Enabling the future.

Prospective action representations

in the human parieto-frontal motor planning system

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Preface

As for the future, your task is not to foresee, but to enable it
Antoine de Saint-Exupery,
"The Wisdom of the Sands"

One of the primary functions of the central nervous system is to make the body move. Whenever we try to find a mating partner, hunt for food or avoid becoming it ourselves, we need to move. No wonder then, that how does a voluntary movement emerge from brain activity has been one of the most extensively studied problems in neuroscience. But, even despite the research effort, the exact mechanisms are still far from understood. In my dissertation I scrutinize a portion of the complex system responsible for transforming thoughts into actions. Specifically, I focus on the interplay between the cognitive and the motor components of action plans and their representations in posterior parietal and premotor cortex. In the first chapter I start by bringing up the psychological theories of how are the mental representations related to motor actions. Next, I briefly review the current state of knowledge about neural correlates of action planning in the primate brain. I concentrate on hand movements as they pose the major challenge in understanding the motor system, being the most complex type of actions the human body is capable of. After having built this general background, I present my own work, where I try to answer three questions about parieto-frontal processing in action planning:

1) Does the brain visually simulate action effects in prior to action execution?

2) Are the reach trajectory plans organized along one, common neural pathway?

3) Are working memory processes modulated by effector preparation?

In the final part of the dissertation I summarize my findings and briefly reflect upon the tangled relationship between the ability to represent and realize ideas, and how it might have shaped the evolution of other remarkable features of the human mind.

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Introduction: From intentions to actions

Predictive encoding of actions

It may appear, that the human motor system has evolved to foresee the future and act upon it. Whenever we try to perform an action in the constantly changing environment, we're racing against time. Our bodies and senses seem too slow to win this race: the several hundreds of milliseconds we need to react to a new event, may be a matter of life and death. This makes the central nervous system compensate for this sluggishness and act ahead so that the slow body catches up with the fast world. Therefore, the brain makes predictions that guide the body to move where it ought to be before the senses can perceive it. Whenever we intend to catch a ball or hit a moving prey, we predict where to aim next, to catch up with the moving target. On the very basic level, these predictions start already in the retina, where laterally spreading transients allow to quickly detect movements and form a simple, cellular-level prediction (Nijhavan and Wu, 2009). Further evidence shows that such predictive coding occurs at various stages of processing within perceptual domain (see e.g. den Ouden et al., 2012; Obleser, 2016). This way, the general orientation of the central nervous system towards representing the future seems to be preserved throughout its ascending pathways up to the highest, cortical centers of perception. Once the information reaches there, the perceptual content needs, however, to be translated into the respective motor programs, that would allow the body to act upon the environment. This translation allows binding information between several perceptual and motor modalities into a common computational framework, even though the initial information coding may be different between those modalities (as the cortical ensembles in the primary visual cortex obviously encode different features than the ones in the primary motor cortex). This binding process, called sensorimotor integration is the key problem to solve by the nervous systems of virtually all animal species (Sperry, 1952).

It appears that the central nervous system's ability to "foresee" the future should allow it to effectively act upon these predictions and, moreover, to shape the environment to fulfill the organism's needs. This shaping has to start off by defining some specific desired state that the action should lead to: *an intention*. The action, when performed, leads to a certain consequence, which may be either just the final state, or the action itself (as both can differ, see Study 2). This consequence then is compared to the intention, either using external sensory feedback or by internal efference copy loops, allowing for correcting potential errors (e.g. Sperry, 1950; Cisek, 2007). Thereby, one can define intentions as a specific sort of predictions, that reflect an ultimate, desired effect of an action. If it wasn't for this prospectively defined intention to which the actual outcome can be compared to, any action would have to be performed on trial-and-error basis, a very costly strategy.

As described by Wolfgang Koehler in his classical works on problem solving in chimpanzees, such waste of energy is not the case indeed (Koehler, 1921). Koehler noted that the way chimpanzees acted in order to get food indicated that they were led by some idea of desired future state allowing them to creatively transform environment to match that state, in a process he called *insight*. This observation was in strong opposition to its contemporary theories of learning, especially Thorndike's concept of instrumental conditioning which assumed trial-and-error basis in learning stimulus→outcome associations (Thorndike, 1911). A prospective visualization of intention is crucial, as plethora of different means may be available to achieve the same goal, requiring a process of selection and evaluation of their effectiveness. Some of these means may emerge in the process of problem solving, like the insight studies of Koehler demonstrated, and usually present a variety of parallel options to achieve the goal. Evaluation and selection of the eventually applied action is encapsulated in a complex, multi-level process and will be briefly discussed later in this and the next chapters.

Psychological foundations of action planning

The formation of the prospective action plans has been approached experimentally with a variety of paradigms, with the most widely used ones being delayed response tasks. First proposed by Rosenbaum (1980), these paradigms base all upon the common principle of temporal separation between action cue (e.g. movement goal) and movement execution. The time in between is a fundamental epoch, where brain activity should – in theory – reflect the definition and the rehearsal of an action plan. First experiments by Rosenbaum demonstrated, that such pre-planning of a response, allows a faster action (Rosenbaum, 1980; compare e.g.: Lindner at al., 2010). The question remains open, however, whether this paradigm constitutes the only way to pinpoint the planning processes in the brain, as some researchers were able to isolate planning activity immediately preceding actions with no delay (Ames et al., 2014). I will return to this problem in Study 1.

The delayed response paradigms have been used widely to disentangle a variety of processes that altogether constitute the umbrella term "action planning", such as target localization (Galetti et al., 1993), target selection (Cisek, 2007), effector selection (Leone et al., 2014), applying motor context (Westendorff et al., 2010), or predictive encoding of the expected consequences of an action (see Study 1).

This last element has been of particular importance for the general topic of my research presented in this thesis and has been of interest to several different psychological theories of sensorimotor binding. Two of them: the ideomotor theory and the theory of event coding (the latter being an extension of the former) seem to provide an interesting conceptual framework for the general problem of binding between intentions and actions leading to them. Both extend the basic concepts of sensorimotor integration to encompass, much more elusive, cognitive processes mediating between sensory inputs and actions. The ideomotor theory bases upon a central notion that every (conscious) action triggers a related mental event (an idea) and vice versa: every thought leads to its related, either

proximate or distal action (James, 1890; Hommel, 2001). For example, an intention to open an application window on a computer screen is equivalent to preparing an action of clicking a mouse button with the cursor pointing to a respective icon. And, conversely, clicking the mouse button leads to an expectancy that it should be followed by a window opening. One may suspect, just like Rosenbaum's findings suggested, that having some prior cognitive (sensory) representation of an action should necessarily shorten reaction times needed to initiate that action. Similarly, matching sensory modalities between stimuli and actions yield shorter reaction times, when compared to unmatched modalities (Greenwald, 1970). A more elusive concept implicated by the ideomotor theory says that the action's goal determines also the action itself by triggering cognitive operations that may lead to obtaining this goal. Therefore, the ideomotor approach made the weight shift from the behavioristic dogma of externally-generated and passively-perceived stimuli, mechanistically processed by stimuli-response mappings, to the internally generated cognitive processes that determine future actions. It is noteworthy, that the theory in principle applies only to voluntary and conscious movements, and not to the many motor reflexes or other involuntary movements the human body is capable of (Rosenbaum, 2009). In their extensive review on the topic Hommel and colleagues (2001) list weaknesses of the classical variants of ideomotor theory and its limited value in convincingly demonstrating the cognitive mechanisms responsible for mapping intentions to actions. For that reason he proposes an expanded variant, which he calls a theory of event coding (TEC). As the authors phrase it themselves, the basic concept of TEC assumes "that perception, attention, intention, and action share, or operate on, a common representational domain" (Hommel et al., 2001, p. 859). This assumption speaks for a common code in processing information between both perceptual and motor domains, although the TEC itself does not provide many hints on the actual neural implementation for such "code" and Hommel et al. do not dwell into this problem. The TEC, however,

notably proposes that binding of multimodal information relies on some common, abstract frame (Prinz, 1990; 1997) responsible for "distal coding", which can be mediated by several different neural mechanisms (see e.g. Singer, 1994; Reichenbach et al., 2014). Furthermore, Hommel et al. (2001) propose an interesting distinction between an action's target and its goal, where the former can be viewed as a mere external sensory stimulus, while the latter as an internal representation of the action, together with its expected (sensory) consequences. These concepts seem somewhat related to the process of binding across different reference frames in which action features can be represented in, as discussed extensively by e.g. Andersen and Buneo (2001) or by Medendorp (2008; Beurze et al., 2010) who also provide empirical support to their view on how can the common reference frame be realized in the brain. I will return to the problem of different reference frames later, as it poses one of the most important challenges all approaches to action planning must face. Apparently, within TEC, the common coding facilitates exchange of information between perceptual and motor modalities in order to optimize their performance, and incomplete visual information may trigger a manual or other bodily action such as changing viewing perspective in order to gather more information (Hommel et al., 2001). In this way, the TEC seems to take into account the older theories of ecological perception, postulating that perceiving is not a passive process, but rather an active one, where the organism interacts with the environment in order to explore it and use its features in an optimized way (e.g. Gibson, 1979).

Interacting with the environment relies foremost on recognizing the potential use of objects (for which Gibson coined the term "affordances"), as well as recognizing consequences of such use, like when holding a stick extends our reach range (compare: Maravita and Iriki, 2004). This in turn appears to require an ability to integrate the tool into the body's own actions, as various tools may require different motor programs to induce the same or similar effects (c.f. Umilta et al., 2008). This specific way of adapting motor plans to

subserve the desired visual consequences may be a more general, inherent feature of the human motor system. Indeed, several studies have consistently demonstrated that the system aims at producing the consequences no matter of the means that lead to them (Janczyk et al 2014; Shin et al. 2010; Kühn and Brass, 2010; Hommel, et al., 2001; Elsner et al., 2002; Wolpert and Ghahramani 2000; Kuang and Gail, 2015). In Study 1 I will discuss this particular problem more extensively.

The theories described above, despite providing a conceptual framework for explaining certain behavioral markers, do not let one delineate any physiological basis for action planning. In the next chapters I will traverse from the vast space of slightly elusive concepts of ideomotor theories to the somewhat more concrete world of the brain functions. I will focus on the cortical motor planning areas, as their role is most relevant for the current work. Moreover, I will discuss each area's functions more specifically in the relevant chapters describing my own studies on the parieto-frontal motor planning system.

The parieto-frontal "planning network"

Among the primate brain regions considered to be important for the sensorimotor integration, the key role has been attributed to the posterior parietal cortex (PPC). The region's placement between the visual and the sensorimotor areas of the cortex, allows it to both receive inputs from and project to multiple sensory, motor and higher-order processing areas (like prefrontal cortex). This anatomical clue has suggested that PPC may be the site for sensorimotor integration in the brain, linking information from different sensory modalities with respective actions. Moreover, lesions to the region result directly in disorders of motor actions like optic ataxia (Hwang et al., 2012) or apraxia (Geschwind and Damasio, 1985; Gross and Grossman, 2008). All this makes PPC a good counterpart for the other motor planning areas located in the frontal lobe (like premotor or supplementary motor cortex). These frontal regions have been demonstrated to play a crucial role in hand

movement planning in a variety of domains, ranging from representing targets hand (Hocherman and Wise, 1991; Crammond and Kalaska, 1989; Messier and Kalaska, 2001) to planning of complex actions (Hocherman and Wise, 1991; Umilta et al, 2008; Pearce and Moran, 2012). The fact that many aspects of planning are shared between parietal and frontal regions suggests a rather complex interplay between them.

The advent of brain imaging studies, allowing to record whole-brain activity has further confirmed the common engagement of frontal and posterior parietal regions in planning of motor actions (see Figure 1.1). It appears that the premotor and posterior parietal areas form a very 'typical' pattern of roughly correlated planning activity (for this reason sometimes called frontoparietal network). More specifically, motor planning tasks conducted in functional magnetic resonance (fMRI) usually yield and elevated signal during the delay phase of a trial, as contrasted with baseline activity (compare to Connolly et al., 2002, 2003; Gallivan et al., 2011; Lindner et al., 2010). Related signal patterns are observed using other methods of measuring brain activity (not relying on blood flow), such as magnetoencefalography where planning activity results in sustained desynchronisation of low-frequency bands (see e.g. Medendorp et al., 2007) or increased single-cell activity in non-human primates (NHP's) (see e.g. Crammond and Kalaska, 1989; Kalaska and Crammond, 1995; Batista and Andersen, 2001; Westendorff et al., 2010). This speaks for consistency in the local increases of neural activity during movement preparation. Although the activity patterns show an apparent correlation between the large-scale regions in a huge variety of tasks, there has been a significant amount of evidence highlighting differences between and within these regions (Gallivan and Culham, 2015; Cavina-Pratesi et al., 2018). Apparently, the "nodes" of the alleged parieto-frontal network differently process the intention in order to realize it. In the next chapters I will review the most important findings describing functional organization of motor planning in the parieto-frontal network, highlighting differences and similarities between its main components.
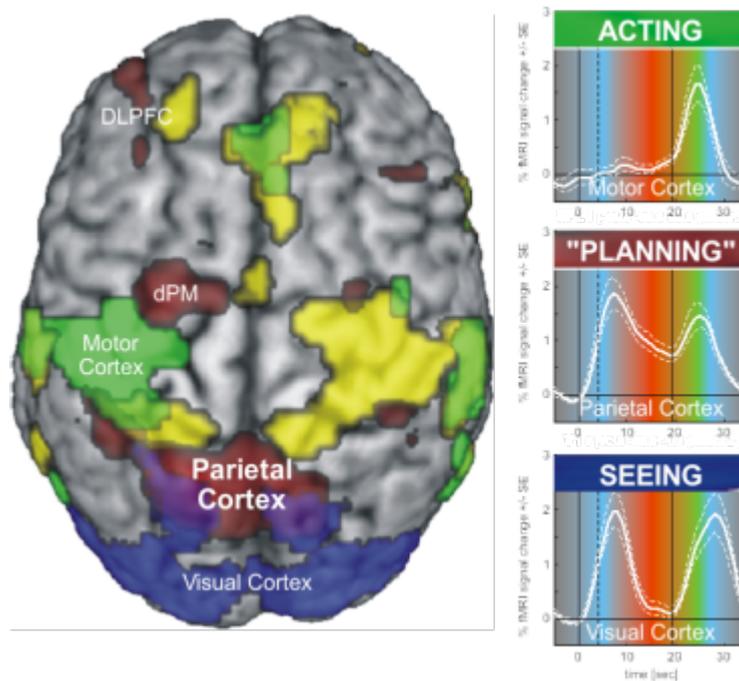
Figure 1.1 Brain organisation of areas responsible for vision (blue), action planning (red) and execution (green). From Lindner et al., 2008, with permission.

At this point it is worth to emphasize an inherent feature of all planning tasks, namely the fact that each planned but deferred action has to be maintained in the working memory until it's executed. This correlation between the retrospective and prospective processes engaged in action planning results in a large spatial overlap between the the parietal and frontal areas engaged in motor planning and working memory maintenance (see e.g. Lindner et al., 2010; Eriksson et al., 2015; Gallivan & Culham, 2015), leaving open the question about how do the two large cognitive building blocks of motor planning interact. I will scrutinize this problem in Study 3.

Posterior parietal cortex

As I mentioned before, the associative role of PPC results from its anatomical organization yielding connections to virtually all other cortical areas (Johnson et al., 1996; Battaglia-Mayer et al., 2015). This means that its engagement in planning of motor actions is complex and thus hard to exhaustively describe. Nonetheless, decades of research on PPC have yielded some principles of its functional anatomy.

The PPC is located anterior to the occipital sulcus and posterior to the postcentral sulcus and is divided into superior and inferior portions by intraparietal sulcus. It has been traditionally considered a part of the dorsal stream of processing visual information, whose primary role is to localize objects and perform actions to them (Ungerleider and Mishkin, 1982; Goodale and Milner, 1992). This "where" stream has therefore a primary importance for the two main types of voluntary, object-directed movements that primates (most importantly humans) can perform: eye movements and reaching/grasping. The hand movements will be in focus for the rest of my thesis, although many concepts may be applicable to other types of actions (such as eye movements) as well. Most of the research showing effector-related distinctions has been performed in macaque monkeys, trained to perform either saccades or reaches in the aforementioned, "classical" delayed response paradigms. Irrespective of the target locations, the neurons in lateral intraparietal cortex respond more strongly, whenever saccade has to be planned (Platt and Glimcher, 1999) and neurons in medial and medio-dorsal portion of the PPC encode rather reaches than saccades (Snyder et al., 1997). On this basis, it has been postulated that the main functional division of the posterior parietal cortex seems to adhere to this basic distinction between planned movement types, with the medial bank of the intraparietal sulcus seems to be devoted to planning and control of the hand and arm movements, and the lateral bank to planning and control of the eye saccades (Andersen and Buneo, 2001).

The direct translation of non-human primate (NHP) findings to humans seems to be limited by the missing exact relationship between the monkey and human anatomy of the PPC. There have been, however, successful attempts to draw similarities and delineate putative cross-species homologues within this region (see e.g. Orban, 2016 for a recent review). The most prominent finding seems to be the definition of a putative homologue of parietal reach region (PRR) on the medial bank of the superior parietal lobule, anterior to the parieto-occipital sulcus (Connoly et al., 2003). The divisions between parietal eye and

hand planning regions seem to be less clear in humans than in NHP's (Heed et al., 2011; Gallivan et al., 2011). Moreover, in both humans and NHP's the prehension and finger control are more clearly represented in the anterior parts of the intraparietal sulcus, than in other regions of the PPC (Cavina-Pratesi et al., 2010; 2017). This cross-species coherency in organization of parietal cortex speaks for the same principles in organization governing the primate motor systems and will be important for the speculations I will allow myself to draw in the last part of the thesis.

The crucial role of parietal motor planning areas seems to be their engagement in representing actions prospectively, rather than in terms of retrospective maintenance of action plans (c.f. Lindner et al. 2010). It is natural to think that this function requires some sort of mental simulation of the motor actions in prior to their execution and it has been speculated, that one of the functions of the posterior parietal lobe is to provide neural basis for such simulation. Neuroimaging studies have shown that posterior parietal lobe is one of the key regions engaged in motor imagery, together with frontal motor areas (Stephan et al., 1995; Aflalo et al., 2015; Klaes et al., 2015; Pilgram et al., 2016). The parietal involvement in the motor imagery seems, however, crucial for the process: as demonstrated by Sirigu et al. (1996), posterior parietal lesions lead directly to impairment in motor imagery, whereas lesions in frontal motor areas do not. Moreover, later findings point to that posterior parietal cortex stimulation is sufficient to evoke an internal feeling of performing an action, even though no action is in fact performed (Desmurget et al., 2009). Other findings show parietal cortex engagement in other imagined visuo-spatial actions like mental rotations (Harris et al., 2000) or navigating a maze (Jerde et al., 2007).

Premotor cortex

In contrast to the posterior parietal cortex, the functional anatomy of premotor areas seems to be generally less understood. The region overlaps with the Brodmann area 6,

although the dorso-medial part of area 6 is defined as supplementary motor area (SMA). The actual anatomical divisions present in the premotor cortex are far from being clearly defined, although there is some evidence suggesting that the dorsal part of the region represents more the proximal muscles of the arm (Scott et al., 1997; Davare et al., 2006, the ventral part – the distal muscles of the hand, responsible for finger control and prehension (Rizzolatti et al, 1996; Matelli and Lupino, 2001; Davare et al., 2006), and the anterior part is a supposed human frontal eye field (see e.g. Paus, 1996). A newer, prominent voice on the premotor functional organization comes from Graziano (2007a; 2007b), who suggests that, the effector representations in the premotor cortex are rather functionally than anatomically organized, and reflect the movements to be performed, rather than the body parts themselves, spreading across boundaries traditionally defined by functional anatomy of frontal motor areas. This shows that premotor cortex role in action planning is not just to represent the effectors themselves. There seems to be a widespread consensus that the actual functions of the region fall far beyond that.

The elusive role of supplementary motor area

The supplementary motor area (SMA) has been considered to play a supporting role in action execution. Located on the medial bank of the BA 6, within the longitudinal fissure and anterior from the motor cortex, the SMA it is well connected to the other sensorimotor areas, including parietal cortex (Vergani et al., 2014; Battaglia-Mayer et al., 2015). It also contains a rough body map in monkeys (Woolsey et al., 1958), with the apparent representations of body parts overlapping and yielding rather complex relationships (Mitz and Wise, 1987; Luppino et al., 1991; Graziano and Aflalo, 2007a,b). The functional roles of SMA seem to fall within an extensive range of the behavioral spectrum, ranging from reach planning (Hocherman and Wise, 1991) to speech and language processing (Hertrich et al., 2016). Cona and Semenza (2017) provide an extensive literature review on SMA

role in cognitive and motor functions, where they point out that the most universal contribution of the region appears to be its general involvement in sequence processing. This function seems to be of special importance for motor planning where the role for SMA in organization of sequential actions has been repeatedly demonstrated (Shima and Tanji, 1998; Nakamura et al., 1998). The involvement of SMA in many distinct tasks seems to suggest that, indeed, its engagement in behavioral control may be of general nature, providing computations needed for different domains.

PPC and PM as complementary parts of one "planning system"

The roles for parietal and frontal areas representation of action plans (goals) seem to be overlapping to a large extent. Yet, several different lines of research seem to point out that the roles of both sub-systems in bridging between intentions and actions are indeed complementary. Very notably, electrophysiological recordings in rhesus monkeys have uncovered that representations of reach targets do differ significantly between the two areas, signaling that they form a hierarchy in processing goals. As Crammond and Kalaska demonstrated, the planning-related neuronal discharges in posterior parietal cortex represent all potential target locations (Kalaska and Crammond, 1995), even if a no-go cue eliminated them as targets. A similar finding was reported by Lindner et al. (2010), who found that PPC encodes – apart from spatial locations to reach to – also the locations that were to be avoided. Although the same is true for PMd, as soon as a location is no longer expected to become a target for next movement, the neurons representing it stop discharging (Cisek and Kalaska, 2002). On this basis, Cisek (2007) suggested a model for action planning and selection (the so-called "affordance competition hypothesis"), where potential goal representations are maintained in the planning areas as long as accumulation of information for selecting the actual goals is needed. Thereafter only the representations of actions to be executed are promoted, with the irrelevant goals being

suppressed and only the ultimate goals are represented in the PMd. Cisek further hypothesized, that the mechanisms for such goal selection are based on modulatory projections from prefrontal cortex and basal ganglia, where processes like goal evaluation take place. Cisek's model may be a good approximation of the computational processing that results in selection from among equivalent actions.

Reference frames

One of the main problems in translation of intentions to action are different neural codes between modalities. The problem has been first described by Head and Holmes (1911) who proposed that the brain possibly contains a single representation of the body allowing to combine information originating in different sensory and motor modalities. As already mentioned before, multi-modal transformations needed to translate the code of perception and, even more elusive, internal representations of intentions into a specific series of motor commands, pose an understandably difficult challenge for an exhaustive theory of motor planning. Even a rather simple problem of target localization requires a strict cross-modal coherence, as coordinate frames used to guide a hand to an object are substantially different from those needed to saccade to the same point in space. As the main role of posterior parietal cortex is to localize a target and plan a movement to it, the problem seems to be of high importance. Contrary to the intuitive notion, that posterior parietal cortex, as a high-level sensorimotor area may represent just a general frame of reference for all effectors, the evidence shows that this is not the case. Experimental data demonstrate that, in PPC, actions are represented in body, head, hand and eye coordinates (and their appropriate combination, e.g. through "gain field" modulation) (Snyder et al., 1998; Xing and Andersen, 2000; Andersen and Buneo, 2001). This speaks for multiplicity of reference frames in action representation, but does not solve the main problem of how are these different reference frames combined into a coherent

representation of actions in space. Andersen and Buneo (2001) suggest a somewhat radical answer: actions are subject to binding into one, common reference frame, a retinotopic (visual) one. This view seems to provide an inspiring conceptual model for the representation of action intentions on the highest level in a sensory, visual space. Further exploring this idea human fMRI findings of Heed et al. (2010) show that reference frames seem to shift from the eye- to body-centered coordinates, whereas the former are represented more prominently in the parietal, and the latter in the frontal motor areas related to motor execution. Another study from the same group suggests, moreover, that the effector-based reference frames are rather loose, and the organization of the posterior parietal cortex seems to be functional (Heed et al., 2013), possibly reflecting the translational nature of the region in organizing complex motor programs. Interestingly, Graziano and Aflalo (2007a; 2007b) draw a similar view of the frontal motor areas, where effector representations (and thus their reference frames) are seemingly organized in a much more complex manner than traditionally considered. Dating back to the XIX century works of Frisch and Hitzig (1870) and Ferrier (1874) who made first discoveries on the motor representations of limb movement pattens in the dog's cortex, the organization of the motor areas may seem to be subject to complex patternisation involving movements of different complexity. Graziano and Aflalo propose, that the cortical organisation in the frontal motor areas should be described in terms of specific movement intentions, less the body parts engaged. In other words, the actual cortical representations of movements spread across the, traditionally defined, discrete "fields" in order to reflect the complexity of motor repertoire.

Tools and their incorporation into action plans

Humans count among the very narrow range of species able to use (and make!) tools (for a review on tool use within the animal kingdom (see: Seed and Byrne, 2010). This rare

ability has to be reflected in the organization of our motor system: reaching for an object with a hand certainly requires a different set of motor programs than the same action performed with a stick. Although the action target remains the same, the ways to achieve it have to change dramatically. It appears, that the motor system copes with this need for changes in motor programs by adjusting the natural movements of the body to ensure the desired performance of the tool. As already mentioned, the multi-modal areas within the PPC can temporarily modify their representations of the body, allowing to incorporate a tool into the motor repertoire (Iriki et al., 1996, Marawita and Iriki, 2004). It appears then, that the way tools are represented can be guided by the same principles that govern the rest of the motor actions. The universal reference frame for representing actions may subserve this function by maintaining a high-level representations of goals, independent of the means to achieve them. It seems to be the case indeed: monkey electrophysiological studies show that premotor area F5 neurons code the perceptually-defined goal, no matter of the actual motor programs engaged in action (Rizzolatti et al. 1988; Umilta et al., 2008). This putatively reflects the fact that some neurons in area F5 seem to encode actions in the visual, not the motor, reference frame (Mushiake et al., 1997). Similarly, the medial posterior parietal cortex function does not seem to be influenced by the actual hand dynamics required for a movement, but rather processes more the visual (intentional) aspects of it, while the dorsal premotor areas seemingly represents the dynamics (Kalaska, 1989). More recent human fMRI works suggest further that the fronto-parietal cortical regions mediating tool use may form a complex system, where tools modulates activity in some regions, while other areas maintain hand-related plans without being affected by the actual effector in use (Gallivan et al., 2013). This shows that tool representations do not get incorporated (or embodied) in a strict sense and the CNS maintains an internal distinction between the bodily, naturally controlled, and "temporary", artificial effectors.

Tools of the future - motor neuroprosthetics

The relationship between natural and artificial effectors has become of special importance in recent decades, mainly due to the development of neurally-guided prostheses. The simplest devices base on reading out the efferent peripheral nerve signals which poses an obvious problem as they require intact spinal and corticospinal tracts. More advanced interfaces, relying on intracortically implanted electrodes, were from the beginning (Fetz, 1969) placed mainly in the primary motor cortex (Lebedev and Nicolelis, 2006; Moxon and Fofani, 2015) and therefore relied on signals related to lower-level motor programs which, as pointed out by Andersen and Buneo (2002), may limit their use for guiding prostheses not resembling human effectors and – importantly – affect the use of feedback signals for on-line movement error monitoring. Although it is worth noting, that some closed-loop motor neural prostheses have successfully been used to incorporate artificial tactile feedback through microstimulation delivered to someatosensory cortex (c.f., O'Doherty et al., 2009; 2011), it remains an open question, whether these approaches suffice for correcting motor errors in more complex actions, and whether signals from motor cortex provide sufficient control over the interfaces that do not resemble the human body. It appears, that readouts from higher-level motor planning areas, representing action intentions, could present a substantial solution to this problem. The prostheses driven by signals from parietal planning areas have been developed only very recently, first in monkeys (Hauschild et al., 2012) and next in humans (Aflalo et al., 2015; Klaes et al., 2015), opening up a new possibility to leverage operation of brain-machine interfaces by providing a source of signals not directly depending on effector-specific motor programs. This advancement seems to open up a great opportunity in creating novel, multi-level control system for neural prosthetics.

One of the main future challenges in the field would lie in the tighter embedding of actions

offered by prostheses into the natural motor repertoire. We may speculate, that neural processes similar to the ones responsible for incorporation of tools into the body schema may also govern the embodiment of prostheses or other artificial body partsj (Ehrsson et al., 2005; 2007; Limanowski and Blankenburg, 2016). As has recently been demonstrated, the degree of such embodiment may be somewhat limited, resulting in worse performance of artificial vs. natural limbs (Gouzien et al., 2017). One may wonder therefore, how deeply the embodiment processes for artificial effectors mimic the representations of natural body parts, and whether the limited incorporation may actually be a feature of the motor system allowing it to use different effectors for the same purpose. In any case, for the future development of neural prostheses and other neurally-guided devices driven by the high-level signals from areas representing motor intentions (c.f. Aflalo et al., 2015; Klaes et al., 2015), embodiment may be one of the key problems to solve. In order to ensure effectiveness of actions using artificial effectors, understanding the complex interplay between the intentions and physical components of movement will be necessary.

Summary

The behavioral and neural data together demonstrate that the central nervous system realizes action intentions via a complex machinery operating at very different levels of processing, ranging from abstract goal representations to most detailed motor programs. This complexity in organization likely reflects the behavioral flexibility in adapting to environment, often providing a variety of ways for achieving the same goal. Thus, the motor system seems to operate according to the main rule: define goals as abstract, sensory representations and then realize them by adapting motor programs to produce the desired sensory consequences. It appears that these abstract sensory representations of actions occur first in posterior parietal cortex, and then frontal motor areas design more detailed plans, more closely related to the motor output. Yet, albeit tempting, this model is not as clear, as it could appear. The presence of neurons encoding sensory

representations of actions in premotor cortex, raises questions about whether these representations are indeed formed only in posterior parietal cortex. Moreover, the aforementioned disparity between PPC and PMd in representing action goals, yields suspicion that these regions may form complimentary subsystems, and contain substantially different action plans that are utilized depending on situational demands. Finally the apparent prospective information coding in the posterior parietal cortex raises concerns about the nature of its involvement in processing retrospective, mnemonic information. These problems can be summarized by the following questions:

1) Does the brain visually simulate action effects in prior to action execution?

2) Are hand reaching plans organized along one, common neural pathway?

3) Do the prepared motor actions affect related working memory processing?

In the next chapters I will try to provide answers to these problems, and put them in a more general model of action planning that emerges from both the studies described above and my own work. I present three own studies where I used the benefits of human functional magnetic resonance imaging (fMRI) to provde new insights into how do frontal and parietal areas interact in processing action intentions and transforming them into movements. In Study 1 I show, that visual intentions are an early component of the motor planning processes, and that the accompanying motor programs sub-serve the function of producing the visualized intentions. In particular, my findings demonstrate that visual consequences of movement are represented in both posterior parietal and dorsal premotor cortex in the early planning activity. This finding leads to the conclusion that the sensory representations of movement consequences are transferred down to the premotor cortex, even though some previous evidence suggested this doesn't need to be the case. In Study 2, I scrutinize how planning of reach trajectories differs from merely representing reach targets. I show that the trajectory representations change dramatically across the parietal and dorsal premotor areas, with the former representing only simple reach paths aimed at

a goal, while the latter – also represent complex paths the hand has to follow. These results demonstrate an apparent processing hierarchy between parietal and frontal areas in reach planning. In Study 3 I ask whether the retrospectively maintained working memory information is affected by the motor context in which this information is going to be used. I demonstrate that the effector-specific motor preparation does indeed influence the working memory activity in posterior parietal cortex, shedding a new light on the interplay between retrospective and prospective processes in action preparation. Finally, in General Discussion I briefly draw general conclusions based on the results of both my own studies and the research discussed above. Furthermore, I present my own view on how the ideomotor cognitive architecture could could have led to the emergence of the unique mind of anatomically modern humans.

Study 1. How will it look like? Human posterior parietal and dorsal premotor cortex encode the visual properties of an upcoming action

INTRODUCTION

Reaches are realized through complex movements of individual joints. Despite that fact hand trajectories do look surprisingly straight and have simple (single peak) velocity profiles. This holds true even if the contributing joints move in a much more complex manner (Morasso, 1981). Observations like this suggest that the central nervous system adapts motor plans to produce desired visuospatial properties of movements. In fact, Wolpert and colleagues (1995) confirmed that notion by an experiment, in which a mismatch between the actual hand position and the visual feedback thereof was manipulated. Despite this mismatch subjects reached along visually straight trajectories. Similarly, related work by Mechsner and others (2001) revealed that subjects automatically preferred movements that led to visually symmetrical action-effects, even if the actual actions needed to generate these effects were not symmetrical. This suggests that movement plans aim at producing desired sensory outcomes and that these outcomes have to be represented before the movement plans are ultimately formed (Janczyk et al 2014; Kunde, 2003; Shin et al. 2010; Kühn and Brass, 2010; Hommel, et al., 2001; Elsner et al., 2002; Wolpert and Ghahramani 2000). If this view is true, one should also be able to delineate a neural substrate that contains a prospective representation of these sensory consequences as part of an action plan. Kühn and colleagues (2011) provided a valuable piece of evidence to support this hypothesis, demonstrating that preparing hand vs. face actions also increases activity in visual areas related to the perception of body parts vs. faces, respectively (compare also to: Kühn et al., 2010). However, evidence that would demonstrate such prospective representation of sensory outcomes (or visual imagery) in the sensorimotor areas engaged in planning such actions in the first place is scarce.

One candidate brain area that could sub-serve such function in humans is the

posterior parietal cortex (PPC) as it plays a crucial role in forming movement intentions (Desmurget et al., 2009) and visual motor-imagery (Crammond, 1997; Sirigu et al., 1996). In particular the medial portion of human PPC has been considered a main substrate for reach planning (e.g. Lindner et al., 2010), possibly constituting the human homologue of macaque parietal reach region (PRR) (Connoly et al., 2003). Importantly, PRR and its putative human homologue thereby represent reach targets and effectors in a common visual reference frame (Andersen and Buneo, 2002; Buneo et al., 2002; Heed et al., 2011; Medendorp et al., 2008). In addition, other studies suggest that PPC/PRR processes also more detailed aspects of upcoming movement, such as trajectory information (Hauschild et al., 2012; Torres et al., 2013, Aflalo et al., 2015). Unfortunately, however, these studies did not specify whether or not the trajectory is represented in a visual frame of reference. Most direct evidence for a role of PPC in the prospective coding of expected sensory consequences during action planning comes from a recent electrophysiological study in monkeys by Kuang et al. (2015). They combined anti-reach and prism adaptation paradigms in order to tease apart the motor and the visual properties of a reach. By using reversing prisms they were able to separate the visually perceived target location from the physical reach endpoint. Moreover, by using anti-reaches they also could separate retrospective representations of the visible target cue from prospective planning. This manipulation allowed them to demonstrate, in one monkey, that at least some PPC neurons do encode the predicted visual properties of an upcoming reach during planning. It is still an open question whether such coding might be also present in human PPC and, moreover, whether such visual representations may also exist in other regions of the brain, as for instance in premotor cortex.

The latter is an obvious question as dorsal premotor cortex (PMd) has been shown to closely work together with PPC in several aspects of action planning, execution and monitoring (Desmurget and Sirigu, 2009; Hoshi and Tanji, 2000; Westendorff et al., 2010;
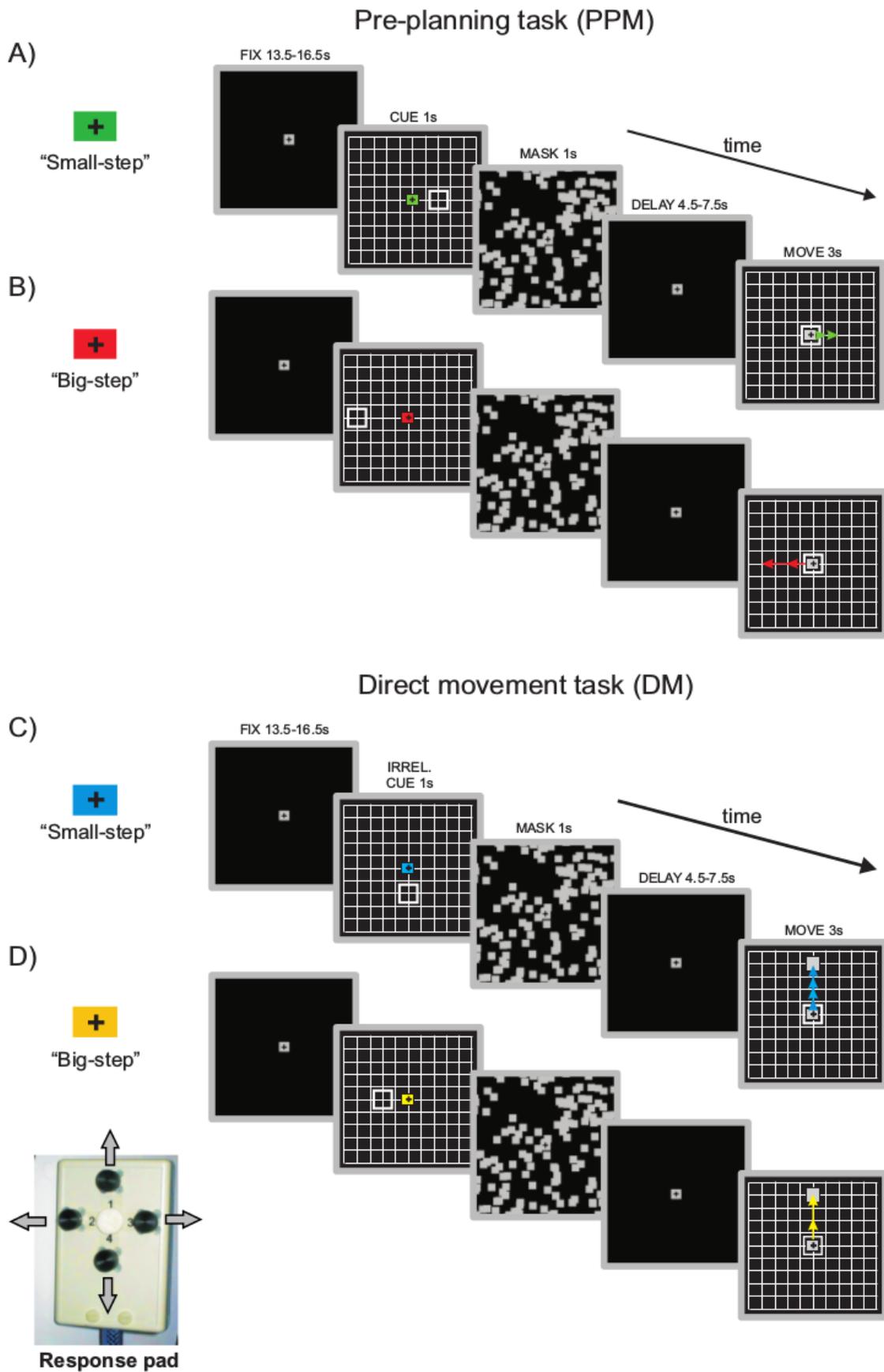
Figure 2.1. Experimental Tasks.
Schematic trial timelines showing each combination of task (DM, PPM) and movement gain ("small step", "big step").

Lindner et al., 2010) Moreover, as demonstrated already, PMd prospectively encodes not only hand-target vectors in visual coordinates (Pesaran et al., 2006; Ochiai et al., 2002) but also any initial direction of movement to circumvent obstacles while reaching (Pearce and Moran, 2012). These findings yield some resemblance to the described functions of the posterior parietal cortex in representing movements. The similar properties of PPC and PMd suggest that during reach planning both areas could initially represent visual action-consequences (i.e. desired reach trajectory) and that the motor programs required to produce these desired consequences are adapted later in the processing stream. Here we attempted to investigate the relationship between the visual consequences of an action and their underlying motor plans. To address this question we performed a functional magnetic resonance imaging (fMRI) study in which human subjects performed an action planning experiment. In this experiment subjects were required to plan and execute "virtual reaches" by moving a button-controlled cursor on a response-grid. In half of the trials, subjects carried out a delayed response task (Rosenbaum, 1980): they were instructed to remember a target location presented during the initial cue epoch and plan a movement towards it. Then, after an intervening delay epoch from which on the target was no longer present, they had to execute the pre-planned movement during a movement epoch. In these trials, it was crucial to plan a movement prior to the movement epoch, hence we named this task "*pre-planned movement task*" (PPM). In the other half of the trials, subjects were told to ignore the initial cue and to instead wait until the movement epoch of that trial when they had to move the cursor to a new, visually instructed target location, randomly placed on the response grid. The latter task was named "*direct movement task*" (DM) and differed from the PPM in that both movement planning and execution took place in the experimentally defined movement epoch (Ames et al., 2014), while in PPM a movement could be already prepared during the delay epoch. In both tasks, we used relatively short delays between initial cue- and movement epochs (e.g. compare to Lindner
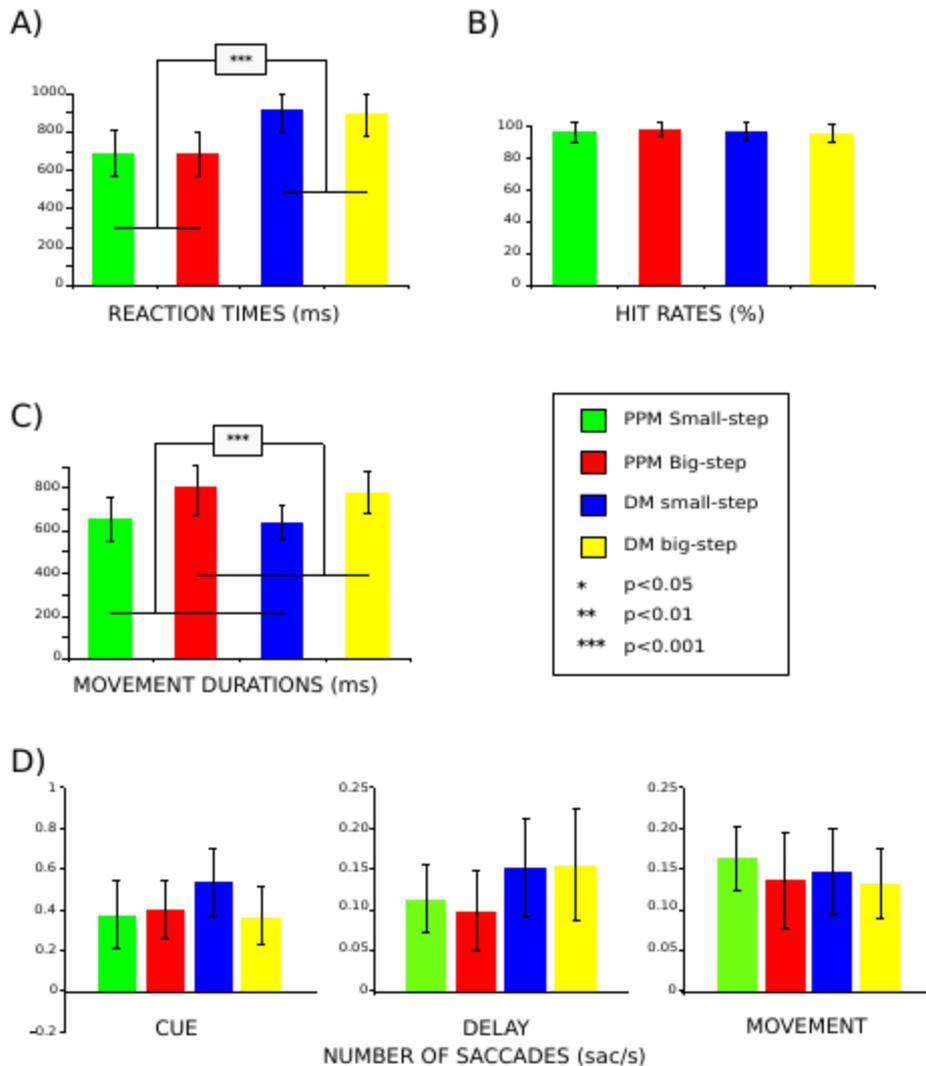
Figure 2.2. Behavioral Performance.
Average manual and oculomotor performance in PPM and DM trials. Error bars denote standard deviations. **A** Manual reaction times in PPM trials were significantly shorter than in DM trials, indicating that planning resulted in a reaction time benefit in PPM. **B** Hit rates did not differ significantly between PPM and DM, nor between movement gains, implying balanced movement difficulty. **C** Movement durations were on average significantly longer in "big-step" trials than in "small-step" trials, regardless of task. This difference was explained by the longer movement animation of the visual end-effector in "big-step" trials (see "Study 1 – Materials and methods") **D** The frequency of fixational saccades during delay and movement epochs did not differ between PPM and DM and also did not vary with gain context. In the cue epoch there were significant effects of "movement gain" and "gain"x"task" interaction.

et al., 2010) in order to minimize a potential influence of higher cognitive (e.g. mnemonic) strategies on movement planning. Furthermore, subjects were instructed to maintain central gaze fixation throughout the whole trial. This should help us to avoid, potentially confounding, eye-movement related brain activity.

To be able to disentangle the visual consequences from the motor components of a planned movement, we manipulated the gain of the visual cursor in both tasks. Namely,

after each single button press, the cursor could perform either a "small step" (i.e. jump to the next intersection of the response grid) or a "big step" movement (i.e. jump to the second-next intersection). Information about which movement gain was actually applied in a given trial was indicated to participants during the cue epoch of the trial (see Figure 2.1) and they needed to incorporate this information into their motor plan in order to perform accurately within the time limit of the movement epoch.

In all conditions we only cued target locations that could be reached by either one, two or four button-presses, allowing us to investigate brain activity as a function of motor sequence length. In addition, by also changing the movement gain ("big" or "small" step) for each given sequence length, we could keep a sequence's motor demands constant while, at the same time, varying its visual consequences.

We expected to reveal a representation of motor sequence length in both human PRR/PPC and PMd during movement planning and execution, a representation that we and others have already described previously (see e.g.: Haslinger et al., 2002; Lindner et al., 2010). More importantly, since previous fMRI studies revealed that the blood oxygenation level dependent (BOLD) signal amplitude correlates positively with the amount of (anticipated) visual motion (Lindner et al., 2006; also compare Schubotz and von Cramon, 2002), we hypothesized that if the visual consequences of a movement are indeed defined during the planning of that movement in PRR/PPC or PMd, then the brain activity in these areas should reflect these visual aspects. Specifically, the "big-step" motor sequences should on average produce stronger planning-related BOLD signal as compared to the "small-step" sequences, due to an overall larger amount of "predicted" visual motion.

RESULTS

Behavioral performance

We controlled several behavioral variables relevant for the interpretation of our fMRI data (Figure 2.2). Specifically, to demonstrate that subjects prepared their movement plans prior to the movement epoch in PPM trials, we analyzed subjects' reaction times (see "Study 1 - Materials and Methods" for details). Reaction times in PPM trials were contrasted to those revealed in DM trials, as in the latter trials planning could take place only in the movement epoch (i.e. after the target had been presented) allowing us to estimate the reaction time benefit through pre-planning (c.f. Rosenbaum 1980). As expected, manual reaction times were on average significantly shorter in pre-planned movement trials (PPM) than in direct movement trials (DM) (2x2 repeated measures ANOVA, main effect "Task" (PPM vs. DM): $p < 0.001$; main effect "Movement gain" ("small-step" vs. "big-step"): $p > 0.05$, n.s.; interaction: $p > 0.05$, n.s.) (Figure 2.2A).

Hit rates were constant across both tasks and movement types (2x2 repeated measures ANOVA, main effect "Task": $p > 0.05$, n.s.; main effect "Movement gain": $p > 0.05$, n.s.; interaction: $p > 0.05$, n.s.), indicating that movement difficulty across conditions was balanced (Figure 2.2B).

Average movement durations showed an expected effect for the factor "movement gain" (i.e. "big-step" sequences produced significantly longer durations because of the way the cursor movement was animated (see "Experimental Design" for details), but no "task" and interaction effects were present (2x2 repeated measures ANOVA, main effect "Movement gain": $p < 0.001$; main effect "Task": $p > 0.05$, n.s.; interaction: $p > 0.0.5$, n.s) (Figure 2.2C).An eye movement data analysis yielded no significant difference between both tasks and movement types with respect to the number of fixational saccades during delay and movement epochs (2x2 repeated measures ANOVA, main effect "Movement gain": $p > 0.05$, n.s.; main effect "Task": $p > 0.05$, n.s.; interaction: $p > 0.05$, n.s) (Figure 2.2D).
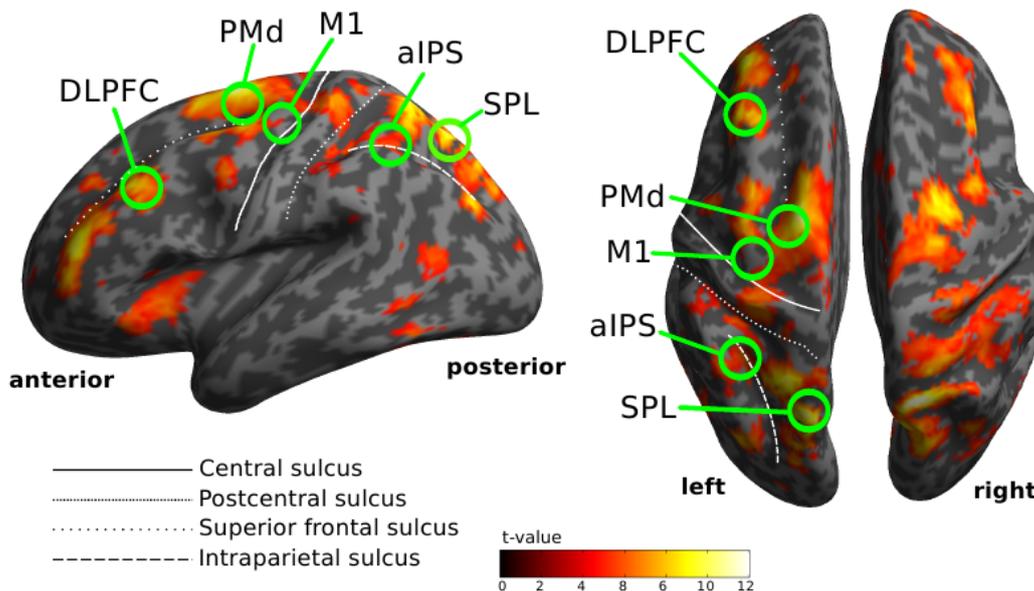
Figure 2.3. Areas of planning-related fMRI activity representing motor sequence length in an exemplary subject. The statistical parametric map is thresholded at p<0.05, fwe corrected for multiple comparisons (see "Study 1 - materials and methods" for a detailed description of the roi selection criteria).

This ensured that fMRI activity in these epochs was not differentially influenced by varying oculomotor behavior across conditions. The saccade rates were, however significantly different across conditions in the cue phase, as an ANOVA revealed a significant main effect of "Movement gain" (F=5.056, df=11, p=0.046) and a "Task"x"Movement gain" interaction (F=11.694, df=11, p=0.006). As we will discuss later in the text, these effects cannot explain the reported fMRI results.

Planning activity encodes visual properties of upcoming movement

For studying planning-related brain activity we decided for region of interest (ROI)-based approach to focus on the areas that were previously demonstrated to contain prospective representations of motor sequences (Lindner et al. 2010) and these motor representations we assumed likely to be modulated by expected visual properties of actions. First, we performed a whole-brain analysis in single subjects to define for each subject the brain areas that exhibited significant modulation of planning activity by motor sequence length during the delay epoch of PPM trials (see "Study 1 - Materials and methods" for details; also compare: Lindner et al. 2010). The following regions exhibited such modulation of
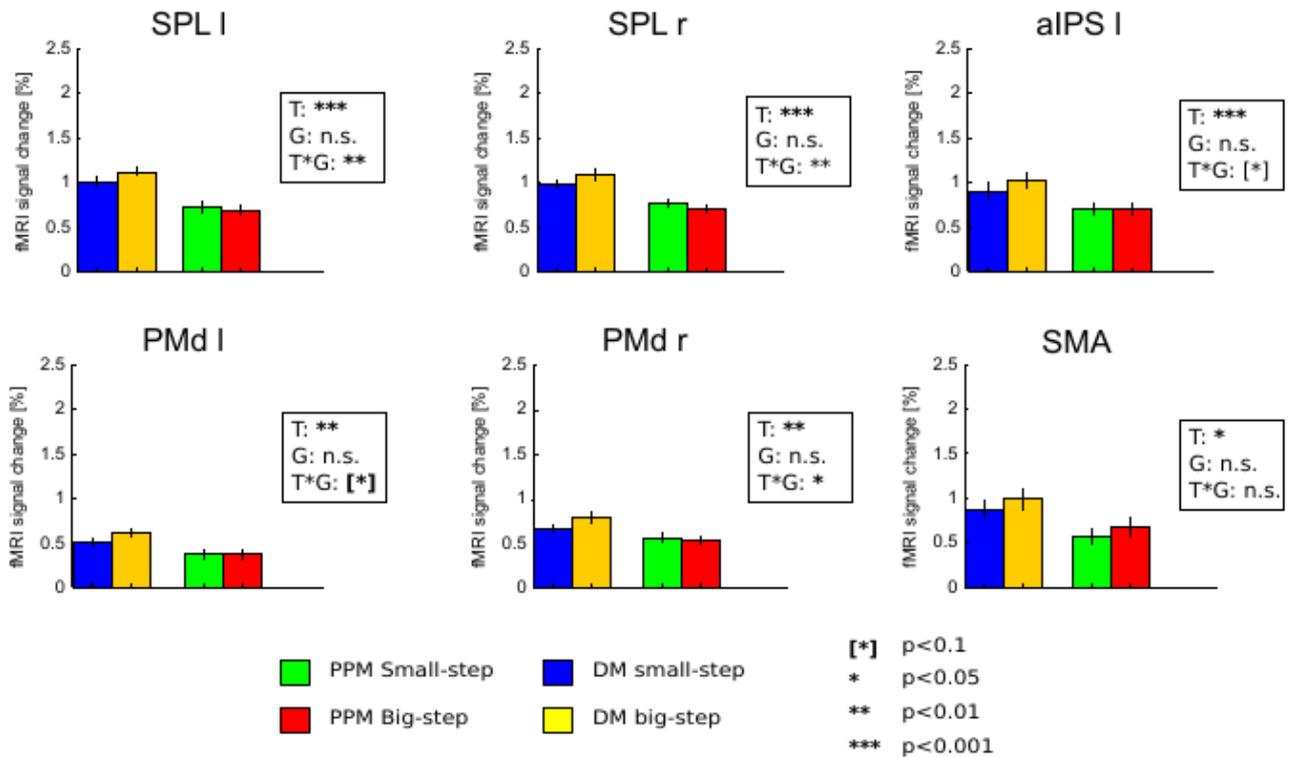
Figure 2.4. BOLD activity in all ROIs during the movement epoch. Signal increases in DM with respect to PPM reflect planning processes (compare main text). Signal differences between "big-step" and "small-step" trials in left and right SPL and in right PMd refer to an influence of (planned) visual movement distance. All values represent averages calculated across subjects' mean activity +/- SEM.

planning activity in all subjects: superior parietal lobule (SPL, bilateral), dorsal premotor cortex (PMd, bilateral) and anterior intraparietal sulcus (aIPS, left) (Figure 2.3). On the basis of previous research (Lindner et al., 2010) we assumed that such activation pattern is characteristic for areas contributing to the prospective planning of goal-directed motor sequences and that – in a second step – we could test whether activity in these ROIs is modulated by movement gain. In addition, we included dorsolateral prefrontal cortex (DLPFC, left), the hand area of left and right primary motor cortex (M1) and area V1 as additional control ROIs. It is worth to note, that our functional ROI selection criterion was independent to the tested hypothesis and thus allowed us to avoid circularity in subsequent analyses.

ANOVAs performed on the activity estimates (i.e. the normalized beta weights) extracted from these ROIs for the movement phase revealed a significantly stronger BOLD signal in DM than in PPM in several areas, namely left and right SPL, left and right PMd, and M1 (Figure 2.4). We consider these task-related changes an indicator for planning

processes in DM: any pre-planning during the delay would strongly reduce the cognitive load needed to plan and execute actions in the movement phase of PPM. On the other hand, planning was still needed during the movement phase in DM, thus elevating related BOLD signal amplitudes in DM as compared to PPM.

Most importantly, in both medial PPC and PMd putative planning activity in the movement phase of DM was additionally modulated by movement gain: the "big-step" motor sequences elicited on average significantly higher BOLD signal amplitudes than did the "small-step" sequences in left and right SPL and right PMd, as indicated by the significant interaction of the factors "Task" and "Movement gain" (Figure 2.4). This indicates that the visual aspects of upcoming movements were represented in these regions. It is noteworthy that there was also a trend for this effect in left PMd (p=0.088), implying a bilateral representation of the visual movement consequences in that area as well. A similar trend was also observed in left aIPS (p=0.09).

No such movement gain-related pattern was present in the movement epoch of PPM in these (and all other) ROIs, indicating that it is not the visual motion *per se* that would explain the signal differences between "big step" and "small step" movements (Figure 2.4). We neither did observe a gain-related modulation of brain activity in the movement epoch of DM in primary motor cortex nor in dorsolateral prefrontal (Figure 2.6). Area M1 is primarily engaged in preparation and execution of motor programs (see eg. Hocherman and Wise, 1991), and, at least to our knowledge, there is no evidence that it could process any visual information about the upcoming action. The dorsolateral prefrontal cortex, in turn, has been demonstrated as being engaged in retrospective mnemonic processes rather than in prospective planning (e.g. compare Lindner et al. 2010). Therefore the lack of signal modulation due to movement gain in these particular ROIs is in line with our main hypothesis (see discussion).

It is also worth to note that both in PMd (in PPM and DM trials) and PPC (in DM
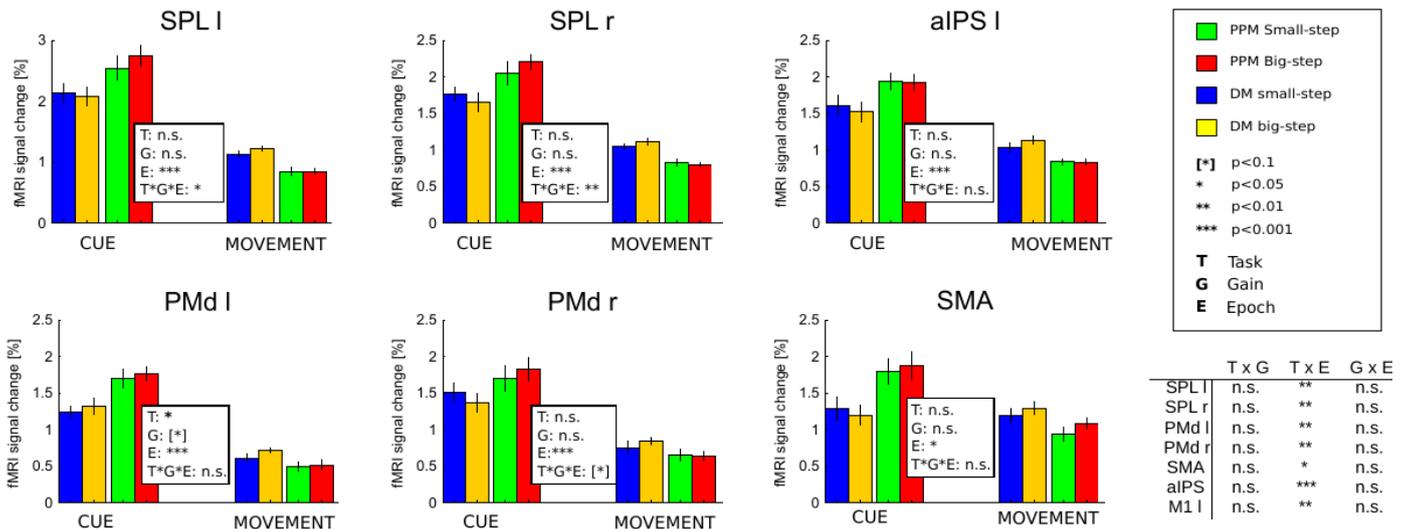
Figure 2.5. BOLD activity at early planning stages. Cue epoch of PPM and movement epoch of DM are grouped together as "planning" conditions. The Task(T) x Gain(G) x Epoch(E) interaction demonstrates presence of visual consequences representation in the left and right posterior parietal cortex (SPL). A significance-nearing trend is present also in the right PMd. The additional table contains interaction effects for all the depicted ROIs. Task x Epoch interaction demonstrates a significantly higher activity in the Cue epoch of the PPM trials and Movement epoch of DM trials, likely reflecting initial planning processes in these epochs/conditions.

trials) visual modulation of planning activity was easier to observe on the ipsilateral but not the contralateral side (with respect to the effector). This suggests that ipsilateral representations of movement may organize information more in terms of the abstract (visual) motor plan, whereas the contralateral representations might process information in a way that more directly refers to effector's motor action. While we cannot reliably test this hypothesis on the basis of the current dataset, it seems at least to be supported by findings of Krasovsky et al. (2014) who also reported that representations of sensory action-outcomes are rather ipsi-, than contralaterally organized.

Comparisons of activity estimates for the delay epoch did neither reveal any significant gain-related differences in any of our planning ROIs nor any differences between movement tasks, i.e. PPM vs. DM (see Figure 2.6).

The lack of a difference between PPM and DM during the delay, which contrasts previous studies (e.g. Lindner et al. 2010), could result from the comparatively short delay epochs in our study. This suggests that such short delays apparently not allow a full separation between the cue- and delay-related BOLD-signals and can be also susceptible to any

instruction-independent default planning (Snyder et al., 2006) in response to the irrelevant target cues that were presented during the cue epoch of DM trials. Irrespective of these clear limitations of our design with short delays, the difference in movement gain could still be reflected by sustained BOLD-signals in the delay phase of PPM. In our view, our inability to observe such effect demonstrates one potential weakness of using the classical delayed response paradigm in fMRI research, namely its limited capacity to capture brain responses related to rapid, early planning processes. This speculation is supported by aforementioned findings of Kuang et al. (2015) who demonstrated, that the relative amount of visual planning neurons is significantly higher early during the planning stage of an action and is becoming less pronounced later during the delay, in the sustained neural response.

Differences between tasks were, however, present in control ROIs: Interestingly, activity in the left motor cortex was significantly stronger in the PPM than in DM (p=0.0027), apparently reflecting unspecific effector preparation processes. This is confirmed by the lack of such modulation on the ipsilateral side (see Supplementary Figure 2.7). Likewise, in DLPFC there was a significant influence of task, namely a stronger activity in PPM as compared to DM too. This area might be engaged in mnemonic aspects of motor planning (e.g. a retrospective representation of the movement target), as was suggested by previous findings of Lindner and colleagues (2010).

The lack of a gain effect in activity of planning ROIs during the delay epoch in PPM trials prompted us to look more closely at early planning activity in these trials. For this purpose, we estimated an alternative GLM in which we now also focused on gain-related changes during the cue epoch (as compared to the response epoch). This is because early planning processes might be already reflected in the integrated BOLD-signal during the cue-epoch. Furthermore we wanted to contrast such early planning in PPM during the cue epoch with early planning in DM during the movement epoch. Therefore we ran a

three-way repeated measures 2x2x2 ANOVA with the factors "Task" (PPM and DM), "Movement Gain" ("small-" and "big-step") and "Epoch" ("Cue" and "Movement"). We assumed that the visual effect ("big-step" > "small-step") should be visible in the cue epoch of PPM and in the movement epoch in DM, as would be confirmed by a three-way interaction of the three factors (Figure 2.5). Indeed, this analysis uncovered that the early planning response in left and right SPL do show the expected effect of visual movement properties as dependent on task and trial epoch (Left SPL: $F=5.469$, $df=11$, $p=0.0393$; right SPL: $F=10.946$, $df=11$, $p=0.0070$). In right PMd we revealed a clear trend for the same effect ($F=4.476$, $df=11$, $p=0.0580$). The gain effect was however absent in left PMd ($F=0.249$, $df=11$, $p=0.6273$).

DISCUSSION

Prospective representation of visual movement consequences

Our experiment represents an alternative approach for studying planning-related fMRI-activity of the human brain. Instead of only focusing on delay-related planning activity between instructive cue and action initiation (e.g. compare Lindner, 2010), we chose to compare movement sequences that had been already pre-planned (PPM) to those that required planning directly before execution (DM) (compare Ames et al., 2014).

Using this approach, we were able to exhibit increases of fMRI-activity during the movement epoch in DM as opposed to PPM trials. We observed such increase in planning ROIs, which had been independently identified by exhibiting motor preparatory activity during the instructed delay in PPM trials. Moreover, we observed an additional modulation of DM activity by the visual consequences of a movement in the same ROIs. Activity was the stronger the more visual motion the same movement sequences produced due to the gain manipulation. This effect was apparent in areas previously demonstrated to contain prospective representations of action plans (PPC and PMd; see: Lindner et al. 2010). Yet,

it was absent both in primary motor cortex and in DLPFC, which has previously been demonstrated to mainly maintain a retrospective memory of visual movement targets (Lindner et al., 2010) . The modulation of planning activity by movement gain was present also in early cue-related brain responses but not during the delay period. This suggests that target localization for movement and characterizing a movement plan in terms of a visual movement consequence, is a transient process, occurring at the earliest stages of motor planning.

Our results are consistent with the idea that motor planning activity in PPC and PMd initially represents the visual consequences of an upcoming movement while the required motor program needed to realize such visual action plans arises at later stages of sensorimotor processing and it seems likely that exclusively this motor program is maintained in memory until it's ultimately put into action.

Alternative paradigms for dissociating vision and manual action

Apart from the gain manipulation that was applied in our study, other experimental paradigms have been used to alter the interrelation between hand movements and visual information. These paradigms could potentially provide us with additional clues about whether the visual consequences of manual actions are embedded in an action plan. One such paradigm is the so-called anti-reach task in which subjects need to perform reaches towards a location opposite to a pre-cued visual target location (Crammond, Kalaska, 1994; Westendorff et al. 2010). While this task clearly allows distinguishing activity related to the direction of a visual target vs. activity related to the direction of movement, it cannot discern whether any movement-related activity would refer to the visual or to the bodily direction of movement as both are identical. Another class of paradigms that seems related engages inverting prisms (Helmholtz, 1909; Clower 1996). The use of prisms can clearly help to dissociate bodily motion from its visual consequences (e.g. through

inverting prisms). Yet, when monitoring brain activity during such paradigms particular care has to be taken to disentangle whether activity truly reflects the visual consequences of movement rather than any visual stimulus itself (or the memory thereof), as visual movement- and target- direction are identical. So far there is only one electrophysiological study on action planning in monkeys that has engaged both paradigms and that therefore could account for the aforementioned limitations (Kuang et al., 2015; for details see "Study 1 - Introduction"). In our own human fMRI experiment the visual movement consequences and the location of the visual goal were also tightly coupled, but our specific experimental findings still allowed us teasing apart these factors as will be discussed in the following paragraph.

Potential limitations of interpretation

Before answering what action components determined the gain-related modulation of the BOLD signal in the early planning activity, some potential confounding factors need to be considered.

In our eye movement analysis we revealed a significant influence of experimental condition on saccadic frequency but during the cue phase, only. Here, saccades were most frequent in the "small-step" DM condition. However, when assuming that saccade rates are positively correlated with the amplitude of the BOLD response (see eg. Kimmig et al., 2001) this saccade effect can hardly account for the pattern of gain-dependent planning activity in PPC and PMd during the cue phase, namely the change in PPM-related activity (compare Figure 2.3D and Figure 2.5). Moreover, as there was no difference in saccade rates in the movement phase, saccadic eye movements also cannot explain the gain-related modulation of planning activity in DM during this task epoch.

Another factor deals with the problem of dissociating visual target cue eccentricity from movement distance. As it may be argued, the more eccentric the visual cues, the

more activity they can evoke, due to the repeatedly demonstrated over-representation of visual periphery in the parietal cortex (e.g.: Colby et al., 1988; Baizer et al., 1991; Motter and Mountcastle, 1981). In our present research target eccentricity itself was inevitably correlated with the length of the visual trajectory of the end-effector (i.e. the placement of targets in the "big-step" conditions was more eccentric than in the "small-step" conditions). Therefore the increase in BOLD-signal that we observed in the early planning could have equally likely reflected any of these aspects. We argue, however, that this effect should then be also visible in the cue phase of the DM trials, and, potentially, in the primary visual cortex. Both were clearly not the case. Hence the eccentricity of the visual target cue is unlikely to explain the observed result.

Movement duration can be considered yet another potential confounding factor. Movements towards more visually distant locations lead to longer lasting sensorimotor representations, which in turn may lead to higher BOLD activity (due to the long time constant of the BOLD-signal such change in motor duration will foremost surface as a change in signal amplitude). In our current study, however, this should again affect not only signal amplitudes during the movement epoch of the DM, but also those of the PPM. Moreover, duration-related signal changes should be visible also in primary motor cortex. Yet, such effect is lacking as well. Finally, movement durations cannot explain the gain effect we see in the CUE phase of the PPM trials. It thus seems plausible to conclude that the observed BOLD-signal modulation during the cue epoch in PPM and during the movement epoch in DM does solely reflect visual differences in the planned movement.

Finally, was the gain-related modulation of the BOLD-signal in DM related to movement planning or due to movement execution? The lack of gain-related BOLD signal modulation during the movement epoch of PPM trials suggests that the observed modulation in DM is rather related to planning differences between "big-step" and "small-step" conditions (present in DM) than to any immediate sensory or somatosensory

feedback about the target or the actual movement (present both in DM and PPM).

For the above reasons we believe that that the gain-related modulation of BOLD-responses in PPC and PMd, occurring during the movement epoch of the direct movement condition and during the cue epoch of the pre-planning condition, is best explained by early planning processes, reflecting the visual consequences of upcoming movement.

Visual action planning in PPC and PMd and its putative implications

The presence of a visual modulation of planning activity in human PPC and PMd is well in line with the known properties of both areas, as has been laid out in detail in the introduction. More generally, it supports the view that the visual movement consequences are a superordinated kinematic component of movement planning, determining the choice of appropriate dynamics in order to move the effector along the desired visual trajectory (Wolpert, 1995; Morasso, 1981).

The representation of visual consequences of a planned action was more robust in PPC than in PMd. If we assume a processing hierarchy between these areas, our findings suggest that PPC delineates a rather general and abstract action plan in visual terms, which is subsequently translated into more specific motor programs by PMd (Desmurget and Sirigu, 2009; Kalaska and Crammond, 1995; Cisek and Kalaska, 2002; also compare Westendorff et al., 2010). Such high-level visual representation of an intended movement's consequences seems to be important for planning, namely to assess a desired trajectory through visual simulation. This is of particular importance, e.g. when movements need to avoid obstacles and an appropriate trajectory has to be planned upfront. Moreover, it can serve as a stable reference for planning whenever effector efficiency is altered (i.e. due to fatigue or injury). This of course means that the desired visual trajectory, as defined in parietal and premotor cortex, also requires an appropriate adaptation of motor programs that considers the current efficacy of the motor system. The latter is possibly realized via

reciprocal cerebro-cerebellar connections and without involvement of awareness (Blakemore and Sirigu 2003). Planning of motor actions, which builds on a simulation of the visual consequences they produce, is supposedly also one of the vital components of effector selection, and tool use. Actions engaging different end-effectors such as one's bare hand or a tool obviously require different motor programs, even if the goals to be achieved are the same. To optimally select between these different motor programs, as might become necessary in certain situations, we need a predictive representation of actions' outcomes to avoid acting on a trial and error basis. A plan representing these sensory outcomes, as supposedly implemented by PPC and PMd, would perhaps fulfill such prerequisite and allow modifying the natural motor repertoire by incorporating the available end-effectors (e.g. tools or even computer interfaces) to achieve a desired sensory outcome. Such flexibility in planning would then broaden the spectrum of potentially available goals and actions (Gallivan et al., 2013; Haruno et al., 2001; Iriki et al., 1996; Maravita and Iriki, 2004) permitting a more efficient selection of both.

Finally, it could be further speculated that a representation of the visual consequences of planned actions in PPC and PMd also underlies our capacity to distinguish self- from externally- produced visual events (e.g. compare Synofzik et al. 2006). While this distinction has been mainly thought to be drawn from a comparison of an efference-copy based prediction of the visual consequences of self-action with the actual visual afference (Sommer and Wurtz, 2002), others suggest that this capacity may likewise refer to a comparison between *desired* and *actual* visual action outcomes (Bahcall and Kowler 1999; Synofzik et al. 2006).

Certainly, the exact role of PPC and PMd in these abovementioned functions remains to be determined. Yet, it is important to stress that a seemingly simple principle, i.e. the planning of action based on desired visual consequences, could have implications for a wide variety of functions extending beyond the motor domain.

Conclusions

Our findings suggest that early planning activity in human posterior parietal cortex represents the visual consequences of planned actions independent of the actual motor programs required to realize these plans. Moreover, we found similar activity in human dorsal premotor cortex, suggesting that the two brain regions may collaborate in representing a visually defined action plans and, potentially, in translating them into appropriate motor commands. At this stage we may speculate that posterior parietal cortex, a region bridging between visual and motor areas might serve as the main driving force of this fronto-parietal planning system, utilizing information from both sources in order to create an effective movement plan.
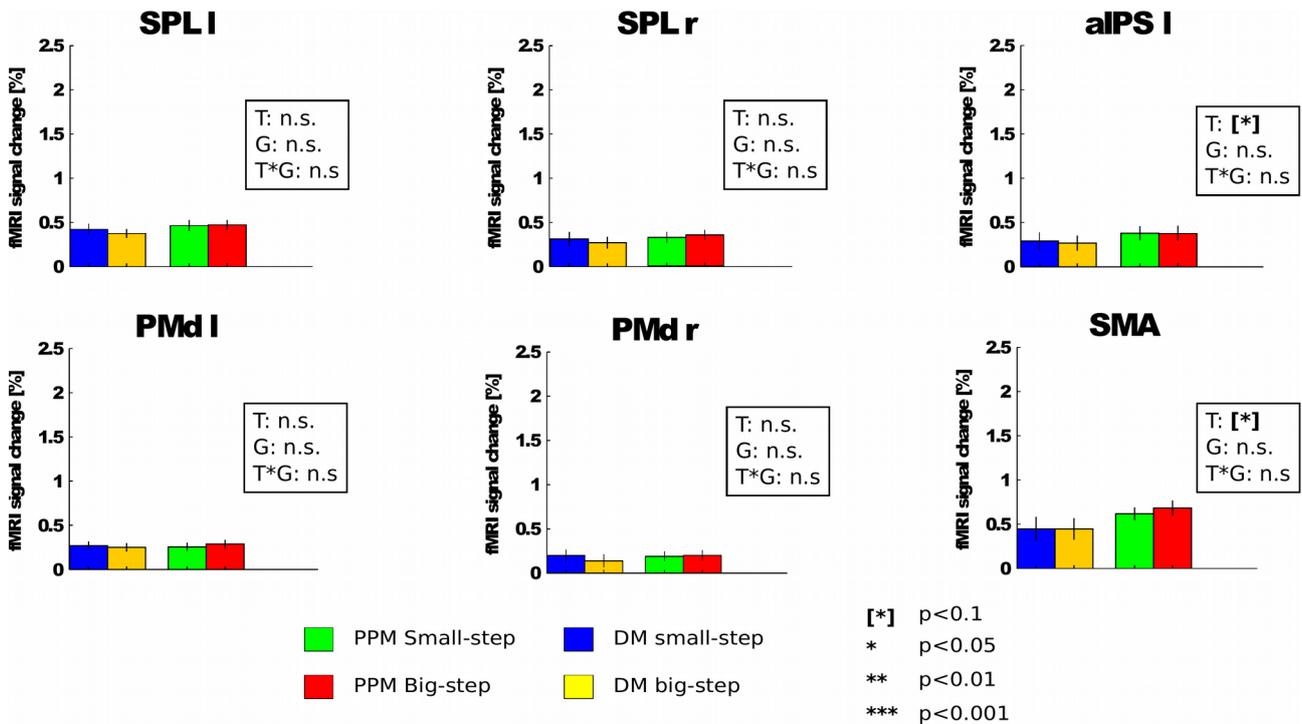

Figure 2.6. BOLD activity in all ROIs during the delay epoch. Sustained activity was present in all ROIs. Signal increases in PPM with respect to DM in M1 could relate to unspecific motor preparation. All values represent averages calculated across subjects' mean activity +/- SEM.
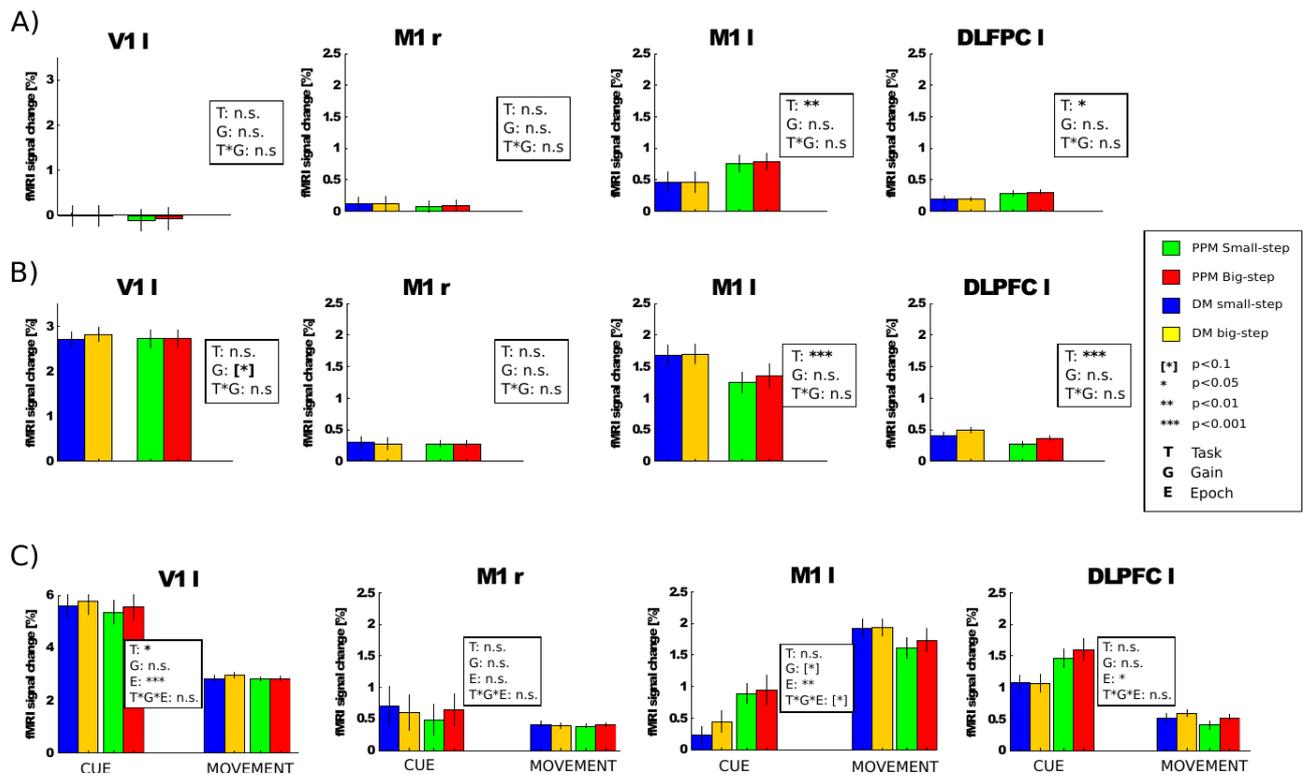
Figure 2.7. Delay (A) and movement epoch (B) betas extracted from primary visual and right primary motor areas. The V1 activity shows a weak trend related to movement gain in the movement epoch of DM trials. C) Control ROI betas extracted in the cue and movement phases, used to capture early planning activity. All values represent averages calculated across subjects' mean activity +/- SEM.

Study 2. When the path is the goal. Distinct representations of reach trajectory plans in human frontal and posterior parietal cortex

INTRODUCTION

Goal-directed eye saccades and hand reaches share many commonalities. Both movement types are prepared based on target and effector representations in a visual (retinal) reference frame and even the neural correlates responsible for their programming do partially overlap (Andersen and Buneo, 2002). According to a well-established view, the motor plans for saccades are thereby defined by coding a difference vector between the current position of the eye and the desired saccade endpoint (Bruce and Golberg 1984; 1985; Zee et al. 1976; Hallet and Livingstone, 1976). As there are no objects in the eye socket that would interfere with the rotation of the eyeball, such simple planning scheme seems optimal for its purpose. In many cases hand movements are executed in a similar point-to-point fashion, such as when catching a ball or swatting a fly. In these latter situations the hand movement could likewise be determined by a difference vector between target and hand (Beurze et al., 2010). Yet, such method would not always suffice: imagine you'd like to reach for your pen, but a mug of coffee sits right between the pen and the hand. In such situation your eye could still saccade straight towards the pen while any hand movement aimed just at the endpoint (the pen) would cause your hand to bump into the mug with severe consequences. Therefore, to allow the hand to circumvent the obstacle, an appropriate reach trajectory needs to be programmed. It seems likely, that such ability to precisely plan hand trajectories is not only required to avoid obstacles, but it perhaps does also underlie our ability to perform the endless variety of highly-complex and skillful movements such as drawing or handwriting.

Electrophysiological research in monkeys has yielded some important clues about where and how the planning of reach trajectories could be realized by the brain. A
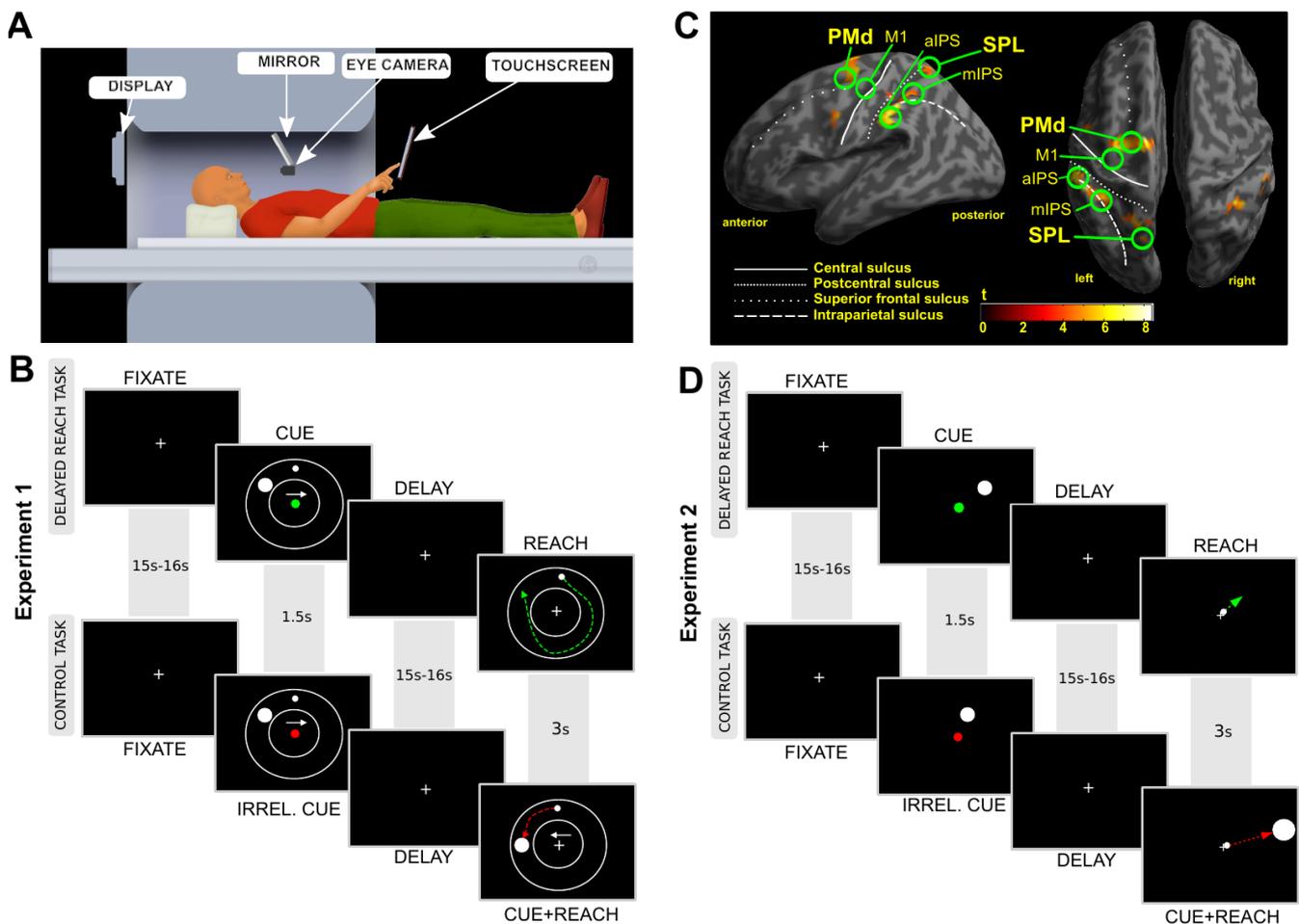
Figure 3.1: A) MRI-compatible virtual reality reach setup. B) Timeline of the delayed reach task (DRT) and the control task (CT) of Experiment 1. Subjects were supposed to reach the target (filled large circle) by moving their finger from the starting position (filled small circle) either clockwise or counter-clockwise, as was specified by the white arrow cue. These cues were shown in the CUE period of both conditions but were relevant only in the DRT. In the CT all cues were irrelevant and the ultimate movement was instructed by a new set of cues presented during the REACH phase. Colored dashed lines illustrate putative reach trajectories in both tasks. Additional masks presented after CUE and REACH screens are not shown (see "Study 2 – Materials and Methods" for details). The objects are plotted not to scale. C) Planning Activity. Inflated cortical surface with an overlay of the statistical contrast of delay-related planning activity (DRT>CT) obtained from 12 subjects in Experiment 1 (p<0.001, uncorrected; t-value>4.0). Labels identify regions of interest that were included in our ROI analyses. Major anatomical landmarks are labeled in addition. D) Timeline of an exemplary delayed reach (DRT) and control trial (CT) in Experiment 2 (see text and compare to B for details).

prominent candidate for reach trajectory planning is dorsal premotor cortex (PMd), as neurons in this brain area are not merely interested in target location or the hand-target difference vector but do represent information relevant for trajectory coding. For instance, in the presence of obstacles PMd does not only code movement plans towards the target location itself but it also represents the initial direction of movement that is needed to circumvent any obstacle (Pearce and Moran, 2012) . Moreover, Hocherman and Wise (1991) have demonstrated, that some neurons in macaque premotor cortex (as well as

primary motor cortex and supplementary motor area) exhibit firing patterns that correlate with the curvature of the trajectory of an upcoming reach. Premotor coding of reach curvature may – along with the coding of initial movement direction - support the ability to circumvent obstacle. In accordance with this interpretation, ablation of premotor cortex disables monkeys' ability to avoid obstacles and they instead attempt to reach directly towards the target (Moll and Kuyspers, 1977). This latter experiment not only directly supports a role of PMd in trajectory planning. It also highlights that planning of straight, direct reaches is still preserved despite PMd lesions and hence such vector-like reach planning must be maintained by other brain regions.

Reach-related areas within the posterior parietal cortex (PPC), namely the parietal reach region (PRR) in the medial wall of the posterior intraparietal sulcus (IPS) of macaque monkeys and its functional human homologue in neighboring parts of superior parietal lobule (SPL), are likely substrates that could subserve vector-like, straight reaching. In fact, monkey PRR and human SPL have been demonstrated to represent reaches in terms of hand-target difference vectors (Beurze et al., 2010; Buneo et al., 2002), i.e. in an optimal format for coding straight reach paths. Several electrophysiological studies demonstrated that these reach planning regions in PPC may also contain trajectory-related information beyond vector coding. Note, however, that unlike to the work on PMd, most of these studies focused on neural activity during reach execution(Aflalo et al., 2015; Mulliken et al., 2008a; Mulliken et al., 2008b; Hauschild et al., 2012) but not on planning. A notable exception is the study of Torres and colleagues (2013), who utilized a simplified obstacle avoidance task. They demonstrated that single cells in monkey PRR modulated their activity prior to the reach whenever a barrier blocked the direct reach path. It was unclear, however, whether the modulation observed in this study truly reflected initial reach direction or, alternatively, strategical chances in initial hand posture present during the planning stage. Taken together, previous research on

reach planning in monkey posterior parietal cortex has highlighted its role in the vector-like coding of reach movements. It is unclear, however, whether it also contributes to the planning of complex trajectories.

Here we tried to reveal how trajectory information is represented prior to movement execution in reach-related areas of the human brain, namely areas SPL and PMd. We intended to examine how trajectory representations change when a movement plan could theoretically be constructed by just defining a vector between the initial hand position and a target as compared to situations when these difference vectors are identical but the movement paths vary. Based on previous research we expected to reveal representations of trajectory plans in human SPL (Mulliken et al., 2008a; 2008b; Hauschild et al., 2012; Torrees et al., 2013; Kadmon-Harpaz et al., 2015) and PMd (Hocherman and Wise, 1991; Kadmon-Harpaz et al., 2015; Pearce and Moran, 2012) and, possibly, in primary motor cortex (Hocherman and Wise, 1991; Philip et al., 2013) as well as supplementary motor area (Hocherman and Wise, 1991; Kadmon-Harpaz et al., 2015). On the basis of the abovementioned research, we assumed that the trajectory representations in SPL and PMd would likely differ depending on the type of the movement required. Specifically, we hypothesized that while PMd should contribute to the preparation of complex trajectories, SPL would be exclusively engaged in planning straight and direct paths.

RESULTS

To address our hypotheses, we conducted two human functional magnetic resonance imaging (fMRI) experiments where subjects had to plan and execute finger reaches towards visually cued targets. Two groups of twelve and seven volunteers took part in Experiments 1 and 2, respectively. All of them were right handed, had no history of neurological disease and had normal or corrected to normal vision. All volunteers gave their written informed consent according to the Declaration of Helsinki prior to the

experiment, and the study was approved by the local ethics committee. In Experiment 1 we varied the length of complex (curved) reach trajectories while keeping the hand-target vector constant across conditions. This experiment mimicked situations that enforce the programming of detailed trajectories (like during obstacle avoidance). In Experiment 2 we varied the distance to the target, and thus the length of the hand-target vector, while instructing subjects to perform simple, straight reaches towards it. We expected that if neural representations of reach trajectories are represented prior to movement, the increasingly larger neural populations should be recruited to represent certain trajectory properties subject to scaling (i.e. length or complexity) and the average BOLD signal amplitudes extracted from a given region should increase with these properties as they scale up (Üstün, 2016).

For the purpose of our experiments, we constructed a virtual-reality reach environment, consisting of an MR-compatible resistive touchscreen panel and a rear projection display system allowing subjects to receive visual feedback about their reaching finger position in approximate spatio-temporal correspondence with the true movement (Figure 3.1A). Subjects were positioned with their head tilted forward inside the head coil to allow them to naturally look in the direction matching their fingertip position albeit without a direct vision of their hand.

4.2.1 Experiment 1 - planning circular reaches

The first experiment (Figure 3.1B) consisted of a circular reaching paradigm comprising of two task variants: the first variant was a delayed reach task (DRT), which was used to trace reach-trajectory-related activity during planning and execution. The participants were required to remember an initially cued target location ("CUE"-phase), and then, after a delay ("DELAY"-phase), a "go" cue appeared that prompted the participants to move their finger to the now invisible target location ("REACH"-phase). The DRT was contrasted with
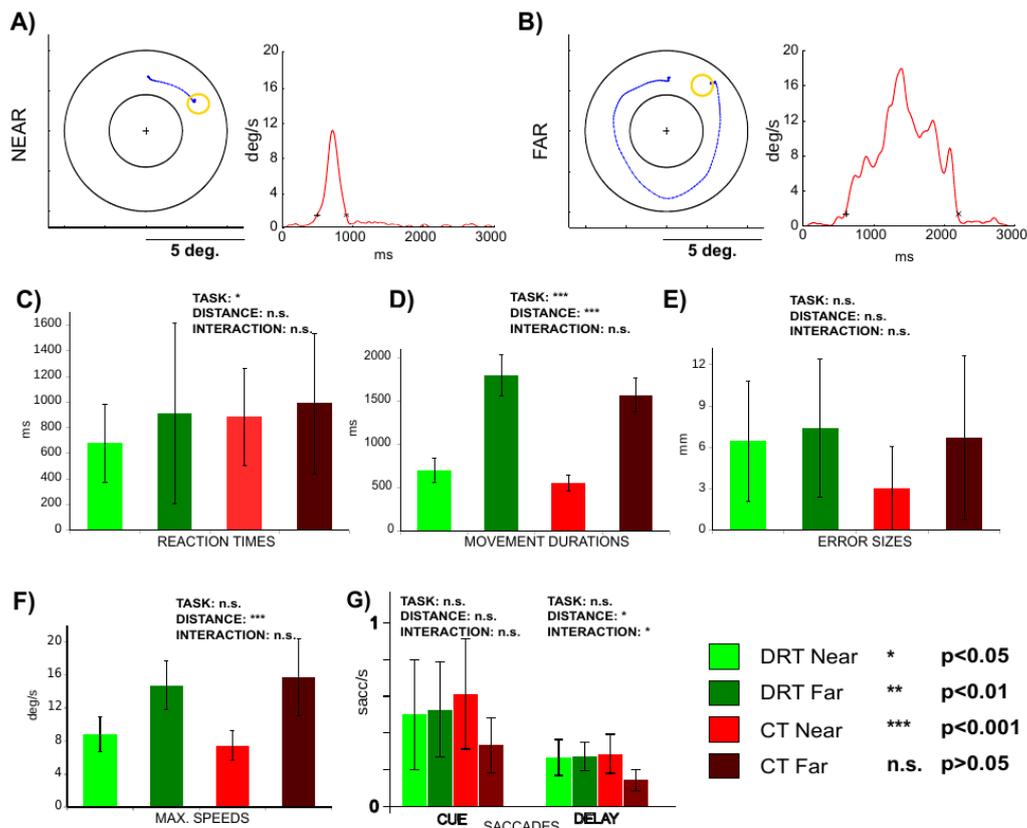
Figure 3.2. Movement performance in Experiment 1. A and B) Exemplary reach trajectories from a single subject (left panels) and the respective speed profiles throughout the REACH phase (right panels) for both a "NEAR" (F) and a "FAR" (G) condition are depicted. C-G) The individual panels show our estimates of behavioral performance as a function of "TASK" and "DISTANCE" and report the influence of these factors on the respective estimates as well as their interaction, as was assessed by two-way repeated measures ANOVAs (n.s. not significant; * p<0.05; ** p<0.01; *** p<0.001). C) Reaction times were significantly shorter in DRT than in CT. D) Movement durations were significantly longer in DRT than in CT and for "FAR" trajectories than "NEAR". E) Error sizes were constant across all conditions. F) Maximal speeds were higher for "FAR" reaches. G) Average frequencies of fixational saccades in CUE an DELAY epochs of respective conditions. Saccades were less frequent in CT "FAR" than in all other conditions. Error bars represent SEM. See text for detailed statistics.

a second task, namely a control task (CT), in which subjects' goal was to ignore the initial spatial cue and, after a delay, to move to a visible target presented at a new location. The key difference between both tasks was that in the DRT, the subjects had to plan a movement well before its execution (during the delay epoch), whereas in the CT, the movement was only planned after the "go" cue appeared, namely when the actual target was presented. The key idea is that during the delay period of the DRT one can assess planning activity in the absence of the varying sensory cues and before a movement is being executed. By contrasting the respective activity estimates in the DRT with the CT one can further control for processes common to both tasks such as task-unspecific motor

preparation (e.g. compare Lindner et al., 2010).

In both tasks the finger starting location was the topmost position between two large circles indicating the circular movement space. The current location of the finger was indicated by a small dot visible during the CUE and the REACH phase only. An arrow cue indicated either a clockwise (right pointing arrow) or a counter-clockwise movement (left pointing arrow) towards the target cue. Accordingly, reaches needed to be executed along a circular path of varying distance (see Figure 3.1B; also compare Figure 3.2 A and B). This allowed us to capture trajectory-related information and to isolate it from information related to a hand-target vector and an eye-target vector, which both were (on average) kept constant in this task. Moreover, this procedure ensured that the target and any retrospective memory thereof would be the same across conditions while reach distance (and complexity) and any related prospective processes engaged in reach planning would vary. In the CT the initial cues were irrelevant and the circular movement was specified by independently selected directional and target cues displayed during the movement epoch (Fig. 3.1B).

As a first step, we analyzed subjects' behavior in Experiment 1 in terms of subjects' reaction times as well as the duration, speed, endpoint error of movement and frequency of residual saccades. In brief, 2x2 (repeated measures) ANOVAs with the factors TASK and DISTANCE were performed on subjects' average behavioral estimates. The respective statistical analysis of subjects' reaction times (Figure 3.2 C) yielded significantly shorter reaction times in the DRT condition than in the control condition (Rosenbaum, 1980), indicating that the movements were actually pre-planned in the DRT (factor TASK: df=11, F=6.8, p=0.024, eta^2_G=0.0207; all other effects were not significant: DISTANCE: df=11, F=2.5, p=0.140, eta^2_G=0.0287; TASK*DISTANCE: df=11, F=1.5, p=0.252, eta^2_G=0.0041). Movement durations were significantly longer in DRT (TASK: df=11, F=27.7 p=0.0003, eta^2_G=0.235) and for longer trajectories (DISTANCE: df=11, F=701.4, p<0.0001,
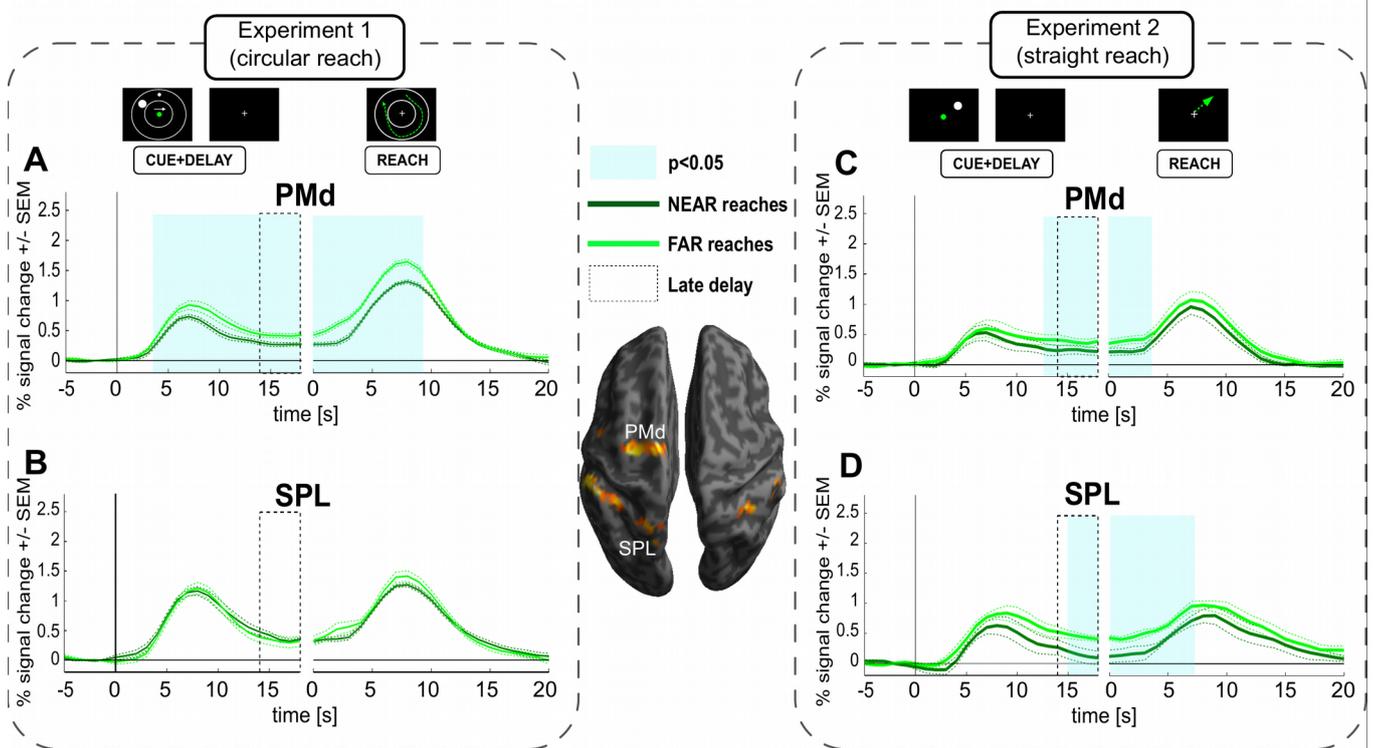
Figure 3.3. ROI timecourses extracted from PMd (A & C) and SPL (B & D), comparing the fMRI-signal in the delayed reach task of Experiments 1 and 2 (A & B vs. C & D, respectively). Cyan-shaded areas represent time epochs during which paired t-test comparisons of signal amplitudes between "NEAR" and "FAR" reaches revealed statistically significant differences ($p<0.05$) for at least three neighboring time-points. Such differences were considered indicative of an influence of trajectory. PMd shows different planning-related signal amplitudes in both experiments (leftward part of the panels A and C, aligned to CUE onset). SPL shows trajectory planning signal modulation in Experiment 2 only (D). PMd shows significant modulation in the reach phase in both experiments (A and C, right panels, aligned to REACH onset), whereas SPL shows such statistically significant difference only in Experiment 2 (D) although a hint of the same effect might be present in Experiment 1 as well (B). Dotted gray boxes indicate late delay phase, in which activity merely represents planning but no longer CUE-related activity. This period was also used for a subsequent statistical comparison between PMd and SPL.

eta^2_G=0.908). It is noteworthy that the latter effect was driven by much larger duration differences (see Figure 3.2 D). There was no interaction between the two main factors (TASK*DISTANCE: df=11, F=1.7, p=0.21, eta^2_G=0.014). Endpoint error (see Figure 3.2 E) was constant across tasks and distances (TASK: df=11, F=2.4, p=0.148, eta^2_G=0.050; DISTANCE: df=11, F=3.5, p=0.087, eta^2_G=0.062; TASK*DISTANCE: df=11, F=3.1, p=0.104, eta^2_G=0.023). Maximal movement speed (Fig. 3.2F) did not differ across tasks (TASK: df=11, F=0.14, p=0.72, eta^2_G=0.001). It was however higher for longer trajectories (DISTANCE: df=11, F=57.87, p=0.00005, eta^2_G=0.589). The interaction effect was not significant (TASK*DISTANCE: df=11, F=2.71, p=0.13, eta^2_G=0.037). Finally, the frequency of saccades (Fig. 3.2 G) was indistinguishable between DRT and CT in the CUE phase
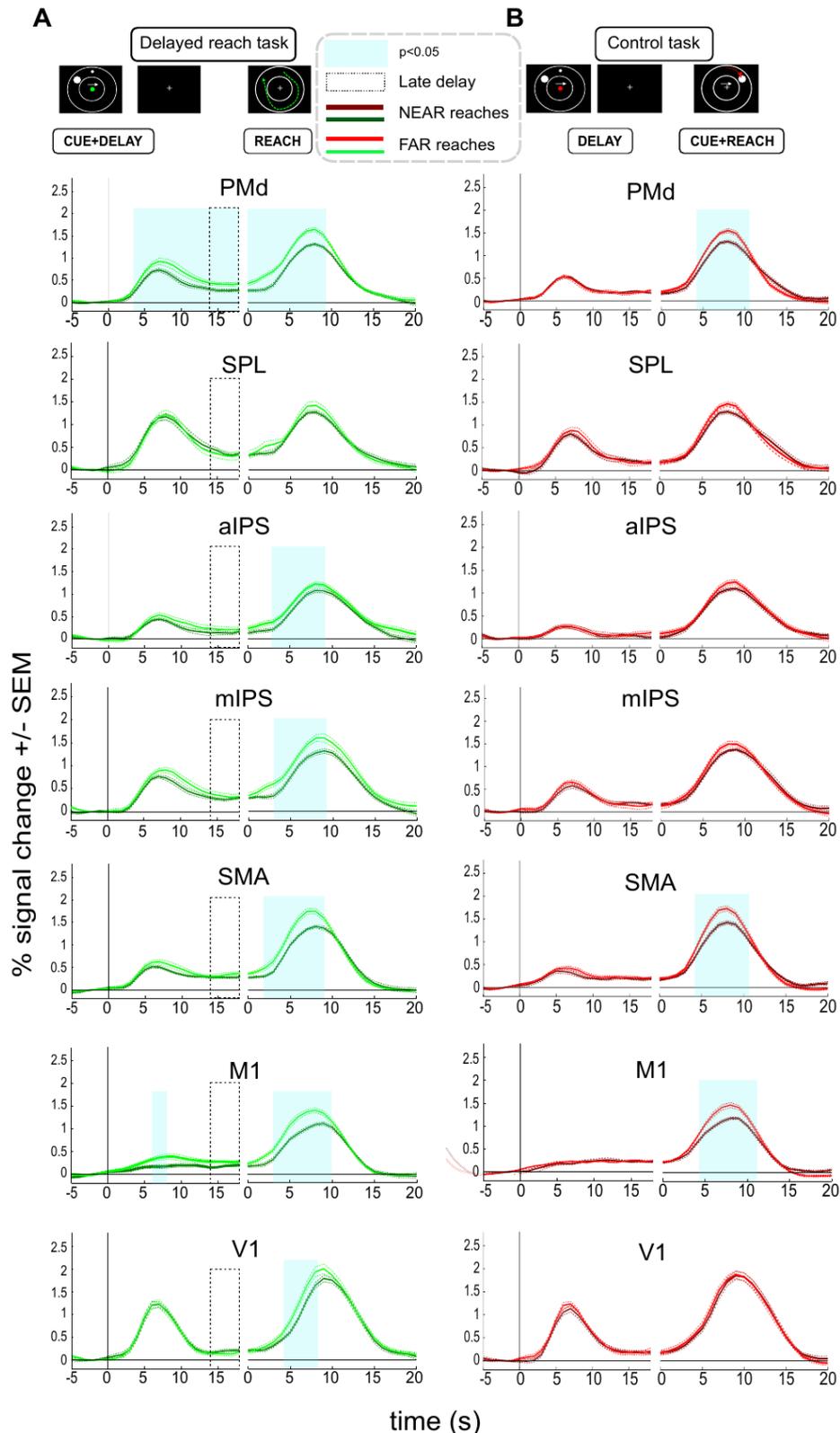
Figure 3.4. Timecourses of fMRI signals extracted from ROIs in the delayed reach (A) and control tasks (B) in Experiment 1. Left panels are aligned to CUE onset while right panels are aligned to REACH onset. Cyan-shaded areas represent time epochs during which paired t-test comparisons of signal amplitudes between "NEAR" and "FAR" reaches revealed statistically significant differences at p<0.05 for at least three neighboring time-points. Such differences were considered indicative of an influence of trajectory. In the DRT both PMd and M1 showed transient trajectory representation during the planning stage (leftward part of the panels, aligned to CUE phase onset). PMd, M1, SMA, mIPS, aIPS and V1 showed differences between the two types of trajectories during the reach stage (rightward part of the panels, aligned to REACH phase onset). **B)** No ROI shows planning-related differences in the CT. As in the DRT, PMd, SMA and M1 exhibit execution-related differences.

(TASK: df=9, F=0.14, p=0.72, eta^2_G=0.00061; DISTANCE: df=9, F=0.23, p=0.64, eta^2_G=0.00169; TASK*DISTANCE: df=9, F=1.85, p=0.21, eta^2_G=0.01130), and was lower for CT "FAR" reaches than in all other conditions in the DELAY phase (TASK: df=9, F=2.8, p=0.127, eta^2_G=0.010; DISTANCE: df=9, F=6.1, p=0.035, eta^2_G=0.039; TASK*DISTANCE: df=9, F=7.2, p=0.025, eta^2_G=0.021). Most importantly, the saccade rates in both CUE and DELAY phase of DRT did not differ for our trajectory manipulation ("NEAR" vs. "FAR").

Subjects' task-related brain activity was assessed with fMRI. Experiments were performed in a 3T Siemens Trio scanner. Functional imaging was done using EPI sequences with 2s temporal resolution and 3x3x4 mm voxel size. Functional data were analyzed using SPM8 and were modeled using a general linear model, in which we included the following regressors of interest: the main epochs of a trial ("CUE", "DELAY", "REACH") were modeled separately for each experimental task (DRT vs. CT) and for each trajectory length ("NEAR" vs. "FAR"). In order to assess correlates of trajectory planning in SPL and PMd we chose a region of interest- (ROI-) based approach. In the first step we delineated a set of brain regions recruited in movement planning by contrasting delay epochs of DRT and CT. This was done by contrasting activity estimates during the delay epochs of DRT vs. CT both within the group and within in each individual. Single subjects statistical contrasts combined with anatomical criteria were used to adjust the ultimate ROI selection in order to account for inter-individual differences in functional brain organization (see "Study 2 – Materials and methods" for details).

Figures 4.1C and 4.7 depict the resulting statistical parametric map of the group analysis, exhibiting planning regions. These figures focus on our *main ROIs*, namely PMd and SPL, defined on the basis of previous research consistently demonstrating their involvement in reach trajectory coding (see introduction of Study 2). For the sake of completeness we included other areas engaged in hand movement planning: intraparietal sulcus (IPS) and supplementary motor area (SMA). We considered these latter areas as

complementary planning ROIs. In addition we included primary motor cortex (M1) due to its potential engagement in trajectory representation (compare Hocherman and Wise, 1991), as well as primary visual cortex (V1), which served as a *control ROI* allowing us to monitor task-unspecific brain activity reflecting visual stimulation during all trial phases. From every ROI we next extracted timecourses of BOLD-signal change throughout a trial at 1s temporal resolution. Within each individual we then separately averaged timecourses for each experimental condition. Statistical comparisons were performed across subjects' average timecourses and between experimental conditions. Activity-timecourses were compared for trajectories of varying length/complexity and separately for each condition. Specifically, we engaged a time-resolved analysis by recruiting multiple paired t-tests performed separately for each time point. We decided for the ROI-based time-course analysis to be able to scrutinize the dynamics of activity changes in planning areas as we expected those to potentially reflect trajectory plan representations. Similar to previous research (Gallivan et al., 2011), the activity maps in our subjects were clearly contra-lateralized with respect to the reaching hand (see Figure 3.1C). Accordingly, we focused in our analyses only on these left-hemispheric areas.

Figure 3.3 A & B show respective timecourses (averaged across all subjects) that were obtained during the DRT task for both main ROIs (A: PMd; B: SPL). The leftward part of each panel depicts the timecourses aligned to CUE onset while the rightward part represents the same timecourses but aligned to the onset of the REACH-phase. Note that we assume a typical delay in time to peak of the event-related haemodynamic response in the human brain (DeYoe et al., 1994; Handwerker et al. 2004), amounting to to 5-6 seconds. Changes in planning activity in the absence of any residual CUE-related activity can be directly inspected during the late DELAY-phase (the last 4s of the delay period, indicated by dashed boxes in Figures 4.3, 4.4 and 4.5), when all the activity related to visual target and cue processing is absent (compare to V1 activity in Figure 3.4) and when

activity is not yet affected by movement execution. During this time period we observed a significant increase in BOLD activity during planning of longer/more complex trajectories in PMd (Figure 3.3A; cyan shaded area). Note that this difference emerged already early after cue presentation and already then might have reflect a trajectory-related difference in planning at early stages. However, as was pointed out before, additional CUE-related modulations of the fMRI-signal can – even if unlikely – not be completely ruled out. Finally, the difference between conditions was also present during the REACH-phase. Note, however, during this period signal modulations are contaminated by systematic differences between conditions such as movement duration or speed (compare the results of behavioral analyses) and the related differences in visual movement feedback. In contrast to PMd, trajectory-related signal modulation was virtually absent in SPL (Figure 3.3B). Finally, we did not observe any trajectory-related variation of BOLD-signals in the DELAY phase of the control task in neither of our main ROIs (Figure 3.4B). Also in the REACH-phase PMd exhibited a significantly higher signal amplitude during FAR as opposed to NEAR reaches (Figure 3.4B). As was mentioned before for the DRT, this activity pattern is likely accounted for by the systematic differences in movement execution and movement feedback.

In none of our additional ROIs we could reveal a significant signal-difference between NEAR and FAR during the late DELAY-phase. It is noteworthy, however, that in M1 we also observed a significant effect of trajectory but only early during the DELAY-phase (Figure 3.4A). Finally, like for PMd we observed an effect of reach trajectory during reach execution in V1, M1, SMA, mIPS and aIPS (rightward panels of Figure 3.4A). In all cases activity was higher for the more complex/longer trajectory. Note, however, the presence of these effects is not necessarily related to planning. It might be rather explained by the systematic differences in movement and - as is clearly indicated by V1 activity - by the respective amount of visual motion that we provided as feedback about
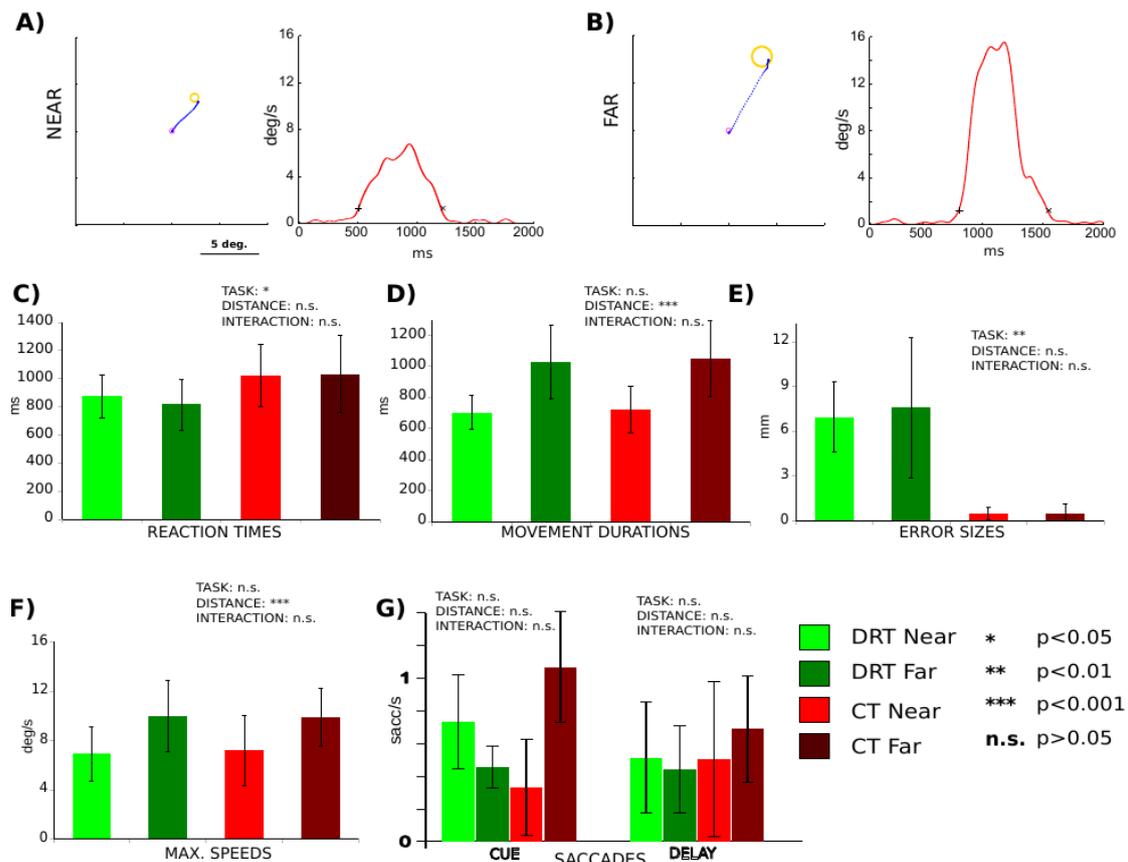
Figure 3.5. Movement performance in Experiment 2. A & B) Exemplary reach trajectories of a single subject (left panels) and the respective speed profiles (right panels) for both a "NEAR" (A) and a "FAR" (B) condition. C-G) The individual panels show our estimates of behavioral performance as a function of "TASK" and "DISTANCE" and report the influence of these factors on the respective estimates as well as their interaction, as was assessed by two-way repeated measures ANOVAs. Error bars represent SEM. C) Reaction times were significantly shorter in DRT than in CT. D) Movement durations were significantly longer for "FAR" trajectories than "NEAR". E) Error sizes were larger for DRT. F) Maximal speeds were higher for "FAR" reaches. See main text for detailed statistics. G) Average frequencies of fixational saccades in CUE an DELAY epochs of CT and DRT. The rates of fixational saccades were constant across all conditions.

subjects' movements. As was true for PMd and SPL, we did not see any trajectory-related variation of BOLD-signals in the DELAY-phase of the control task in either of the additional ROIs, but only during the REACH-phase (Figure 3.4B).

In summary, the results of Experiment 1 are consistent with the idea that PMd – and potentially also M1 – represent plans for upcoming reach trajectories: Planning activity reflected differences in the length of curved trajectories despite the initial hand-target difference vectors were identical across trials. In the next experiment we'll compare planning activity from the same ROIs to a situation in which movements were directed straight towards a target and, thus, could – at least potentially – be defined by a hand-

target difference vector. In other words, there would be no explicit need to represent trajectories during movement planning.

Experiment 2 – planning straight reaches

In the second experiment the overall design was similar to the one used in Experiment 1 in that we contrasted a delayed reach planning task with a direct reach task. This time, however, we used a simple center-out reaching task (compare Figure 3.1D). Such task should allow us to see whether the potential trajectory-related scaling of the BOLD-signal would be seen in brain activity even if a given reach trajectory could be defined by a simple difference vector between target and hand, as such vector-based programming has been suggested at least by behavioral findings (see Todorov and Jordan, 2002; Hoff and Arbib, 1993; Ijspeert et al. 2003 but compare Wong et al., 2016). We manipulated reach amplitude by positioning the targets at two different distances and at randomly chosen radial positions in the upper-right quadrant of the visual field (see Figure 3.5A & B for examples). The idea behind this manipulation was to additionally uncover potential trajectory representations for simple, straight reach plans, while the planning of longer trajectories should result in higher BOLD signal amplitudes (see introduction of Study 1).

Similar to Experiment 1, reaction times (Figure 3.5C) were significantly shorter in the DRT ("TASK": df=6, F=7.8, p=0.031, eta^2_G=0.0039) suggesting that subjects preplanned their movements in this condition. The other effects were not significant ("DISTANCE": df=6, F=1.2, p=0.322, eta^2_G=0.1786; "DISTANCE*TASK": df=6, F=1.9, p=0.220, eta^2_G=0.0073). As in Experiment 1, movement durations (Fig. 3.3D) were significantly longer for longer trajectories ("DISTANCE": df=6, F=42.8374, p=0.00061, eta^2_G=0.45535). All other effects were not significant ("TASK": df=6, F=0.5772, p=0.47619, eta^2_G=0.00360; "DISTANCE*TASK": df=6, F=0.0014, p=0.97177, eta^2_G=0.00001). The endpoint error sizes (Fig 3E) were significantly higher in the DRT ("TASK":df=6, F=34.17, p=0.0011,
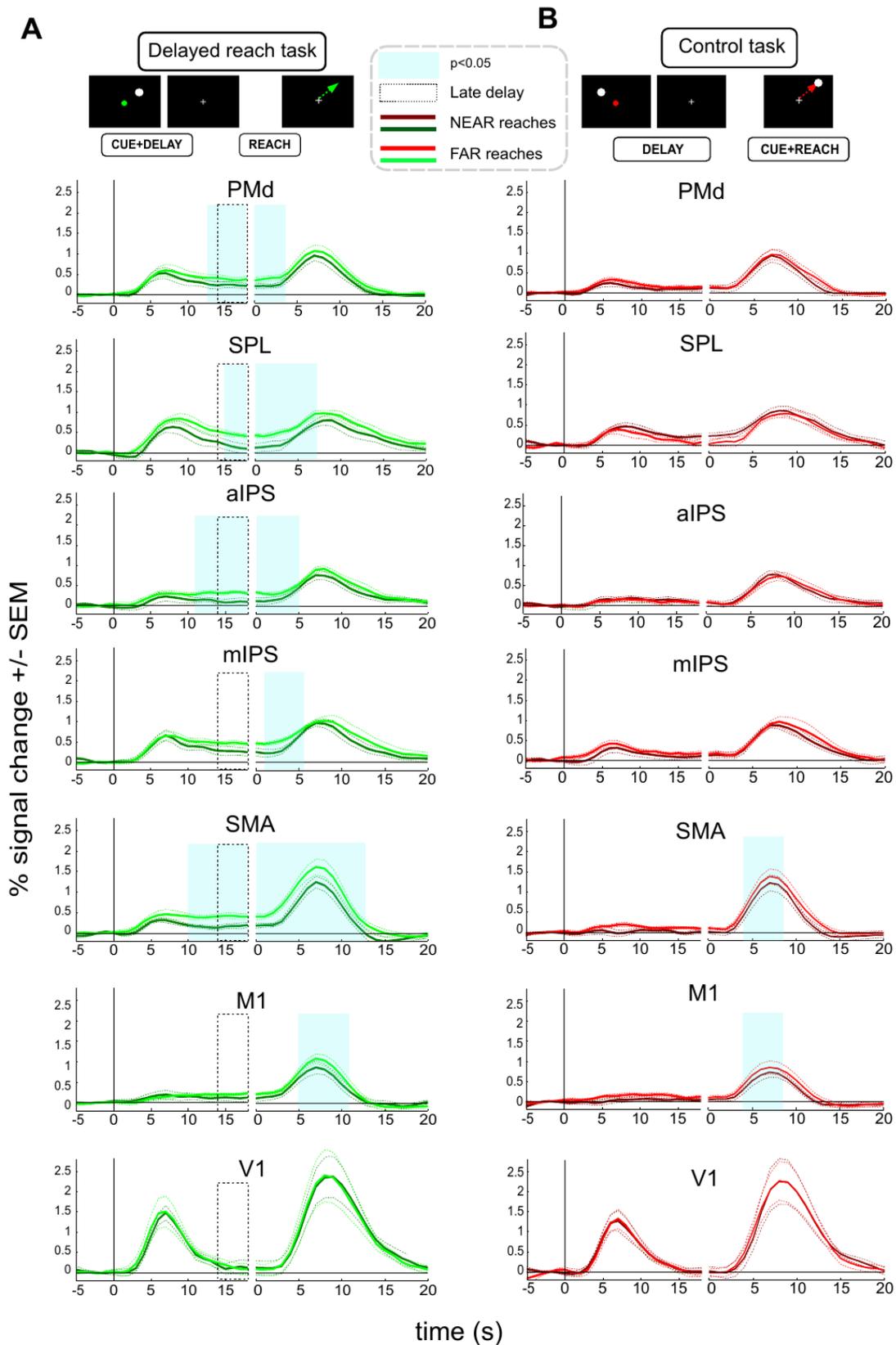
Figure 3.6. Timecourses of fMRI signals extracted from ROIs in the delayed reach and control tasks in Experiment 2. Left panels are aligned to CUE onset while right panels are aligned to REACH onset. Cyan-shaded areas represent time epochs during which paired t-test comparisons of signal amplitudes between "NEAR" and "FAR" reaches revealed statistically significant differences at $p<0.05$ for at least three neighboring time-points. A) PMd, SPL, SMA and aIPS show significant signal differences during the planning epoch in DRT. All areas except V1 show differences during the reach epoch.. B) In the control task, no ROI showed planning-related differences. Both SMA and M1 exhibited differences during the reach stage.

eta^2_G=0.6545). This difference likely resulted from lower precision of memory- vs. visually-guided reaches. Most important for our study, both the factor distance and its interaction with task were not significant ("DISTANCE": df=6, F=0.20, p=0.6735, eta^2_G=0.0045; "DISTANCE*TASK": df=6, F=0.13, p=0.7326, eta^2_G=0.0045). Maximal speeds (Fig. 3.3F) were significantly higher for longer trajectories ("DISTANCE": df=6, F=77.86, p=0.00012, eta^2_G=0.26356). All other effects were not significant ("TASK": df=6, F=0.20, p=0.67151, eta^2_G=0.00043; "DISTANCE*TASK": df=6, F=0.47, p=0.51874, eta^2_G=0.0014). Finally, saccade frequencies (Fig. 3.3G) were not different across conditions both in the CUE ("TASK": df=4, F=1.1, p=0.358, eta^2_G=0.043; "DISTANCE": df=4, F=4.8, p=0.093, eta^2_G=0.090; "DISTANCE*TASK": df=4, F=4.1, p=0.114, eta^2_G=0.112) and in the DELAY phase ("TASK": df=4, F=0.91, p=0.39, eta^2_G=0.0041; "DISTANCE": df=4, F=0.51, p=0.51, eta^2_G=0.0034; "DISTANCE*TASK": df=4, F=1.50, p=0.29, eta^2_G=0.0048).

We will next consider task-related changes of brain activity in our main and in the complimentary planning-related ROIs. Note that we used a similar procedure for ROI selection to the one used in Experiment 1. The actual brain regions selected for further ROI analyses were practically the same as in Experiment 1 (see Figure 3.7, compare also Supplement 2 for further details on ROI selection).

The BOLD signals in these ROIs during the reach phase of the DRT were quite similar to those observed in Experiment 1: longer trajectories yielded larger signal amplitudes in PMd, SPL aIPS, mIPS, SMA and M1 (see Figure 3.3C&D and Figure 3.6A, rightward part of panels). More importantly, for our main ROIs the planning-related BOLD signals extracted during the late DELAY phase of the DRT were markedly higher for longer trajectories not only in PMd but this time in the SPL too (Figure 3.3 C & D; compare time period indicated by the dashed box in the leftward part of each panel). Higher delay-related BOLD signals for longer trajectories were also observed in two of our complimentary ROIs: SMA and aIPS (Figure 3.6A). No planning-related signal modulation

was observed in M1 or in any other additional ROI. In the control task, no ROI showed any trajectory-related activity during the DELAY phase (Figure 3.6B). Only during the REACH phase, M1 and SMA exhibited a modulation of the BOLD-signal as a function of trajectory (Figure 3.6B). This resembled their respective signal changes during the REACH phase in DRT (Figure 3.6A) and likely can be attributed to the systematic differences in movement execution (also compare Experiment 1). The lack of similar V1 modulation likely results from the much lower amount of visual motion as shown by the smaller movement duration differences between trajectories (Fig. 3.4D).

Contrasting Planning activity (in SPL and PMd) across Experiments

Finally, to directly test for the difference in the activation pattern in our main ROIs, SPL and PMd, across the two experiments, we performed an additional mixed model ANOVA with the factors "Experiment", "DISTANCE" and "ROI", comparing the activity estimates of the late delay phase of the DRT trials. These estimates captured the average activity during the last four seconds of the DELAY phase (see dashed boxes in Figure 3.3). The analysis revealed a significant three-way interaction (F=7, df=17, p=0.17, eta^2_G=0.03), further confirming that SPL and PMd exhibited diametrically distinct patterns of planning activity in both tasks, namely a (stronger) contribution of PMd to the planning of complex trajectories in the DRT of Experiment 1, while both areas represented the straight, vector-like movement trajectories in the DRT of Experiment 2.

In order to further scrutinize the apparent differences in activations between the PMd and SPL across experiments, we calculated Bayes factors for each of these ROIs in both experiments (see "Materials and methods" for details). The use of conventional statistics reduced our ability to control for type II errors as strictly as for type-I-errors (Jeffreys, 1961), and, in consequence, did not allow us to quantify whether the differences between ROIs highlighted by ANOVA may have overlooked the actual signal similarities in

Experiment 1, potentially resulting in type II error. To account for this limitation, we additionally calculated Bayes factors to determine for each experiment whether the planning activity estimates of our primary ROIs during the late delay (dashed boxes in Fig. 3.3) are the same for trials with different trajectory length (null hypothesis) or whether they are different (alternative hypothesis). A Bayes factor value below 0.33 provides strong evidence for a lack of signal differences while values above 10 indicate strong evidence in favor of signal differences between NEAR and FAR conditions (Jeffreys, 1961). Bayes factors for Experiment 1 equaled to 60.79 for PMd and 0.22 for SPL. This result is consistent with a role of PMd in planning complex reach trajectories of varying length. Moreover, Bayes factors further show that planning activity in SPL did not differ for curved trajectories that varied in length and complexity but aimed at identical targets. In Experiment 2 the Bayes factors were 10.34 for PMd and 201.29 for SPL. The strong evidence in favor of signal differences parallels previous statistical analyses and shows trajectory representations in both main ROIs during straight reach planning.

DISCUSSION

In Experiment 1 we showed that different reach trajectories for targets kept at the same visual locations produce differential planning responses in dorsal premotor cortex but not in SPL. Experiment 2 allowed us to further demonstrate that trajectories are represented in PMd even if reaches could, at least in principle, be coded by a simple hand-target difference vector. Moreover, we show that the activity was modulated by the trajectory of straight reaches in the medial portion of SPL. Comparing the results from these two experiments, we may note that while PMd contains representations of trajectories irrespective of their complexity, SPL (and perhaps also supplementary motor area) primarily encode trajectory plans for simple reaches directed straight towards a target.

Note that we ensured the reported differences could not be accounted for by

subjects' residual eye movements (Fig. 3.2G & 3.4G). Moreover, constant error rates across conditions, as were present in both experiments (Fig. 3.2E & 3.4E), suggest that the different planning-related signals did not simply result from increasing task difficulty, but rather reflected parameters of planned trajectories. The particular design of Experiment 2 further ensured that such differences in task difficulty between "NEAR" and "FAR" should not arise in the first place (compare "Study 2 – Materials and methods" in appendix). Finally, in Experiment 1 we instructed the same target locations (across conditions) while varying the way to the target (i.e. the trajectory). This allowed us not only to keep initial eccentricity/direction of target location balanced across conditions but this also guaranteed that any attention towards the target locations (or cues), or any retrospective memory thereof, would likewise be identical across tasks. Hence, the reported differences in brain activation should exclusively relate to the process of planning different reach trajectories.

Alternative views on reach trajectory planning

Does reaching always require planning of trajectory? One alternative possibility, suggested by prior literature, is that a reach is initially defined by a vector pointing either towards the final target location or, alternatively, towards the initial direction of movement (Pearce and Moran, 2012). Then, during reach execution, the hand would be guided on-line by a feedback-based control system (todorov and Jordan, 2002; Hoff and Arbib, 1993), allowing even for guiding more complex reach shapes (Ijspeert et al, 2002). This way, only the first desired state (goal) and not the whole trajectory would need to be planned in advance. As an alternative to the above, it may be hypothesized that the reach trajectory is constructed and represented as a whole at the initial stages of reach planning (Üstün, 2016) and only then, this initial plan is being converted to respective motor commands during movement execution while likewise allowing for on-line corrections for potential movement

inaccuracies. As mentioned in the introduction, most previous research on trajectory coding concentrated on the movement execution stage, albeit with some exceptions which (also) focused on reach planning. On the basis of the results provided by these studies, however, one could not determine whether the changes in planning activity reflect any global trajectory parameter such as the overall movement path. Conversely, they could also represent only initial components of trajectory like the initial hand posture (Torres et al., 2013) or the initial movement direction enforced by additional cues, e.g. obstacles (Hocherman and Wise, 1991; Pearce and Moran, 2012). These latter studies, in which representations of such specific parameters were reported, the remaining parts of movement planning and execution could still be guided by the aforementioned on-line control system.

In fact, findings of Pearce and Moran (2012) are compatible with this notion, as in their study the population activity in PMd seemingly encodes the initial direction of an upcoming movement regardless of the target position, although one cannot infer anything about representation of the remaining parts of trajectory. Hence, the currently available physiological data leave it open whether or not there is an explicit neural coding of global trajectory parameters during reach planning. Our results, in turn, seem to support the idea that PMd does code global trajectory parameters prior to a movement. We exhibited a modulation of the averaged BOLD response during planning of varying reach trajectories even if target and initial movement directions were constant. PMd activity represented trajectory information not only when the situation required the precise programming of more complex movement path (Experiment 1), but even if planned trajectories were straight and direct (Experiment 2). This highlights a vital and general role of premotor cortex in trajectory planning.

Limitations of the study

Given the nature of our experimental design and of our recording methods, however, we cannot further detail the precise global trajectory parameters underlying the signal changes that we revealed. Yet, as we have already argued above, it is at least highly unlikely that the observed signal differences can be explained by specific spatial parameters such as initial difference vector or obstacle location (also compare our discussion in the next paragraph). Due to the relatively coarse spatial resolution of our BOLD signal recordings (see "Study 2 – Materials and Methods"), the activity estimates averaged within the regions-of-interest covered large neural populations. This approach allowed us to avoid the problem of measuring only specific correlates of trajectory (such as initial direction), but, in turn, does not allow us to attribute the changes in planning activity to any of the specific kinematic parameters correlated to the trajectory length, such as reach durations, numbers of intermediate segments/points or exact path shapes (compare Üstün, 2016). These detailed properties of trajectory planning have to be addressed using more sensitive methods. Our findings also leave open the question about the actual local topographic distribution of trajectory coding neural populations within the ROIs. The earlier electrophysiological findings of Messier and Kalaska (2000), who reported that individual PMd neurons code both reach amplitude and direction, may present important hints to address this issue.

Superior parietal lobule encodes straight reach paths

Similar to PMd, superior parietal lobule activity increased during the planning of straight, direct reaches towards more eccentric targets in Experiment 2. Different to PMd, however, SPL planning activity did not differentiate between the more complex trajectories of Experiment 1, where the hand- and eye-to-target initial difference vectors were kept equal regardless of trajectory. These results are consistent with the notion that SPL could chiefly

represent straight reach plans. One might further ask whether SPL thereby encoded indeed an initial difference vector (similar to saccades) or the straight trajectory defined along such vector, as the two features were inherently correlated in Experiment 2. As is suggested by anatomical studies, SPL (and other parietal regions) has a relative over-representation of the visual periphery as compared to visual areas (see Colby et al., 1988; Baizer et al., 1991; Motter and Mountcastle, 1981; but compare Ben Hamed et al., 2001). The mere coding of the difference vector could, accordingly, recruit larger neural populations representing more peripheral targets, and potentially lead to an increase in the total BOLD signal for more eccentric target locations in Experiment 2. However, as was demonstrated by Kimmig et al. (2001) in their study on saccades, the coding of larger difference vectors (or rather topological coding of more eccentric target locations) themselves is not sufficient to modulate the amplitude of the BOLD signal in the way we observed here, as it probably does not need recruiting increasingly larger neural populations the longer the vector. The same argument likewise accounts for movement durations as the larger saccade amplitude, the longer its duration. Clearly, the cortical planning of reaches and saccades is distinct, yet it shares several common principles. It is hard to see why the chosen target distances and movement durations alone should lead to gross amplitude differences in the BOLD response, especially given the fact that comparable parameters did not lead to BOLD signal differences in a saccade planning task. Adding to this, even though some data suggest existence of a relative over-representation of the periphery, there is still an absolute over-representation of the central visual field in posterior parietal cortex (Ben Hamed et al. 2001), predicting a weaker representation of more peripheral locations. For these various reasons we propose an alternative explanation of our results. In our view, the observed increase in SPL activity for more eccentric reaches in Experiment 2 is consistent with the idea that this region's role is to localize the target and, moreover, to initially represent a "simple" trajectory aimed

directly at the target (e.g. through interpolated intermediate points, see: Üstün, 2016). It well might be that such direct and straight trajectory representation is encoded by neural populations in SPL by default and no matter what sort of movement path is actually required in a given context. This, in turn, could explain why monkeys with lesions of premotor cortex and intact posterior parietal cortex cannot plan complex hand trajectories that would allow to effectively avoid obstacles. Instead, these monkeys still try to reach straight towards targets and bump into obstacles (Moll and Kuyspers, 1977). Moreover, recent findings showed that PPC inactivation in monkeys impairs their ability to reach along straight paths and the reaches become significantly curved (Battaglia-Mayer et al., 2012). Such automatic planning of simplified, straight trajectories by SPL could be useful in various everyday situations and crucial whenever a rapid response is required (e.g. when swatting a fly). We admit, however, that there may still exist differences between the straight movements executed in this experiment and certain other fast, reflexive hand movements performed in more natural settings, where adhering to the flat surface of a touch-panel is not required.

Potential interactions between PPC and PMd in reach path planning

Given the obvious difference in movement plan representation between PMd and SPL, as was described here, one could conceive a hierarchical model in which an initial trajectory plan is formed in SPL based on the difference vector pointing directly towards the target location. As information transfer from posterior parietal cortex to M1 is faster than to PMd (Innocenti et al., 2014), the simple movement plan may be quickly put into action. If required, this initial plan is "overwritten" by other frontal areas (such as PMd), which possibly consider additional spatial constraints that would interfere with execution of the reach along the initially defined, direct path - like information about obstacle locations (Torres et al., 2013; Pearce and Moran, 2014; Lindner et al., 2010). PMd might incorporate

such additional information to construct a global (potentially more complex) trajectory plan, which is passed on to areas responsible for its further processing and execution (like M1). In fact, as we already described above, lesions to premotor cortex of macaque monkeys make them unable to avoid obstacles or, alternatively, to update their initial motor plan (Moll and Kuyspers, 1977). In addition, PMd has been shown to highlight those motor plans that are actually selected for execution, rather than merely representing all the possible plans. This does further imply a role of PMd in forming the ultimate trajectory (Kalaska and Crammond, 1995; Cisek e al. 2002). It is worth to note, that several authors postulated that PMd may additionally play a governing role in the sensorimotor system, modifying motor plans as required by given context (Westendorff et al., 2010; Archambault et al., 2011). Such detailed hierarchy amongst the cortical areas engaged in planning reach trajectories could not be assessed on the basis of our experiments. The nature of the BOLD signal would not allow us distinguishing incoming neural signals from local ones (Logothetis et al. 2001) - a distinction which is critically needed to establish hierarchy. Moreover, such distinction is perhaps particularly challenging when considering posterior parietal and premotor areas that are linked by single-synapse pathways (Pandya and Kuyspers, 1969; Jones and Powell, 1970; Kurata, 1991; Johnson et al., 1996; Bataglia-Mayer et al., 2003). To further detail how exactly trajectory information is represented and transferred throughout the network of areas engaged in sensorimotor processing, causal methods could be utilized in the future to disrupt information flow between specific regions.

Possible involvement of other areas in trajectory planning

In accordance with earlier studies, we did observe trajectory information encoded in M1 activity during movement execution (Hocherman and Wise, 1991; Kadmon-Harpaz et al, 2014; Hatsopoulos et al., 2007). The results revealed in Experiment 1 further suggest that M1 might encode trajectory information already at the very early stages of planning

reaches along complex paths. In Experiment 2 we did not observe any M1 modulation of this kind, while in this experiment trajectories did not differ with respect to their complexity. The overall findings suggest that only trajectories of greater complexity may require engagement of M1 well before movement execution.

Another interesting finding is the involvement of supplementary motor area in the planning of straight but not of circular movements (see "Supplementary results"). This result parallels earlier findings of Hocherman and Wise (1991) who also reported more SMA neurons involved in coding straight than curved reach paths, as evident from the number of neurons responding to either of those. Hence, similar to SPL, SMA seems to be more involved in coding direct, straight trajectories. Yet, it still remains to be determined what exact role the SMA plays in this process and whether our observation can be confirmed.

Concluding remarks

Our study suggests that global trajectory information is represented in premotor and posterior parietal areas of the human brain well before movement execution. Moreover, we reveal differences in the representation of planned reach trajectories across these areas. Specifically, premotor cortex can seemingly encode complex reach trajectories while posterior parietal cortex (and possibly supplementary motor area) rather represent plans for movement along a simplified, straight and direct path. Such a parallel and distinct representation of two fundamentally different types of trajectory plans would clearly ask for a meaningful functional interpretation. It is conceivable that emergence of two disparate reach planning subsystems is desirable from an ecological point of view by offering a high degree of flexibility in adjusting hand movement control to situational demands. This way a parietal subsystem could allow to rapidly reach straight towards an object, whereas a frontal subsystem would take over whenever movements have to be performed with more finesse and when moving along the right path is an integral part of the motor goal.

Supplementary results

While the qualitative assessment of the signal patterns in our additional ROIs suggested at first, that the SMA and aIPS encode the movement plans in similar way as the SPL does. To test this, we performed an additional analysis of variance comparing the PMd activity against SMA, aIPS and mIPS. The three-way interaction effect was present only in SMA activity (df=17, F=9.25, p=0.007, eta^2_G=0.02) but not in any of the intraparietal ROIs (mIPS: df=17, F=2.24, p=0.15, eta^2_G=0.003; aIPS: df=17, F=2.42, p=0.14, eta^2_G=0.009). Those, in turn showed a significant main effect of distance (mIPS: df=17, F=9.34, p=0.007, eta^2_G=0.01; aIPS: df: 17, F=10.45, p=0.005, eta^2_G=0.12).

In the next step, similar to comparing activity across experiments between PMd and SPL, we additionally calculated Bayes factors for SMA, aIPS and mIPS to assess presence of trajectory representations in these ROIs across experiments. For Experiment 1, the Bayes factors were: SMA: 0.4; aIPS: 0.34; mIPS: 0.34. This showed no evidence for engagement of any of these areas in complex trajectories planning. Bayes factors for Experiment 2 were: SMA: 32.13; aIPS: 65.62; mIPS: 4.10. The results for SMA were in agreement with the t-test and ANOVA analyses and showed strong evidence for engagement of SMA in planing of straight, but not curved trajectories. The apparent representation of straight trajectories in aIPS was confirmed by Bayesian analysis, showing strong evidence in favor of aIPS representing the straight reach trajectories. Apparently, however, the fact that the additional ANOVAs in both IPS regions did not reveal a significantly differential pattern across experiments as it did in our other ROIs, suggests that IPS representation of trajectories plans was rather similar across tasks. We suspect that this may have likely resulted from the specific setting of our reaching task, relying on flexion of fingers and wrist muscles critically involved in prehension, and other precise hand movements. On the basis of other lines of research, we may speculate that the actual role for IPS subregions here was to represent the oncoming hand movement in terms of the general finger motion-related processes, less the actual trajectory (Culham et al., 2006; Schaffelhoffer et al, 2015; Jeannerod et al., 1995; Fogassi and Lupino, 2005; Fogassi et al., 2001).
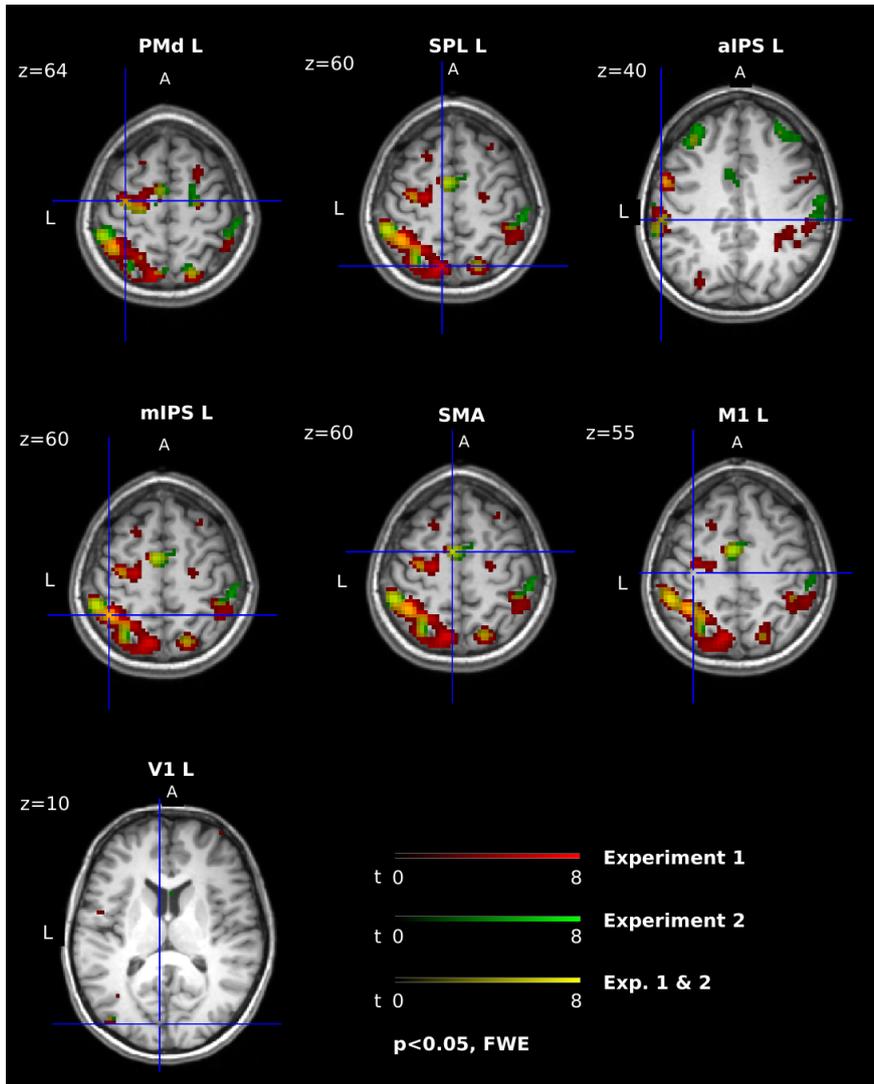
Figure 3.7. Comparison of planning regions recruited by our two experiments in a representative subject (DRT>CT; the overlaid maps of activity were thresholded at p<0.05, FWE-corrected for multiple comparisons). Red and green shaded regions denote clusters of planning activity specific to the delay phase of Experiments 1 and 2, respectively. Yellow shaded regions represents areas active in both experiments. Blue crosshairs indicate centers of clusters selected for subsequent ROI analyses (compare "Study 1 – Materials and methods").

Study 3. Future of the past: evidence for effector-dependent modulation of working memory activity in posterior parietal cortex

INTRODUCTION

Working memory is the key cognitive process allowing an organism to link previously encountered information to a future action. As much as it's popular, the term "working memory" (WM) has been not clearly defined and its detailed brain mechanisms and cognitive components remain somewhat elusive (for reviews see e.g. D'Esposito & Postle, 2015; Eriksson et al., 2015). One of the traditional views on working memory architecture bases upon Baddeley and Hitch (1974) concept of separate storages modules, assuming that mnemonic information is maintained with respect to its sensory modality within specialized modules (e.g. visuomotor sketchpad). Recently, brain imaging studies, supported this view, showing that processing of different mnemonic content engages its respective domain-specific cortical areas, such as fusiform face area for faces (Ranganath et al., 2004) or visual cortex for other visual forms (Harrison & Tong, 2009; see also: Wager & Smith, 2003). It has been suggested that domain separation in cortical topography may be also reflected in behavioral performance, as different WM "storages" seemingly possess independent processing capacities, see e.g. Myerson et al. (1999) who demonstrated that verbal and spatial memory domains yield independent memory spans in subjects tested (compare also: Logie, 1990).

The classical concept of separate memory processing modules relates to the retrospective aspect of memory, focusing on the nature of the information stored. However, as information is always learned to be used for future actions, whether in laboratory setting or real life, it can be hypothesised that the way mnemonic information is processed does not build solely upon the exact type of information, but also to ensure its efficient use in a given context. For example, the probability that we'll have to use visuo-spatial information

for motor actions (e.g. making a reach) is usually much higher than that for using this information for a verbal recall. One may suspect that working memory processing can at least partly build upon a relevant action by which the information is likely to be used/reproduced, either due to different rehearsal or to action-specific preparatory processes.

If this view was true, working memory functions should be affected by specific motor "context" in terms of its use, i.e. by the relevant effector (motor modality). Indeed, several lines of research have demonstrated that the type of effector used has an influence on subject performance in working memory experimental tasks, in particular where manual responses were employed (Hale et al. 1996; Lawrence et al. 2001). Apparently, this results in task difficulty being artificially higher for certain groups, such as older adults, only due to the effector used to respond, affecting the measured working memory performance. As demonstrated by Emery et al. (2006), the working memory tasks employing verbal responses do not seem to elicit any age-related decrease in performance, as opposed to tasks where the response requires pressing buttons on a keypad. These findings may trigger questions of how do the motor components necessary for retrieval influence the working memory maintenance processes.

Conceptually speaking, an interplay between the mnemonic and the motor components of working memory tasks seems to be especially likely given the major spatial overlap between the areas engaged in working memory and the ones controlling motor planning, mostly in frontal and parietal lobes (see e.g. Lindner et al., 2010; Eriksson et al., 2015; Gallivan & Culham, 2015). This likely reflects the fact that both prospective and retrospective processes are tightly inter-related: every action planning experimental task, apart from prospective components like goal or action representation, must contain a retrospective component (i.e. an instruction or target cue). And conversely, as already discussed above, a typical working memory task contains also a prospective component
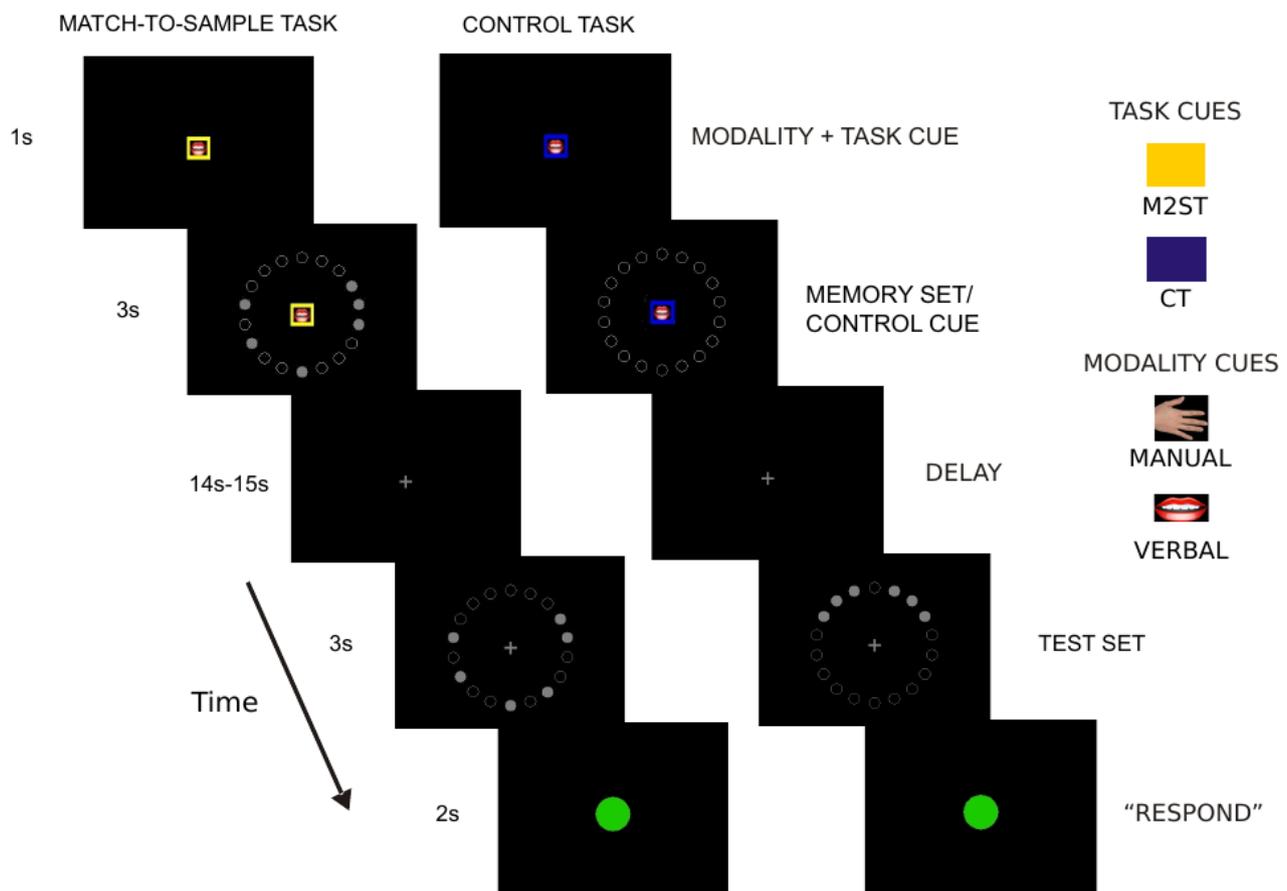
Figure 4.1. Timelines of example working memory task (M2ST) and control task (CT) trials. Each trial started with a color cue and an icon symbolizing the current task and response modality, respectively. After displaying a memory or a control cue the delay began, after which the test set appeared. A green "go" cue indicated response onsets. Please note that the visual mask screens were removed from the timeline for clarity. See text for further details.

(i.e. a potential use for the memorized information). In most experimental settings the latter is represented by the task instructing volunteer to respond in a specific way. It is then conceivable, that activity of the brain areas typically highlighted in working memory research (assumed to process information retrospectively) can also represent the prospective processes, such as preparing an effector for an upcoming answer. Yet, to our best knowledge, to date none of neuroimaging works addressed this particular problem.

Here, we scrutinized the potential relation between retrospective memory and prospective motor preparation processes, by asking whether in a spatial working memory task, memory-related fMRI activity is modulated by the effector used to respond. We expected, that in a WM task the BOLD signals representing working memory maintenance will be influenced by effector modality, potentially resulting in different amplitude of signal in

respective areas due to them representing different levels of congruency between the material to be memorized and the effector. Specifically, we expected the hand effector to have impact on activity in parietal areas, demonstrated to carry prospective information for manual actions in visuospatial planning tasks (see e.g. Lindner et al., 2010) as well as retrospective visuospatial working memory content (see e.g. Pisella et al., 2004).

RESULTS

Experimental tasks

Our experiment was comprised of two basic paradigms: a working memory, match-to-sample task (M2ST) and a control task (CT). The first one was a classical working memory paradigm with delayed response, where subjects were required to remember a pattern of circles on the screen and then after a delay indicate whether the pattern has changed or not ("same" vs. "different"). Crucially, we instructed the subjects before each trial to answer either manually (by button pressing) or verbally (compare: Figure 4.1; see "Study 3 – materials and methods" for details) to manipulate effector-specific processes. The choice of such spatial memory task additionally allowed us to avoid sequential item ordering, which could lead to different strategies of encoding and recall. In the control task (CT) we manipulated a similar effector instruction, but the subjects' role was simply to judge the visual symmetry of circles presented on the screen ("symmetric" vs. "asymmetric"). This allowed us to assess activity related to task-unspecific preparation of an effector (Snyder et al., 2006). Thirteen volunteers took part in the experiment. All of them were right handed, had no history of neurological disease and had normal or corrected to normal vision (see "Study 3 – Materials and methods" for details). All volunteers gave their written informed consent according to the Declaration of Helsinki prior to the experiment, and the study was approved by the local ethics committee. All the behavioral analyses were performed using R (R Foundation for Scientific Computing). All the fMRI analyses were
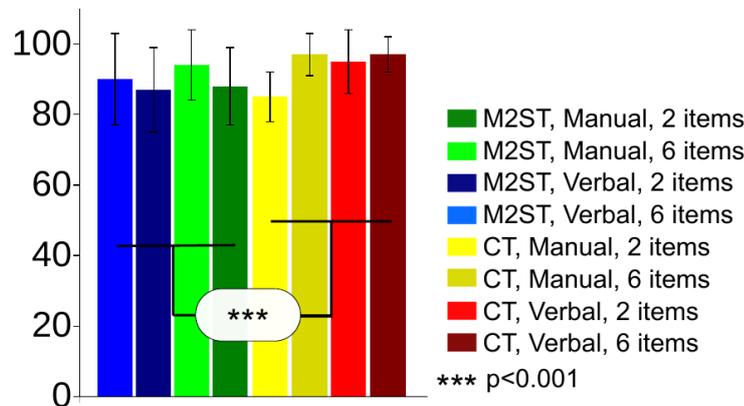
Figure 4.2. Average manual and verbal performance in PPM and DM trials. Error bars denote standard deviations. Hit rates differed significantly between M2ST and CT, but not between loads or effector modalities.

performed using SPM8 (Wellcome Center for Neuroimaging), R and custom Matlab (MathWorks) routines.

Behavioral performance

We analyzed the behavioral performance using a 2x2x2 ANOVA with the factors "task"x"modality"x"load". Analyses of hit rates performed across all conditions revealed a significantly higher accuracy in the control task as compared to the memory task (see Figure 4.2; main effect of task: df=12, F=23, p=0.0004, eta^2_G=0.075). There was also a statistical trend suggesting that higher memory load in the M2ST could lead to decreased task performance (task x load: df=12, F=3.5, p=0.0853, eta^2_G=0.016). All other effects were not significant (load: df=12, F=0.63, p=0.44, eta^2_G=0.003; modality: df=12, F=1.1, p=0.32, eta^2_G=0.03; modality x task: df=12, F=0.21, p=0.65, eta^2_G=0.003; modality x load: df=12, F=0, p=1, eta^2_G<0.001; task x load x modality: df=12, F=0.064, p=0.8, eta^2_G<0.001).

Whole brain activity

Figure 4.3 shows a representative subject (A) and group-level maps (B) of activity increases during the delay phase in the M2ST as compared to CT. The M2ST resulted in higher activity in a number of fronto-parietal areas typical for working memory and action planning tasks. These areas were: superior parietal lobule (SPL), anterior intraparietal
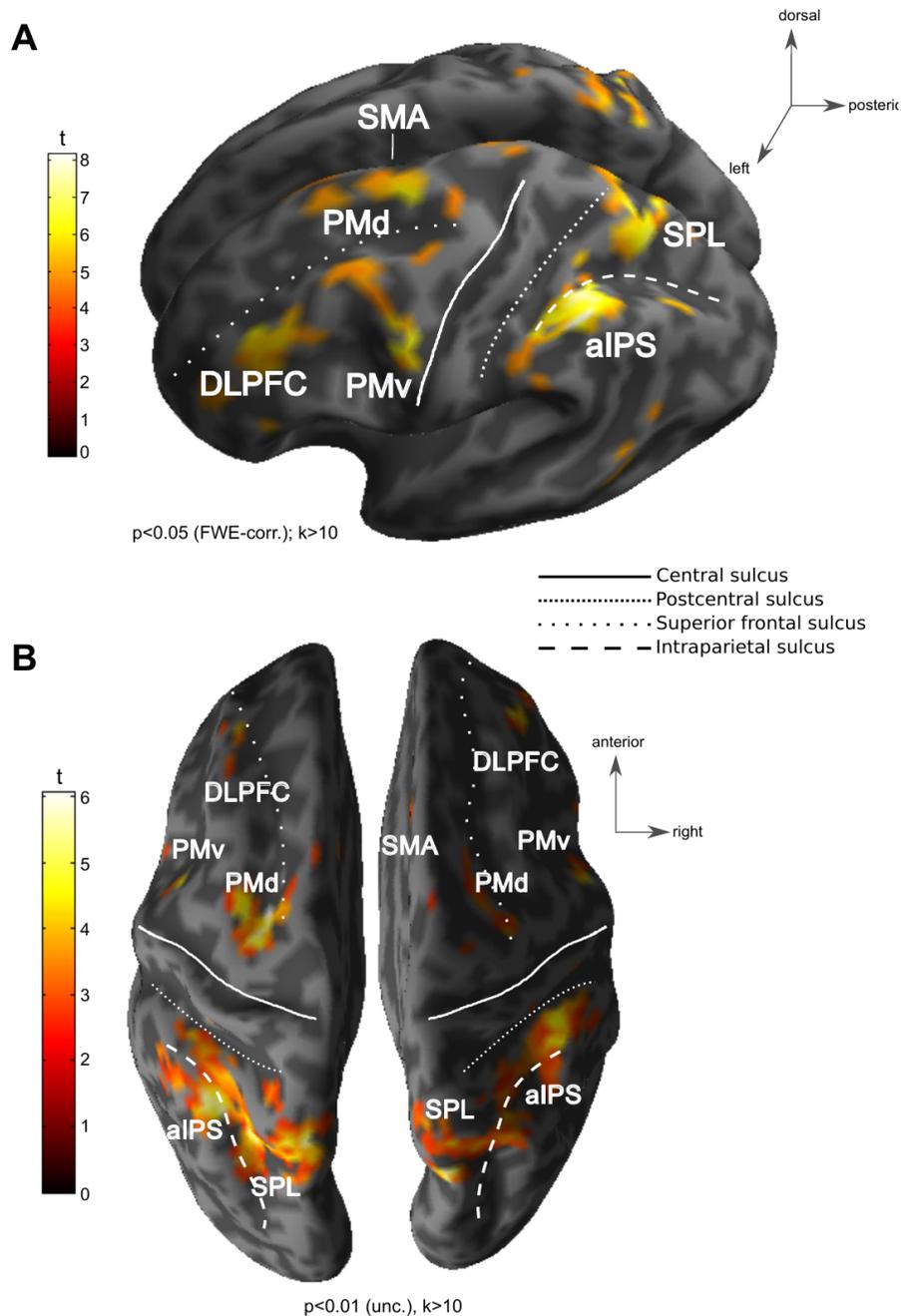
Figure 4.3. Areas of working-memory-related activity defined by M2ST>CT delay contrast. A) An exemplary subject's MW activity maps. B) Group-level activity maps resulting from a random-effects analysis in SPM. White lines denote major anatomical landmarks.

sulcus (aIPS), dorsal premotor cortex (PMd), ventral premotor cortex (PMv), dorsolateral prefrontal cortex (DLFPC) and supplementary motor area (SMA). Moreover, we included hand (M1h) and mouth (M1m) representations in the left primary motor cortex as control areas. All these areas were treated as regions-of-interest (ROIs) in the subsequent analyses (see also "Study 3 - Materials and Methods" for further details).
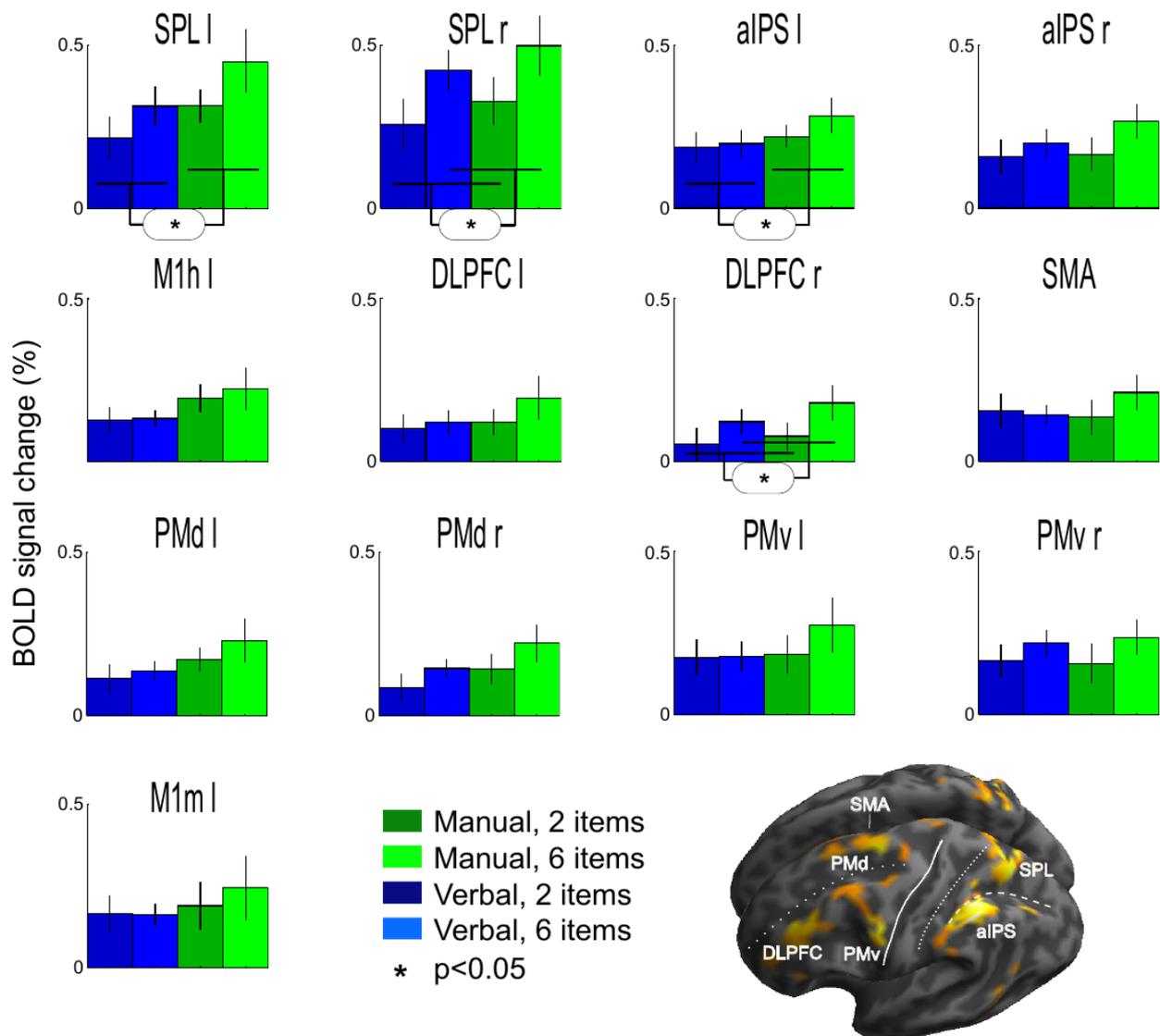
Figure 4.4. BOLD activity in all ROIs during the memory epoch. Blue and green colors denote verbal and manual response modalities, respectively. Brighter shades refer to higher memory loads. Signal differences between "verbal" and "manual" trials in left SPL and in left aIPS refer to an influence of prepared hand response. The right SPL and DLFPC show an increased signal reflecting higher memory loads. See main text for detailed statistics. All values represent averages calculated across subjects' mean activity +/- SEM.

Region-of-interest results

From the aforementioned ROIs we extracted group-averaged beta weights which were then analyzed using 2x2 ANOVA (with factors "Modality" and "Load") in the M2ST and a paired t-test in CT (for factor "Modality"). Figure 4.4 shows the mean signal amplitudes in the delay epoch of the M2ST task. Figure 4.5 depicts the mean BOLD-signal timecourses extracted from respective ROIs in the M2ST and CT. The analyses of variance performed
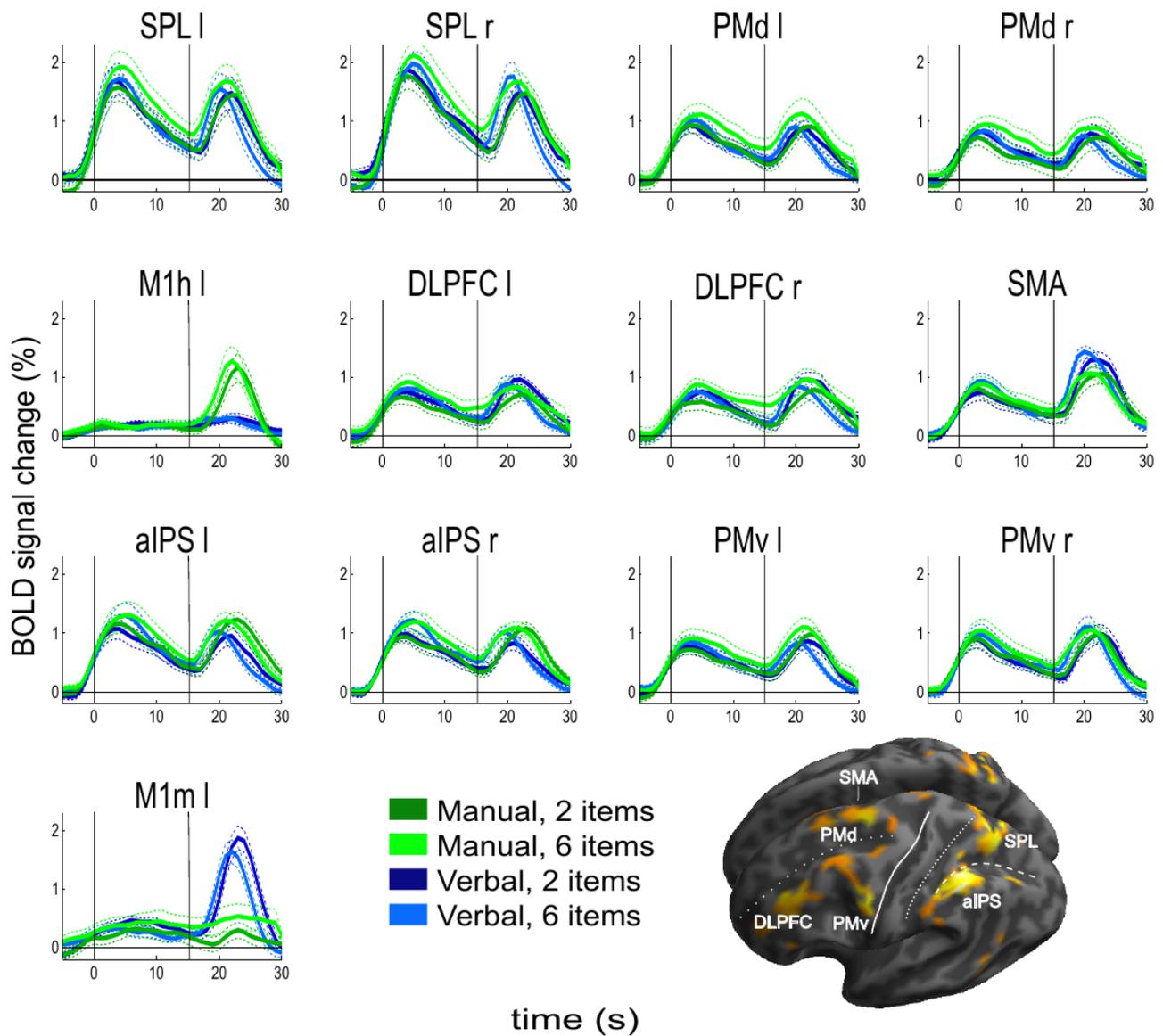
Figure 4.5. Timecourses od BOLD activity during M2ST trials, divided across response modalities and memory loads. Vertical bars denote onsets of delay and test set epochs. All values represent averages calculated across subjects' mean activity +/- SEM.

on the memory-related signals for M2ST trials showed, that the modality-dependent changes in activity were present in the posterior parietal areas SPL and aIPS in the left hemisphere, with both regions showing higher activity for "hand", as compared to "mouth" trials (SPL: main effect of "Modality", df=12, F=5.42, p=0.038, eta^2_G=0.05; aIPS: main effect of "Modality", df=12, F=5.8, p=0.034, eta^2_G=0.03). This effect was not present in the contralateral counterparts of these areas. Noteworthy, a trend for the same effect was also present in the left M1 hand area (df=12, F=4.71, p=0.051, eta^2_G=0.06). In addition, we observed a significantly higher activity for higher WM load in right-hemispheric areas: SPL, aIPS and DLPFC (SPL, main effect of "Load", df=12, F=5.99, p=0.031, eta^2_G=0.09; aIPS:
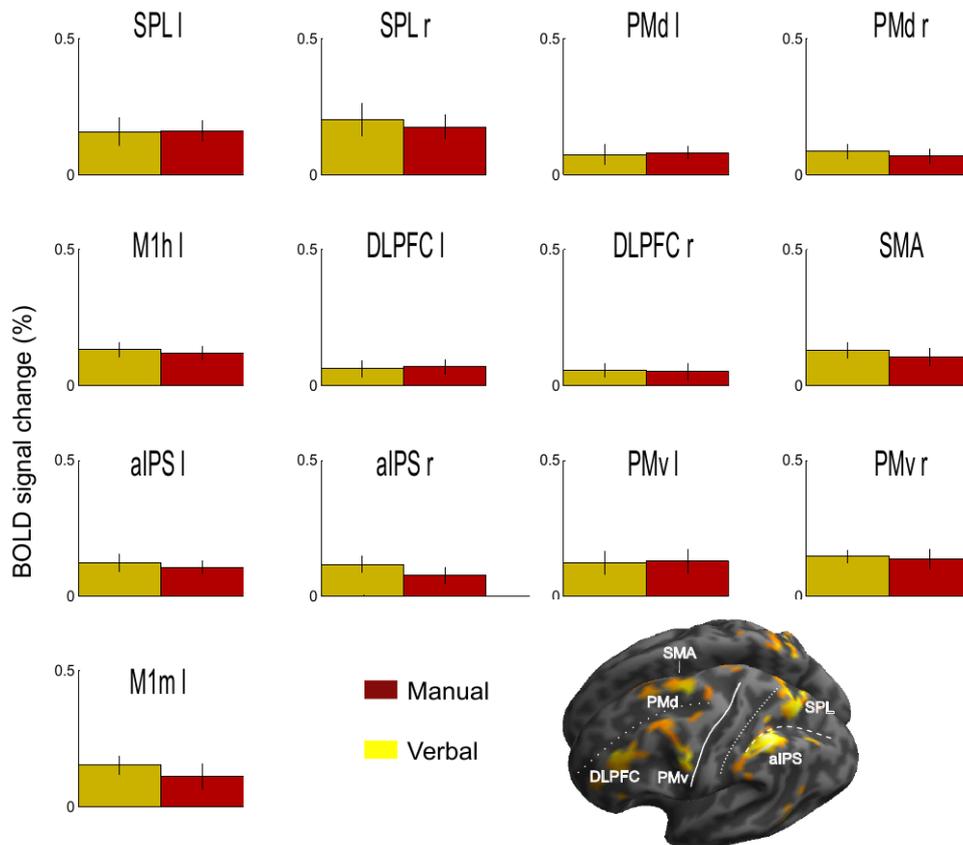
Figure 4.6. BOLD activity in all ROIs during the delay epoch of the control task. Yellow and red colors denote verbal and manual response modalities, respectively. No differences between preparatory signals related to response modalities were observed in any of the ROIs. All values represent averages calculated across subjects' mean activity +/- SEM.

main effect of "Load", df=12, F=6.3, p=0.027, eta^2_G=0.04; DLPFC: main effect of "Load", df=12, F=4.48, p=0.037, eta^2_G=0.064). We did not see an effect of "Modality" neither in M1h nor in M1m. In none of the areas we observed a significant interaction effect between "load" and "modality" (TABLE 5.1). We did not see the effect of "modality" in any ROI during the delay phase of the control task (TABLE 5.2, Figure 4.6).

DISCUSSION

In our study we observed changes in the gross amount of the working-memory-related BOLD signal in posterior parietal regions being influenced by the effector used for subjects' subsequent behavioral answer. This effect was not present in the control task, hence is not merely attributable to unspecific effector preparation. The major implication from these results is of practical nature: task-related brain activity in working memory studies may be affected in the parietal regions by the effector used for providing a response. How is it

possible, however, that the effector influences the working memory representations?

As the effector modality-specific processes were present already during the delay, we can speculate, that they were specific to the memory maintenance, and not recall processes. This may also shed a new light on results reported by Emery et al. (2006) who observed a WM performance deficit in older adults who were required to perform manual responses in a working memory task, as compared to verbal responses. One could question whether in that research the apparent deficit was caused by the older adults' lower ability to use more complex manual response interfaces (such as button boxes), or to altered motor preparation processes related to such responses. As in our own research we observed increased brain activity in the areas responsible for manual action planning specifically for the manual response trials, we can lend support for the latter notion: response preparation remains tightly linked to the working memory processing. Therefore, the way that parietal system processes the mnemonic content appears to be influenced by the future use of the information. Can one determine however, that the observed pattern of activity indeed reflects the prospective processes of the task? The answer may be partially suggested by previous research from Manelis and Reder, who showed that frontal and parietal areas activity is modulated by anticipated difficulty in the n-back task (Manelis & Reder, 2015). In another study, Lindner and colleagues (2010), demonstrated the prospective (preparatory) role of parietal cortex in manual tasks. In that study, the PPC activity, in a task that required both prospective and retrospective processing, appeared to be driven mainly by the preparatory processes, less by retrospective ones. In turn, the dorsolateral prefrontal cortex activity exhibited involvement in working memory maintenance, regardless of the prospective components. This confirmed the notion raised by multiple other researchers, suggesting that prefrontal cortex plays the leading role in organizing the working memory rehearsal in the other areas (see e.g.: Fuster, 2009; Eriksson et al., 2015; D'Esposito & Postle, 2015), with its own activity arranged along a posterior-to-anterior gradient, the

more abstract the level of processing is required (Badre & D'Esposito, 2007). This abstract processing remains in stark contrast to the role of posterior regions (i.e. the parietal cortex), where the WM content appears to be processed in more tight relation to future actions. We ourselves did observe that memory load modulates the activity in the dorsolateral prefrontal cortex, suggesting regulatory role of that region. Moreover, the fact that the load effect was also present in right IPS and SPL indicates that DLPFC might effectively modulate the function of the parietal regions in order to cope with the increased memory demand (see: Raabe et al., 2013; compare: Hoeller-Wallscheid et al., 2017).

Potential limitations and future directions
In this experiment we report higher involvement of posterior parietal cortex in representing spatial items in a working memory task when they sub-serve the generation of an upcoming manual (rather than verbal) behavioral response. The main explanatory limitation of our study lies, apparently, in the congruency between the visuospatial memory and the manual response modality, as the regions of posterior parietal cortex where we observed the effect of hand response preparation, are also crucially involved in processing spatial WM content (Pisella et al., 2004; Hamidi et al., 2008; Lindner et al., 2010). On the basis of our current data we can not predict whether a similar pattern of parietal activity increase like the one reported here for manual responses could be observed also for different memory modalities, e.g. verbal content. It appears possible, that the patterns of activity could then shift towards areas representing the response effector more congruent with the memory content, such as Broca area for verbal items. To scrutinize the links between working memory and response preparation in other content modalities than the ones presented here, more research is necessary.

Our results suggested, that the BOLD activity underlying working memory tasks is affected by the way a task-response is given. This effect was prominent in posterior parietal cortex, repeatedly demonstrated to be involved in prospective processing of actions. Whether the

parietal cortex is bridging retrospectively processed mnemonic content with its future use, and how exactly parietal function is modulated by inputs coming from the frontal cortex, remains to be answered. The influence of a motor-preparatory component on the activity traditionally attributed to working memory maintenance sheds a new light on the actual structure of the working memory network and its links to other brain systems engaged in goal-directed actions, yet portrays the working memory as the key pivot bridging the sensory past with the motor future.

Table 5.1

ANOVA results for mean delay-related betas extracted from each individual ROI, comparing "modality" and "load" main effects and their interactions in the match-to-sample task (M2ST).

ROI	Effect	DFn	DFd	F	p	p<.05	ges
SPL l	load	1	12	3.35	0.092		0.05
	modality	1	12	5.42	0.038	*	0.05
	load:modality	1	12	0.36	0.561		0.00
SPL r	load	1	12	5.9876	0.031	*	0.09
	modality	1	12	2.4913	0.14		0.02
	load:modality	1	12	0.0042	0.949		0.00
PMd l	load	1	12	1.11	0.31		0.02
	modality	1	12	3.12	0.1		0.05
	load:modality	1	12	0.62	0.45		0.00
PMd r	load	1	12	0.24	0.632		0.00
	modality	1	12	4.71	0.051		0.06
	load:modality	1	12	0.29	0.6		0.00
M1h l	load	1	12	1.7	0.22		0.02
	modality	1	12	1.2	0.3		0.02
	load:modality	1	12	1	0.33		0.01
DLPFC l	load	1	12	5.48	0.037	*	0.06
	modality	1	12	0.95	0.348		0.02
	load:modality	1	12	0.56	0.47		0.00
DLPFC r	load	1	12	1.11	0.313		0.01
	modality	1	12	0.61	0.451		0.00
	load:modality	1	12	3.76	0.076		0.02
SMA	load	1	12	1.11	0.313		0.0085
	modality	1	12	0.61	0.451		0.0048
	load:modality	1	12	3.76	0.076		0.0168
antIPS l	load	1	12	1.8	0.206		0.01
	modality	1	12	5.8	0.034	*	0.04
	load:modality	1	12	2.2	0.167		0.01
antIPS r	load	1	12	6.3	0.027	*	0.04
	modality	1	12	3.2	0.098		0.01
	load:modality	1	12	3.7	0.078		0.01
PMv l	load	1	12	1.2	0.3		0.01
	modality	1	12	1.7	0.22		0.01
	load:modality	1	12	2.6	0.13		0.01
PMv r	load	1	12	3.168	0.1		0.03
	modality	1	12	0.018	0.9		0.00
	load:modality	1	12	0.365	0.56		0.00
M1m	load	1	12	0.24	0.63		0.0031
	modality	1	12	0.64	0.44		0.0122
	load:modality	1	12	1.33	0.27		0.0036

Table 5.2

T-test results for each individual ROI, comparing mean delay-related betas for "hand" and "verbal" modalities in individual ROIs in the control task (CT).

ROI	df	t	p
SPL l	12	-0.071	0.945
SPL r	12	0.612	0.552
PMd l	12	-0.277	0.786
PMd r	12	0.858	0.407
M1h l	12	1.017	0.329
DLPFC l	12	-0.204	0.841
DLPFC r	12	0.103	0.920
SMA	12	0.714	0.489
antIPS l	12	0.661	0.521
antIPS r	12	1.551	0.147
PMv l	12	-0.150	0.883
PMv r	12	0.267	0.794
M1m l	12	1.297	0.219

General Discussion: Intentions embodied

Parieto-frontal stream for processing intentions

In the three studies described in the previous chapters I demonstrated different processes that bind action intentions to the motor outcome. In the first experiment I outlined the role for visual simulation of the movement consequences and the relationship between this simulation and the respective motor programs. My findings suggests that the representations of visual action consequences are embedded in the early stage of planning activity, and that these early representations are present both in parietal and in dorsal premotor cortex. The parietal cortex seemed to be, however, more prominently engaged in representing sensory action consequences than its premotor counterpart. Next, I showed that action plans differ between parietal and frontal motor control areas with respect to reach planning strategies. Importantly, I uncovered that while posterior parietal cortex holds vector-based, simple reach plans, premotor cortex is capable of representing reaches following complex paths. Apparently, the latter capability allows for sophisticated hand movements, extending beyond simple, reflex-like ones. In the last study, I was able to demonstrate the role of parietal areas in translating retrospective mnemonic information into a future-oriented motor plan. In particular, I showed, that brain activity putatively reflecting mnemonic rehearsal in the parietal areas is influenced by the effector that will be used for responding in the working memory task. This finding suggests, that the intentional aspect modulates all levels of cognitive processing.

Taken together, these three studies demonstrate that posterior parietal cortex represents various prospective aspects related to upcoming actions, ranging from representing the expected actions' consequences to maintaining the mnemonic content in an effector-optimized form. Interestingly, the representation of the visual consequences of an action seems to be duplicated across PPC and PMd which raises a further question about the mechanisms underlying this redundancy. This gets at least partially answer in Study 1,
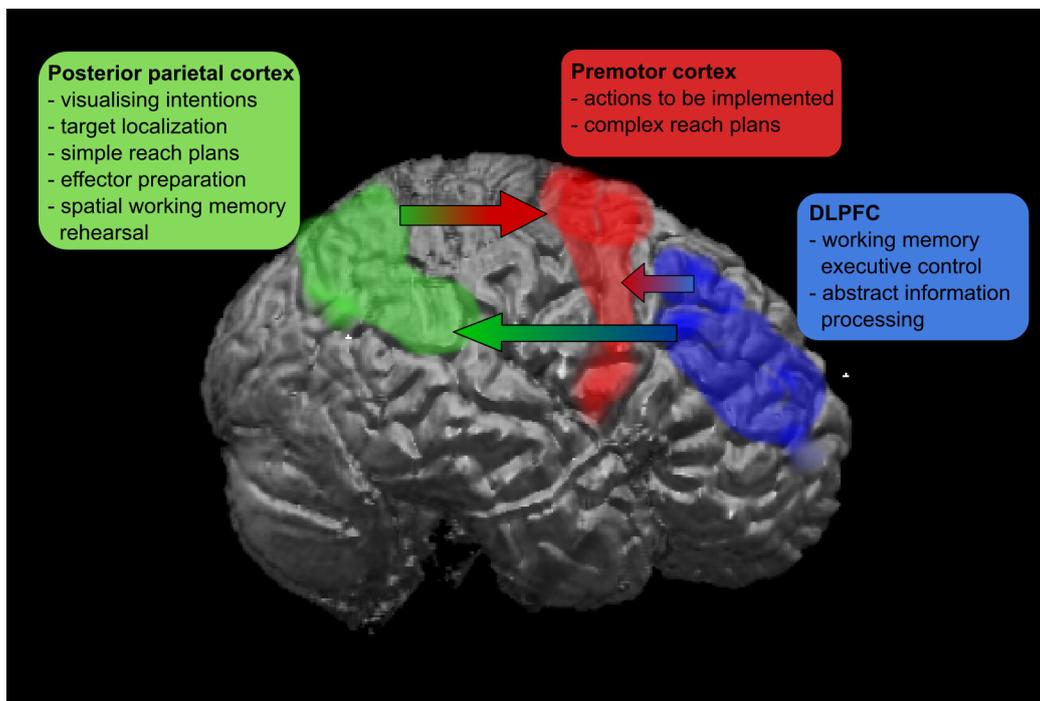
Figure 5.1. Suggested functional division and hypothetical scheme of primary information flow between PPC, PM and DLPFC, based on three experiments described in previous chapters.

showing, that PPC and PMd show dramatically different representations of goals and actions leading to them, whenever the two become detached. Posterior parietal cortex represents the action's target, while the premotor cortex seems then to represent the actual plan of movement that will be executed. This corroborates suggestions from numerous previous studies on motor planning, demonstrating that the frontal motor planning areas do represent more physical aspects of an action, while the parietal cortex contains a more abstract, idealized representation of goals and intentions. It seems therefore that the path between perception and action is composed of complex, multi-level transformations, functionally distributed across the parietal and frontal motor areas. Based on the empirical findings, we can dare to delineate a general view on this cascade of information flow, where the initial intention, building upon visuospatial information, is prospectively defined in posterior parietal cortex (as shown in Study 1). This intention can be subject to modulation by the current state of the body, such as presence of tools that may extend the reach range (Maravita and Iriki, 2004), or the current motor context (Westendorff et al., 2010) that may change the sensory outcome of a given motor

Figure 5.2 Representative forms of visual art of Homo sapiens. (Upper- and middle left): rock paintings dated ca. 5000-3000 BC near Hassi Laouinate, Western Sahara. (Upper right): A horse painting from Lascaux Cave, ca. 17000 BC, France. Photo: public domain. (Lower left): a carving depicting an antelope (dating unknown) near Smara, Western Sahara. (Lower right): Michaelangelo's La Pietà, Vatican City, Rome. Photo: Stanislav Traykov, Wikimedia Commons.

program, such as turning the steering wheel leads to different outcome while driving a car forward vs. in reverse. On the basis of expected outcomes, the final action plan has to be first selected from among the range of viable alternatives (c.f. Cisek, 2007; Lindner, 2008 or Gallivan, 2017) and only then the selected plan is translated into appropriate motor commands. Representing alternative action plans appears to be the basis for ensuring flexibility of behavior in response to varying environmental demands and allows for mental evaluation of a plan before trying it out. The ability to mentally represent intentions prior to realizing them seems to be a pivotal property of the human motor system. It ensures choosing optimal action plans, allows for manipulating physical objects within one's imagination and, furthermore, the use of tools extending the set of available actions. We

can suspect that although such ability is not unique to our own species, its impact on the human mind extends far beyond the domain of motor control. I will conclude this work by drafting a slightly provocative hypothesis on how did the neural architecture of the human motor system lay the groundwork for the modern human mind.

Making ideas come true – the evolution of actions, the evolution of mind

I will start this last part of my thesis by noting that we, humans, are the only species capable of creating art representing external objects. Even our closest cousins – chimpanzees can, at best, splash and smear paint on the canvas, without being able to give it any aesthetic form. Any anecdotal reports about elephant "paintings" remain just an effect of brutally enforced reflexes, without the elephant conceptualizing the overall picture it is supposed to "paint", but rather trying to avoid punishment administered by its captors (English et al., 2014). All other frequently called forms of "animal art", such as bowerbird courtship rituals, especially its amazing skills in ornamenting nests, remain an example of stereotyped behavior. Even if one argues for a creative element in these behaviors, such creativity is limited to fluctuations modifying the basic form, making it bigger or fancier, rather than aimed at any kind of original creation, completely distinct from the exemplar. In brief: no other species than humans possesses the ability to create art, especially in its visual, figurative forms. Now, could this uniquely human trait build on the ability to reproduce the contents of imagination, as offered by our motor system? According to Mithen's (1994; 1996) theory of cognitive evolution, the minds of our early human ancestors were composed of several independent modules, evolving at relatively different paces in different hominin species. Therefore, the archaic humans, such as Neanderthals, may had possessed a "swiss-knife" of mind, where the modules performed each their own functions with limited transfer between them. Mithen uses a metaphor of a chapel with all aisles tightly separated with walls. Although the Neanderthal mind was possibly more oriented towards visuospatial operations (Gregory et al., 2017), it lacked extended social

capacities, which is considered the leading cause that influenced the easiness by which Chatelperronian (late Neanderthal) culture was subdued by the spreading Homo sapiens. But what was the basis for this alleged the social inferiority of Neanderthals responsible for their eventual demise in confrontation with much more numerous and advanced cousins? As it has been speculated (Bettinger, 1991; Harari, 2011), the ability of Homo sapiens to form large social groups has been mediated by our ability to employ symbols and ideologies, for which the works of art are a mean of expression. As Mithen further hypothesises, the evolutionary leap of our own species has taken place thanks to the emergence of language, which broke through the metaphoric walls of the primitive mind's chapel and allowed conceptually linking the information stored in the – previously separated – modules of the mind (Mithen, 1994; 1996; see also: Arbib, 2005; 2009). On the other hand, several hints suggest that early forms of symbolic thinking and language were already present in pre-Neanderthal hominins, such as *Homo naledi* (de Waal, 2015) and other varieties of Homo erectus, whose endeavours like ocean sailing imply that they needed to possess primitive language for coordinated group actions (Everett, 2017; 2018). Interestingly, the ability to use tools has been suggested to underlie development of symbolic thinking, as tools can be processed as early precursor of symbols – forms evoking semantic associations (i.e. affordances), yet physically distinct from their direct purpose (Everett, 2017). No matter when exactly did hominins develop the ability to express the symbols and communicate them, such communication could develop only thanks to the appropriate means of expressing symbols and ideas. While speech is certainly a key prerequisite, it allows only for communication within groups of limited size, where personal interactions are possible and frequent. Where this is not the case (for example in large, sparse or nomadic populations), or where oral communication does not allow for expressing more complex ideas like religious/mystic symbols, other forms of expressions are needed. These are visual arts and – more recently - writing, the two byproducts of motor system's ability to shape the environment according to a pre-

visualised intention (see Study 1). Both have enabled humans to universally communicate rules, myths, beliefs and stories, the key components of the human culture. It appears that these forms of expression draw heavily from the existing brain wiring allowing for manual actions. Apparently, the process of visualising an action plan and moving a hand in order to match it, made a good basis for skills like painting or toolmaking, and on this basis even much more sophisticated processes could build. The areas of human posterior parietal cortex responsible for combining representations from different sensori-motor domains, allowed for creating completely novel visual forms or combining old ones (Wynn, Coolidge and Bright, 2009). It is conceivable, and has been repeatedly suggested (see e.g. Wynn, Coolidge and Bright 2009), that object representations in parietal areas are modulated by prefrontal abstract-thinking functions with such modulations allowing further to attribute meanings to objects and recombine them in novel ways. This possibility is reflected already in the earliest examples of human art, with notable example of the Löwenmensch, a prehistoric figurine combining both human and animal-like properties. Such unusual combination of visual forms indicates that imagination and abstract thinking of the prehistoric sculptor had to enable them to mentally combine the body of an animal with that of a man in order to create the hybrid form, possibly symbolizing some mysterious belief. This differs from merely representing external objects and shows that the creator combined their available imaginations of a lion and a man to give them a new, abstract meaning. History of writing reflects a similar process in which pictorial forms were gradually replaced by more abstract ones, allowing texts to contain abstract and complex concepts. These examples clearly demonstrate that human expression of ideas crucially depends on symbolic and abstract thinking. But, in addition, we learn that the cognitive ability to represent ideas and concepts would be nearly useless if there were no means of expressing them. There would be no Venus of Hohle Fels if its unknown sculptor was unable to envision what he was to carve, and, conversely, there would be no cave paintings of Lascaux without the elaborate neural machinery that allowed the painter to

skillfully move the hand in order to reproduce the content of their imagination. The uniquely human forms of artistic expression built upon how the motor system evolved and how it allows us to transfer the visualized intentions into the physical world, be it through reaching for an apple or painting a horse on a cave wall. This ability to materialize the content of imagination has gradually evolved from creating very simple forms to astonishingly complex ones, from the primitive rock carvings to La Pieta. Apparently, to a large extent we owe this progression to the organisation of the primate motor system. Thanks to the way this complex neural machinery has evolved, we possess a stable basis for the crucial trait that made us, humans, so unique: the ability to express, share and immortalize ideas.

APPENDIX

Study 1 – materials and methods

Subjects. 14 healthy subjects (8 females) participated in the study. All of them had normal or corrected to normal vision. All except one subject were right-handed. The subjects provided informed consent in accordance with the Declaration of Helsinki and with the guidelines of the local ethical committee, and were reimbursed for their participation. Two of the subjects were excluded from the final sample (see "Behavioral performance analysis" for details).

General task design. To study planning-related brain activity we conducted a functional magnetic resonance imaging (fMRI) study, in which human subjects performed an action planning experiment (Figure 2.1). During this experiment subjects needed to plan and execute "virtual reaches" by moving a button-controlled cursor on a response-grid. In half of the trials, subjects carried out a delayed response task (Rosenbaum, 1980): they were instructed to remember a target location presented during the initial cue epoch and plan a movement towards it. Then, after an intervening delay epoch during which the target was no longer present, they had to execute the pre-planned movement during a movement epoch. In these trials, it was necessary to plan a movement prior to the movement epoch, hence we named this task "*pre-planned movement task*" (**PPM**). In the other half of the trials, subjects were told to ignore the initial cue and instead to wait until the movement epoch of that trial. Then they had to move the cursor to a new, visually instructed target location, randomly placed on the response grid. The latter task was named "*direct movement task*" (**DM**) and differed from the PPM in that both movement planning and execution took place directly during the movement epoch. Contrasting both types of trials allowed us to access brain processes related to movement planning. First, comparing delay-related brain activity in PPM vs. DM should allow one to isolate activity due to movement pre-planning in PPM (Rosenbaum, 1980; Lindner et al., 2010). Second, contrasting the estimates of brain activity during the movement epoch for DM vs. PPM

should exhibit activity related to initial, fast planning processes that still need to be accomplished in DM but that are already completed in PPM (c.f. Ames et al., 2014).

To further address whether any of the planning activity revealed would reflect the desired visual properties of a planned movement independent from the motor components of that movement, we additionally manipulated the visual movement gain of the cursor in both tasks. This meant that after each single button press, the cursor could perform either a "small step" (i.e. jump to the next intersection of the response grid) or a "big step" movement (i.e. jump to the next, and then to the second-next intersection). Targets were positioned in such a way that they required sequences of 1, 2 or 4 button presses to be reached, in each of the "gain" conditions. By changing the movement gain ("big" or "small" step) for each given movement sequence length, we could keep a sequence's motor demands constant while at the same time vary its visual consequences (the visual distance of the movement). This was meant to allow us capturing planning activity that would specifically co-vary with the amount of upcoming visual motion. Since the number of trials with each sequence length was balanced, the only difference between the "big" and "small step" conditions in each task was the amount of visual motion the sequences produced.

Information about which movement gain was actually applied in a given trial was shown to participants during the cue epoch of the trial (see Figure 2.1) and they needed to incorporate this information into their motor plan in order to perform accurately within the time limit of the movement epoch. For every participant, color cues indicating conditions were the same.

Using our approach we expected to reveal a representation of the upcoming motor sequence during movement planning in PPM, a representation that we have already described previously for both PPC and PMd (Lindner et al., 2010). Areas that would exhibit such a prospective representation of the motor plan (and hence not just a retrospective memory of the target) were considered in a subsequent region of interest (ROI) analysis

(see below), in order to reveal whether their planning activity contains information about the visual consequences of an upcoming movement (i.e., it should represent the "visual way to the goal" in addition to the motor sequence). Previous fMRI findings revealed, the amplitude of the blood oxygenation level dependent (BOLD) signal correlates positively with the amount of (anticipated) visual motion (Lindner et al., 2006). Therefore we hypothesized that if the visual consequences of a planned movement are indeed defined in PPC or PMd, the brain activity in these areas should reflect these visual aspects of the movement. Specifically, the "big-step" motor sequences should on average produce stronger planning-related BOLD signals as compared to the "small-step" sequences, due to an overall larger amount of expected visual motion.

Stimulus presentation. Stimuli were presented using Cogent Graphics Toolbox (Laboratory of Neurobiology at the Wellcome Department of Imaging Neuroscience London, UK) running on a Windows^{TM} -based PC and delivered to the subject using a LCD projector (1024x768 pixels, 60Hz refresh rate), a translucent screen and a set of mirrors attached to the head coil of the MRI scanner.

Each trial started with a baseline epoch (13500, 15000 or 16500ms), which required the subject to fixate their gaze upon the centrally positioned fixation cross (1.1 deg visual angle). The fixation cross remained visible for the whole time course of a trial and subjects were instructed to fixate it at all times. This should help us to avoid, potentially confounding, eye-movement related brain activity. After the baseline epoch ended, the cue screen was presented for a fixed time of 1000 ms. The cue screen consisted of the movement space grid (9x9 squares, see Figure 3,1; size of each square was approx. 1.7 deg) and an empty square representing target location (approx. 1.7 deg). The fixation cross was replaced by a color cue, that indicated both the movement gain ("big-step" vs. "small-step" movement) and the task (PPM or DM). Subsequently the scene was masked for 1000ms to prevent afterimages of the visual targets and then the delay epoch began. The delay epoch was of variable length (4500, 6000 and 7500ms). These delay times

chosen were much shorter than those used in previous studies of our group (e.g. compare Lindner et al., 2010). We did this to reduce subjects ability to use retrospective mnemonic strategies and from engaging in task-unrelated cognitive activities (such as any sort of mind-wandering) during the delay epoch. Subsequently, the response grid was presented, and subjects were supposed to execute the movement to the remembered target location in case of PPM or to a filled square (1.1 deg), indicating the actual target in DM. Specifically, subjects used a response pad (see Figure 2.1) held in their right hand in order to move a button-controlled square cursor to the designated target area. The cursor moved in the direction that corresponded to the button pressed (either left, right, up or down), skipping between intersections along the vertical or horizontal lines of the grid, respectively. Depending on the movement gain, a single press of the button could either lead to a "small-step" movement of the cursor (so that the cursor moved from one intersection on the grid to the next) or a "big-step" (in this case the cursor jumped twice in the same direction, with a 100ms time delay between successive cursor steps). Time for completing the motor response was limited to 3000ms. After the time limit was reached, the screen was masked again, and the next trial began after an inter-trial interval of 2000ms.

Subjects practiced the task before scanning until they reported satisfactory performance. During scanning subjects performed 36 trials for each of our four conditions in total. These trials were acquired during three experimental blocks, each consisting of 48 trials. The conditions were randomized within a block.

Oculomotor behavioral control. Eye movements were monitored at 50Hz sampling rate with an infrared operated, MR-compatible eye tracking camera (SensoMotoric Instruments) and the ViewPoint software (Arrington Research). All eye movement analyses were performed off-line using custom routines written in Matlab (MathWorks). In brief, eye position samples were filtered using a second-order 10 Hz digital low-pass filter. Saccades were detected using an absolute velocity threshold (20 degrees per second).

Since our experiment required subjects to maintain fixation on the central fixation point, we excluded 2 of our 14 participants who did not comply to this instruction and frequently performed large saccades (amplitude > 3 degrees visual angle away from the fixation point in more than 20% of the trials). In both excluded subjects, this behavior was equal to gaze shifts towards the target location in the cue epoch, or towards the moving cursor during the movement epoch of a trial, or towards both.

Manual performance analysis. Manual performance was assessed in terms of hit rate, movement durations and reaction times. Those trials were classified as hits, in which the cursor was positioned over the correct target location at the end of the movement epoch. Movement duration captured the time from the first button press until the cursor reached its final position. Reaction time was defined as the interval between the onset of the movement epoch and the time at which the first button in a sequence was pressed.

All behavioral data were analyzed statistically using 2x2 repeated measures ANOVA with factors "task" and "movement gain".

fMRI acquisition and SPM analysis. MRI images were acquired on a 3T Siemens TRIO scanner using a twelve-channel head coil (Siemens, Ellwangen, Germany). For each subject, we obtained a T1-weighted magnetization-prepared rapid-acquisition gradient echo (MPRAGE) anatomical scan of the whole brain (176 slices, slice thickness: 1 mm, gap: 0 mm, in-plane voxel size: 1 x 1 mm, repetition time: 2300 ms, echo time: 2.92 ms, field of view: 256 x256, resolution: 256 x 256) as well as T2*-weighted gradient-echo planar imaging scans (EPI): slice thickness: 3.2 mm + 0.8 mm gap; in-plane voxel size: 3 x 3 mm; repetition time: 2000 ms; echo time: 30 ms; flip angle: 90°; field of view: 192 x 192 mm; resolution: 64 x 64 voxels; 32 axial slices. Overall, we obtained 2100 EPIs per subject, which were collected during the three consecutive runs of about 20 min length each. A single EPI volume completely covered the cerebral cortex as well as most subcortical structures. Only the most inferior aspects of the cerebellum were not covered in several of our subjects.

Functional data were analyzed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK). In every subject, functional images were spatially aligned to the first volume in a series, and then coregistered to the T1 image. After that, a non-linear normalization of the structural image to a T1 template in MNI space was performed. Parameters obtained with this normalization were then applied to all functional images. In the last step of data preprocessing, we smoothened all the functional images with a Gaussian filter of 8 mm x 8 mm x 8 mm FWHM.

In subject-specific fMRI analyses we specified two general linear models for each individual. The first model included all the four conditions ("task" x "movement gain") and for each condition we modeled trial epochs (cue+mask, delay, response) as separate regressors. Cue was modeled as a single regressor, regardless of the condition. Sequence length was modeled as a linear parametric modulator, thus capturing any relative difference in BOLD-signal amplitudes related to the number of button presses required to reach targets at different distances. This parametric modulator was included separately for all conditions and for both delay and movement epoch. Head motion parameters were included in the model as six independent regressors (x, y, z translation and x, y, z rotation). Inter-trial intervals, as well as fixation epochs weren't modeled explicitly and thus served as an implicit baseline.

The second GLM was constructed in order to obtain reliable cue-related betas for each of the experimental conditions (see "results"). To this end we modeled cue epoch the same way as other epoch regressors, namely defining "task" and "movement gain" separately. The other regressors we modeled as described above.

ROI analysis. For each subject we identified a set of regions that contribute to the prospective planning of motor sequences (Figure 2.2). We decided for this region-of-interest (ROI) approach in order to avoid inter-individual variation in functional anatomy and specifically look at planning related activity in the relevant areas. Towards this end we first calculated the statistical parametric map capturing areas that show a parametric

modulation of their BOLD activity by the planned number of button presses (motor sequence length) during the delay epoch of "pre-planning" trials in each individual. Based on coordinates of movement sequence planning regions that were described by Lindner et al. (2010), we selected our ROIs by looking for areas showing a statistically significant linear increase in BOLD intensity during the delay phase of PPM trials within a search radius of 20mm around the respective coordinates ($p<0.05$, FWE-corrected for multiple comparisons within the search volume). These areas were: left and right superior parietal lobule (SPL), left and right dorsal premotor cortex (PMd) and anterior intraparietal sulcus (aIPS). Since for the left aIPS we were only able to identify these areas in 9 out of 12 subjects, we applied a more liberal threshold ($p<0.001$ uncorrected) in the remaining 3 subjects to provide a more representative sample. In addition to these planning ROIs we included several control ROIs: (i) The hand representation in the left and right primary motor cortex (M1) was identified based on anatomical criteria (Yousry et al., 1997) to control for motor response-related activity and for effector preparation.(ii) DLPFC was mapped according to the same criteria as described for our planning ROIS. As for aIPS, a more liberal threshold ($p<0.001$ uncorrected) was applied in three subjects. In only one subject we were not able to reliably localize DLPFC using the latter criterion. Data from that subject's DLPFC were therefore extracted using group-based coordinates. (iii) Finally, we additionally included area V1 as a control ROI in order to capture activity reflecting visual input stemming from the target cue or the cursor movement. We we are not aware of any findings showing its specific engagement in reach planning.

As our functional ROI definition did not differentiate between "movement gain" conditions (i.e. maps were calculated for both "small-step" and "big-step" movements taken together), the ROI selection was not biased in favor of our hypothesis (i.e. stronger planning activity in "big-step" conditions). In the next step, for each of our ROIs and in each of our subjects, we extracted the normalized mean beta weights of our main GLM regressors from a 3mm radius sphere created around the ROIs center coordinate, each

single ROI consisting of 7 voxels in total. The extracted betas of the first GLM were analyzed separately for the delay and the movement epoch using a 2x2 repeated measures ANOVA with the factors "task" and "movement gain". The GLM was analyzed using the added additional factor ("epoch") in a 2x2x2 repeated measures ANOVA.

Study 2 – materials and methods

Participants

Twelve healthy, right-handed participants (11 females) in the age range of 20-32 years (mean age 25 years), participated in Experiment 1. Seven healthy, right-handed volunteers (6 females, age range 20-31 years, mean age 25 years) took part in Experiment 2. Out of these, five subjects had also participated in Experiment 1 (two of them had completed Experiment 2 first). The over-representation of female subjects in both experiments resulted from spatial constraints given our setup (especially touchscreen size and its position, see Figure 3.1A), which required particularly slim subjects.

The number of participants was guided by a power analysis (power=0.80; alpha=0.05) that was informed by the descriptive statistics of a timecourse analysis on a previously published, similar fMRI dataset. In that study, planning activity varied as a function of movement sequence length (Lindner et al. 2010) . For the power analysis we considered the within-subject activity difference during the late delay period (last 4 sec) in left PMd, namely for a delayed response task that required the planning of a less complex (2 targets) vs. a more complex (4 targets) movement sequence. This analysis suggested a sample size of 11 subjects (two-tailed tests). For Experiment 2 we relaxed this criterion (one-tailed tests), as we had a directional hypothesis (the stronger the activity the more complex trajectory planning). Note that here we measured each experimental condition 20 times per individual, while the study that informed our power analyses only comprised of 9 repetitions per condition.

MR-compatible reach setup

We realized our experiments in a custom made MRI-compatible virtual reality reach setup, in which we could record 2D movements of subjects' right index finger and could provide subjects a virtual visual representation of their finger on a stimulus screen (see Figure 3.1A). Specifically, visual stimuli were projected via an LCD projector onto a translucent

screen, mounted directly behind the head coil of the scanner (1024x768 pixels; 60Hz refresh rate). Subjects viewed the stimulus screen via a mirror, positioned in front of the participant. Viewing distance was approximately 82cm and roughly matched the distance from participants' eyes to the touchscreen. To track subjects' finger movements we used a MRI-compatible motion capture system, utilizing a resistive touchscreen panel from MAG (www.magconcept.com), mounted on a plastic board. This touchscreen-board was placed on top of a plastic rack onto which the stimulus-mirror, a camera for eye movement recordings and the display screen were mounted in addition. Limited by the spatial constraints of the scanner environment, we always tried to approximate a parallel alignment between the touchscreen and the display to guarantee approximate spatio-temporal correspondence between measured finger position and visual feedback thereof. Subjects were positioned with their head tilted forward inside the scanner head coil, so that they could directly look towards their pointing finger. Ultimately, direct vision of the hand was blocked by both the mirror and additional masks and subjects had to rely on the virtual visual feedback about their finger position instead. All reaches were performed in darkness and the only visual information provided was the one projected through the display system. In order to minimize potential disturbances of the magnetic field by hand and arm movements we stabilized each subject's arm, elbow and shoulder with foam cushions and adhesive tape, so that only wrist and finger movements were made possible. To minimize movement friction we had subjects wear a cotton glove on their reaching hand.

Each of our experiments was preceded by a training session during which the subjects familiarized themselves with the tasks demands. All subjects were additionally required to practice the experiment for a minimum of 10 minutes inside the scanner once the MRI setup had been completed.

Eye recordings

Eye fixation was monitored at 50Hz sampling rate with an MR-compatible combined

camera and infra-red illumination system (MRC Systems) using the ViewPoint software (Arrington Research). Due to technical difficulties of recording eye movements in the experimental environment (extensive video capture noise, too long setup time) we were only able to perform systematic eye-recording analyses in 10 out of 12 subjects in Experiment 1 and in 5 out of 7 subjects in Experiment 2. All eye movement analyses were performed off-line using custom routines written in Matlab (MathWorks). In brief, eye position samples were filtered using a second-order 10Hz digital low-pass filter. Saccades were detected using an absolute velocity threshold (20 degrees per second), and blinks were defined as gaps in the eye position records caused by eyelid closure. Time periods with blinks were excluded from subsequent analysis. We instructed the subjects to continuously fixate on the central spot. While our subjects fulfilled this requirement in the majority of trials, we still assessed the frequency of residual saccades (amplitudes ≥ 1 deg visual angle) on a trial by trial basis and compared saccade frequencies in the CUE and in the DELAY epoch across conditions to control for potential eye movement-related confounds.

Experiment 1

The detailed paradigms of Experiment 1 are depicted in Figure 3.1B. Each trial started with a 15s/16s fixation period (FIXATE), during which subjects were instructed to fixate a centrally positioned fixation cross. In addition, subjects were required to perform "finger fixation" by placing their right index finger on a tactile cue on the touchscreen. This tactile cue also defined the starting position for reaching and it would corresponded to a location at the topmost position between the circles marking the reaching space. Eye blinks were allowed though discouraged during this period. Next, a CUE screen appeared for 1.5 seconds, indicating the experimental condition (a red central cue indicating CT and a green cue indicating DRT), a target location, reach direction (an arrow indicating clockwise or counterclockwise direction), eye and finger fixation points and instructed reach space boundaries (compare Fig. 3.1B). Both the starting location and all targets were positioned

at a constant radius of about 3deg visual angle from the fixation point. We used a predefined set of four target locations, placed in the upper-portion of the reach space either at 10 o'clock (-60°), 10.30 o'clock (-40°), 1.30 o'clock (+40°) or 2 o'clock (+60°). Note that the starting position corresponds to 0° (12 o'clock). This way, by manipulating reach direction and target location, we could alter the movement trajectory, without affecting target eccentricity and, accordingly, the hand-target difference vector. In the DRT condition subjects were required to remember the target location and to plan a movement to it according to the arrow cue. Subjects were told to ignore target and arrow cues in the CT condition, as the relevant cues would be delivered only later in the REACH phase. In both conditions subjects were asked to maintain fixation and avoid blinking during this CUE period. Next, we presented an image for 500ms, which was made up of (400) randomly positioned, black and white circles approximately the size of the cursor, to mask any after-images of the cues (not shown in Fig. 3.1B). This mask was followed by a DELAY period lasting 15s-16s. During the DELAY subjects were instructed to keep fixation and, again, blinking was allowed though discouraged during that period. Note that we assume that correlates of goal-directed movement planning should be present during this phase in DRT but not in CT. Finally, the response screen appeared for 3s signaling the REACH phase. In the DRT subjects had to move their right index finger to the pre-cued target location as fast and accurate as possible through a single, smooth movement of their finger. In the CT subjects were presented a new target location and a new arrow cue, and had to immediately perform a movement according to these cues. Once reaching the instructed goal, subjects had to stay at the final location until the response screen disappeared. Then, a blank screen appeared for 4s (not shown in Figure 3.1B) and subjects had to return their finger to the tactile cue. They were also encouraged to blink specifically during this period to reduce corneal drying in the face of prolonged periods of fixation. Note that visual feedback about finger position was only provided during the CUE and REACH phases of a trial. All experimental conditions were presented randomly

interleaved and were repeated 20 times across 5 consecutive scanning sessions per subject.

Experiment 2

The overall design of Experiment 2 was similar to Experiment 1 (compare Fig. 3.1D). Each trial started with a 15-16 seconds fixation epoch. The points of fixation of eye and finger overlapped spatially and corresponded to the center of the display. Then, a CUE screen was displayed for 1.5s, with a task cue presented centrally at the fixation point (a red cue indicating CT and a green cue indicating DRT), and a target cue in periphery at about 3.2deg or 7.2 deg visual angle for NEAR and FAR conditions, respectively. Target size in NEAR conditions was 0.8 deg visual angle. To accommodate for an increase in movement difficulty (ID) with increasing distance (D), we increased the size of the target (W) in the FAR conditions according to Shannon's formulation of Fitts' Law (MacKenzie, 2013), expressed as:

$$ID = \log 2\left(D/W + 1\right)$$

In DRT trials, subjects were instructed to remember the target cue and plan a movement to it, whereas in CT trials they were told to ignore the initial cue. The CUE screen was then masked for 500ms and a DELAY period followed, lasting 15-16 seconds. Ultimately, the REACH screen appeared for 3s and subjects had to move the cursor to the remembered target location in DRT, or to the newly cued target location in CT. After the instructed target location was reached they had to maintain their finger position at this location until the end of this task period. Then the screen was blanked and subjects had to return to the starting position. Subjects were required to perform straight movements, without lifting the finger off the touchscreen and they were told to be "as fast and as accurate as possible". Else they did not receive any additional instructions on how to plan/perform their reaches, as we did not want to bias their natural planning strategies. As in Experiment 1, we presented all experimental conditions randomly interleaved and repeated them 20 times across 5 consecutive scanning sessions per subject.

Finger movement analysis

Finger movement data were preprocessed using custom routines programmed in Matlab (MathWorks) and analyzed statistically using R (R Foundation for Statistical Computing). In brief, during preprocessing we applied a digital low-pass filter (1st-order Butterworth filter; 6Hz cut-off frequency). Data were analyzed to provide estimates of reaction times, movement accuracies, maximal velocities and movement durations. Reaction time was operationalized as the temporal difference between the onset of the movement epoch and the moment when finger velocity exceeded a threshold of 11mm/s. Movement error sizes were characterized as the linear distance between the finger endpoint (calculated as average of the last five samples of the finger position during the REACH phase) and the border of the target circle.

fMRI acquisition and analyses.

MRI images were acquired using a 3T Siemens TRIO scanner using a twelve-channel head coil (Siemens, Ellwangen, Germany). For each subject, we obtained a T1-weighted magnetization-prepared rapid-acquisition gradient echo (MPRAGE) anatomical scan of the whole brain (176 slices, slice thickness: 1 mm, gap: 0 mm, in-plane voxel size: 1 x 1 mm, repetition time: 2300 ms, echo time: 2.92 ms, field of view: 256 x256, resolution: 256 x 256) as well as T2*-weighted gradient-echo planar imaging scans (EPI): slice thickness: 3.2 mm + 0.8 mm gap; in-plane voxel size: 3 x 3 mm; repetition time: 2000 ms; echo time: 30 ms; flip angle: 90°; field of view: 192 x 192 mm; resolution: 64 x 64 voxels; 32 axial slices. Overall, we obtained 2050 EPIs per subject in Experiment 1, which were collected during five consecutive runs. In Experiment 2 we collected again 2050 EPIs per subject over five runs. A single EPI volume completely covered the cerebral cortex as well as subcortical structures, apart from the most inferior aspects of the cerebellum which were not covered in several of our subjects. Functional data were processed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK). In every subject, functional images were spatially aligned to the first volume in a series, and then coregistered to the

T1 image. After that, a non-linear normalization of the structural image to a template in MNI space was performed. Parameters from normalization were then applied to the functional images. In the last step of data pre-processing, we smoothened all the functional images with a Gaussian filter of 6mm x 6mm x 8mm FWHM.

In subject-specific fMRI analyses we next specified a GLM for each individual including our four experimental conditions ("task" [DRT, CT] x "movement distance" ["NEAR", "FAR"]). Each condition was modeled separately for each of our three trial epochs (CUE+MASK, DELAY, REACH). The regressor duration was defined according to respective epoch duration. The regressors were convolved with the canonical HRF-function of SPM8. Head motion parameters were included in the model as separate regressors. Fixation epochs weren't explicitly modeled and served as an implicit baseline. To consider each subject's individual functional brain organization, we detected planning areas significantly more active during the delay epoch in DRT than the respective epoch of CT trials in each subject (for that step, single subject activity maps were thresholded at p<0.001, uncorrected).

We additionally performed a group-level analysis to delineate the areas commonly activated by reach planning in our experiments. For this purpose we entered the respective (first level) contrast images in a second-level group analysis (one-tailed t test). In this step, we used a minimal cluster-size criterion (k>10 voxels) and a statistical threshold of p<0.001, uncorrected.

Region of Interest Analyses

We used the results of the group-level analysis and anatomical landmarks (see below) to initially identify reach planning-related areas. Our ROI set consisted of two main areas: left dorsal premotor cortex located at the posterior end of the superior frontal sulcus, anteriorly to the hand area of M1 (PMd); the left posterior-medial portion of superior posterior lobule (SPL; Conolly et al., 2003). The additional movement planning ROIs included were: the left anterior end of the intraparietal sulcus (aIPS); the left middle intraparietal sulcus (mIPS);

and left supplementary motor area (SMA). For each of these ROIs and for each individual we next identified the coordinate of the voxel exhibiting the local maximum of the individual subject statistical contrast DRT>CT that was closest to the respective ROI group-coordinate. In addition we anatomically identified the hand area of left primary motor cortex (Yousry et al., 1997) due to its potential engagement in reach planning (Hocherman and Wise, 1991) as well as left primary visual cortex (V1). The latter area served as a control for any activity related to visual stimulation, also because we are not aware of any findings showing its specific engagement in reach planning or execution. To avoid biasing our ROI-selection in individual subjects across both Experiments, as they were planning different movement types in each (circular [Exp. 1] vs. straight [Exp. 2]), in those subjects that participated in both of our experiments, we used the ROI coordinates of Experiment 1 also for Experiment 2 (5 out of 7 subjects, compare Figure 3.7). Please note that our ROI definition meets the criteria described by Kriegeskorte et al. (2009) to avoid circularity in data analysis. For ROI analyses we always considered the average activity of voxels within a 3mm radius around the ROI center coordinate. We decided for univariate signal analyses, as it was sensitive enough to capture signal changes scaling up with trajectory parameters in our ROIs. We consider this to be the most direct and reliable way to make inferences about trajectory plan representations.

Time-resolved fMRI analysis

Using custom protocols written in Matlab (MathWorks) (compare ref. 33), we extracted and analyzed BOLD-signal timecourses for each of our ROIs. Importantly, we separately analyzed timecourses during the CUE and DELAY vs. the REACH epoch: timecourses for the CUE and DELAY phase were aligned to the onset of the CUE, and normalized to the baseline defined as a time window of -5s to -3s preceding CUE onset. As planning processes are likely to take place beginning as early as the presentation of the target cue we analyzed both trial epochs together. The signals for the REACH epoch were aligned to the onset of the REACH phase and normalized to the same baseline period as above. The

timecourses were filtered with a digital high-pass filter (128s cutoff frequency) and interpolated at 1s temporal resolution (given the temporal jitter in our design).

To examine the effect of trajectory on the BOLD signal in each of the ROIs, we performed a time-resolved analysis of the timecourses with respect to their relative amplitude over the principal trial epochs (CUE/DELAY and REACH) using paired t-tests (compare "RESULTS" section). Only the significant differences spanning over three or more consecutive time points were taken into consideration and we limited the interpretation of results only to the late-delay phase of trials (see "RESULTS") as the most relevant. The additional comparison between the main ROIs was done with mixed-models ANOVA in R. In order to additionally control for type-II-error usually harder to capture with the classical statistics like ANOVA, we additionally calculated Bayes factors for our main and selected additional ROIs, using the method described by Dienes (2011). These factors allowed for comparing the hypotheses that planning signals are the same vs. different during late delay with respect to the trajectory conditions (NEAR vs. FAR) in each experiment. In particular, we assumed the signal differences to be approaching 0, when there is no difference between trajectory representations (null hypothesis), and diverging from 0 if the trajectory signals are different (alternative hypothesis). Specifically, for every ROI tested, we determined the Bayes factor based on subjects' signal differences between FAR and NEAR conditions during the late delay period in each experiment. The alternative hypothesis was modeled by a uniform distribution (>0 to maximal signal difference observed within individual subjects for a given ROI). Bayes factors above 10 were considered as strong support for the hypothesis that trajectory-related planning signals differ, while values below 0.33 indicate strong support for the null hypothesis (no trajectory-related signal differences).

Study 3 – materials and methods

Subjects.

Thirteen subjects (two males; eleven females; mean age: 25) participated in this study. All of the participants had normal or corrected-to-normal visual acuity and were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). None of them suffered from chronic, neurological or psychiatric diseases and took any medication. All subjects gave written consent in accordance with the declaration of Helsinki. Furthermore, this experiment was approved by the local ethics committee. Subjects received 10 Euro per hour for their participation.

Task.

We applied functional magnetic resonance imaging (fMRI) while our participants worked on either a delayed match-to-sample task in which subjects had to memorize dot patterns or a control task in which they had to judge if a given dot pattern is axially symmetrical (Figure 4.1). Each trial started with a baseline period (14,000 or 15,000ms) in which subjects were asked to keep central fixation on a fixation cross. Then, a cue (1000ms) indicated a) if the current trial was a memory trial (yellow square) or a control trial (blue square) and b) if subjects would have to respond verbally (picture of a mouth) or manually (picture of a hand) in the end of the trial. After this cue period, an encoding period (3000ms) started in the memory trials in which subjects saw 18 small circles that were arranged in a circle around the cue. Either two or six of these circles were marked and their positions within the big circle served as the memory items that subjects had to keep in memory during the subsequent delay period (14,000 or 15,000ms). Then, we either presented the very same dot pattern of the encoding period or a different one (3000ms). Subjects had to wait until they saw a green go-cue and had to indicate within 3000ms if this dot pattern equaled the one of the encoding period or not by either saying 'same' or 'different', respectively in the verbal conditions or by pressing the right or left button of a button box, respectively in the manual conditions. The control condition differed from the

memory condition after the cue period insofar as a circle consisting of 18 unfilled circles was solely presented around the cue so that subjects could not maintain any memory content during the subsequent delay period (14,000 or 15,000 ms). Then, we presented a circle of 18 small circles after the delay period. Again, either two or six of these circles were filled. Subjects waited until the green "go" cue and indicated if this dot pattern was axially symmetrical to the vertical middle line of the big circle or not by either saying "same" or "different", respectively, in the verbal conditions or by pressing the right or left button of a button box in the manual conditions.

Our subjects worked on five consecutive blocks in which each of the 4 main conditions (2 modalities (verbal vs. manual) x 2 tasks (memory vs. control) was randomly presented twice resulting in 20 repetitions of each modality condition.

Stimulus presentation.

We created the visual stimuli on a Windows based PC using MATLAB R2007b (The MathWorks, Inc.) and Cogent Graphics developed by John Romaya at the LON at the Wellcome Department of Imaging Neuroscience. They were projected onto a translucent screen (size of the projected image: 28 deg x 37 deg visual angle; viewing distance: 92 cm) by means of a video projector (frame rate: 60 Hz; resolution: 1024 x 768 pixels). Our participants watched the projected stimuli on the translucent screen being placed behind them with the aid of a mirror that was mounted on the head coil.

We displayed the fixation cross of the baseline and delay phases in Arial font and a 2.44 degrees visual angle font size. The color cue square side was 2.44 deg. The modality cue images were 1.95deg x 1.76deg. The spatial cues (dots) were placed at 4.9deg radius from the central fixation point and were approximately 1 degree in diameter each.

Data acquisition.

Eye tracking. Our subjects were supposed to maintain central fixation during the whole trial besides the response phases to ensure that the fMRI activity that we analyzed was not significantly influenced by eye movements. We recorded eye-movements with a

MRI-compatible infrared eye-camera (SMI SensoMotoric Instruments) and the ViewPoint Eye Tracker system (Arrington Research Inc.; sampling rate: 50 Hz) and performed on-line visual inspection of the eye image to ensure that subjects adhered to the fixation instruction.

Hit rates. In the verbal conditions, we recorded our subjects answers with a MRI-compatible microphone (Optoacoustics Dual-Channel Microphone, Optoacoustics Ltd., Israel; sampling rate: 8 kHz). The manual responses were recorded with a button box with two buttons indicating either "same" (left button) or "different" (right button). All recordings were analyzed off-line using self-written scripts in MATLAB R2007b (The MathWorks, Inc.).

fMRI data acquisition. We collected the MR images with a 3-Tesla MR-scanner Trio gradient system and a twelve channel head coil (both: Siemens, Erlangen, Germany). A T1-weighted magnetization-prepared rapid-acquisition gradient echo (MP-RAGE) structural scan of the whole brain was assessed from each subject (number of slices: 176, slice thickness: 1mm, gap size: 0 mm, in-plane voxel size: 1 x 1 mm, TR: 2300 ms, TE: 2.92 ms, FOV: 256 x 256 mm, resolution: 256 x 256 voxels). Moreover, we acquired T2*-weighted gradient-echo planar imaging (EPI) scans (slice thickness: 3.2 mm, gap size: 0.8 mm, in-plane voxel size: 3 x 3 mm, TR: 2000 ms, TE: 30 ms, flip angle: 90°, FOV: 192 x 192 mm, resolution: 64 x 64 voxels, 32 axial slices). 330 EPIs were collected from each participant during five consecutive blocks of 11 minutes each. Cerebral cortex and most sub-cortical structures were completely covered by the EPI-volume but we did not record from the most posterior parts of the cerebellum in several of our subjects due to brain size.

Behavioral performance analysis.

We statistically analyzed our behavioral data using SPSS (IBM SPSS Statistics, version 22) and R (R Foundation for Statistical Computing). Furthermore, functional MRI data were analyzed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK) and R (R Foundation for Statistical Computing). The group size was guided by power

analyses performed on a similar, previously published fMRI dataset (Lindner et al. 2010), comparing working memory and motor planning planning activity in the frontal and parietal cortices. At preselected relevant parameters values (power of 0.80 and alpha of 0.05) this analysis suggested a sample size of 11 subjects (two-tailed tests).

Hit rates. To investigate if the performance level was influenced by the modality, the task and/ or the load level, we analyzed the percentage value of correct answers by means of a three-way repeated measures ANOVA with the factors 'modality' (2 levels: verbal vs. manual), 'task' (2 levels: memory vs. control), and 'load' (2 levels: 2 vs. 6).

fMRI data analysis.

Pre-processing. The pre-processing of our functional images was done in SPM8 (Wellcome Department of Cognitive Neurology, London, UK). Separately for each subject, we realigned all functional images by using the first scan of the first session as a reference. Then, we spatially coregistered the T1 anatomical image to the mean image of the functional scans and normalized our subjects' mean anatomical images to the SPM T1 template in MNI space (Montreal Neurological Institute). The resulting normalization parameters were also applied to all functional images for spatial normalization. Finally, all functional images were smoothed by using a Gaussian filter (6 x 6 x 8 mm^3 full-width at half-maximum) and high-pass filtered (cutoff period: 100 ms).

First-level analysis

In the subject-level fMRI analysis we first specified a GLM for the M2ST with the eight conditions (task x response type x load) and three trial epochs (cue+mask, delay, response) modeled as separate regressors. Load was additionally modeled in the control condition (defined as the number of symmetry test items visible in the response phase) but wasn't used for subsequent analyses as not relevant. Head motion parameters were included in the model as six independent regressors (one for each specific head rotation and translation). Fixation epochs weren't modeled directly and served in the model as an implicit baseline. For each subject we calculated statistical parametric maps showing an

effect of increase in BOLD signal by the working memory activity during the delay phase of "working memory" trials, i.e. delay M2ST > delay CT.

Group-level analysis

Group-level activity maps were plotted on the basis of a 2nd level random-effects analysis from the first level statistical parametric maps of activity related to the delay regressors in the CT and the M2ST. In the latter we additionally examined contrasts related to the effector modality effect. We thresholded statistical parametric maps at $p<0.001$, uncorrected for multiple comparisons to ensure that our exploratory analysis of the whole brain activity does not omit any substantial activity during the delay phase.. The resulting parametric maps were then overlayed on the standard MNI T1 template image as provided by SPM8 in order to anatomically define the regions of activity. Note that we used these maps only for visualization and aiding in selecting group-based coordinates for subsequent ROI selection in some individual subjects.

ROI analysis

We focused the analyses on comparing activity in specific cortical areas involved in our working memory task. For the analysis of signal amplitudes, we selected areas that showed statistically significant effect of increase in BOLD intensity during the delay phase of working memory trials (as compared to control trials), reflecting the working memory activity in single subjects. To these maps we applied a statistical significance threshold of $p<0.05$, corrected for family-wise error. The maps were then overlaid on each subject's T1 images, thus allowing precise assessment of their anatomical location. Whenever this threshold was too strict and did not yield any clusters of activation in a given subject, we used group coordinates to define a ROI. As we did not differentiate between the "response modality" at this stage (i.e. the maps were calculated for both modalities taken together), such approach ensured that our region-of-interest (ROI) selection was not biased in favor of our hypothesis (compare Kriegesorte, 2009). The ROIs were first defined as the local maxima of t value within major clusters of working memory related BOLD activity. In

particular, these were: left and right superior parietal lobule (SPL), left and right dorsal premotor cortex (PMd), left and right dorsolateral prefrontal cortex (DLPFC), left nad right ventral premotor cortex (PMv), and left and right anterior intraparietal sulcus (aIPS). To complete our ROI set and allow observing any task-unspecific effector preparation we included anatomically defined functional representations of hand (Yousry et al., 1997) and vocal organs (Simonyan and Horvitz, 2011) in the left primary motor cortex (labeled as M1h and M1m, respectively).

In the next step, for each of ROIs in each of our subjects we extracted normalized, mean beta weights related to every regressor, from a 4mm sphere around the ROIs center coordinate. For each ROI these beta weights were then statistically analyzed on the group level, using a repeated measures 2x2 ANOVA model, with factors response type x load in the M2ST. Moreover, we compared response type in the CT using a paired, two-tailed t-test. In addition to the beta analysis, we extracted and plotted BOLD-signal timecourses for each of our ROIs for all the conditions of interest, using custom protocols written in Matlab.

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General Discussion

Arbib, M. A. (2005). From monkey-like action recognition to human language: an evolutionary framework for neurolinguistics. Behav. Brain Sci. 28, 105-124-167.

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Statement of contributions

This thesis is partly composed of three manuscripts that have been or will be submitted for publication as peer-reviewed journal articles. The following persons contributed to those manuscripts:

Study 1

fMRI study on visual properties of planned actions.

Artur Pilacinski: designed the experiment, collected and analyzed data, wrote the manuscript.

Melanie Wallscheid: co-analyzed eye data.

Axel Lindner (thesis supervisor): co-designed the experiment, collected and analyzed data, co-wrote the manuscript.

Study 2

fMRI study on planning of reach trajectories.

Artur Pilacinski: designed the experiment, collected and analyzed data, wrote the manuscript.

Axel Lindner (thesis supervisor): co-designed the experiment, collected and analyzed data, co-wrote the manuscript.

Study 3

fMRI study on motor preparation modulation of working memory activity.

Artur Pilacinski: designed the experiment, collected and analyzed data, wrote the manuscript.

Melanie Wallscheid: designed the experiment, collected fMRI and behavioral data, analyzed behavioral and eye data, co-wrote "materials and methods".

Axel Lindner (thesis supervisor): aided in all the above steps, edited the manuscript.

Fotini Scherer aided in MRI scanning of volunteers in all the above studies.