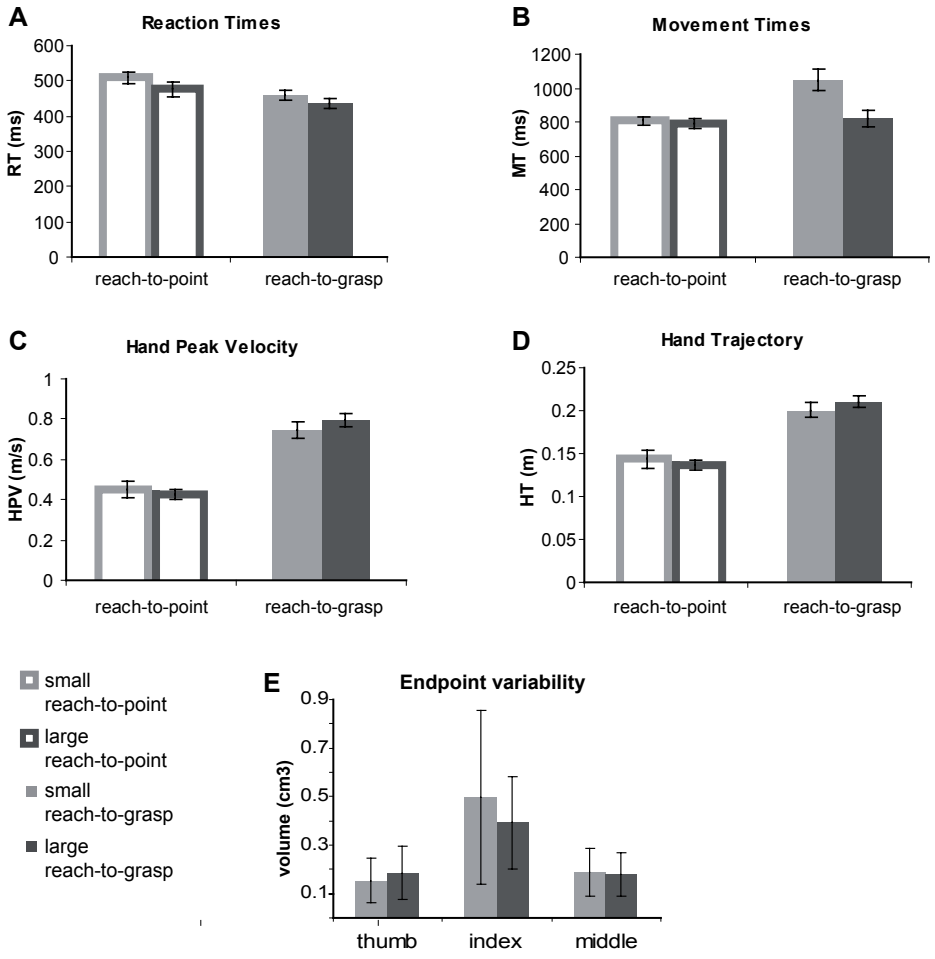

Figure 2. Behavioral results - kinematic control experiment
Movement parameters (A–D) during reaching-to-point (bold lining) and reaching-to-grasp (no lining) trials and the endpoint variability (E) during reaching-to-grasp trials toward the small (light gray) and large (dark gray) objects are shown. A–D, The histograms illustrate the group means (±SEM) as a function of movement type and object size for the following movement parameters: A, RT; B, MT; C, HPV; D, HT; E, Histogram illustrates the group mean (±SEM) as a function of object size of the three-dimensional 95% confidence intervals of the end-point position of the thumb, index finger, and middle finger.

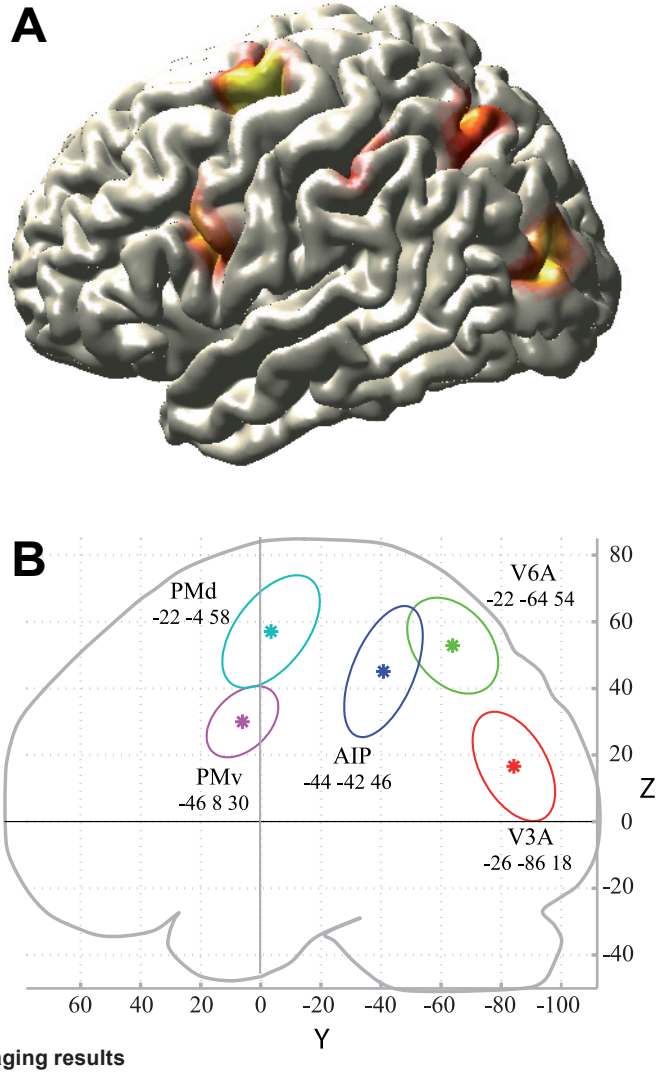

Figure 3. Imaging results

A. Random effects analysis

Cerebral activity of the random effects conjunction analysis (RFX) within the Volumes of Interest used by the DCM on a three-dimensional rendered brain.The RFX showed extensive common cerebral activity over occipital, parietal, and frontal regions (FWE-corrected, $p < 0.05$).

B. Subject-specific Volumes of Interest

Average group coordinates (*) of the single subject VOIs in the y and z directions and variability of the single subject coordinates (95% confidence intervals for each of the five regions). In the x direction, the average group coordinates for AIP and V6A and for PMd and PMv are separated by 22 and 26 mm, respectively.

Effective connectivity

Table 2, column 1, summarizes the average rate constants (Hz) for the intrinsic connections and input over subjects. During preparation and execution of a visually-guided grasp, the strength of each intrinsic connection, both forward and backward, within our model was significantly different from zero. Table 2 also shows the average rate constants over subjects for the modulatory effects of executing a grasping movement towards a SMALL (column 4) or LARGE (column 7) object. It is useful to interpret the magnitude of these modulatory changes in relation to the values of the intrinsic connections. For example, the coupling estimate for the connection from V3A to V6A increases from 0.47 to 0.57 when grasping the small object, which corresponds to an increase in coupling strength of 21% (note that the modulatory effects are additive; see Eq. 1). For completeness, the rate constants in table 2 are expressed both in real values and in percentage change relative to the intrinsic connectivity. Figure 5 shows the percentage change in connection strength for connections in which the modulatory effect was significantly different from zero. Within the dorsomedial circuit, grasping movements towards both the SMALL (Fig. 5A in green) and LARGE (Fig. 5B in red) object increased the coupling from V3A to V6A significantly, while the connection from V6A to PMd was enhanced significantly during LARGE only (see Table 2 for p-values). In contrast, within the dorsolateral circuit, the couplings, from V3A to AIP, and from AIP to PMv, were significantly enhanced only when the SMALL object was grasped.

A contrast (SMALL vs LARGE) on each of the bilinear terms, testing for differences between modulatory effects on each connection, showed a significantly stronger modulation of the interregional coupling during SMALL than during LARGE for three of the four connections. First, the forward connection between V3A and V6A was significantly more enhanced by grasping a small object than a large object ($T_{1,16}$ = 1.8; p = 0.045). In addition, the coupling from V3A to AIP was significantly more modulated by SMALL ($T_{1,16}$ = 1.97; p = 0.032); the same was true for the connection from AIP to PMv ($T_{1,16}$ = 2.03; p = 0.03). The coupling between V6A and PMd did not significantly differ between conditions ($T_{1,16}$ = .17; p = 0.379).

Table 2. Effective connectivity.
Intrinsic connectivity (column 1-3): Average rate constants (rate of change of neuronal activity (Hz) in one area as induced by another) over subjects for the intrinsic connections and their p-values. The intrinsic connectivity refers to the impact that one region exerts over another on the basis of the overall experimental context, rather than in relation to a precise experimental perturbation.

Modulation of SMALL (column 4-6) and LARGE (column 7-9): The modulatory effects of object size on the forward connections over subjects, i.e. changes in connection strength. Rate constants are expresses in real values and in percentage change relative to the intrinsic connectivity.

SMALL vs. LARGE (column 10/11): A contrast (SMALL vs. LARGE) testing whether the interregional couplings are more strongly modulated during grasping a SMALL than during grasping a LARGE object. *significant results that would not survive Bonferroni-correction.

Connections	Intrinsic connectivity			Modulation of SMALL			Modulation of LARGE			SMALL vs. LARGE	
	Rate constants	SEM	p values	Rate constants	SEM	p values	Rate constants	SEM	p values	Rate constants	p values
V3A to V6A	0.468	0.064	0.000	0.099 (21%)	0.030	0.004	0.031 (7%)	0.011	0.015*	0.068	0.045*
V3A to AIP	0.216	0.078	0.014*	0.066 (31%)	0.023	0.010	0.003 (1%)	0.021	0.895	0.064	0.032*
V6A to PMd	0.421	0.068	0.000	0.019 (5%)	0.011	0.100	0.014 (3%)	0.005	0.009	0.004	0.379
AIP to PMv	0.251	0.093	0.016*	0.026 (10%)	0.008	0.007	0.007 (3%)	0.006	0.230	0.019	0.030*
AIP to V3A	0.073	0.019	0.001	-	-	-	-	-	-	-	-
V6A to V3A	0.111	0.032	0.003	-	-	-	-	-	-	-	-
PMv to AIP	0.038	0.012	0.006	-	-	-	-	-	-	-	-
PMd to V6A	0.068	0.020	0.003	-	-	-	-	-	-	-	-
INPUT to V3A	0.158	0.028	0.000	-	-	-	-	-	-	-	-

Model selection

One might wonder whether the connectivity architecture of our model is optimal and whether alternative models might account better for the data than our model. To address this issue, we formally compared a series of alternative models (Penny et al., 2004) to select the optimal balance between accuracy and complexity of the model.

The alternative models we tested are shown in figure 4. For instance, it might be argued that the dorsomedial and dorsolateral streams are not anatomically segregated as suggested in the literature. Recent findings in macaques indicate that V6A is interconnected with AIP (Passarelli et al, 2007). We therefore estimated an alternative model (model A1) including reciprocal connections between V6A and AIP and allowed both SMALL and LARGE conditions to modulate the couplings in both directions (model A1). Table 3 shows the Group Bayes Factors (GBF) and the positive evidence ratio (PER) for each alternative model in comparison to our original model. The model comparison between model A1 and the original model shows there is strong evidence (Bayes factor ≥ 150) in favor of the original model. The positive evidence ratio (PER) for our original model over model 1 was 9:2, which concurred with the GBF in suggesting that the current model accounted better for the data than the alternative model A1.

Furthermore, F2 and F5 (the monkey homologues of PMd and PMv) are mutually interconnected (Marconi et al., 2001; Matelli et al., 1986). We therefore estimated an alternative model including reciprocal connections between PMd and PMv (model A2). We allowed both SMALL and LARGE conditions to modulate the couplings in both directions between PMd and PMv. It has also been suggested that the grasping-related activity observed in V6A could constitute an efference copy of F2 activity (Galletti et al., 1997). Therefore, we tested whether considering a modulation of object size on the feedback connection from F2 to V6A could improve the model (model A3).

Another way of allowing communication between the streams is through backward connections. In model A4 we tested whether the backward connection between AIP and V3A would be modulated by object size as well. In model A5 we allowed all the backward connections to be modulated by object size. Finally, we wanted to test whether the most complete model (model A6), which included all possible connections and modulations, would be better than our original model. Table 3 summarises the results from all model comparisons and shows that there is strong evidence (Bayes factor ≥ 150) that the original model is better than any of the alternative models.

Table 3. Model comparison - Group Bayes factors
GBF = Group Bayes factor. PER = the positive evidence ratio (PER), i.e. the number of subjects where there is positive (or stronger) evidence for the original model divided by the number of subjects with positive (or stronger) evidence for the alternative models A1 to A6. All criteria provide strong evidence in favor of the original model.

	Original vs. A1	*Original vs. A2*	*Original vs. A3*	*Original vs. A4*	*Original vs. A5*	*Original vs. A6*
GBF	309.43	1.85×10^{18}	2.34×10^{9}	2.26×10^{8}	3.62×10^{19}	1.06×10^{48}
PER	9:2	12:1	14:2	14:2	14:1	13:1

Discussion

We used DCM to evaluate whether and how the inter-regional couplings of an occipito-parieto-frontal network were modulated by grasping objects of different size, while keeping the object position relatively constant. We show that performing prehension movements alters the effective connectivity between occipital, parietal, and frontal regions (Table 2), generating stronger inter-regional couplings during the prehension of smaller objects (Fig. 5). Grasping large objects increased the connectivity of the dorsomedial circuit, whereas grasping small objects increased the connectivity of a mainly dorsolateral circuit, with a degree of overlap between these two circuits (Fig. 5). These findings suggest that the specification of prehension parameters involves different portions of the parieto-frontal network. In the following sections we elaborate on the implications of these findings for models of the neural control of prehension movements.

Behavioral performance

The experimental manipulation evoked different types of prehension movements, with different planning and execution phases for the different objects. It might be argued that grasping the large object might have minimized the grasping requirements, making this condition functionally equivalent to a pointing movement. However, the results of directly comparing the kinematics of reaching-to-grasp and reaching-to-point movements towards the large and small objects argue against this possibility. For instance, the movement execution times were sensitive to the size of the object to be grasped, but not to the size of the object to be pointed at (Fig. 2B). Movement planning times and early kinematics parameters like the peak velocity of the hand were also different during the two types of movements (Fig. 2C). These results indicate that, in this experiment, the act of grasping the large object does not reduce to a pointing movement.

It might be argued that grasping objects of different size could generate differences in movement accuracy. Control measurements of the endpoint variability of the thumb, index finger, and middle finger during the reaching-to-grasp movements argue against this possibility (Fig. 2E).

Connectivity in the dorsolateral circuit (V3A-AIP-PMv)

Several imaging studies have localized neurovascular responses evoked during visually-guided grasping movements, reporting increases in activity from a region located at the junction between the intraparietal and the inferior postcentral sulci [AIP: Culham et al., 2003; Toni et al., 2001b], and from a ventral portion of the precentral gyrus [PMv: Toni et al., 2001b]. Related studies found similar activities during object manipulations (Binkofski et al., 1999; Ehrsson et al., 2000; Johnson-Frey, 2004). Here, we show that there are specific, differential changes in effective connectivity between AIP and PMv during reaching-to-grasp movements. This finding fits with the general notion that the dorsolateral circuit is concerned with controlling grasping parameters of the prehension movement (Jeannerod et al., 1995).

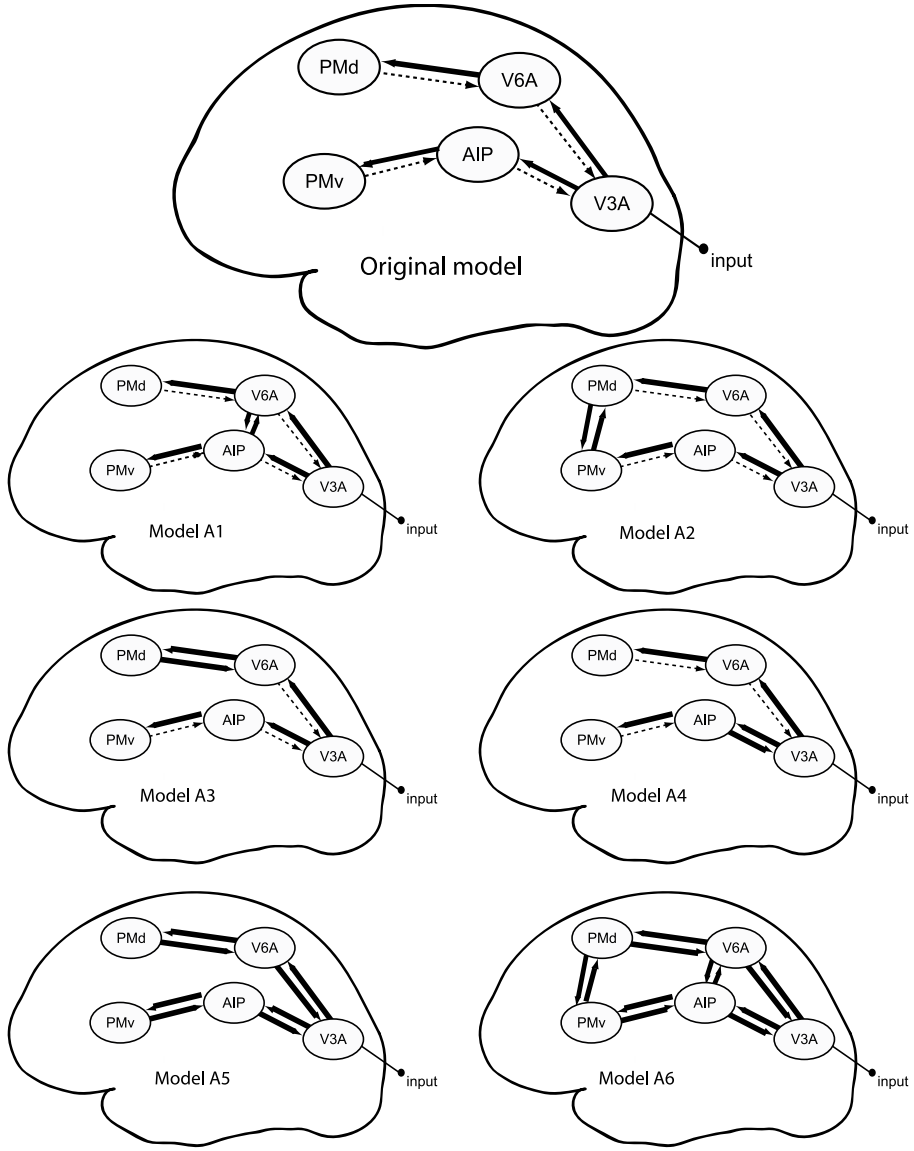

Figure 4. Model comparison
Original and alternative models for the DCM model comparison. Thick black arrows represent connections that are allowed to be modulated by both SMALL and LARGE.
Dashed arrows are intrinsic connections not allowed to be modulated. All driving inputs are the instruction cues (INPUT) that triggered the preparation of the appropriate motor program. The INPUT is fed into V3A. The resulting perturbation is allowed to propagate throughout the model via interconnections from V3A to V6A, terminating in the dorsal premotor cortex (PMd); and from V3A to AIP, terminating in ventral premotor cortex (PMv). In the original model we tested whether the forward connections in this model were differentially modulated by object size (SMALL or LARGE) during the execution of the movement. The alternative models are described in detail in the Model selection section.

On the other hand, the couplings between AIP and PMv increased more during the execution of a movement towards a small object than towards a large one. This finding is difficult to reconcile with the notion of dedicated parieto-frontal circuits for reaching and grasping.

We suggest that this increased connectivity might reflect the increased on-line control required by grasping small objects. It is known that prehension of objects with small surfaces (relative to finger size) requires a larger degree of visual feedback (Bootsma et al., 1994), and that the kinematic profile of the hand is disproportionally altered when grasping small objects without visual guidance (Chieffi and Gentilucci, 1993). Berthier et al. (1996) also showed that as visual information and object size decreased, subjects had longer movement times, slower speeds, and more asymmetrical hand-speed profiles. We suggest that, during the prehension of small objects, AIP could increase its coupling with PMv in order to transform object-centered target representations (Murata et al., 2000) into motor space (Kurata and Hoshi, 2002) on the basis of incoming visual information of the moving arm (Ochiai et al., 2005). This suggestion follows the notion that the ventral premotor cortex supports a difference vector between the current state of an effector and the target of the movements (Shadmehr and Wise, 2005). The emphasis here is on control, as the modulatory influences of object size on this dorsolateral circuit are related to the execution phase of the prehension movement. This interpretation is in line with recent TMS reports on the crucial role of the anterior intraparietal region and ventral premotor cortex during reaching-to-grasp movements (Davare et al., 2006; Rice et al., 2006; Tunik et al., 2005), where TMS was only disrupting the movement during the execution phase and not during the planning phase (Rice et al., 2006). It has also been shown that PMv activity reflects dynamical motor parameters specifically during the execution of a movement, and not during its preparation (Xiao et al., 2006).

Connectivity in the dorsomedial circuit (V3A-V6A-PMd)

We found significant increases in effective connectivity between V3A and V6A during movements directed towards both small and large objects, and a small but significant change in coupling strength between V6A and PMd during movements towards the large object. The involvement of area V6A in prehension movements is supported by its anatomical connectivity, i.e. direct projections to premotor regions controlling complex proximal and distal arm movements (Raos et al., 2003). Furthermore, it is known that both V6A and PMd are involved in processing visuospatial information for visual control of arm-reaching movements (Fattori et al., 2001; Fattori et al., 2005), and that patients with occipito-parietal lesions show severe impairments in both reaching and grasping (Jeannerod et al.,1994; Milner et al., 2003). Similarly, controlled lesions of V6A in monkeys provoked deficits in reaching, wrist orientation, and grasping (Battaglini et al., 2002). Fattori et al. (2004) recently showed that some V6A cells are specifically modulated during the grasping of visual objects. The increased effective connectivity we observed within the dorsomedial circuit during both types of prehension movements fits with the properties of V6A, and with the general notion that the dorsomedial circuit is concerned with specifying arm movements in space (Burnod et al., 1999). On the other hand, the coupling between V6A and PMd increased during reaching-to-grasp towards large objects, but not towards small objects (note however that the direct comparison between the two conditions did not reveal a significant difference). This finding is not immediately compatible with the notion of a

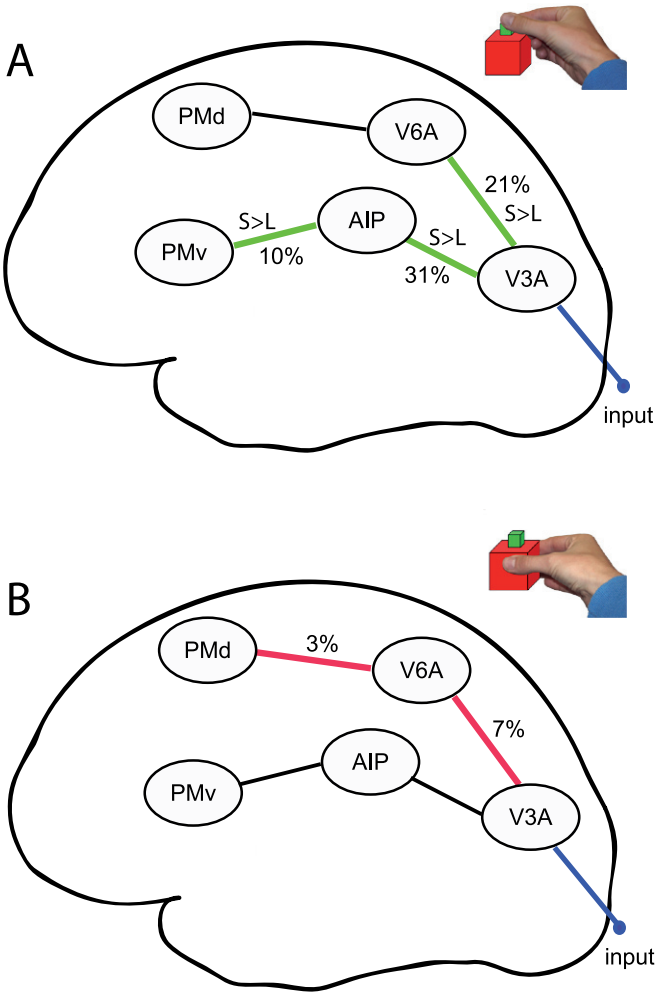

Figure 5. Effective connectivity
Modulatory effects (i.e. significant changes in connection strength) of object size on forward connections in the model (over subjects).
A: modulatory effects of executing a prehension movement towards a SMALL object (green).
S > L: The interregional couplings that are significantly stronger modulated during grasping a SMALL than during grasping a LARGE object.
B: modulatory effects of executing a prehension movement towards a LARGE object (red).

dorsomedial circuit dedicated to reaching movements. We suggest that this increased connectivity might reflect an increased reliance on advance information allowed by grasping large objects. It is known that the dorsal premotor cortex supports movement preparation and execution on the basis of advance information (Wise et al., 1997). Under the assumption that the prehension of objects with large surfaces available for finger contact can rely to a larger degree on a pre-specified motor plan (Chieffi and Gentilucci, 1993; Berthier et al., 1996), we suggest that the eye-centered, automatic motor plan generated by the superior parietal lobule irrespectively of target characteristics (Pisella et al., 2000, Medendorp et al., 2003) could be forwarded to PMd in order to incorporate the relative position of target, hand, and eyes (Pesaran et al., 2006) as well as associative rules if necessary (Toni et al., 2001b).

Interpretational limitations

These results are to be interpreted within the limitations of our modelling approach. Rather than exploring the whole space of model configurations (given our five anatomical VOIs), we used formal model selection procedures (Penny et al. 2004; Stephan and Penny, 2007) to compare models with anatomical plausibility and parsimony. An example of the latter is the choice to feed the external visual input directly into the last common node of the dorsomedial and dorsolateral streams (i.e., V3A), rather than modelling the whole retino-geniculo-striatal pathway. Analogously, we have chosen to avoid modelling primary motor cortex and the cortico-spinal motor output. These simplifications are necessary to make the models computationally tractable and enable us to focus on the most important aspects of the pathways we are interested in, but may limit the scope of interpretation.

In our second-level analyses we investigated multiple DCM parameters. Strictly speaking, this necessitates a correction for multiple comparisons. The conventional Bonferroni correction can be too severe a correction when applied to parameter estimates of dynamic system models, because it assumes complete independence between the entities tested. In dynamic system models, however, it is not infrequently the case that conditional dependencies exist amongst the parameters. Inspection of the posterior covariance matrices of our models revealed low dependencies, thus ensuring good model identifiability. Most of our significant results remained significant after applying Bonferroni correction, including the significant modulation of connections by object size (see table 2). However, the differential effect of modulation by SMALL versus LARGE did not survive correction.

Conclusions

We have explored the pattern of inter-regional couplings during a reaching-grasping task. Analysis of the changes in effective connectivity in an anatomically grounded occipito-parieto-frontal network during task performance revealed that dorsolateral and dorsomedial portions of the parieto-frontal network are modulated differently by prehension movements with different degrees of on-line control. These results argue against a strict dichotomy between the cerebral control of reaching and grasping in humans, as suggested by the two visuomotor channel hypothesis (Jeannerod et al., 1995). We suggest an alternative hypothesis, in which the relevance of the dorsolateral and the dorsomedial circuits for prehension is a function of the degree of on-line control required by the movement.

Chapter 6

SUMMARY AND CONCLUSIONS

This thesis investigated how sensory information influences the motor system through different pathways in voluntary action. Standard and non-standard sensorimotor mapping activate different neural circuits. The common goal of the experiments described in the preceding chapters was to distinguish which of these circuits is involved in what circumstances and what the mutual interactions between the areas in these circuits can tell us about the functions these pathways represent. The first two chapters investigated the question whether the routes by which visual information reaches the motor cortex changes under the influence of learning. With fMRI it was investigated whether parietal areas would become involved during arbitrary visuomotor learning if the associations would be sufficiently overlearned. To further define the role of the PPC in arbitrary visuomotor mapping, the nature of the representation of the overlearned associations was tested in a psychophysics experiment.

The last two chapters of this thesis each described novel approaches used to respectively acquire and analyse fMRI data of visually-guided reach-to-grasp movements. The first approach was concerned with solving the technical challenges associated with grasping in the scanner. The other approach was the introduction of analyses of effective connectivity into the field of motor control, asking whether reaching and grasping are distinct processes represented along anatomically segregated parietofrontal pathways. The current chapter summarizes the conclusions from the experimental chapters and gives suggestions for future research.

PPC in arbitrary sensorimotor mapping

In chapter 2 was investigated whether arbitrary visuomotor associative behavior, either next to or independent from its reliance on frontostriatal and frontotemporal circuits (Toni et al., 2001a, Wise and Murray, 2000, Canavan et al., 1989; Passingham, 1993; Toni and Passingham, 1999), involves the dorsal stream for the guidance of the motor response, when these mappings become overlearned. We speculated that the neural distinctions between arbitrary visuomotor associative behavior and spatially-guided movement (Milner and Goodale, 1995, Toni et al, 2001a) might not be structural in nature. As on one side the object affordances that automatically drive spatially-guided movements (Grezes et al, 2003) are suggested to be the end result of a learning process that abstracts relevant stimulus features (Oztop et al., 2004), and on the other side arbitrary mappings can be trained to a high degree of automaticy (Shadmehr and Wise, 2005; Packard and Knowlton, 2002; White and McDonald, 2002; Graybiel, 1995;), it is possible that standard and non-standard sensorimotor mapping are instances of the same phenomenon measured in different stages of its evolution. We hypothesized that when arbitrary visuomotor associations become automatic, PPC might become involved in arbitrary visuomotor mapping as it is in spatially-guided movement (Sakata et al, 1995).

To test this hypothesis, fMRI was used to compare cerebral activity during different stages of learning arbitrary visuomotor associations. Subjects were either learning novel arbitrary visuomotor associations, overlearning known mappings, or attempting to learn frequently changing novel mappings. Crucially, rather than comparing the average strength of the neurovascular signal evoked during these conditions, we have isolated differential time-dependent modulations to define cerebral activity associated with the dynamic process of learning. We were specifically interested in the neural consequences of overlearning arbitrary visuomotor associations, testing whether and where changes in cerebral activity support the automatization of performance as compared to initial learning of new associations.

We found that frontal, striatal, and intraparietal regions revealed consistent time-dependent increases in activity while subjects were performing overlearned associations. Crucially, during overlearning increases in cerebral activity were observed while at the same time behavioral performance was time-invariant. Learning or attempting to learn novel associations resulted in decreased or stable activity in these same areas, together with increases in ventral-occipital and temporal regions.

These data confirm and extend earlier findings that suggest frontostriatal and frontotemporal circuits to play a crucial role in visuomotor associative learning. The learning-related increases in ventro-occipital and temporal areas are consistent with the necessary ventral stream involvement in the identification of the visual stimuli. The learning-related decreases and increases in the striatum in different phases of learning support both early and late changes in striatal responses that have been reported (Hadj-Bouziane and Boussaoud, 2003; Pasupathy and Miller, 2005; Brasted and Wise, 2004) and confirm the role of the striatum during overlearned performance of arbitrary visuomotor associations (Nixon et al., 2004b). Previous imaging studies failed to show significant learning-related changes in activity in the dorsal premotor cortex (Boettiger and D'Esposito, 2005; Deiber et al.,

1997; Toni et al., 2001b; Toni and Passingham, 1999). The opposite dynamics generated in PMd during different learning stages confirm that this region contributes to both initial learning and retention of arbitrary visuomotor associations (Halsband and Freund, 1990; Kurata and Hoffman, 1994; Petrides, 1997).

PPC activity showed a learning-related decrease during initial learning, confirming previous reports (Deiber et al., 1997; Toni et al., 2001b). The same PPC cluster increased its activity during overlearned performance. Interestingly, performance did not change during overlearning. This finding illustrates how a rich cerebral dynamics can lie beneath a stable behavior. When we would have considered the average activity measured during overlearning as compared to new learning instead of changes in trial-by-trial activity as we have done now, we would have seen the parietal signal decreasing. This shows that imaging in some cases can provide more sensitive measures of cognitive change than behavior (Wilkinson and Halligan, 2004).

Together, these results suggest that different but not completely segregated circuits support visuomotor mappings at different stages of task proficiency. Crucially, the dynamics of parietal activity indicate that, once the mappings are becoming automatic, this region might join fronto-striatal circuits and contribute to the performance of arbitrary visuomotor associations. Once visuomotor associations become robust to interference, PPC might start to convey relevant sensory information towards the motor cortex.

It remains to be seen whether the information that PPC conveys relates to the identity of the visual cue or to the selection of the motor response. The fact that we can arbitrarily couple almost any stimulus to any response suggests that arbitrary visuomotor associations are represented at a high level and not bound to a specific sensory or motor system. Moreover, these movement representations are believed to be independent of the actual presence of the visual information or the execution of the motor response (Toni et al., 2002b). The PPC seems to be able to dissociate between different courses of action defined by the visual stimuli specifying the arbitrary movements, regardless of whether the visual stimuli are followed by an actual movement (Thoenissen et al., 2002). Research seems to indicate that PPC is able to encode spatial information both in hand-centered and head-centered reference frames and is thought to transform target locations directly between these reference frames (Andersen and Buneo, 2002). The parietal involvement found in chapter 2 suggests that overlearned visuomotor associations could come to rely on a spatial framework, similarly to spatially-guided movements. Alternatively, it is possible that the PPC contribution to overlearned visuomotor associations is non-spatial in nature, as suggested by the finding that after extensive training this region can encode non-spatial features of instructions that are relevant to the task (Sereno and Maunsell, 1998; Toth and Assad, 2002).

Accordingly, in chapter 3 was investigated whether overlearned arbitrary visuomotor associations are represented in a motor or in a spatial framework. The nature of the movement representation of motor skill has been explored for spatially guided movement and motor sequence learning, but not for arbitrary visuomotor mapping. An interference procedure was applied to see how performance of extensively trained arbitrary visuomotor associations depends on the effector used to provide the response.

After an initial extensive training on performance of these associations, subjects were asked to perform the same task in a novel setting that interfered with either the spatial or the motor coordinates of their performance. Following this manipulation, we

also tested whether performing the visuomotor associations in the original training setting was influenced by the type of interference experienced by the subjects. We found that performance was influenced by this experimental manipulation, with stronger interference effects following spatial alterations in the relationship between visual instructions and finger movements that preserved the instruction-to-finger mapping. This result suggests that extensively trained arbitrary visuomotor associations are retrieved using a spatial framework. These data are compatible with the notion that overtrained arbitrary mapping come to rely on a spatial framework linking visual instructions with locations in space (the buttons of the keypad). It can also be inferred that these arbitrary mappings become independent from direct couplings between stimuli and finger movements, i.e. they come to rely on an effector-independent representation.

Motor sequences, after sufficient learning, can be performed irrespectively of visual instructions, whereas in arbitrary visuomotor mapping each instruction remains necessary for selecting the correct response. Accordingly, the findings in chapter 2 support the observation that overlearned visuomotor associations might not only rely on a frontostriatal circuit for deciding on the action to perform in a certain context (Toni and Passingham, 1999; Wise and Murray, 2000; Nixon et al., 2004;). They also seem to come to rely on portions of the posterior parietal cortex known to be involved in spatially guided behavior (Sakata et al., 1995) to determine how actions are performed. In addition, the findings in chapter 3 suggest that once the coupling between a stimulus and the spatial location of the associated motor response has become automatic, the movement of the finger towards this location might start to resemble a spatially-guided movement.

To summarize, during learning arbitrary visuomotor associations the increased coupling of the stimulus to its location in space might change the arbitrary mapping into a more spatially-guided movement, calling for involvement of the posterior parietal cortex in overlearned visuomotor behavior, while frontostriatal circuits are still important for deciding which action to undertake.

Further experiments are necessary to confirm the learning-related nature of the cerebral changes reported in chapter 2. Investigating the evolution of arbitrary visuomotor learning over significantly longer timespans could further elucidate the issue of whether arbitrary and spatially-guided movements are veritably instances of the same time-varying phenomenon instead of structurally different. To identify the common denominators and differentiating features underlying arbitrary sensorimotor mapping, the learning of different mappings should be explored by systematically varying the coupling between different kinds of sensory stimulation (visual, auditive, tactile) and motor outputs (different effectors).

Although the associations learned in chapter 2 have no semantic meaning, we found a time-dependent decrease in BOLD signal during the learning of novel associations, followed by an increase during the first blocks of automatic performance, in an area localized within the probabilistic borders of BA44/45. This result confirms previous reports on the involvement of this region in the initial learning and the long-term retention of arbitrary visuomotor associations. This area has been associated with orthographic-to-phonologic transformations, a particular class of arbitrary visuomotor transformations (Indefrey and Levelt, 2004; Nixon et al., 2004a). By exploring the continuum between visuomotor mappings as implemented in our experiments and orthographic-to-phonologic transformations we could investigate the role of orbital prefrontal areas in arbitrary mapping, as this map-

ping ability may have been of crucial importance in the evolution of human language (Wise and Murray, 2000).

It has been suggested that both effector-dependent and effector-independent representations play a role in learning motor skills, with a relative contribution that varies as a function of the learning stage (Nakahara et al., 2000, Bapi et al., 2000, Hikosaka et al., 1999). Fast improvements in accuracy early in learning have been associated with effector-independent representations, while slow improvements in speed later in learning could rely on effector-dependent representations. Accordingly, it could be argued that our observation window was biased towards fast (effector-independent) changes, rather than towards slow (effector-dependent) changes. To be able to assess whether a more slowly evolving effector-dependent representation has been learned concurrently to the effector-independent representation reported in chapter 3, spatial and motor representations have to be manipulated at different stages of learning. It furthermore might be interesting to assess with fMRI the changes in cerebral activity in PPC in respons to changing the spatial or the motor relationship between visual instructions and finger movements of overlearned associations.

PPC in standard sensorimotor mapping

In chapter 4 a new protocol was described for studying visually-guided reach to grasp movements in an fMRI experimental setup. The usefulness of this protocol was illustrated by describing how its application allowed to investigate a couple of questions with fMRI data acquired during natural visually-guided grasping. The combination of specific scannerproof mechanical devices, experimental design, and image analysis makes it feasible to study visually-guided reach to grasp movements using standard MR equipment and accessories, while allowing subjects to perform ecologically relevant movements with free gaze. We showed that the experimental setup resulted in natural prehension movements as the visually-guided reach-to-grasp movements in the experiment had comparable kinematic properties as were observed in previous psychophysical studies (Dijkerman and Milner, 1998).

The sensors on the mechanical grasping devices allowed to identify different phases of the movement, enabling to differentiate between cerebral activity during movement planning and during movement execution. This was of crucial importance for the study performed in chapter 5. With a simple diagnostic tool assessing the temporal relationship between task events and head motion we could evaluate the severity of the head movement artefacts. Meaningful BOLD activity related to the experimental task could be dissociated from other sources of variance including the direct and indirect effects of moving the hand in the MR-environment. Modelling the head movements and the global signal changes generated by arm and hand motion during image acquisition greatly improved the statistical model. This protocol was developed and tested in the context of another study investigating dorsal and ventral stream contributions to visuomotor transformations (Verhagen et al, in preparation) and was applied to another grasping experiment investigating

the role of immediate and final goals in action planning (Majdandžić et al, 2007). In the study by Verhagen et al. (In preparation) it is hypothesized that when movement-related visual information is absent *and* perceptual information is necessary for planning a correct movement, i.e. under monocular vision, the ventral stream has to increase its relative functional integration with the dorsal stream. As it was found that PMv and LOtv increase their effective connectivity with AIP during monocular trials as the deviation of the target object from the vertical increased, it is suggested that the dorsolateral stream, consisting of AIP and PMv, is involved in the visuomotor process, operating on the basis of perceptual visual information provided by LOtv.

The study of Majdandžić (2007) showed that a different fronto-parietal circuit is involved when planning a sequence of movements on basis of a desired end-goal than when performing the same action by selecting movements spatially compatible with given object properties.

The grasping data of this last dataset were analysed in a novel analysis focusing on prehension movements towards objects of different size. As described in the introduction, dedicated parietal areas have been found to be involved in either reaching or grasping movements, leading to the two-visuomotor-channel hypothesis (par 1.2.1). This hypothesis suggests that a functional dichotomy exists between reaching and grasping along respectively a dorsomedial pathway, consisting of V6A and dorsal premotor cortex, and a dorsolateral pathway, from AIP to ventral premotor cortex. In chapter 5 an alternative possibility was tested, namely that the relative contribution of these parietofrontal circuits to reaching-grasping behavior is related to the degree of online control required by the prehension movement. Functional imaging had identified the areas involved in prehension, but had not yet explored the effective connectivity within this circuits. Hence, the knowledge about the neural activity associated with prehension movements was combined with the available knowledge about the connectional structure binding the areas involved together, resulting in a occipito-parieto-frontal network shown in fig.5.7. We used Dynamic Causal Modelling (DCM, Friston et al., 2002) to evaluate whether and how the inter-regional couplings of this network were modulated by grasping objects of different height and width, while keeping the object position relatively constant.

We show that performing prehension movements alters the effective connectivity between occipital, parietal, and frontal regions, generating stronger inter-regional couplings during the prehension of smaller objects. Grasping large objects increased the connectivity of the dorsomedial circuit, whereas grasping small objects increased the connectivity of a mainly dorsolateral circuit, with a degree of overlap between these two circuits (Fig. 5.7). These findings suggest that the specification of prehension parameters involves different portions of the parieto-frontal network. The specific, differential changes in effective connectivity between AIP and PMv during reaching-to-grasp movements fit with the general notion that the dorsolateral circuit is concerned with controlling grasping parameters of the prehension movement (Jeannerod et al., 1995). On the other hand, the couplings between AIP and PMv increased more during the execution of a movement towards a small object than towards a large one. This finding is difficult to reconcile with the notion of dedicated parieto-frontal circuits for reaching and grasping. We suggest that this increased connectivity might reflect the increased on-line control required by grasping small objects.

In addition, we found increased effective connectivity between V3A and V6A during

movements directed towards *both* small and large objects, and a small but significant change in coupling strength between V6A and PMd during movements towards the large object, but not towards the small object. The first finding fits with the properties of V6A, and with the general notion that the dorsomedial circuit is concerned with specifying arm movements in space (Burnod et al., 1999). However, the second finding is not immediately compatible with the notion of a dorsomedial circuit dedicated to reaching movements.

It is known that prehension of objects with small surfaces (relative to finger size) requires a larger degree of visual feedback (Bootsma et al., 1994). We suggest that, during the prehension of small objects, AIP could increase its coupling with PMv in order to transform object-centered target representations (Murata et al., 2000) into motor space (Kurata and Hoshi, 2002) on the basis of incoming visual information of the moving arm (Ochiai et al., 2005). We suggest that the increased connectivity between V6A and PMd during the grasping of the large object might reflect an increased reliance on advance information allowed by grasping large objects. It is known that the dorsal premotor cortex supports movement preparation and execution on the basis of advance information (Wise et al., 1997). Under the assumption that the prehension of objects with large surfaces available for finger contact can rely to a larger degree on a pre-specified motor plan (Chieffi and Gentilucci, 1993; Berthier et al., 1996), we suggest that the eye-centered, automatic motor plan generated by the superior parietal lobule irrespectively of target characteristics (Pisella et al., 2000, Medendorp et al., 2003) could be forwarded to PMd in order to incorporate the relative position of target, hand, and eyes (Pesaran et al., 2006) as well as associative rules if necessary (Toni et al., 2001b).

In summary, these results showed that investigating effective connectivity provides a new perspective on the two visuomotor channel hypothesis. Analysis of connectivity revealed that dorsolateral and dorsomedial portions of the parieto-frontal network are modulated differently by prehension movements with different degrees of on-line control. These results argue against a strict dichotomy between the cerebral control of reaching and grasping in humans. Alternatively, we suggest that the relevance of the dorsolateral and the dorsomedial circuits for prehension is a function of the degree of on-line control required by the movement.

It might be argued that grasping the large object might have minimized the grasping requirements, making this condition functionally equivalent to a pointing movement. Kinematic results have indicated that, in the experiment of chapter 5, the act of grasping the large object does not reduce to a pointing movement. Nevertheless, it might be worth to explore the effective connectivity of the parietofrontal circuits in a novel version of the fMRI experiment with an additional pointing condition only consisting of an arm movement towards the object. Manipulating the object distance together with the manipulation of object size might further elucidate the mechanisms underlying prehension.

Although the two-visuomotor channel theory expresses a clear systems-level perspective, until the event of effective connectivity analyses it had not been possible to address the important questions regarding this theory experimentally. Although we had means to measure anatomical connectivity and cerebral activity in segregated brain areas, we lacked methodological and analytical tools to investigate functional interactions between areas in dedicated circuits. The findings of chapter 5 clearly show how our research can be enriched by incorporating these analyses into our research practice.

Naturally, effective connectivity analyses, like DCM, have their limitations. One of the

strenghts, but equally one of the drawbacks of DCM is its model-driven nature. Our results are bound to the validity of our model. We can only include a limited amount of areas in our models, so the question always remains whether we have erroneously omitted an area that significantly influences the areas included in the model. Furthermore, the anatomical connectivity we use to build our model on, is mainly inferred from tracer studies in non-human primates. In the connectivity database CoCoMac (http://www.cocomac.org) thousands of data from tracing studies in macaque monkeys are described. However, defining clear homologies between the macaque and human brain has proven to be complicated. As DCM models the effective connectivity as a propagation of activity through these anatomical connections, ill-defined models or inaccurate anatomical connectivity between the nodes in the network under study can result in erroneous inferences about the effective connectivity. One solution to this problem might come from diffusion tensor imaging (DTI) that allows us to study large white matter tracts in the human brain in vivo. Combining the individual patterns of cerebral activity with the subject-specific tractography might improve the anatomical plausibility of the DCM's. Unfortunately, DTI tractography in its current state is not able yet to yield sufficiently reliable results, suffering as this technique still is from the amount of false positive and false negative results and coarse spatial resolution (Roebroeck, 2006). Other steps forward could come from the combination of model-driven and exploratory effective connectivity methods, like Granger Causality, that could guide the selection of nodes for the network model to test. Another important concern is that fMRI data are always an indirect measure of neural activity. In time, the simultaneous acquisition of fMRI and EEG or MEG that have a much higher temporal resolution might solve some of the current problems.

But although analyses of effective connectivity still have a long way to go, I am convinced the future of neuroimaging lies in framing our questions in terms of pathways and circuits, instead of focussing on the functional properties of single areas.

Resuming: parietofrontal circuits in sensorimotor mapping

The fundamental question in neuroscience that this thesis tried to contribute to, is the question how sensory cues influence the motor system (Toni and Passingham, 1999, Passingham et al., 1998). It is well established that different circuits in the brain allow visual information to reach the motor system. It was shown that the parietofrontal circuits involved in standard and non-standard visuomotor mapping are not functionally segregated in the way they are generally believed to be. The first two chapters showed that the routes by which visual information reaches the motor cortex change under the influence of learning. The findings in chapter 2 and 3 led us to conclude that the performance of overlearned visuomotor associations does not only rely on frontostriatal circuits for deciding what action to perform in a certain context, but also on the posterior parietal cortex to determine how actions are performed. Chapter 4 showed that it is feasable to study ecologically valid reach-to-grasp movements in a scanner environment. The studies to which the proposed protocol for studying visually-guided grasping was applied, indicated that the routes by

which visual information reaches the motor cortex can also change under the influence of the amount of depth information available for vision and are subject to the level at which a visually-guided action is planned. Chapter 5 argues against a strict dichotomy between the cerebral control of reaching and grasping along dorsoventral and dorsomedial pathways, as suggested by the two visuomotor channel hypothesis (Jeannerod et al., 1995). It is suggested that the relevance of the dorsolateral and the dorsomedial circuits for prehension is a function of the degree of on-line control required by the movement. The results of chapter 5 clearly show how important it is to investigate the brain from a systems-level perspective and explore the functional interactions between brain areas by methods of effective connectivity.

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DUTCH SUMMARY

Een belangrijke vraag binnen de cognitieve neurowetenschappen is de vraag hoe visuele informatie het motorische systeem beïnvloedt (Toni and Passingham, 1999, Passingham et al., 1998). Visuele informatie kan via verschillende paden in de hersenen het motorische systeem bereiken. Twee corticale paden houden zich bezig met visuele perceptie: een dorsaal ('rugwaarts') visueel pad met de visuele sturing van beweging; een ventraal ('buikwaarts') pad met de waarneming en herkenning van objecten (Ungerleider and Mishkin, 1982; Goodale and Milner, 1992). Deze paden zijn onderdeel van een veel groter netwerk en er zijn dan ook veel onderlinge verbindingen tussen de paden gevonden.

Welk pad of circuit in of voor welke situatie gebruikt wordt, hangt af van de aard van de informatieverwerking die nodig is voor het omgaan met de situatie waarin we ons op dat moment bevinden. Zo kan het motorische systeem op allerlei verschillende manieren reageren op de binnenkomende visuele informatie. We kunnen een rechtstreekse beweging in de richting van de locatie van een object maken, zoals wanneer wij een deurknop vastpakken om een deur te openen. Maar als zich naast de deur een grote rode knop bevindt, kunnen wij de deur ook indirect openen door op de rode knop te drukken.

Wanneer de locatie van een object onze beweging rechtstreeks aanstuurt, zoals in het geval van de deurknop of wanneer we een kopje van de tafel pakken, dan noemen wij dit standaard visuomotor mapping (Wise et al., 1996a). Als de associatie tussen het object en de beweging niet gestuurd wordt door de spatiële informatie, maar willekeurig is - zoals in het geval van de rode knop of wanneer het rode verkeerslicht op groen springt en wij hard op het gaspedaal trappen - dan wordt dit niet-standaard of willekeurige visuomotor mapping genoemd (Wise and Murray, 2000).

Verschillende netwerken zijn betrokken bij deze soorten beweging, met een zekere mate van overlap tussen de netwerken. Standaard visuomotor mapping, ofwel spatieel gedreven beweging, wordt aangestuurd door een specifiek netwerk tussen gebieden in de pariëtale en frontale hersenschors (een pariëto-frontaal netwerk; Milner and Goodale, 1995). Van willekeurige visuomotor associaties wordt aangenomen dat ze vooral gerepresenteerd zijn in een netwerk tussen gebieden in de frontale hersenschors en het striatum (een fronto-striataal netwerk; Wise and Murray, 2000; Toni et al, 2001a). Deze onderwerpen worden uitgebreid beschreven in de inleiding, zie daarvoor hoofdstuk 1.

In dit proefschrift ligt de nadruk op de verschillende pariëto-frontale circuits die een rol spelen bij zowel standaard als willekeurige visuomotor mapping. De hoofdstudies waarvan in dit proefschrift verslag wordt gedaan, zijn uitgevoerd met functionele magnetische resonantie imaging (fMRI), een moderne beeldvormingstechniek, waarmee het mogelijk is om hersenactiviteit te meten terwijl een proefpersoon een taak uitvoert. Het is daarbij van groot belang om niet alleen te achterhalen welke hersengebieden actief zijn bij het uitvoeren van een taak, maar ook om te zien hoe deze gebieden met elkaar communiceren. De directe invloed van het ene gebied op het andere wordt effectieve connectiviteit genoemd. Theorieën over bewegingssturing worden vaak verwoord in termen van netwerken en

circuits. Echter, door een gebrek aan geschikte methoden en analyses zijn veel vragen die vanuit dit systeemgerichte perspectief ontstonden experimenteel onbeantwoord gebleven. Naast standaard fMRI analyses zijn in dit proefschrift daarom ook connectiviteits-analyses uitgevoerd om de functionele koppeling tussen de hersengebieden binnen de pariëto-frontale circuits te verkennen en nieuwe hypothesen over de functie van deze circuits te testen.

In hoofdstuk 2 en 3 van dit proefschrift wordt beschreven hoe is onderzocht in hoeverre de routes waarlangs visuele informatie de motor cortex bereikt veranderen onder invloed van leren. In hoofdstuk 2 ligt de nadruk op de vraag in hoeverre langdurig geoefende willekeurige visuomotor associaties, naast fronto-striatale en fronto-temporale circuits (Toni et al., 2001a, Wise and Murray, 2000), het dorsale pad gebruiken om de beweging te sturen. Het bovengenoemde neurale onderscheid tussen willekeurige visuomotor associaties en spatieelgedreven bewegingen hoeft niet structureel te zijn. Het zou ook een uiting van eenzelfde fenomeen in verschillende ontwikkelingsfasen kunnen zijn. Men heeft eerder gesuggereerd dat de automatische object affordances (= het impliciet besloten zijn van een bepaalde handeling in een object) die een beweging sturen (Grezes et al, 2003) het eindresultaat van een lang leerproces zijn (Oztop et al., 2004). Daarnaast is het mogelijk om willekeurige associaties te leren tot zij in hoge mate automatisch zijn (Shadmehr and Wise, 2005). De verwachting was dat de posterior pariëtale cortex (PPC), waarvan we weten dat het actief is bij spatieel gedreven beweging (Sakata et al, 1995), dan ook actief zou worden zodra willekeurige visuomotor associaties geautomatiseerd werden.

Met fMRI werd de hersenactiviteit in verschillende fasen van het leren van de visuomotor associaties met elkaar vergeleken. In het experiment leerden de proefpersonen nieuwe associaties, voerden associaties uit die ze al lang getraind hadden (overlearning) waren en probeerden daarnaast ook associaties te leren die regelmatig veranderden. Om te hersenactiviteit te kunnen bepalen die met het dynamische leerproces samenhangt, werden de tijdsafhankelijke veranderingen in hersenactiviteit met elkaar gecontrasteerd.

Frontale, striatale en intrapariëtale gebieden lieten consistente tijdsafhankelijke toenames in activiteit zien wanneer proefpersonen automatische associaties (overlearning) uitvoerden. Nieuwe associaties leren of deze proberen te leren, resulteerde in afnemende of stabiele activiteit in dezelfde gebieden, naast toenames in ventraal-occipitale en temporale gebieden. Deze resultaten sluiten aan bij eerdere bevindingen dat fronto-striatale en fronto-temporale circuits een cruciale rol spelen in visuomotor associatief leren. PPC activiteit liet een leergerelateerde afname zien tijdens initieel leren, wat eveneens eerdere rapportages bevestigd (Deiber et al., 1997; Toni et al., 2001b). De activiteit in hetzelfde PPC cluster nam toe tijdens overlearning. De taakprestatie veranderde hierbij niet, wat laat zien dat een rijke cerebrale dynamiek ten grondslag kan liggen aan stabiel gedrag en dat imaging in sommige gevallen een gevoeligere maat voor cognitieve verandering is dan gedrag (Wilkinson and Halligan, 2004).

Samenvattend suggereren deze resultaten dat visuomotor associaties in verschillende fases van taakbekwaamheid door verschillende, maar niet losstaande circuits worden gerepresenteerd. In het bijzonder lijken de dynamische veranderingen in pariëtale activiteit erop te wijzen dat, zodra de associaties overlearned zijn, dit gebied zich aansluit bij fronto-striatale circuits om de uitvoering van willekeurige visuomotor associaties te ondersteunen. Zodra visuomotor associaties zo automatisch zijn dat ze bestand raken

tegen interferentie, begint de PPC mogelijk met het doorgeven van relevante sensorische informatie aan de motor cortex.

De gevonden PPC activiteit wijst erop dat overlearned visuomotor associaties gerepresenteerd zouden kunnen zijn in een spatieel schema, net als spatieel gedreven bewegingen. Aan de andere kant zijn er aanwijzingen dat dit gebied na training niet-spatiële taakrelevante kenmerken kan coderen (Sereno and Maunsell, 1998; Toth and Assad, 2002). Daarom werd onderzocht of langdurig geoefende visuomotor associaties in een motorische of een spatiële structuur gerepresenteerd zijn. Hoofdstuk 3 bevat de belangrijkste bevindingen uit dit onderzoek.

Na intensieve training van de associaties werd de proefpersonen gevraagd om dezelfde associatietaak in een nieuwe opstelling uit te voeren, waarin ofwel de spatiële danwel de motorische relatie tussen de visuele instructies en vingerbewegingen was veranderd. Na deze manipulatie werd getest of de taakprestatie in de originele trainingsopstelling werd beïnvloed door het type interferentie waaraan de proefpersonen werden onderworpen.

De resultaten gaven aan dat taakprestatie werd beïnvloed door de experimentele manipulatie, met sterkere interferentie-effecten na spatiële veranderingen in de relatie tussen visuele instructies en vingerbewegingen, waarbij de motorische koppeling tussen instructie en vinger hetzelfde bleef. Dit suggereert dat langdurig getrainde willekeurige visuomotor associaties gerepresenteerd worden in een spatiële structuur waarin de visuele instructies aan locaties in de ruimte (de toetsen van de knoppenbox) gekoppeld worden, onafhankelijk van de directe koppeling tussen stimuli en vingerbeweging.

Hoofdstuk 4 en 5 richten zich op de pariëto-frontale circuits die betrokken zijn bij het oppakken van voorwerpen. Bij het oppakken van een voorwerp moet zowel visuospatiële informatie over de extrinsieke kenmerken (de spatiële locatie) als de intrinsieke kenmerken (grootte, vorm en oriëntatie) van het voorwerp verwerkt worden. Dienovereenkomstig kan een grijpbeweging verdeeld worden in een reikcomponent, die de hand richting het voorwerp leidt op basis van de extrinsieke kenmerken, en een grijpcomponent, die de vingers voorvormt op basis van de intrinsieke kenmerken. In neurale termen lijkt deze tweedeling weerspiegeld te worden in, respectievelijk, een dorsomediaal “reik-circuit”, bestaande uit gebied V6A en de dorsale premotor cortex (PMd), en een dorsolateraal “grijp-circuit” gevormd door de anterior intrapariëtale cortex (AIP) en de ventrale premotor cortex (PMv) (Jeannerod et al., 1995). Deze theorie wordt de “twee visuomotor kanalen hypothese” genoemd.

Het is niet triviaal grijpbewegingen te bestuderen in een fMRI-scanner. Daarom wordt in hoofdstuk 4 een nieuw protocol beschreven dat, door middel van een combinatie van specifieke voor de scanner geschikte apparaten, experimenteel design en data-analyse, het haalbaar maakt om grijpbewegingen te bestuderen met gebruikmaking van de standaard MR uitrusting en accessoires, terwijl het tegelijkertijd voor de proefpersonen mogelijk is zo natuurlijk mogelijke bewegingen uit te voeren met vrij zicht op het te pakken voorwerp. De toegevoegde waarde van dit protocol is in hoofdstuk 4 uitgelegd en geïllustreerd met voorbeelden van toepassingen. Dit protocol is eveneens gebruikt om de data te verzamelen die in hoofdstuk 5 zijn geanalyseerd.

De “twee visuomotor kanalen hypothese” is niet eerder getoetst door middel van het bestuderen van de effectieve connectiviteit binnen deze circuits. In hoofdstuk 5 wordt beschreven hoe Dynamic Causal Modelling (DCM, Friston et al., 2003) is gebruikt om te

evalueren of en op welke manier de interregionale interacties binnen het bovengenoemde occipito-pariëto-frontale netwerk gemoduleerd worden door het grijpen van voorwerpen van verschillende grootte, terwijl de positie van het object constant blijft. Het blijkt dat het uitvoeren van grijpbewegingen de effectieve connectiviteit tussen occipitale, pariëtale en frontale gebieden verandert, waarbij sterkere regionale interacties optreden tijdens het pakken van kleinere objecten. Het pakken van het grotere object verhoogde de connectiviteit van het dorsomediale “reik” circuit, terwijl bij het pakken van een kleiner object de connectiviteit in voornamelijk het dorsolaterale “grijp” circuit toeneemt, met een bepaalde mate van overlap tussen de twee circuits.

Deze bevindingen suggereren dat bij de specificatie van de bewegingsdetails voor reik-grijpbewegingen verschillende delen van het pariëto-frontale netwerk betrokken zijn. De specifieke, differentiële veranderingen in effectieve connectiviteit tussen AIP en PMv tijdens reik-grijpbewegingen sluiten aan bij het algemene idee dat het dorsolaterale circuit zich bezighoudt met het vaststellen van de grijpparameters van de pakbeweging (Jeannerod et al., 1995). Echter, de interactie tussen AIP en PMv blijkt meer toe te nemen tijdens het uitvoeren van een beweging richting het kleine object dan bij een beweging in de richting van het grote object. Dit gegeven is moeilijk te integreren in de theorie van aparte pariëto-frontale circuits voor reiken en grijpen. Daarnaast is een toename in effectieve connectiviteit tussen V3A en V6A geobserveerd tijdens bewegingen zowel richting grote als kleine objecten. Ook is een kleine, maar significante verandering in de sterkte van de koppeling tussen V6A en PMd tijdens het pakken van het grote, maar niet het kleine object, geconstateerd. Dit eerste resultaat sluit aan bij eerdere bevindingen dat V6A betrokken is bij zowel grijpen als reiken (Fattori et al, 2004) en bij de theorie dat het dorsomediale circuit zich bezighoudt met het specificeren van armbewegingen in de ruimte (Burnod et al., 1999). De tweede is daarentegen niet compatibel met het idee van een dorsomediaal ‘reik’-circuit. Onze resultaten gaan daarom in tegen een strikte tweedeling in een grijp- en reikcircuit, zoals in de twee visuomotor kanalen hypothese wordt gesteld.

Het is bekend dat het pakken van objecten met een kleinere oppervlakte (in verhouding tot vingergrootte) een hogere mate van online controle behoeft (Bootsma et al., 1994). Wij suggereren dat tijdens het pakken van kleine objecten AIP haar koppeling met PMv verhoogt, om zo de objectgerichte doelrepresentaties (Murata et al., 2000) te transformeren naar de motorische ruimte (Kurata and Hoshi, 2002). Dit op basis van de inkomende visuele informatie van de bewegende arm (Ochiai et al., 2005). Daarbij komt dat de toegenomen connectiviteit tussen V6A en PMd tijdens het pakken van het grote object erop lijkt te wijzen dat men zich bij het grijpen van grotere objecten meer verlaat op informatie die van tevoren aanwezig is. Het is bekend dat PMd bewegingsplanning en –uitvoering ondersteunt op basis van informatie vooraf (Wise et al, 1997). Onder de aanname dat het pakken van objecten met grote oppervlaktes in grotere mate wordt ondersteund door een vooraf gespecificeerd motorisch plan (Chieffi en Gentilucci, 1993; Berthier et al., 1996), suggereren wij dat het automatische motorische plan dat door de superior pariëtale cortex wordt gegenereerd, los van de kenmerken van het doel (Pisella et al, 2000; Medendorp et al;, 2003) doorgezonden wordt naar PMd om de relatieve positie van doel, hand en ogen te integreren en vast te leggen. In dit proefschrift wordt daarom gesuggereerd dat de relevantie van dorsomediale en dorsolaterale circuits voor grijpbewegingen een functie is van de mate van online controle benodigd voor de beweging.

Samenvattend laat het onderzoek in dit proefschrift zien dat na langdurig leren van een willekeurige koppeling tussen een visuele stimulus en een beweging ook pariëtale gebieden in de hersenen actief worden die betrokken zijn bij volautomatische bewegingen zoals iets oppakken. Daarnaast lijken grijpen en reiken niet onafhankelijk van elkaar in verschillende pariëto-frontale paden gerepresenteerd te worden; welk pad wanneer geactiveerd wordt, lijkt eerder afhankelijk te zijn van de hoeveelheid online controle die nodig is om de beweging uit te voeren. In het bijzonder laten de resultaten in hoofdstuk 5 zien dat het onderzoeken van effectieve connectiviteit een nieuw licht werpt op de twee visuomotor kanalen hypothese. Dit illustreert hoe belangrijk het is om het brein vanuit een systeemgericht perspectief te onderzoeken en de functionele interacties tussen hersengebieden te bekijken met behulp van connectiviteitsanalyses.

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wens dat de weg dan lang mag zijn (Kavafis)

As you set out for Ithaka
hope the journey is a long one (Kavafis)

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"You are human", was the simple answer of my supervisor Ivan to such a panic attack. Ivan's perfectionism sometimes was the cause of the stress, but at the same time he was the only one really able to convince me of the fact that the world would not collapse right away. Ivan, I believe no one could have taught me as much as you did. We needed some time to get to know each other, but as time passed working together turned out to be very pleasant and fruitful. You are a great scientist indeed. But most important is your never ceasing care and personal commitment to your students. I am glad we will keep on collaborating, so I will still be able to enjoy your peculiar and subtle sense of humor from time to time!

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Next to Ivan and Frans, I got very valuable help from London. Klaas, without your enthusiastic lessons in Dynamic Causal Modelling and your support by phone, email and sms at all times, a large part of this thesis had not been written. I sometimes secretly called you the "DCM messiah", which is meant as a compliment, because it is wonderful to see and share your drive to convince the neuroimaging community to investigate connectivity.

"The F. C. Donders family": I laughed the first time I heard Peter say this, but how mistaken I was. I am glad I could be part of this wonderful centre that buzzes from scientific enthusiasm day and night. I want to thank all colleagues for the motivation, knowledge, (technical) support and friendship I found. Within the Dondersfamily I found a home in the Intention and Action group. Except for the research topic, this group had something else in common: very refined tastebuds. Guys, how I will miss you all and our tasty group dinners! Floris and Rick, jullie discussies hielden me altijd scherp. Rogier, leuk dat we nog

samenwerken. En heel veel dank voor al je proefschrifthulp!

Jasminka, lieve paranimf, dank voor je groot hart, steun en gezelligheid. Ik mis onze samenwerking, en onze lange treinreizen waarin geen onderwerp onbesproken bleef: de grappige of angstaanjagende emails van onze supervisors, de toestand van het weer of onze vriendjes, onze eindeloze hoeveelheid hobbies, en, uiteraard, onze soms hoogoplopende discussies over de interpretatie van onze data. Ik hoop dat jij en Wouter een mooi plekje vinden met een scanner, een IJslands paard en een flink aantal bergen. Ik kom graag langs!

Lennart, het was niet echt gepland dat ik je zou begeleiden bij je stage, maar het liep als vanzelf zo. Ik zie je nog mijn kantoor binnenspringen om een vraag te stellen waarna je al weer wegrende zonder het eind van mijn weloverwogen (en dus te uitgebreide) antwoord af te wachten. Ik was blij dat je voor het AIO-schap koos en dat we gingen samenwerken, want je bent een gedreven wetenschapper. Even gedreven ben je als het gaat om koken. En praten… Een van de meest uitgewisselde zinnen met Ivan is: “Any idea where Lennart is?” Niet al te gefocust worden! Jouw enthousiasme maakt je tot iemand om graag in de nabijheid te hebben. Dank voor alles!

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Although one could never be sure if and when I would be at my desk, a lot has been shared with my office colleagues. Sabine (always nice to be at the Berg-en-dalseweg), Tessa, Christian and Ian, thanks! Jan Mathijs, and Guido, na vijf jaar naast jullie, ben ik er nog niet aan gewend dat ik jullie niet zie als ik me omdraai in mijn nieuwe kantoor. Waarom is sneeuw niet zwart maar wit?

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Stef, je bent niet voor niets mijn paranimf. Onze vriendschap is dit jaar volwassen geworden (18 jaar). Na zoveel jaar kan die vriendschap dan ook nooit meer stuk. Dank voor alles, maar vooral voor dat je er onvoorwaardelijk voor me bent.

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Edda, ik realiseer me steeds opnieuw hoe belangrijk en bijzonder het is om een zus te hebben die je zo nabij is. Jij hebt ook het een en ander aan hindernissen moeten overwinnen en daar heb ik veel van geleerd. Ik ben trots op ons!

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Ithaka gaf je de mooie reis.
Was het er niet, dan was je nooit vertrokken,
verder heeft het je niets te bieden meer.

En vind je het er wat pover, Ithaka bedroog je niet.
Zo wijs geworden, met zoveel ervaring, zul je al
begrepen hebben wat Ithaka's beduiden.

Ithaka gave you the marvellous journey.
without her you would not have set out.
She has nothing left to give you now.

And if you find her poor, Ithaka won't have fooled you.
Wise as you will have become, so full of experience,
you will have understood by then what these Ithakas mean.

(Vertaald door Hans Warren en Mario Molengraaf, Gedichten, Amsterdam 1991, p. 25.)
(Translated by Edmund Keeley and Philip Sherrard)

CV AND PUBLICATION LIST

Curriculum Vitae

Meike Jorinde Grol was born on the 10th of august 1976 in Nijmegen, The Netherlands. After attending secondary education at the Stedelijk Gymnasium Nijmegen (VWO), she moved to Utrecht in 1995 to study Cognitive Artificial Intelligence (CKI). In- and outside the study she became active in several committees and teached as a teaching assistant. Amongst other things she was praeses of the Utrecht Student Choir and Orchestra (USKO). During her traineeship at the Departement of Psychiatry of the University Medical Center Utrecht she got acquainted with fMRI-research and became intrigued by the plasticity and connectivity of the human brain. She wrote her M. Sc thesis about brain connectivity under supervision of Frans Verstraten and started her Ph.D under his supervision at the department of Experimental Psychology at the University Utrecht. In October 2002 she started working at the projects of this thesis at the F. C. Donders Centre for Cognitive Neuroimaging in Nijmegen supervised by her co-promotor Ivan Toni. She is currently working as a postdoc at the Leiden Institute for Brain and Cognition at the departement of Radiology, Leiden University Medical Center, and the department of Psychology, University of Leiden, The Netherlands.

Publication list

Articles

Grol, M.J., Majdandžić, J., Stephan, K.E., Verstraten, F.A.J., Toni, I. (2007). Parieto-frontal connectivity during visually-guided grasping. *Journal of Neuroscience,* 27: 11877-11887. (Chapter 5 of this thesis)

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Verhagen, L., Grol, M.J., Dijkerman, H.C., Toni, I. Studying visually-guided reach to grasp movements in an MR-environment. *Manuscript submitted.* (Chapter 4 of this thesis)

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Grol, M.J. (2003, December) Posterior Parietal contributions to the learning of visuomotor associations’, Talk given at the Winter Conference of the Dutch Psychonomics Society, Egmond aan Zee, The Netherlands.

Grol, M.J. (2003, October) Connectivity: overview of concepts and methods. Talk given at the Psychiatry department, University Medical Centre, Utrecht, The Netherlands.

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Appendix A

SUPPLEMENTARY MATERIAL OF CHAPTER 4

Subjects

Ten healthy, young men (25±4 years, mean±standard deviation) participated in experiment 1 after giving written informed consent according to institutional guidelines of the local ethics committee (CMO region Arnhem-Nijmegen, The Netherlands). All participants had normal or corrected-to-normal vision and were right-handed (Edinburgh Handedness Inventory, Oldfield, 1971; 89±14%). Subject details of experiment 2 can be found in chapter 5.

Image acquisition

Images were acquired on a 3 Tesla Trio MRI system (Siemens, Erlangen, Germany), using a standard circular polarized head coil for radio-frequency transmission and signal reception. BOLD-sensitive functional images were acquired using a single shot gradient EPI sequence (TR/TE 2060 ms/40 ms, 28 transversal slices, interleaved acquisition, distance factor 17%, effective voxel size 3,5 x 3,5 x 3,5 mm). Following the experimental session, high-resolution anatomical images were acquired using an MP-RAGE sequence (TR/TE/TI 1960 ms/5.59 ms/1100 ms, voxel size 1 x 1 x 1 mm). Image acquisition details of experiment 2 can be found in chapter 5.

Image analysis

In both experiments imaging data were analyzed using SPM2 (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm). The first five volumes of each participant's data set were discarded to allow for T1 equilibration. Prior to analysis, the image time series were spatially realigned using a sinc interpolation algorithm that estimates rigid body transformations (translations, rotations) by minimizing head-movements between each image and the reference image (Friston et al. 1995a). The time series for each voxel were temporally realigned to the middle slice in time to correct for differences in slice time acquisition. Subsequently, images were normalized onto a custom MNI-aligned EPI template (based on 24 male brains acquired on the Siemens Trio at the F.C. Donders Centre) using both linear transformation and 16 iterations of non-linear transformation and resampled at an isotropic voxel size of 2 mm. Finally, the normalized images were spatially smoothed using an isotropic 10 mm full-width-at-half-maximum Gaussian kernel. Each participant's structural image was spatially coregistered to the mean of the functional images (Ashburner and Friston, 1997) and spatially normalized by using the same transformation matrix applied to the functional images.

The fMRI time series were analyzed using an event-related approach in the context of the General Linear Model. Using standard multiple regression procedures (Friston et al. 1995b) in experiment 1, we considered three main sources of experimental variance: GRASP (prepare and reach to grasp movement), HAND-RETURN (the time interval during which the hand moved back from the object to the home-key), and MISSES (trials with responses exceeding the response time cut-off (i.e. reaction + movement, 1000 ms). Each effect was modelled on a trial-by-trial basis as a square-wave function. The onsets of the GRASP and

MISSES were time-locked to the opening of the liquid crystal goggles, and the offsets were time-locked to the first contact between the subject's fingers and the target object. The onset of the HAND-RETURN effect was time-locked to the onset of the auditory cue instructing the return of the hand, and the offset was time-locked to the moment the home-key was pressed. The variance associated with the orientation of the target object was modelled as a first order (linear) parametric modulation of the GRASP effect. These regressors were convolved with a canonical haemodynamic response function and its temporal derivative (Friston et al. 1998).

In experiment 2 single subject models consisted of separate regressors describing planning stages for the different levels of Cue, Object, and Orientation. Trial-by-trial measures of this planning stage were extracted from the behavioral measurements during the experiment. In addition, we separately modelled movement execution (split into distinct regressors for grasping the large and the small part of the object), rotation of the device, and error trials.

Each effect was modelled on a trial-by-trial basis as a concatenation of square-wave functions, with onsets time-locked to onset of the LED cue, and offsets time-locked to the release of the hand from the home key. Each of these 12 square-wave functions were then convolved with a canonical haemodynamic response function and its temporal derivative, and down-sampled at each scan in order to generate 24 regressors modelling the main effects described above (Friston et al., 1995b).

Head movement effects were accounted for as described in Friston et al. (1996) by including a Volterra expansion of the 6 rigid-body motion parameters as nuisance covariates (Worsley and Friston, 1995), which consisted of linear and quadratic effects of the 6 realignment parameters belonging to each volume and also included spin-history effects as linear and quadratic effects of motion parameters in the previous volume, giving a total of 24 regressors (Lund et al., 2005). Three further regressors, describing intensities in white matter (WM), cerebrospinal fluid (CSF), and residual compartment (section outside the brain and skull, RC) were added. This was done to account for image intensity shifts due to movement of the hand within the main magnetic field of the scanner as described in chapter 4 (Culham et al., 2006; Verhagen et al., 2006). The statistical significance of the estimated evoked haemodynamic responses in experiment 2 was assessed using t-statistics in the context of a multiple regression analysis. Contrasts of the parameter estimates for planning stages were calculated, and entered into a one-way, within-subjects analysis of variance (ANOVA). The authors were specifically interested in assessing effects of Cue (Final Goal, Immediate Goal) on brain activity during the planning stage before movement onset. For this purpose, SPMs of the T statistic for these effects were created, with the degrees of freedom corrected for nonsphericity at each voxel. Reported are the results of a random effects analysis, with inferences drawn at the cluster level, corrected for multiple comparisons using family-wise error correction ($p < 0.05$, corresponding to a cluster extent threshold of 100 contiguous voxels, given an intensity threshold of $t > 3.5$ (Friston et al., 1996)).

Behavioral analysis experiment 2

For each trial, the following behavioral measures were obtained: Reaction time (RT; time from cue onset to release of the home key), Reaching time (ReT, time from release of

home key to taking off the object from the side), Transport time (TrT, time from taking off the object to putting the object in its end position in the slot), and Return time (time from putting the object into its end position to return of the hand on the home key). In addition, it was recorded whether the object manipulation that was performed was correct.

RTs, ReTs, and TrTs measured during the scanning session were analyzed separately using SPSS Version 14.0 (Chicago, IL, USA), and considered independent variables of a 2 x 2 x 2 repeated measures ANOVA with main effects of Cue [Final Goal, Immediate Goal], Object [Large, Small], and Orientation of the device [1 , 2]. The number of trials was balanced over factor levels, although slight variations occurred due to excluded error trials. Subjects were considered a random factor. Alpha-level was set at $p = 0.05$.

Appendix B

SUPPLEMENTARY MATERIAL OF CHAPTER 5

Subjects

Six healthy right-handed (Edinburgh Handedness Inventory (Oldfield, 1971); 100±0%; mean±SD) volunteers (5 male, 1 female, 27±2 years) were recruited to participate in a kinematic control study. They all had normal or corrected-to-normal vision, and gave informed consent according to institutional guidelines of the local ethics committee.

Experimental set-up

Subjects had to perform pointing or grasping movements while lying supine, in a set-up identical to the one used in the fMRI experiment (see Fig. 1A main paper – apart from the presence of the MR-scanner).

Experimental time course and procedures

The experiment consisted of a total of 80 trials, subdivided into 4 blocks of 20 trials. In the reaching-to-point condition, subjects were asked to reach towards the object and touch it with their thumb without manipulating it. In the reaching-to-grasp condition, subjects were asked to reach and grasp the object and take it out of the rail (as described in the fMRI experiment). Following the prehension movement, and differently from the fMRI experiment, the experimenter placed the object back in its home position in the rail. At the beginning of each block, the subjects were verbally instructed on whether to make reaching-to-grasp or reaching-to-point movements. The object was rotated between blocks. The order of movement type (reaching-to-grasp, reaching-to-point) and object orientation (small object on top, large object on top) was counterbalanced across subjects.

Within each block, trials instructing movements towards the small or the large part of the object were pseudo-randomly intermixed. The colour of a centrally located two-colour LED (green/red) indicated whether the subjects should perform a movement towards the small (green) or the large (red) object. When the LED switched on, subjects had to leave the home key as soon as possible, make the appropriate movement towards the object,, and return to the home key. After 4 seconds, the LED switched off, and an inter trial interval of variable length (1.5–6 seconds) followed. Subjects were instructed to complete their action before the LED switched off. Subjects practised both reaching-to-grasp and reaching-to-point movements before starting the kinematic measurements.

Data acquisition and processing

Participants' hand movements were measured by means of a magnetic recording system, the miniBIRD realtime motion tracking device (Ascension Technology Corporation, Burlington, VT, USA), using small magnetic markers attached to the thumb, index finger, middle finger, and wrist of the right hand of the participants, and connected through an RS232 serial port to a dedicated personal computer (PC). The sampling-rate of the miniBIRD-system was 100Hz and the position resolution 0.5 mm. These data were low-pass filtered using a fourth order Butterworth filter at 10 Hz. A second PC running Presentation version 10.3 (Neurobehavioral Systems, Inc., San Francisco, CA, USA) was used to control the stimuli presentation (LED, object rotation) and to record movement-related

responses (i.e., the release of the homekey, the release of a switch when the object was removed from the supporting rail, the pressing of the homekey following hand return – see Fig. 1A).

We considered the following movement parameters: Reaction Time (RT, the time interval from LED onset to release of the home-key); Movement Time (MT, the time interval from home-key release to movement offset); Hand Trajectory (HT, the distance travelled by the thumb during MT); Hand Peak Velocity (HPV, the maximum speed of the thumb during MT); and Maximum Grip Aperture (MGA, the maximum distance between thumb and index finger during MT). The first two trials of each block were discarded to prevent carry-over effects between conditions, leaving 72 trials per subject. All remaining trials survived an a priori RT exclusion criterion (100 ms < RT < 1000 ms). In one subject, one trial was discarded because the subject made an incorrect response.

As in the fMRI experiment, the onset of each movement was determined by the release of the home-key, and the offset of each reaching-to-grasp movement was determined by the release of a switch when the object was removed from the rail. Since the reaching-to-point trials did not involve any object manipulation, in this condition the offset of each movement was determined on the basis of the velocity profile of the thumb (i.e., the movement was considered ended when the thumb velocity remained below 0.05 m/sec for 0.15 seconds). Hand Trajectory described the sum of the Euclidian distances between the filtered position data during MT. Hand Peak Velocity was calculated as the maximum of the first derivative of the filtered position data during MT. In addition, we also calculated the volume of the ellipsoids representing the three-dimensional 95% confidence intervals of the end-point position of thumb, index finger, and middle finger obtained during the reaching-to-grasp trials (McIntyre et al. 1998).

Statistical inference

For each of the movement parameters described above, we assessed the effects of Movement type [POINT, GRASP], Object size [LARGE, SMALL], and Orientation [ORIENTATION 1, ORIENTATION 2] by means of 2 x 2 x 2 repeated measures ANOVAs. For the reaching-to-grasp trials, we assessed the influence of Object size [LARGE, SMALL] and Finger [THUMB, INDEX, MIDDLE] on the movement endpoint variability by means of a 2 x 3 repeated measures ANOVA. To account for the skewed distribution of the movement endpoints, the three-dimensional 95% confidence intervals of the end-point positions of the fingers were log-transformed prior to statistical inference.

Series
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1. Van Aalderen-Smeets, S. I. (2007). Neural dynamics of visual selection. Universiteit Maastricht, Maastricht, the Netherlands.

2. Schoffelen, J. (2007). Neuronal communication through coherence in the motor systeem. Radboud Universiteit Nijmegen, Nijmegen, the Netherlands.

3. De Lange, F.P. (2008). Neural mechanisms of motor imagery. Radboud Universiteit Nijmegen, Nijmegen, the Netherlands.

4. Grol, M.J. (2008). Parieto-frontal circuitry in visuomotor control. Universiteit Utrecht, Utrecht, the Netherlands.