PLANNING TO REACH GOALS

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ZUSAMMENFASSUNG

Alltäglich führen wir mühelos Zeigebewegungen zu Bewegungszielen in unserem Umfeld aus, beispielsweise wenn wir den Touchscreen unseres Telefons berühren, um einen Anruf anzunehmen. Um eine Zeigebewegung auszuführen und unsere Hand zu der gewünschten Position zu bewegen, erstellt unser Gehirn einen Bewegungsplan. Dieser Bewegungsplan erfordert unter anderem eine Transformation eingehender visueller Informationen in motorische Signale, die an die Muskeln gesendet werden. Ein *frontoparietales Netzwerk für Zeigebewegungen* ist entscheidend an der Bewegungsplanung beteiligt. Das Netzwerk umfasst den dorsalen prämotorischen Cortex (PMd) und Areale im posterioren parietalen Cortex (PPC). Es ist bisher weitgehend unklar, wo im frontoparietalen Netzwerk die Transformation visueller Informationen in motorische Signale stattfindet.

Das erste Ziel dieser Arbeit war es daher, zu untersuchen, ob die Areale des frontoparietalen Netzwerks eine visuelle oder motorische Repräsentation des Bewegungsziels aufrechterhalten. Hierfür wurde eine funktionelle Magnetresonanztomographie (fMRT)-Studie durchgeführt, in der Probanden einen visuellen Reiz dargeboten bekamen und nach einem Bewegungsplanungsintervall eine Zeigebewegung ausführten. Ein Bewegungsplanungsintervall zwischen der Präsentation des visuellen Reizes und der Bewegungsausführung ermöglicht es, die Bewegungsplanung zu isolieren und die planungsspezifischen Gehirnaktivierungen zu messen. Die anschließende Zeigebewegung wurde entweder zu der Position des visuellen Reizes ausgeführt oder zu der achsengespiegelten Position des Reizes. Diese Aufgabe erlaubt es, die motorische Repräsentation des Bewegungsziels von der sensorischen Repräsentation des visuellen Reizes zu dissoziieren. Zudem manipulierten wir, ob während des Planungsintervalls das Bewegungsziel voll spezifiziert oder unterspezifiziert war. So konnte die zweite Fragestellung dieser Arbeit untersucht werden, nämlich wie unterspezifizierte Bewegungsziele im frontoparietalen Netzwerk für Zeigebewegungen repräsentiert sind, und ob auch ein Bewegungsplan erstellt wird, wenn das Bewegungsziel unterspezifiziert ist.

In der ersten Studie nutzten wir univariate Analysen der fMRT-Daten. Während der Bewegungsplanung zeigten sich frontoparietale Aktivierungen, im PMd und in Arealen des PPC, wie dem superioren Parietallappen (SPL) und dem anterioren Sulcus intraparietalis (aIPS). Innerhalb dieses Netzwerks hielt der linke SPL das Bewegungsziel aufrecht. Wenn das Bewegungsziel unterspezifiziert war, waren nur (posteriore) parietale Areale aktiviert, allerdings mit geringerer Aktivierungsstärke.

In der zweiten Studie wurden die neuronalen Aktivierungsmuster weiterer frontoparietaler Regionen desselben Datensatzes mittels sensitiverer multivariater Analysen untersucht. Die Ergebnisse für die spezifizierten Bedingungen zeigten, dass frontoparietale Areale im PMd und SPL vorrangig das Bewegungsziel repräsentieren. Wenn das Bewegungsziel nicht spezifiziert war, war die Position des visuellen Reizes im PMd repräsentiert.

Zusammengefasst zeigen die Ergebnisse, dass frontoparietale Areale bereits während der Bewegungsvorbereitung eine motorische Repräsentation des Bewegungsziels aufrechterhielten. Dies war auch der Fall in Arealen, die anatomisch nahe dem visuellen Cortex und damit früh im visuell-motorischen Verarbeitungspfad lokalisiert sind. Die Ergebnisse unterstreichen die Rolle des frontoparietalen Netzwerks für die Aufrechterhaltung und, möglicherweise, den Aufbau eines Bewegungsplans. Solange das Bewegungsziel unklar ist, hielt der PMd eine sensorische Repräsentation des visuellen Reizes aufrecht, während Areale im PPC eine vorbereitende Aktivierung ohne räumliche Repräsentation aufwiesen. Die Befunde legen nahe, dass keine vollständige Bewegungsplanung stattfindet, wenn das Bewegungsziel nicht spezifiziert ist.

ABSTRACT

In our everyday life, we effortlessly reach towards goal positions in space, like the touchscreen of our phone to accept an incoming call. To do so, the brain sets up a movement plan that will be used to move our hand to the desired position. Among others, such a plan requires incoming visual information to be transformed into a motor command that will be sent to the muscles. On a cortical level, reach planning primarily involves a *frontoparietal reach network* comprising the dorsal premotor cortex (PMd) and areas in the posterior parietal cortex (PPC). It remains widely unclear where in the reach network the transformation from a visual to a motor representation of the reach goal takes place.

The first goal of this thesis was to examine whether frontoparietal reach regions maintain a visual or motor representation of the reach goal. To do so, we conducted a functional magnetic resonance imaging (fMRI) experiment in which participants saw a visual cue and had to reach after a delay either to its actual or to its mirrored position. This allowed for dissociating the sensory representation of the visual cue position from the motor representation of the reach goal position. By inserting a delay between stimulus presentation and reach execution we could analyze brain activation related only to reach planning. We further varied if the movement goal was fully specified or underspecified during the delay. We could thereby address the second main question of this thesis; how underspecified movement goals are represented in the frontoparietal reach network, and if frontoparietal reach regions are also engaged in reach planning when the movement goal is underspecified.

In the first study of this thesis, we used univariate fMRI analyses and found predominant activation in the PMd and in posterior parietal areas like the anterior intraparietal sulcus (aIPS) and the superior parietal cortex (SPL) during reach planning. Within this reach network, the left SPL encodes the inferred reach goal rather than the position of the visual cue. When the reach goal is underspecified, reach regions in the PPC are recruited, but at a lower activation level.

In the second study, multivariate pattern analysis was used on the same dataset to examine in more detail the characteristics of multiple regions within the reach network. In specified conditions, the PMd and regions in the SPL are again biased to maintain the

position of the reach goal rather than that of the visual cue. However, in underspecified conditions, only the PMd, but not areas within the PPC, represents the visual cue position.

Taken together, our results show that frontoparietal reach regions maintain a prospective motor code during reach planning. This highlights the crucial role of this network in maintaining and possibly also in setting up reach plans. When the movement goal is not yet specified, PMd maintains a sensory code rather than the reach goal, while PPC areas elicit non-spatial preparatory activation. This may suggest that the reach plan is only set up once the movement goal is specified.

Figures 1.1, 1.4, 2.2, 2.3, 2.4 and 3.1 show the Montreal Neurological Institute (MNI) 152 template MNI-Colin27 brain template (MNI, Montréal, Canada; Holmes et al., 1998) and were created using the Multi-image Analysis GUI (Mango, Research Imaging Institute, San Antonio, Texas, USA).

CONTENTS

1. THE ONSET

1.1 REACHING SEEMS SIMPLE

In our everyday life, we continuously interact with our environment by executing goal-directed movements towards objects surrounding us. For instance, when the mobile phone rings and one sees that his or her boss is calling, one effortlessly reaches for the phone and presses the touch screen to reject the call. *Reaching* refers to a pointing movement with an additional transport of the hand. In order to perform such a seemingly simple movement, we first need to set up a movement plan that will be used to activate our muscles and move our joints in order to bring our finger to the desired position. However, the plan for this action requires many processing steps.

Before planning a reaching movement to reject an incoming call, we need to perceive that our mobile phone is ringing, by either seeing a color/brightness change on the screen, hearing the ring tone, feeling the vibration, or a combination of those. Thereafter, the process of movement planning can begin. In order to plan a reaching movement towards a single position we need to obtain information about the spatial position of the phone and, more specifically, of the button that we want to press. We also need to integrate this spatial information, for instance with information about the position of our own hand. Even if we only consider these fundamental components of movement planning, the sensory information relevant for the movement needs to be integrated and transformed into motor commands, so that we can execute the desired reach to answer or reject the call. The necessary transformation from sensory to motor information involves cortical brain areas that form a network for reach planning.

1.2 THE BRAIN MAKES THE PLAN

When we want to reach for an object, we usually shift our gaze to its position. The visual signals are transmitted from our retina to the visual cortex, a brain structure responsible for processing visual information. The visual cortex comprises the occipital lobe, located at the posterior part of the brain (Figure 1.1). To reach out for an object, on the other hand, we rely on motor commands that are sent to our muscles. The motor commands are generated in the primary motor cortex (M1) and from there, they are sent to the spinal cord. M1 is located in the frontal lobe of the brain. To be suitable for the motor system, the visual input needs to be transformed to a motor output in between the visual and motor cortex. Two core brain structures are involved in this transformation: the dorsal portions of the premotor cortex (PMd), located in the frontal cortex just anterior to the M1, and the posterior portions of the parietal cortex (PPC; Figure 1.1), located between the visual and primary motor cortex. Due to its anatomical location in between sensory cortices, most importantly just anterior from the visual cortex, the PPC is an ideal hub for several aspects of movement planning, including visuomotor transformations. The PPC comprises the superior parietal lobule (SPL), the inferior parietal lobule (IPL), as well as the intraparietal sulcus (IPS). The frontal and posterior parietal areas involved in reach planning are collectively referred to as the *frontoparietal reach network* (Gail and Andersen, 2006).

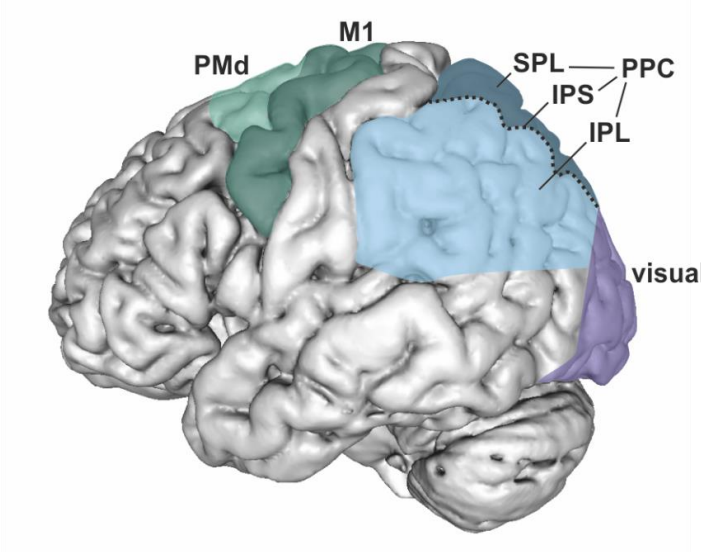

Figure 1.1: Schematic of brain areas involved in reach planning. The posterior parietal cortex (PPC) comprises the superior parietal lobule (SPL), the inferior parietal lobule (IPL), as well as the intraparietal sulcus (IPS), and is located anterior from the visual cortex. The dorsal premotor cortex (PMd) is located anterior from the primary motor cortex (M1) that sends motor commands to the spinal cord.

The essential role of the frontoparietal reach network in reach planning can be illustrated when parts of it are disrupted due to lesions. Optic ataxia for instance is a well-known neuropsychological symptom that occurs after damage to posterior parietal areas. Most patients with optic ataxia have difficulties reaching towards goals in the peripheral visual field (Rossetti et al., 2003) although their perceptual and motor abilities are preserved. Optic ataxia can be further characterized by errors in reaching movements towards goals in the contralesional visual field (*field effect*) and/or errors in movements with the contralesional hand (*hand effect*; Perenin and Vighetto, 1988; Khan et al., 2007; Blangero et al., 2008). It is worth noting that although misreaching can occur also to targets of other sensory modalities, the deficits occur predominantly for visual goals (Perenin and Vighetto, 1988; Blangero et al., 2007). These findings illustrate that optic ataxia may result from deficits in coupling visual input with motor output and they highlight the importance of PPC areas in the process of visuomotor integration.

Studies of single patients have shown that optic ataxia can result from either unilateral (Perenin and Vighetto, 1988; Blangero et al., 2007; Ferrari-Toniolo et al., 2014) or bilateral lesions to the SPL (Pisella et al., 2000, 2004). Nevertheless, more inferior PPC lesions can also lead to optic ataxia (Perenin and Vighetto, 1988). Reports on overlapping lesion sites in a larger sample of patients suggest the intraparietal sulcus (Perenin and Vighetto, 1988) or the parieto-occipital junction (Karnath and Perenin, 2005) as the neural basis of optic ataxia.

Still, the results concerning the neural correlates of optic ataxia are unclear, partly because the PPC lesions are typically widespread and they are located at slightly different anatomical locations, which makes it difficult to compare lesions across patients. As a result of these anatomical differences, there are also differences in the extent and character of functional impairments, such as the occurrence of visual field- and/or hand-effects in different patients. Although studies of optic ataxia patients reveal causal contributions of PPC areas to visuomotor integration, they do not allow for the characterization of precisely circumscribed anatomical areas. Such limitations can be overcome with experiments using electrophysiological recording techniques in non-human primates or neuroimaging techniques in healthy humans.

1.3 THE MACAQUE'S REACH NETWORK

Over the last few decades, the brains of non-human primates, like macaque monkeys, have been regarded as an adequate model of sensorimotor processes in the human brain. When it comes to tasks such as goal-directed movements, macaque monkeys are equipped with skills that are comparable to those of humans and are therefore suitable study subjects. Moreover, macaque monkeys can be subject to electrophysiological recordings that allow for measuring the current produced by neuronal populations (local field potentials), and for the recording of single neurons' firing rates. As a result, neuronal activity can be directly measured in precisely circumscribed brain areas, which gives an important insight into the neurophysiological processes underlying the preparation of movements.

Mountcastle and colleagues (1975) conducted one of the first studies reporting neuronal activity related to the movement behavior of macaque monkeys. In particular, different neuronal populations in area 5 and 7a of the PPC (Figure 1.2) not only respond during saccadic and smooth pursuit eye movements, as well as fixation, but also during passive arm movements, as well as when planning and executing active reaching movements within the immediate extrapersonal space (Mountcastle et al., 1975). These findings motivated numerous studies to investigate the specificity of monkey PPC areas for certain *effectors*, such as the limbs or eyes. For instance, are there regions that are selectively involved in planning and executing movements with the arms? A second important aspect of movement planning is *where* we move. Subsequent research has addressed the question of how areas of the PPC involved in movement planning represent movement goals.

A number of studies have suggested different areas of PPC, particularly in the SPL and along the IPS, for planning and executing movements with different effectors. One way to study effector selectivity is to test if and to what extent neuronal activity represents either the saccade goal or the reach goal. Snyder et al. (1997) examined effector-selectivity in the PPC using a saccade vs. reach paradigm. Their results revealed that the PPC is indeed involved in movement planning, but most interestingly that the activity in different PPC areas depends on the effector the monkey will use to perform the goal-directed movement. For instance, when the monkey has to plan and perform a saccadic eye movement, an area located at the lateral wall of the posterior half of the IPS, the lateral intraparietal area (LIP,

Figure 1.2) is strongly involved in encoding the saccade goal position. On the other hand, when the monkey has to perform a reaching movement, neuronal activity in another area posterior to LIP comprising parts of the medial wall of the intraparietal sulcus (area MIP; Figure 1.2) is strongly tuned to the spatial position of the reach goal. Reach goal encoding was taken as evidence for area MIP being involved in reaching movements and has since been confirmed in numerous studies (Gail and Andersen, 2006; Gail et al., 2009; Westendorff et al., 2010), also for reach sequences (Batista and Andersen, 2001). Moreover, MIP exhibits reach planning activity even if the exact reach goal position is still unknown (Calton et al., 2002), and also when the macaque is not instructed but freely chooses to perform a reach (Cui and Andersen, 2007). Area MIP has therefore been referred to as the parietal reach region (PRR; Snyder et al., 1998). In encoding the reach goal position, PRR neurons do not only take into account the absolute position of the goal. Rather, their firing rates are *gain modulated* by a combination of the reach goal and the hand position (Buneo et al., 2002) as well as the distance between eyes and hand (Chang et al., 2009). It is important to note that reach-related signals do not occur exclusively in PRR, and saccade-related signals do not occur exclusively in LIP (Snyder et al., 1997). Rather than speaking of *effector selectivity*, it is more appropriate to refer to regions as being *preferentially* or *dominantly* involved in or *related* to reaches or saccades.

One main characteristic of reach-related regions like PRR is the extent to which these regions are specialized for representing the reach goal positions and/or the arm to move. Recently, Yttri et al. (2014) inactivated PRR and showed deficits in reaching movements with the contralateral arm independent of the reach goal position, leaving reaches with the ipsilateral arm unaffected. This suggests that PRR specifically represents the arm for an upcoming reach. However, there is also evidence that inactivation of PRR yields specific deficits in reaching to goals contralateral to the lesion site comparable to the field-effect in optic ataxia (Hwang et al., 2012), indicating that the reach goal is represented more strongly in PRR than the effector. Possibly, these contradictory results occur due to differences in the *size* of the lesioned site. However, they may also be caused by differences in the anatomical *location* of the lesion. For instance, the most posterior parts of MIP were lesioned in the former study (Yttri et al., 2014), but the middle portions of MIP in the latter (Hwang et al., 2012). This illustrates the current debate about the anatomical location and extent of PRR.

It is important to note that PRR contains several reach-related cortical regions. Although most studies have focused on area MIP (Buneo et al., 2002; Cui and Andersen, 2007; Hwang et al., 2012), PRR may also be defined as including dorsal aspects of the parieto-occipital visual area 6a (V6a; Fattori et al., 2001) located anterior to the parieto-occipital sulcus (POS; Figure 1.2). In addition to the vague anatomical definition of macaque PRR, selective responses for reach planning have also been found for neurons in the dorsal portions of Brodmann area 5 (area 5d; Cui and Andersen, 2011), and in area AIP (Lehmann and Scherberger, 2013) that is located anterior to LIP, which was previously reported as grasp-selective (Murata et al., 2000). Considering these widespread reach-selective neuronal populations within PPC, it is reasonable to assume a whole network of reach regions throughout macaque SPL and IPS, rather than a single module specialized for reaching movements.

In accordance with their functional specialization for different effectors, the PPC regions also show different patterns of connectivity with frontal regions. Reach-related regions V6a and 5d as well as PRR exhibit the strongest connectivity with PMd via monosynaptical connections (Tanné-Gariépy et al., 2002), underlining the importance of PMd in reach planning and execution (Kalaska et al., 1997; Wise et al., 1997).

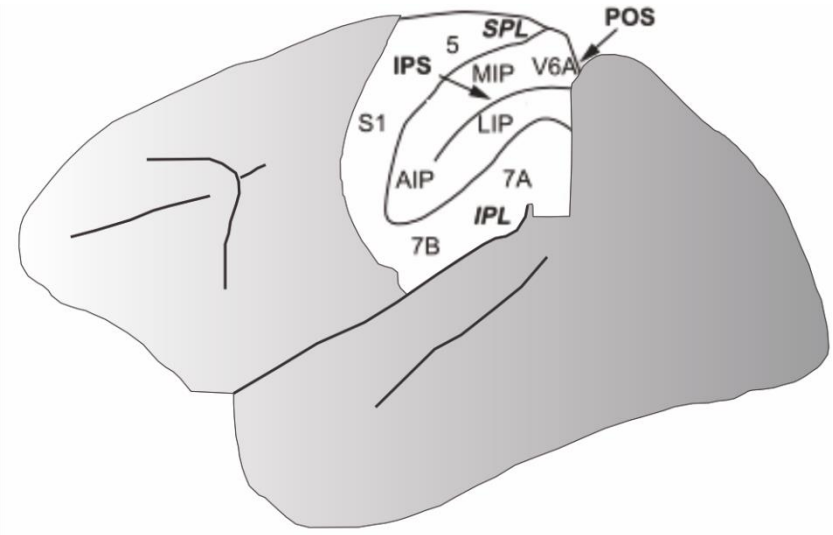

Figure 1.2: Lateral view of the macaque monkey brain showing the posterior parietal cortex (PPC) in white. The PPC is located posterior from the primary somatosensory cortex (S1), and anterior from the occipital cortex, from which it is divided by the parieto-occipital sulcus (POS). It comprises Brodmann areas 7A and 7B in the inferior parietal lobule (IPL), and Brodmann area 5 in the superior parietal lobule (SPL). Crucial for movement planning are the areas located along the intraparietal sulcus (IPS): the lateral intraparietal area (LIP) for saccades, the anterior intraparietal area (AIP) for grasping and reaching, and the middle intraparietal area (MIP) and visual area 6a (V6a) for reaches. Figure adapted from Culham and Kanwisher (2001).

In accordance with the findings in PPC, neurons in PMd encode goals for upcoming reaches (Cisek and Kalaska, 2002; Gail et al., 2009; Westendorff et al., 2010). Similar to PRR, gain-modulated neurons in PMd represent the reach goal relative to the position of hand and gaze (Pesaran et al., 2006). However, the PMd also encodes additional information required to set up a motor command such as the amplitude of the upcoming reach (Messier and Kalaska, 2000). Furthermore, the activity of PMd during movement execution resembles the activity in M1. For instance, PMd activity similar to M1 activity reflects arm orientation and reach trajectory (Scott et al., 1997). Moreover, the preferred direction of neurons in both PMd and M1 representing the reach goal position changes in response to changes of arm orientation (Caminiti et al., 1991). The functional properties of the PMd highlight that in addition to its crucial role in setting up reach plans, the PMd is also important for reach execution and shows a stronger motor-based character than PPC. In accordance, PMd is not only connected to M1 (Dum and Strick, 2005), but is also directly connected to the spinal cord (He et al., 1993).

Taken together, electrophysiological recordings from the macaque monkey show that a frontoparietal network comprising the macaque PMd and PPC areas is involved in reach planning and execution, for instance by representing the position of the goal for an upcoming reach. These findings contribute to our current understanding of neurophysiological mechanisms underlying visuomotor processing. However, the extent to which the macaque and human brain regions are anatomically and functionally equivalent is still under debate (Passingham, 2009). Despite their similarities, macaque and human PPC also show strong anatomical differences (Van Essen et al., 2001). For instance, Brodmann area 7 is located inferior from the IPS in macaques, but superior from the IPS in humans (Figure 1.2 and 1.5). Therefore, the extent to which findings in macaque monkeys can be transferred to humans is unclear.

1.4 THE HUMAN'S REACH NETWORK

While electrophysiological recordings in macaque monkeys allow for the precise characterization of single cell firings as well as responses of neuronal populations at a very high temporal resolution, studies typically examine only a few cortical regions. Moreover, the recordings require electrodes to be implanted in the brain which is not adequate for

studying healthy human brains and has so far only been done in small samples of specific patient groups, such as in a recent study of tetraplegic patients (Aflalo et al., 2015).

On the other hand, non-invasive imaging techniques, such as functional magnetic resonance imaging (fMRI), allow for measuring correlates of brain responses throughout the whole brain, although at a lower temporal resolution than electrophysiological measures. Magnetic resonance imaging (MRI) makes use of the fact that the nuclei of hydrogen atoms have magnetic properties. In an MRI scanner, these nuclei are aligned along the direction of a strong static magnetic field and then they are exposed to a radio frequency magnetic pulse that causes the nuclei to absorb energy and thereby produce a measurable signal. In fMRI, changes in the local oxygenation of blood in the brain are measured, which are assumed to reflect the amount of brain activity; the more active a brain region, the more blood is sent to this region, which leads to a surplus in local blood oxygen. Relative changes in the amount of oxygenated and deoxygenated blood also go along with differences in magnetic susceptibility that can in turn be used to map which brain regions are active. This effect is referred to as the blood oxygenation level dependent (BOLD) effect (Ogawa et al., 1990).

For each individual volume element (*voxel*) of the brain, conventional univariate fMRI analyses determine if changes across time in the measured BOLD signal are related to a particular event, and are significantly more active in response to this event as compared to a baseline condition or another condition. By looking at individual activated voxels or connected clusters of activated voxels, it is possible to map activated regions throughout the brain or to determine the averaged activation within a particular region of interest (Figure 1.4).

To capture the BOLD signal related to movement planning, delayed movement tasks have been used in several studies. Again, monkey research forms the basis of this strategy. The PRR as a core region for reach planning exhibits persistent activity, thereby maintaining the reach goal position even if the onset of the reach movement itself was delayed by several seconds and the reach goal was not visible anymore (Klaes et al., 2011). Likewise, human brain regions associated with reach planning, such as the SPL and PMd, maintain movement goal positions throughout a delay of up to 20 seconds (Toni et al., 2002; Connolly et al., 2002; Lindner et al., 2010; Medendorp, Goltz, and Vilis, 2005, 2006). Moreover, inserting a delay between the presentation of the sensory input, such as a visual cue position, and the movement execution has the advantage of dissociating sensory

representations from motor related representations (Rosenbaum, 1980). Importantly, using such a manipulation for studying sensorimotor processing does not lead to an artificial situation. Although humans usually perform *visually-guided reaches* towards a visually present object, in many cases we need to remember the position of an object, and only reach to the remembered goal position after a delay, which is referred to as *memory-guided reaching*. For instance, one can keep the position of the ringing mobile phone in memory and reach for it, even if in the meantime one is talking to and looking at a person nearby.

Using univariate analyses of fMRI data, a network of human frontoparietal regions has been robustly shown to be involved in both reach planning (Toni et al., 2002; Beurze et al., 2007, 2009; Lindner et al., 2010) and execution (Fabbri et al., 2010, 2014). As shown schematically in Figure 1.1, this network typically comprises the PMd and the PPC, particularly its areas SPL and IPS. Nevertheless, neurons in reach-related regions may also be active during saccade planning, as has been shown in macaque monkeys, where reach-related regions also exhibit some activity related to saccade planning (Snyder et al., 1997). One may then ask to what extent the regions of the human frontoparietal reach network are specific to reach planning.

Human frontoparietal networks for arm and eye movements seem to largely overlap, since these regions show activation during planning and execution of both saccade movements and reaching or pointing movements. Yet reaching movements usually recruit a more widespread network at a higher level of activation such as the PMd, the middle IPS and anterior IPS (aIPS), and the SPL, particularly its medial parts (the precuneus; PCu) extending to the parieto-occipital cortex (Astafiev et al., 2003; Filimon et al., 2009; Beurze et al., 2009; Medendorp, Goltz, Crawford, and Vilis, 2005). To quantify the extent to which frontoparietal regions are specifically involved in reach planning, Beurze et al. (2009) calculated index maps representing the degree to which a region shows stronger activation during reach or saccade planning in humans (Figure 1.3). A preference for reaches was found in the posterior parietal and frontal regions, including the PMd. The preference for reaches becomes stronger in frontal regions, such as the PMd (Beurze et al., 2009; Medendorp, Goltz, Crawford, and Vilis, 2005). These regions are considered to be dominantly involved in reach planning, i.e. they are *reach-related*. It is noteworthy that reach-dominance was determined by comparing reaches and saccades in most studies. A recent study additionally investigated foot movements and found limb-selective rather than reach-selective regions in PPC (Heed et al., 2011). Moreover, effector relatedness may not

be a fixed property in PPC and PMd, but it may rather evolve throughout the process of movement planning. When only the effector but not the movement goal is presented, SPL, IPS, and PMd are recruited, but in an effector-independent manner. Only when the movement goal is also specified, do these regions exhibit effector dominant representations with a preference for hand over eye movements in PPC and PMd as depicted in Figure 1.3 (Beurze et al., 2009).

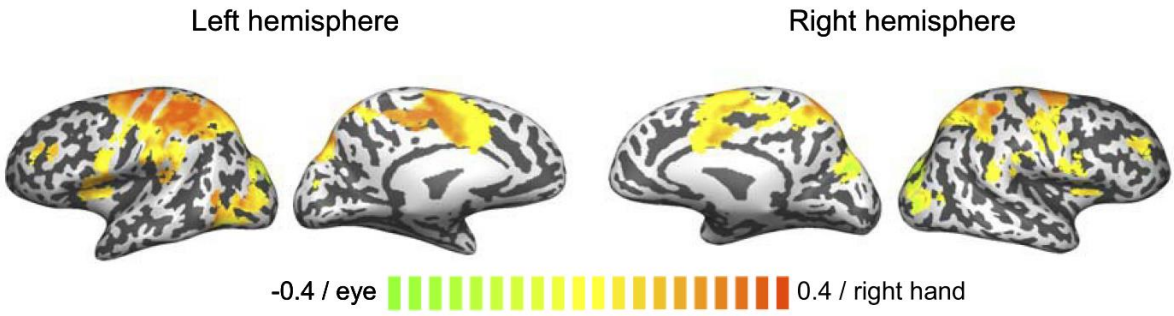

Figure 1.3: Effector-dominance in the network involved in movement planning (Beurze et al., 2009). Significantly stronger activations for reach planning than saccade planning can be seen in the dorsal premotor cortex, in the supplementary and cingulate motor area, in the primary motor cortex, and in the posterior parietal cortex along the intraparietal sulcus. All of these regions show a preference for reaches over saccades.

As described above, traditional univariate fMRI analyses reveal the average activation within a particular region. But they do not take into account the information contained in distributed activation patterns, so they may not be sensitive enough to discover potential differences between effectors. Multivoxel pattern analysis (MVPA) of fMRI data, on the other hand, is well suited to examine the informational content represented in spatial patterns of activation for different experimental manipulations, such as reach versus saccade planning. When one performs MVPA, a classifier is trained on a subset of data in order to learn how voxel patterns represent different conditions (Haxby et al., 2001; Kamitani and Tong, 2005). Then, another subset of the same dataset is presented to the classifier and it is tested on whether it can correctly classify the voxel pattern as representing one of the learned conditions, such as reach or saccade planning. In other words, while univariate analyses of fMRI data reflect the strength of *activation*, multivariate approaches assess the pattern of activation and thus the *information* contained within a region (Figure 1.4). During movement planning, regions in the SPL and IPS, as well as PMd, represent whether the upcoming movement will be a reach or a saccade

(Gallivan, McLean, Smith, et al., 2011). This result indicates that arm and eye movements are represented differently, but information about which effector is predominantly represented is lacking. To gain a better understanding, it is necessary to combine univariate and multivariate fMRI analyses to quantify how strongly a representation is involved in a certain process.

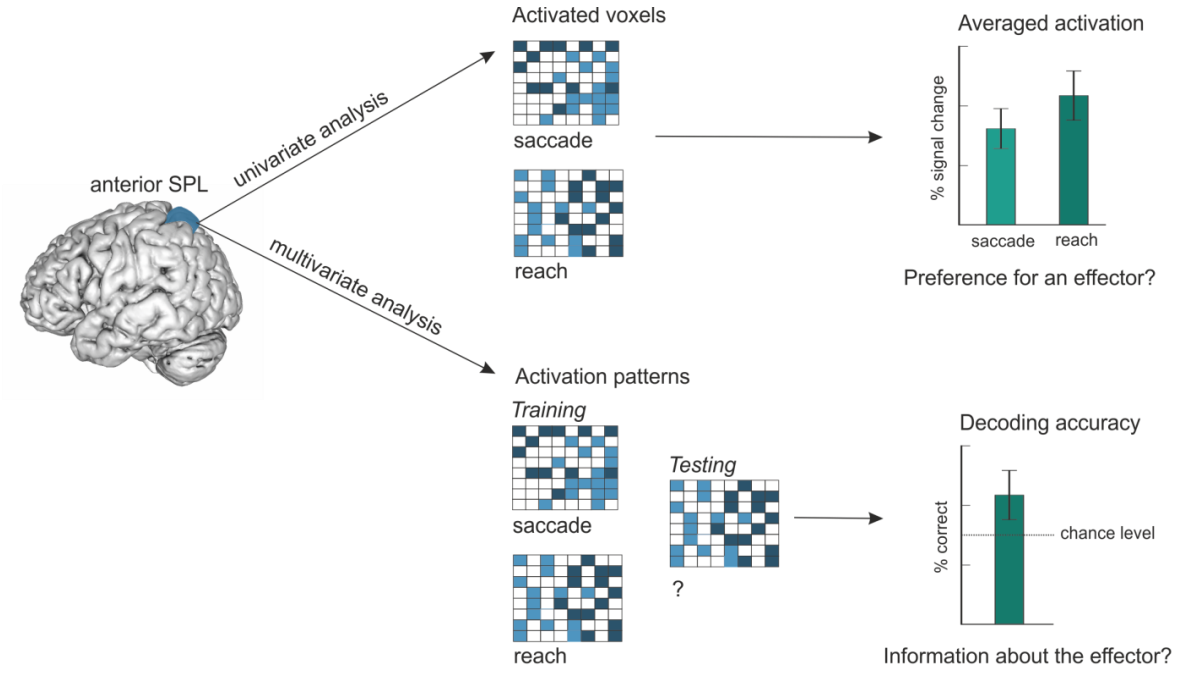

Figure 1.4: Schematic of fMRI analyses in a region of interest (ROI). Effector specificity can be studied via univariate or multivariate analyses in an exemplary ROI, such as the anterior SPL. In the case of a univariate analysis, one possibility is to determine the activation level for each individual voxel (depicted in white, light blue, and dark blue) and then average it across all voxels contained in the ROI. The averaged activation can then be compared across conditions to determine if the region shows a preference for one of the conditions (here, it is between reaches and saccades). In a multivariate analysis, such as multi-voxel pattern analysis, on the other hand, a classifier is trained on a subset of data in order to learn how voxel patterns represent different conditions (Kamitani and Tong, 2005) like reach or saccade planning. Then, another subset of the same dataset is presented to the classifier and it is tested on whether it can correctly classify the voxel pattern as representing one of the learned conditions. If the obtained decoding accuracy is significantly above chance, one can conclude that the region contains information about the effector.

Taken together, previous research shows that there are also areas dominantly related to reach preparation and execution in human PPC. Early human fMRI studies have focused on identifying a homologue of macaque reach-related regions within the PPC. For PRR, they found designated regions in Brodmann area 7 in the SPL (SPL7) for pointing, i.e. finger movements towards a position without an arm movement (Astafiev et al., 2003; Connolly et al., 2003). More recent studies, however, question the concept of one reach-

related region in human PPC (Filimon et al., 2009; Gallivan, McLean, Smith, et al., 2011). As in macaque PPC with reach-related neurons in PRR, V6A, AIP, and area 5d (Snyder et al., 1997; Fattori et al., 2001; Cui and Andersen, 2011; Lehmann and Scherberger, 2013), human PPC likewise contains a complex of reach regions. A broad distinction can be made between two clusters in the SPL7.

A posterior SPL7 cluster comprises the posterior PCu and posterior IPS (Prado et al., 2005; Filimon et al., 2009). This cluster often extends to the superior parieto-occipital cortex (SPOC; Gallivan et al., 2009; Cavina-Pratesi et al., 2010) just anterior or even posterior to the parieto-occipital sulcus (POS). Based on probabilistic histological maps (Eickhoff et al., 2007), this cluster most often falls into the posterior BA7, being labelled as the SPL7P. SPOC processes information not only about the transportation of the hand in reach and grasp movements (Cavina-Pratesi et al., 2010), but also about an object's reachability (Gallivan et al., 2009), the hand orientation (Monaco et al., 2011), as well as the grasp axes (Monaco et al., 2014) for grasping movements. Therefore, SPOC has been discussed as a putative human homologue of macaque area V6A (Gallivan et al., 2009), which not only contains reach-related neurons, but also neurons selective for different grip types (Figure 1.5; Fattori et al., 2010).

An anterior SPL7 cluster is also located medially, in the anterior precuneus (aPCu), sometimes extending to the middle portions of medial IPS (Prado et al., 2005; Filimon et al., 2009; Gallivan, McLean, Smith, et al., 2011; Gallivan, McLean, Valyear, et al., 2011; Bernier et al., 2012). The corresponding probabilistic histological label for this anterior part of BA 7 is SPL7A. Area SPL7A, labelled 'human PRR' by Connolly et al. (2003), likewise plays a crucial role in planning and executing reaching and pointing movements (Figure 1.5; Connolly et al., 2003; Fernandez-Ruiz et al., 2007; Bernier et al., 2012), with and without visual feedback from the hand (Filimon et al., 2009), and it is even engaged in imagined and observed reaching (Filimon et al., 2007).

How do the SPL regions functionally differ from each other? It has been discussed that the SPL exhibits a visual to somatosensory gradient with the posterior cluster relying more on visual input, making it a visuomotor region mostly involved in visually-guided reaches (Filimon et al., 2009). The anterior cluster relies more on proprioceptive information, such as in reaching with closed eyes (Filimon et al., 2009). Similarly, a gradient for the representation of movement goal versus effector representation has been suggested (Beurze et al., 2009), with posterior clusters exhibiting a stronger representation

of the movement goal position (left or right visual field), while the anterior cluster shows a stronger representation of the effector to move (left or right arm, as opposed to the eye). Although these regions encode the movement goal (Beurze et al., 2009), it remains unclear if they weight the visual or motor components differently in their representation of the reach goal.

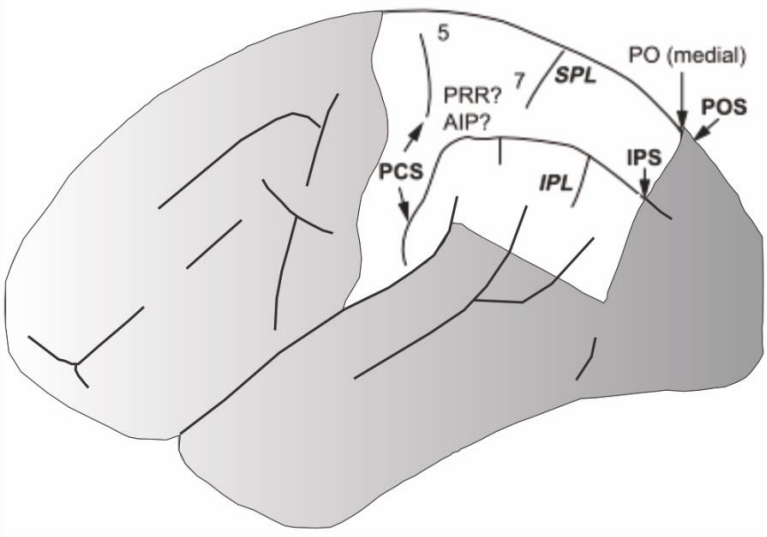

Figure 1.5: Lateral view of the human brain showing the posterior parietal cortex (PPC) in white. The PPC is located posterior from the postcentral sulcus (PCS), and anterior from the occipital cortex from which it is divided by the parieto-occipital sulcus (POS). It comprises Brodmann areas 7 and 5 in the superior parietal lobule (SPL), the inferior parietal lobule (IPL), and the intraparietal sulcus (IPS). The regions located in the SPL are particularly crucial for movement planning. A putative human homologue of macaque PRR is sketched superior from the IPS in the anterior portions of SPL area 7. Putative human area AIP may be located in the anterior parts of the intraparietal sulcus (IPS). The homologue of area V6A (not visible here) is presumed to be located in the medial portions of SPL7 extending to the parieto-occipital region (PO). Figure adapted from Culham and Kanwisher (2001).

In addition to the SPL clusters described above, reaching activates the aIPS (Filimon et al., 2009; Lindner et al., 2010). The aIPS shows stronger activation during grasping even without transporting the arm towards the object (i.e. only opening and closing the grip to grasp an object). It has therefore been suggested that the aIPS may be the human homologue of macaque grasp-selective region AIP (Figure 1.5; Culham et al., 2003; Cavina-Pratesi et al., 2010; for a review see Culham et al., 2006). However, as aIPS also responds to mere arm transport without a grip component, it is unlikely that it is exclusively involved in grasping. Instead, the area may play a more general role in visuomotor control, such as in the on-line control of movements (Tunik et al., 2005; for a review see Tunik et al., 2007).

Taken together, previous research has ascribed functional differences to the regions within the frontoparietal reach network. Putative functional differences among these regions with regards to spatial encoding processes are mostly unclear. That is, do different regions maintain a visual or motor representation of reach goals during reach planning? To address this question, it is essential to dissociate visual and motor representations from each other.

1.5 WHAT YOU SEE OR WHERE YOU MOVE?

In the previous sections, we considered one of the simplest cases of movement planning: planning a reach towards a visually present or memorized goal. However, movements can also be shaped by the context in which a movement goal is placed. It is then important to voluntarily and flexibly adjust our actions to this context. For instance, it is easy to reach for the button of a phone and reject a call, but rejecting the call may only be the desired action in certain situations, like when one's boss is calling. If a friend's name is on the screen, one would rather press the accept button. The same visual input (seeing an incoming call on the screen of the phone) can thus lead to different actions depending on the context (movement of one's finger to one button or the other and accepting or rejecting the call).

The pro-/anti-movement task (Hallett, 1978) is a well suited task to set identical visual inputs into different contexts and, thereby, manipulate the desired motor output. In this task, participants see a visual cue and need to combine it with a context rule in order to infer the movement goal. These context rules either require performing a pro-movement towards the position of the visual cue or an anti-movement to its mirrored position. Pro-movements require a direct sensorimotor transformation because the visual cue position corresponds to the movement goal position. However, for anti-movements the movement goal position is dissociated from the visual cue position. In other words, anti-movements require the suppression of the intuitive pro-movement, as well as the voluntary generation of a movement towards the mirrored position. Under these requirements, the pro-/anti-movement task is well suited to study sensorimotor transformations during the planning of eye and arm movements.

In an immediate reach task, anti-reaches yield longer reaction and movement times and are less precise, as compared to pro-reaches (Westendorff and Gail, 2011). On a

cortical level, anti-pointing causes higher activation in SPL and IPL (Connolly et al., 2000). These behavioral and neurophysiological effects may reflect the additional cognitive processes of movement suppression and re-planning that are required before executing an anti-movement. However, by inserting a delay between the presentation of the instructing cues (the visual cue and the rule cue) and the movement execution, these behavioral differences can be reduced and the advantage of dissociated visual cue and movement goal positions can still be exploited. As a result, a delayed pro-/anti-movement task is ideally suited to study preparatory activation and its nature. Does the activation reflect a retrospective sensory code, the visual cue position, or a prospective motor code, the movement goal position?

Several electrophysiological studies in macaque monkeys used this task design and demonstrated that some neurons in both PMd and PRR encode the position of the visual cue until the context rule cue that specified the reach goal appeared. Importantly, once the context rule is presented and the movement goal is specified, the neurons may dynamically switch to encode the reach goal position (Figure 1.6; Gail and Andersen, 2006; Gail et al., 2009; Westendorff et al., 2010; Klaes et al., 2011). The tuning properties of populations in PMd and PRR are thus not fixed to either the visual cue or reach goal. Rather, they vary throughout the process of reach planning, and their tuning properties are also dependent on the amount of information available.

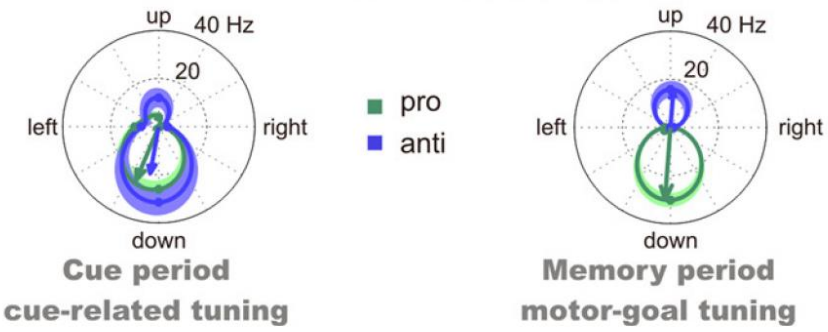

Figure 1.6. Directional tuning of a PRR example neuron (Westendorff et al., 2010). This example motor-goal neuron shows a dynamic switching from cue- to motor-related tuning. The left polar plots show that the neuron is directionally tuned for the visual cue position (down) in both pro- and anti-trials when only a visual cue is known (cue period). During a memory period, when the context rule (pro or anti) is known, the neuron is directionally tuned for the motor goal, in opposite directions in both the pro- and anti-trials (right plot).

Interestingly, PRR shows stronger directional tuning for directly cued pro-reaches, while PMd prefers anti-reach goals (Gail et al., 2009). The context rule thus differently modulates neuronal activity in the two regions and is interpreted as a more stimulus-driven representation of automatic reach plans in PRR as opposed to a predominant representation of inferred movement goals in PMd.

For reach execution, it is known that the SPL is sensitive to both the movement direction (Fabbri et al., 2010, 2014) and the movement goal position (Barany et al., 2014). This region may be involved in sensorimotor transformations as it represents both the input (the visual movement goal position) and the output (the movement direction) to these transformations. PMd, on the other hand, does not contain representations of the movement goal position. It only contains representations of the movement direction, indicating that it may be more important for motor-related than for sensory-related features (Barany et al., 2014). It is noteworthy that the described results are based on the reach execution phase, so the findings may have been biased towards a motor representation.

How the reach goal is encoded during reach planning remains widely unclear, particularly with regard to putative differences between regions within the frontoparietal reach network during assessment of the visual and motor components of the reach goal. For instance, one may hypothesize that posterior parietal regions located near the visual cortex maintain visual representations, while the PMd is located anterior to M1 and may be more motor-related. If a prospective motor code (the reach goal) rather than a retrospective visual code is maintained in frontoparietal regions, this suggests that the regions may be involved in maintaining and potentially setting up reach plans. Yet, it would still be unclear how much information is necessary to set up a movement plan.

1.6 PLANNING TO REACH AMBIGUOUS GOALS

As movement planning relies on the integration of numerous different pieces of information, it is important to understand what happens when one of these pieces is missing. Coming back to the previous example, one would normally always reject a call from one's boss, but always accept a call from a friend. But what happens if one only hears the phone ringing before seeing the screen to realize who is calling? One cannot be sure whether to accept or reject the call before looking at the screen. If the available information is not enough to specify one reach goal, it may be that movements towards both the reject

and accept button are planned simultaneously. Alternatively, reach planning may be delayed until all necessary information is given (seeing the name on the screen) and the reach goal is specified.

Several behavioral studies in humans have addressed this issue using paradigms in which participants were presented with multiple potential reach goals and asked to start their arm movement before the final reach goal was cued (C. S. Chapman et al., 2010; Stewart et al., 2013; Gallivan et al., 2016). Results showed that in ambiguous situations, movement characteristics, such as the reach direction, correspond to an average of movements towards each of the targets presented alone (C. S. Chapman et al., 2010). The authors suggest that this averaged trajectory reflects both the number and the position of all potential movement targets. In addition to averaged reach trajectories, two competing movement goals with different orientations cause an averaged wrist orientation until one of the goals is cued as the final movement goal (Stewart et al., 2013). However, these results leave unclear whether both competing movement plans are fully specified or if one movement plan is specified based on averaged visual-spatial target information. To test both putative hypotheses, Stewart et al. (2014) introduced an obstacle close to one of two possible target positions. The obstacle's position led to a rotation of the initial movement trajectory away from the obstacle. Thus, the movement vector is not just a mere averaged visual-spatial representation of both reach goals, but a motor average of competing movement plans. These findings were interpreted as a simultaneous specification of all potential movement plans, supporting previous reports from electrophysiological studies in macaque monkeys.

Cisek and Kalaska (2002, 2005) were one of the first to demonstrate that neurons in macaque PMd fire when one of two potential reach goals is near their preferred direction. The responses of single neurons were significantly weaker compared to trials with only one reach target at the neuron's preferred direction. Yet at the population level both potential reach directions were encoded until one of the two was selected as a final reach goal. Once the reach goal was specified, neurons tuned for the direction of the goal increased their firing rate while the firing of neurons tuned towards the non-selected potential target was suppressed. Similar results have since been obtained in PRR (Cui and Andersen, 2007; Klaes et al., 2011), and were placed into a theoretical framework, the *affordance competition hypothesis* (Cisek, 2007). According to this hypothesis, frontal and parietal neurons maintain internal representations (*affordances*) for all currently available reach

targets. Importantly, neurons with different directional preferences are mutually inhibiting each other, thus competing with each other, until information biasing this competition towards one of the two goals reaches the respective population from cortical or subcortical regions (Cisek, 2007). It is important to note that this hypothesis does not apply to all reach-related regions in macaque PPC. For instance, area 5d differs from PRR in that it only encodes reach plans after a decision about the movement goal has been made (Cui and Andersen, 2011).

How do macaque PMd and PRR interact when multiple reach goals are available? When selecting among multiple reach goals, activity in PMd populations rises significantly earlier than in PRR, while reaching towards one cued target produces approximately simultaneous activation in PMd and PRR (Pesaran et al., 2008). Also, when a reach goal needs to be remapped, the movement goal representation arises earlier in PMd and significantly later in PRR, presumably because movement goal selection in PMd triggers a reorganization of network activity in PRR towards a movement goal representation (Westendorff et al., 2010). These findings highlight the role of PMd in reach goal selection.

How do reach regions in the human brain behave when the information necessary to plan a movement is ambiguous? Evidence for the simultaneous specification of multiple movement plans comes from an electroencephalographic (EEG) study showing that delay phase activity in (pre)motor cortex is inversely scaled with the number of possible reach goals (Praamstra et al., 2009). This is presumably caused by mutually suppressive interactions between cell populations encoding different movement directions, as suggested by the affordance competition hypothesis (Cisek, 2007).On the other hand, results from an fMRI study with separate cues for the movement goal and the effector (left vs. right arm) showed that conditions in which the effector was specified but the visual movement goal was unknown yield activation in reach-related regions of the PPC (Beurze et al., 2007). However, activations were stronger and broader when both the effector and the movement goal were specified. The authors interpreted these findings as an incomplete state of sensorimotor integration (Beurze et al., 2007), contradictory to the behavioral and electrophysiological studies described above. Similarly, Bernier et al. (2012) cued the effector (left vs. right arm) either before or simultaneously with the presentation of the movement goal. They tested whether frontoparietal reach regions represent the movement goal for both arms when the effector is unknown, or if the movement goal is only formed after the information about the effector is given. They found evidence for the latter case and

concluded that a motor plan is specified only if both the movement goal and the effector information are given. Thus, the specification of the effector to move seems to be necessary to set up a reach plan.

As pointed out above, evidence from behavioral (C. S. Chapman et al., 2010; Stewart et al., 2013; Gallivan et al., 2016) and electrophysiological studies (Praamstra et al., 2009; Tzagarakis et al., 2010; Rawle et al., 2012) instead implies the simultaneous specification of multiple reach plans. However, in these studies, only the movement goal was unknown, while the effector to move was known. This is a crucial difference to the study of Bernier et al. (2012) and suggests that uncertainty about the effector may have a stronger influence on sensorimotor integration than uncertainty about the movement goal. Hence, there is mixed evidence on whether multiple movement plans are set up in parallel when the movement goal is ambiguous. It remains to be answered if and how reach related regions represent ambiguous movement goals.

A delayed pro-/anti-reach task is suitable to introduce different pre-cueing conditions to manipulate the level of movement goal specification (Westendorff et al., 2010). When presenting both the visual cue and the context rule before the delay, the reach goal can be inferred and is specified. On the other hand, when only the visual cue position but not the context rule is known, the reach goal remains ambiguous, because it is unclear whether a pro- or anti-reach is required. The task allows addressing the questions if the visual cue position is sufficient to set up a movement plan, and how underspecified reach goals are represented in the human brain.

1.7 OUTLINE

Specifying the goal for an upcoming movement is essential for successfully executing reaches. Previous studies have emphasized the role of a frontoparietal network in reach planning, particularly in integrating and transforming sensory information to set up and maintain movement plans (Beurze et al., 2007, 2009; Filimon et al., 2009; Lindner et al., 2010; Bernier et al., 2012). The characteristics of different regions of the human frontoparietal reach network are still poorly understood. In this thesis, I address the question of whether certain regions, particularly in PPC, are more specialized for visual or for motor information. Furthermore, it remains unclear how much information is necessary to set up a reach plan. Are regions within the reach network engaged in movement planning

when the movement goal is underspecified? Answering this question can give further insight into the process of sensorimotor integration.

We conducted an fMRI-experiment in which participants planned and performed right-arm reaches in a delayed pro-/anti-reach task. We also introduced different pre-cueing conditions to manipulate the level of movement goal specification. In specified conditions, the context rule that was required to infer the movement goal was presented right after the visual cue and before the delay, resulting in a specified movement goal. In underspecified conditions, on the other hand, only the visual cue was presented before the delay. As the context rule was not yet presented, the movement goal remained underspecified throughout the delay, since the required movement could either be a pro-reach or an anti-reach. The analyses were based on the delay, capturing reach planning activation and excluding reach execution. The two studies presented in this thesis differ in the analyses of the fMRI data (univariate vs. multivariate).

For the first study, presented in chapter 2, we used univariate analyses of fMRI data to investigate whole brain activation clusters in conditions with specified or underspecified reach goals. Moreover, we examined signal strength in designated regions of interest (ROIs) for reach planning, in particular the SPL and the PMd, to determine whether these regions maintain the visual cue or the movement goal position.

In the second study, presented in chapter 3, we focused on the spatial information contained in the voxel patterns within several ROIs. As MVPA has been shown to detect more subtle characteristics of spatial encoding processes during movement execution (Fabbri et al., 2014; Haar et al., 2015) and thus may reveal different results than univariate analyses, we applied this approach to refine and extend our previous study. In this study, we examined several regions of the PPC to account for potential functional differences. Thereby, we extend the results of the first study not only by focusing on the informational content, but also by determining the characteristics of multiple reach regions in the SPL and aIPS of the PPC, as well as the PMd.

2. ACTIVATION IN THE REACH NETWORK

A similar version of this manuscript has been published as:

Gertz, H. & Fiehler, K.(2015). Human posterior parietal cortex encodes the movement goal in a pro-/anti-reach task. Journal of Neurophysiology, 114, 170–83.

Previous research on reach planning in humans has implicated a frontoparietal network, including the PCu, a putative human homologue of the monkey PRR, and the PMd. Using a pro-/anti-reach task, electrophysiological studies in monkeys have demonstrated that the movement goal rather than the position of the visual cue is encoded in PRR and PMd. However, if only the effector but not the movement goal is specified (underspecified condition) the PRR and PMd have been shown to represent all potential movement goals. In this fMRI study, we investigated whether the human PCu and PMd likewise encode the movement goal, and whether these reach-related areas also engage in situations with underspecified compared to specified movement goals. By using a pro-/anti-reach task, we were able to spatially dissociate the position of the visual cue from the position of the movement goal. In the specified conditions, pro- and anti-reaches activated similar parietal and premotor areas. In the PCu contralateral to the moving arm, we found directionally selective activation fixed to the movement goal. In the underspecified conditions, we observed activation in reach-related areas of the posterior parietal cortex, including PCu. However, the activation was substantially weaker in parietal areas and lacking in PMd. Our results suggest that human PCu encodes the movement goal rather than the position of the visual cue if the movement goal is specified and even engages in situations when only the visual cue but not the movement goal is defined.

2.1 INTRODUCTION

Previous research in monkeys has identified two regions being crucially involved in reach planning: the PRR (Snyder et al., 1997; Batista and Andersen, 2001; Gail and Andersen, 2006; for a review see Andersen and Buneo, 2002) and the PMd (Crammond and Kalaska, 1996; Cisek and Kalaska, 2002, 2005). The PRR is located at the medial bank of the intraparietal sulcus (Snyder et al., 1997) and receives direct input from extrastriate visual areas and projects to the PMd (Johnson et al., 1996; Tanné-Gariépy et al., 2002; for a review see Wise et al., 1997). It is thus an important interface between sensory and motor cortices (Mountcastle et al., 1975). A subset of PRR neurons codes both the movement goal for an action and the effector to perform the action, whereas other subpopulations fire in the absence of spatial movement goal information if only the effector is specified and vice versa (Calton et al., 2002). The PMd has likewise been shown to integrate positional information of the movement goal and the effector (Hoshi and Tanji, 2006). Using target-selection tasks, it has been demonstrated that PMd neurons simultaneously encode multiple movement goals if more than one potential reach goal is present (Cisek and Kalaska, 2002, 2005). As soon as the correct movement goal is specified the corresponding directional signal is enhanced while the signals of the non-chosen movement goals are suppressed. Thus, both areas the PRR and the PMd which are reciprocally connected (Johnson et al., 1996) contribute to sensorimotor integration.

A recent inactivation study in PRR found lesion effects specific to contralateral limb movements but independent of the spatial position of the reach goal (Yttri et al., 2014). Based on this result, the authors suggested limb-specific movement planning in area PRR and therefore characterized the PRR as a motor area situated early in the visuomotor pathway. However, other inactivation studies observed stronger lesion effects in a region slightly anterior to PRR for reach goals presented contralateral to the injection site arguing for target-selectivity (Hwang et al., 2012; Battaglia-Mayer et al., 2013).

In contrast to target-selection tasks, rule-selection tasks have been applied to answer the question whether PMd and PRR neurons represent the position of the visual cue or the movement goal. In order to disentangle the position of the visual cue from the position of the movement goal, context rules are applied to the visual cue which either instruct a reach towards the visual cue (rule pro) or towards its mirrored position (rule anti) (Gail and Andersen, 2006; Gail et al., 2009; Westendorff et al., 2010; Klaes et al., 2011). Delay-

related directional tuning signals in PRR neurons revealed selective coding of the movement goal rather than the memorized position of the visual cue irrespective of whether it was directly cued by the physical visual cue (pro-reach) or inferred from the rule applied to the visual cue (anti-reach) (Gail and Anderson, 2006). This suggests that PRR translates current sensory information into reach plans rather than storing the visual cue position in visual memory. Similar results have been revealed for PMd neurons (Gail et al., 2009) indicating an important role of PMd and PRR in space-context integration in order to encode the desired movement goal. By introducing different pre-cueing conditions, it has been shown that movement goal representations in PMd and PRR neurons are modulated by contextual information, i.e. by the information given before the movement planning phase. For example, PRR neurons were stronger engaged in planning of pro-reaches while PMd neurons showed stronger overall activity during planning of anti-reaches (Gail et al., 2009). Moreover, motor-related latencies were shorter for PMd than PRR neurons for inferred movement goals, i.e. during anti-reach planning, suggesting that PMd initiates movement goal remapping in PRR (Westendorff et al., 2010). In these experiments, the point in time when the context rule was given varied between trials; the context rule was either presented before or after a variable instructed delay. This also allowed for differentiating movement planning based on specified movement goals (visual cue and context rule given before the delay) from movement planning based on underspecified movement goals (only the visual cue given before the delay). In the underspecified condition, monkeys were uninformed whether they should perform a reach towards the visual cue (pro-reach) or towards its mirrored position (anti-reach) until an additional rule cue was given after the delay specifying the movement goal. The underspecified movement goal condition yielded spatial tuning preferences for the inferred anti-movement goal in both PRR and PMd (Westendorff et al., 2010). Likewise, a preference for the encoding of the inferred movement goal in underspecified conditions were also observed in free-choice trials where the monkeys were free to choose the pro- or anti-reach goal (Klaes et al., 2011). However, if the free-choice behavior was controlled for by a bias-minimizing reward schedule the delay-phase activity indicated that PMd and PRR simultaneously encoded the two alternative movement plans when only the visual cue was given.

In humans, a broad frontoparietal network, likewise including strongly connected areas of the PPC and dorsal premotor cortex (Tomassini et al., 2007), is involved in the preparation of goal-directed reaching movements (Prado et al., 2005; Beurze et al., 2007;

Busan et al., 2009; Lindner et al., 2010; Parkinson et al., 2010; for a review see Culham et al., 2006). Consistent with electrophysiological findings in monkeys, the human PPC and PMd have been demonstrated to represent both the spatial position of the movement goal and the effector selected for that action, e.g. left vs. right arm (Beurze et al., 2007). Using a sequential cueing task, Beurze et al. (2007) also found activation in the PPC and the PMd even if only information of the movement goal or the effector was available, which is in line with previous findings in monkey PRR (Calton et al., 2002). However, activation in PPC and PMd was more pronounced when both the movement goal and the effector were cued by showing stronger effector- than target-selectivity (Beurze et al., 2007). The double coding of movement goal and effector signals together with stronger activation when both the movement goal and the effector were specified let the authors argue for a role of the human PPC and PMd in sensorimotor integration. Vice versa, the weaker activation in PPC and PMd when only the movement goal or the effector was specified argues for an incomplete stage of sensorimotor integration. One goal of the present study was to examine whether and how PPC and PMd engage in underspecified conditions in a pro-/anti-reach rule-selection task.

Within the human PPC, a dorso-medial area of the SPL seems to be crucially involved in the planning of hand and arm movements and has been discussed as a putative human homologue of monkey area PRR (Astafiev et al., 2003; Connolly et al., 2003; Pellijeff et al., 2006; Fernandez-Ruiz et al., 2007; Hagler et al., 2007; Vesia and Crawford, 2012). Consistent with previous reports on monkey PRR (e.g., Snyder et al., 1997), the 'human PRR' elicits higher activation for the planning of goal-directed pointing movements compared to the planning of goal-directed saccades (Connolly et al., 2003). In the following, we will label this region as PCu, as it gives an anatomical reference.

In order to examine the spatial code maintained in the PCu during movement planning, Fernandez-Ruiz et al. (2007) used left/right reversing prisms. By doing so, they were able to dissociate the visually perceived direction of a pointing movement towards a spatially corresponding visual cue from the actual (physical) pointing direction, e.g., an actual rightward movement to a right visual cue was seen as a leftward movement to a left visual cue. During movement planning, they found higher activation to contralateral visual cues in conditions without the prism and a reversed activation pattern with higher activation to ipsilateral visual cues (which are now visually perceived in contralateral space) in conditions with the prism. This effect was only significant for the left PCu contralateral to

the moving hand. The authors concluded that the PCu encodes the position of the visual movement goal rather than the direction of the actual limb movement, i.e. the physical movement goal. However, this task design does not spatially dissociate the visual cue presented before the delay from the visual movement goal representation since participants always reached to the visual cue, i.e. performed pro-reaches in visual coordinates. Thus, it remains unclear whether human PCu maintains the visual cue in visuospatial memory or represents the visual movement goal. Pro-/anti-reach tasks are suitable to answer this question. Therefore, a second goal of this study was to examine whether the human PCu and the PMd encode the position of the visual cue or the (inferred) visual movement goal by applying a pro-/anti-reach rule-selection task.

We used functional magnetic resonance imaging (fMRI) to investigate whether human reach-related areas, in particular PCu and PMd, represent the visual cue or the visual movement goal, and how strongly these areas are engaged during reach planning when the movement goal is not specified. We applied an adapted version of the pro-/anti-reach rule-selection task from an electrophysiological study in monkeys (Westendorff et al., 2010). This task allows us to (a) dissociate the position of the previously presented visual cue from the position of the (inferred) visual movement goal and (b) compare movement planning activation in situations with specified or underspecified movement goals. First, we hypothesize that visual movement goals are encoded in the human PCu and PMd as it has previously been shown in monkey electrophysiological research (Gail et al., 2009; Westendorff et al., 2011). If the human PCu and PMd represent the visual movement goal, we expect higher activation for contralateral visual cues in pro-trials and a reversed activation pattern for anti-trials, i.e. higher activation for ipsilateral than contralateral visual cues. Second, we hypothesize that PCu and PMd also engage in reach movement planning in underspecified conditions (cf., Westendorff et al., 2010; Klaes et al., 2011). To further specify the characteristics of this engagement we examined the activation strength and lateralization effects in underspecified conditions.

2.2 MATERIALS AND METHODS

PARTICIPANTS

Twenty-five participants participated in this fMRI experiment. We discarded three participants due to motion artifacts and another three participants due to poor performance in the behavioral task (<70 % correct trials), leaving nineteen participants (age range 20–29 years; 11 females). All participants were right-handed as assessed with the Edinburgh Handedness Inventory (Oldfield, 1971), had normal vision, and no history of neurological or psychiatric disorders or chronic diseases. They were financially compensated or received course credit for their participation. All participants gave informed written consent according to the Declaration of Helsinki (2008) before the experiment in accordance with the study procedure approved by the local ethics committee.

EXPERIMENTAL DESIGN AND CONDITIONS

To investigate brain areas involved in movement planning in specified and underspecified conditions, we adapted a delayed reach task with different cueing conditions from an electrophysiological study in monkeys (Westendorff et al., 2010; Figure 2.1B). This task allowed us to separate the position of the visual cue (visuospatial memory) from the position of the movement goal (movement goal encoding) by introducing a context rule (pro- vs. anti-reach) that had to be applied to the visual cue. By applying the context rule either before (specified condition) or after the delay (underspecified condition), we were able to manipulate the amount of information available during the delay resulting in conditions with specified or underspecified movement goals.

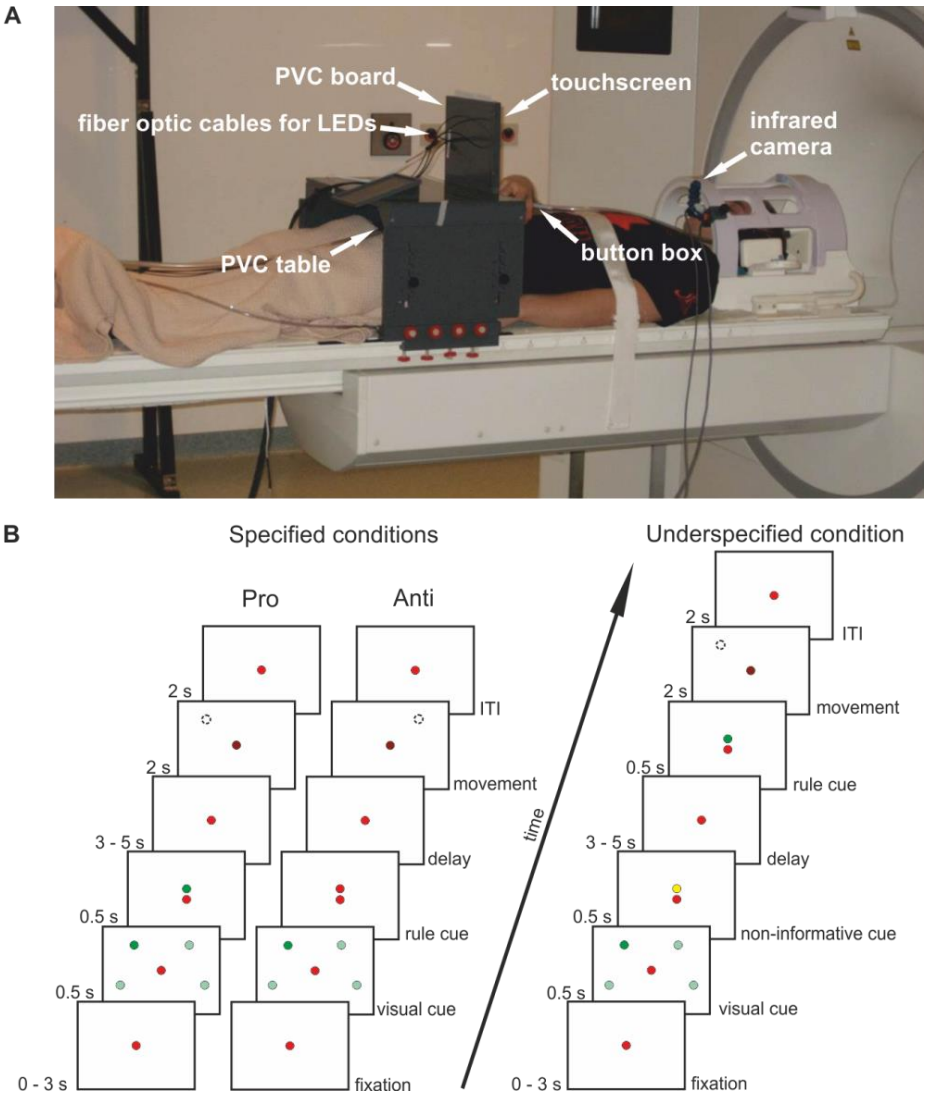

Figure 2.1: Setup and experimental design. **A.** Participants lay in the scanner with their head tilted and their index finger on a button box. Right arm reaches were performed to a touchscreen mounted in front of a PVC board. Also attached to this board were optic fiber cables connected to stimuli LEDs in the control room. The board was mounted to a PVC table placed over the participants' hips. Eye movements were recorded with an infrared camera. **B.** Delayed pro-/anti-reach task with different precueing conditions. Context rules (pro, anti) had to be applied to visual cues at four possible positions to infer the movement goal. All possible cue positions are illustrated here (light green spheres), but were not visible during the experiment. In this exemplary single-reach trial only one visual cue was presented (dark green sphere). A red fixation LED was visible at the center of the screen throughout the whole trial, and a change of its brightness served as a go-cue. In the specified pro condition (left timeline), the context rule was indicated centrally by a green LED above the fixation LED, and reaches were performed toward the position of the previously presented visual cue after a variable memory delay (broken line circle). In the specified anti condition (center timeline), the context rule was indicated by a red LED above the fixation LED. Reaches were performed to the mirror-imaged position of the visual cue (broken line circle). Different precueing conditions were introduced to vary the information available during the memory delay. In the specified pro and anti conditions, both the visual cues and the context rule were available before the delay. In the underspecified conditions (right timeline), only the visual cue was available during the memory delay, whereas the context rule was given immediately after the delay prompting participants to start the respective reaching movement. An additional task-irrelevant yellow cue was presented above the fixation LED before the delay to keep visual input constant. The timeline for underspecified conditions shows an exemplary pro trial, with a green LED above the fixation LED presented after the delay.

Light-emitting diodes (LEDs) served as spatial cues, rule cues and fixation point. Participants were instructed to maintain fixation on a red central fixation LED throughout the trial. Green LEDs served as spatial cues which were presented at one of four possible positions left or right from the fixation point. In addition to the randomized trial structure with jittered delay durations we varied the number of reaches (50% single-reach trials and 50% double-reach trials). We did so to ensure that planning-related activation is not reduced due to predictability of the target position (Berndt et al., 2002; Dassonville et al., 1998). In single-reach trials, one visual cue was presented at one of four possible positions, two positioned in the left and two in the right hemifield (see Stimuli). In double-reach trials, the two visual cues were always presented sequentially. Double reaches were performed from the start position to the (mirrored) 1st visual cue position and from there directly to the (mirrored) 2nd visual cue position following the order of the visual cue presentation. Both reach goals always fell into the same visual hemifield so that all reaches were either performed within the left or right visual field. For subsequent analyses we collapsed data of single- and double-reach trials, and reaches planned to the lower and upper workspace.

In the specified condition, visual cue and rule cue were presented consecutively. The color of the LED located right above the fixation point specified the context rule that participants had to apply to the visual cue in order to infer the movement goal. A green LED indicated that participants had to perform a reach towards the remembered position of the visual cue (pro-reach), whereas a red LED required moving towards the position mirrored to the centrally located fixation point (anti-reach), e.g. to the lower left in case of a visual cue presented at the lower right. In this condition, all information required for building up a movement plan was available during the following delay. Participants started right arm reaches as soon as the central fixation LED was dimmed after the delay (go-cue). In the underspecified condition the visual cue and an additional non-informative cue were presented before the delay. Importantly, the rule cue was presented after the delay. Thus, during the delay participants knew the position of the visual cue but were unaware about the movement goal (pro- vs. anti-reach). We introduced an additional non-informative cue in this condition to keep visual information constant and to inform participants about the underspecified condition with the delay preceding the rule cue. Participants performed reaches after the presentation of the rule cue. Other than that, specified and underspecified conditions were identical and trials were presented interleaved in random order. Participants did not receive feedback about the correct reach goal position.

APPARATUS AND STIMULI

To enable a direct view of the visual stimuli, participants were positioned in the scanner with their head tilted with wedges (~20-30°) inside the head coil. A custom-made MR-compatible PVC table, adjustable in distance and height, was mounted over the participants' hips and fixed to the scanner bed. At the front end of the table a vertical PVC board with six holes with a diameter of 1mm was attached. Inside each hole one fiber optic cable ended which was connected with an LED placed in the control room. One red LED was positioned centrally and served as fixation point and go-cue. Four green LEDs served as visual cues with one LED each positioned at the upper left and upper right workspace (5 cm horizontal and 5cm vertical deviation from the fixation LED) and at the lower left and lower right workspace (8 cm horizontal and 1 cm vertical deviation from the fixation LED). An additional bicolor (green/red) LED right above the central LED indicated the context rule. Directly in front of the PVC board an MR-compatible 10.4" touch screen panel (Magic Touch, Keytec, Inc., Garland, Texas, USA) was attached at an eye-to-screen-distance of about 50 cm to record reaching endpoints with a resolution of 1024 x 768 pixels. To reduce effects of eye movements on brain activation we recorded the eyes using an infrared camera (MRC Systems GmbH, Heidelberg, Germany) attached to the head coil and visually inspected the data offline for constant fixation throughout the trials. Due to the tilted head position we could not conduct eye tracking. Using a camera allowed for a general control of constant fixation but not for a quantitative analysis of single eye movements. However, we instructed and trained our participants thoroughly to maintain fixation, especially during the delay. In addition, the subtle change in brightness of the fixation LED serving as go-cue along with the variable delay interval encouraged participants to fixate until they started the movement. For all remaining participants (see *Participants*) this rough criterion of constant fixation was fulfilled.

The right upper arm was strapped to the bed to minimize movement artifacts during reaching. Yet, it was ensured that participants could freely move their right forearm and reach towards all positions of the touch screen without moving the upper arm or shoulder. Before and after movement execution participants continuously pressed a button of an MR-compatible button box placed on their abdomen with their right index finger. To assess individual reach endpoint errors, we subtracted the observed reach endpoints from the physical position of the visual cue. To this end, all visual cue LEDs were turned on subsequently after the end of the experiment and participants touched each position

accordingly. Based on the individual reach endpoint errors, reaches were classified offline in correct and incorrect movements (description see below). All LEDs and response devices were controlled by Presentation software (Neurobehavioral Systems, Inc., Albany, CA).

TRIAL TIMING

We used a rapid event-related design to study the neural correlates of movement planning. Each trial started with a fixation phase of random duration varying from zero to three seconds with 15 ms steps (repetition time / number of trials = 3s / 192). Then the visual cue was presented for 500 ms. In the specified condition, the visual cue was succeeded by the rule cue (500 ms) and a random delay of 3 s, 3.6 s, 4.3 s or 5 s (Figure 2.1B). After the delay, the go-cue was presented initiating the movement interval (2 s). We varied the duration of the delay in order to minimize the predictability of the movement onset that might reduce activation associated with movement preparation. In the underspecified condition, the visual cue was followed by a non-informative cue (500 ms; Figure 2.1B) and then the delay (3 s, 3.6 s, 4.3 s, 5 s). Afterwards the rule cue (500 ms) and the go-cue were presented successively followed by the movement interval (2 s). In specified conditions and the underspecified condition, a new trial started after an inter-trial interval of 2 s with the next excitation pulse.

After the end of the experiment, a calibration session was run to determine the physical position of the visual cue. To this end, all visual cue LEDs were turned on subsequently and participants were asked to reach to each position accordingly.

One trial lasted on average 10.75 s (8 to 13.5 s). Each condition (specified conditions pro and anti and underspecified condition) consisted of 64 trials, resulting in 192 trials in total and a duration of about 35 minutes. The experiment in the scanner lasted about 1.5 h, including the set-up time, the functional scan, and the anatomical scan. Participants practiced the task on a computer outside the scanner prior to the experiment.

BEHAVIORAL ANALYSES

Behavioral data refer to the movement execution phase. At the time of the go-cue, participants were informed about the movement goal and performed either pro- or anti-reaches depending on the rule cue given before (specified condition) or after (underspecified condition) the delay period. We thus analyzed pro- and anti-reaches separately in the specified and underspecified conditions.

To assess individual reach endpoint errors, we subtracted the observed reach endpoints from the physical position of the visual cue determined in the calibration session (see *Apparatus and Stimuli*). In a first step, we analyzed the rate of correct responses. To do so, we separated the area of the touch screen into individual quadrants (mean size, width x height: 10.06 x 7.9 cm) based on the vertical and horizontal centerlines between the coordinates of the touches to the visible spatial cues acquired during the calibration session after the experiment. Responses were classified as correct if touches fell into the correct individual quadrant. Three participants performed poorly in all conditions with a rate of correct responses of < 70 % and were discarded from further analyses. For the remaining participants (N = 19) the amount of correct responses was compared across conditions using a one-way repeated measures (RM) ANOVA with the factor condition (specified pro, specified anti, underspecified pro, underspecified anti) and an alpha level of 0.05. When the assumption of sphericity was violated according to Mauchly's test for sphericity, F statistics were corrected according to the procedure of Greenhouse-Geisser. Two-tailed post hoc *t* tests were Bonferroni-Holm corrected for multiple comparisons.

Second, we analyzed the response time for all participants, defined as the time elapsed after the onset of the go-cue and until the first touch. We used a one-way RM ANOVA with the factor condition (specified pro, specified anti, underspecified pro, underspecified anti) and an alpha level of 0.05. Corrections for multiple comparisons or for violations of sphericity were carried out as described above.

IMAGING PARAMETERS

Functional and anatomical MRI data were acquired at the Bender Institute of Neuroimaging (Giessen, Germany) using a 1.5-Tesla Siemens Symphony whole-body MRI system with a quantum gradient system (Siemens, Erlangen, Germany) and a standard 1-channel head coil. A gradient-echo field map was measured before the functional run to receive information about inhomogeneities in the static magnetic field. For functional imaging, a total of 794 volumes were registered on average, varying from 786 to 802 volumes due to the combined duration of the randomized trial ordering with jittered fixation intervals and delay phases. A T2*-weighted gradient-echo-planar imaging (EPI) sequence was used with 30 axial slices covering the whole brain (slice thickness: 4 mm; 1 mm gap; descending slice order; echo time (TE): 59 ms; repetition time (TR): 3 s; flip angle: 85°; field of view: 192 mm; matrix size: 64 x 64 mm; voxel size: 3.0 x 3.0 x 4.0

mm). The orientation of the slices was selected to cover superior parietal areas and was tilted to parallel the inferior border of the orbitofrontal cortex in order to reduce signal losses due to susceptibility artifacts. Structural images consisting of 160 sagittal slices were acquired using a T1-weighted magnetization-prepared, rapid-acquisition gradient echo (MPRAGE) sequence (matrix size: 256 x 180 mm; field of view: 250 mm; TE: 4.18 ms; TR: 1990 ms; voxel size: 1.4 x 1.0 x 1.0 mm).

PREPROCESSING

Imaging data were preprocessed and analyzed using the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL; version 5.0.2; http://www.fmrib.ox.ac.uk/fsl). The first four volumes (12 s) were discarded due to an incomplete steady state of the magnetic field. We manually screened the motion parameters (rotations, translation) along the x, y, and z axes of each participant. After realignment and motion correction using FSL's motion correction tool MCFLIRT (Jenkinson et al., 2002) we used a custom-made FSL tool to detect EPI outlier volumes by calculating the mean squared difference in brightness values to the respective adjacent volumes. These deviation scores were thresholded according to an outlier detection method for skewed data (Hubert and van der Veeken, 2008) globally for the whole data set. Three participants were discarded from further analyses due to large motion artifacts defined by more than 10% outlier volumes (Hubert and van der Veeken, 2008).

Non-brain tissue was removed from all images using the FSL's brain extraction tool BET (Smith, 2002). Further preprocessing included the following steps: 1) B_0-unwarping using field maps, 2) spatial normalization to the Montreal Neurological Institute (MNI) space, 3) slice timing correction, 4) spatial smoothing using a Gaussian kernel of 5mm full-width-half-maximum, and 5) temporal high-pass filtering with a cutoff of 144 s to remove low frequency drift.

DATA ANALYSES

Data analyses were performed using the general linear model (GLM) implemented in FSL's FMRI Expert Analysis Tool FEAT v6.00 (Smith et al., 2004). We defined the delay phase as the period of interest for putative movement planning. We modeled one separate delay predictor for each experimental condition (specified conditions pro and anti, underspecified condition) and position of the visual cue (left or right visual field), resulting in six predictors of interest: PRO LEFT, PRO RIGHT, ANTI LEFT, ANTI RIGHT, UNDERSPECIFIED LEFT, UNDERSPECIFIED RIGHT. In addition to these delay regressors, we defined the fixation interval (FIX), the presentation of the spatial cue (SPATIAL), the presentation of the rule cue (RULE), and the movement phase (MOVE) as predictors of no interest. Each predictor was defined as a boxcar function with the value 1 for the duration of the respective event. Regressors were convolved with a double-Gamma hemodynamic response function in order to model the late undershoot. We also included the temporal derivative to our model to achieve a better fit to the data (Friston et al., 1998).

We conducted three different types of analyses. To identify brain areas active during the delay in the specified and underspecified conditions, we performed whole-brain voxelwise analyses. Additionally, we performed a conjunction analysis across the specified and underspecified conditions to extract activation in common brain regions. Finally, we conducted ROI analyses based on our prior hypotheses about cortical areas involved in movement planning.

VOXELWISE ANALYSES

Whole-brain voxelwise analyses were conducted using standard multiple regression procedures. We calculated one baseline contrast for each experimental condition to test our hypothesis that areas of the reaching network are involved in specified and underspecified conditions. The two delay regressors of each condition were combined and compared to the fixation interval: (PRO LEFT + PRO RIGHT) > FIX, (ANTI LEFT + ANTI RIGHT) > FIX, and (UNDERSPECIFIED LEFT + UNDERSPECIFIED RIGHT) > FIX. Additionally, we identified differences in activation strength between conditions by calculating the differential contrasts: (ANTI LEFT + ANTI RIGHT) > (PRO LEFT + PRO RIGHT) and vice versa, (PRO LEFT + PRO RIGHT) > (UNDERSPECIFIED LEFT + UNDERSPECIFIED RIGHT), and (ANTI LEFT + ANTI RIGHT) > (UNDERSPECIFIED LEFT + UNDERSPECIFIED RIGHT).

For individual analyses, *z* statistic images were thresholded at $p < 0.05$, corrected for multiple comparisons using Gaussian random field theory (GRF; Worsley et al., 1996). For group-level analyses, parameter estimates were assessed with a mixed effects model, with the random effects component of variance estimated using FSL's FLAME stage 1 procedure (Beckmann et al., 2003; Woolrich et al., 2004). Before thresholding, the statistical images were masked by a maximum probability gray matter mask based on the Harvard-Oxford cortical structural atlas provided by the Harvard Center for Morphometric Analysis (http://www.cma.mgh.harvard.edu/fsl_atlas.html) available with FSL. We did so to restrict our analyses to gray matter and thereby reduce the cluster criteria for statistical significance. *Z* (Gaussianized T) statistic images were generated using a *z* statistics threshold of 2.1 and a corrected cluster probability threshold of $p = 0.05$ using GRF (Worsley et al., 1996).

We applied a custom-made FSL tool to locate signal peaks of clusters and label anatomical regions according to the Juelich probabilistic cytoarchitectonic atlas (Eickhoff et al., 2007).

CONJUNCTION ANALYSIS

To identify a general reaching network being involved in movement planning independent of the context rule we conducted a second-level conjunction analysis on baseline contrasts from specified conditions pro and anti: [(PRO LEFT + PRO RIGHT) – FIX] ⋂ [(ANTI LEFT + ANTI RIGHT) – FIX]. A custom-made FSL tool was used to create a minimum *z* image from the second-level *z* statistics images ($z > 2.1$, $p = 0.05$) of the respective contrasts and to perform a cluster wise test. Note that for easier reading the conjunction analysis will be denoted as pro ⋂ anti.

ROI ANALYSES

We conducted second-level ROI analyses on three regions that were activated during movement planning in the specified conditions as revealed by previous whole-brain analyses: the left PMd and left and right PCu. We defined the ROIs independently of our analyses on the basis of the study by Lindner et al. (2010), who found sustained activation in PMd and PCu during the delay phase associated with reach movement planning. ROIs were created by specifying spheres with a radius of 5 mm centered at the reported

coordinates (left PCu: -17.6 -64.9 60.0; right PCu: 17.6 -64.9 59.6; left PMd: -26.6 -8.6 58.1).

In a first step, we confirmed our ROI selection by testing for a main effect of condition using the following contrasts: (PRO LEFT + PRO RIGHT) > FIX, (ANTI LEFT + ANTI RIGHT) > FIX, (UNDERSPECIFIED LEFT + UNDERSPECIFIED RIGHT) > FIX. *Z* statistic images were thresholded at p=0.05, corrected for multiple comparisons using GRF (Worsley et al., 1996). For further analyses we extracted the mean percent signal change (%SC) per participant for each delay regressor from each ROI using Featquery (http://fsl.fmrib.ox.ac.uk/fsl/fsl4.0/feat5/featquery.html). We hypothesized that movement goals are encoded in PCu and PMd leading to higher %SC in response to contralateral visual cues in condition pro, but higher %SC for ipsilateral visual cues in condition anti (indicating a contralateral movement goal). To test this assumption we conducted a 2 x 2 RM ANOVA with the factors condition (pro vs. anti) and visual field (left vs. right) with an alpha level of 0.05. One-tailed post-hoc *t* tests were Bonferroni-Holm corrected for multiple comparisons, if necessary.

Second, we tested how activation strength changed in the underspecified condition compared to specified conditions in areas which showed a main effect for all three conditions, namely the left and right PCu. To do so, we analyzed %SC as a function of condition (three levels: pro, anti, underspecified) in a one-way RM ANOVA with an alpha level of 0.05. When the assumption of sphericity was violated according to Mauchly's test for sphericity F statistics were corrected according to the procedure of Greenhouse-Geisser. Two-tailed post-hoc *t* tests were Bonferroni-Holm corrected for multiple comparisons, if necessary. Finally, we examined if the left and right PCu show a preference for the left or right visual cue by testing for lateralization differences performing two-tailed paired sample *t* tests.

2.3 RESULTS

In the present study, we first analyzed brain activations in the specified conditions pro and anti to examine whether the brain encodes the reach movement goal or the physical position of the visual cue. Here, we focused on three regions of the reaching network, the left PMd and the left and right PCu. Second, we investigated how delay phase activation differs if the movement goal is underspecified compared to when it is specified. In the

following, we provide an overview of the behavioral results, and then report the results of the voxelwise whole-brain group analyses and the ROI analyses.

BEHAVIORAL ANALYSES

Across all conditions participants' reaches fell into the correct quadrant of the touch screen in 85.8 % of all trials (90.2 % for the specified condition pro, 83.7 % for the specified condition anti, 86.0 % for the underspecified condition pro, and 83.1 % for the underspecified condition anti), with a mean deviation across all trials of 2.1 cm ± 1.9 cm. There was no significant effect of condition on the percentage of correct responses ($F_{(3, 54)} = 1.954$, $p = 0.146$). Response time did also not differ between the four conditions ($F_{(3, 54)} = 1.115$, $p = 0.318$), specified pro ($M = 1299$ ms, $SD = 261$), specified anti ($M = 1317$ ms, $SD = 295$), underspecified pro ($M = 1254$ ms, $SD = 483$), and underspecified anti ($M = 1369$ ms, $SD = 519$).

PLANNING PRO- AND ANTI-REACHES IN SPECIFIED CONDITIONS

To identify brain areas active during the delay in the specified conditions, we performed baseline contrasts for the specified conditions pro and anti on the group data. The activation of both conditions with labels of the signal peaks according to the Juelich cytoarchitectonic atlas (Eickhoff et al., 2007), MNI coordinates and *z* scores are listed in Table 2.1.

For the planning of pro-reaches, we calculated the baseline contrast (PRO LEFT + PRO RIGHT) > FIX and found activation in frontoparietal areas comprising the reaching network (Figure 2.2A). Specifically, the left and right SPL were activated. The cluster included the PCu comprising the medial portions of the SPL, anterior to the parieto-occipital sulcus. This region has previously been suggested as putative human homologue of monkey area PRR (Connolly et al., 2003; Fernandez-Ruiz et al., 2007; Fabbri et al., 2010). Moreover, activation occurred in the left and right IPL, the left and right aIPS and adjacent primary somatosensory cortex (S1), the left M1, and the left PMd spreading into the left superior frontal gyrus (SFG). We also found activation in the left frontal pole extending into the left middle frontal gyrus (MFG), and in the right frontal pole spreading into the right MFG and SFG.

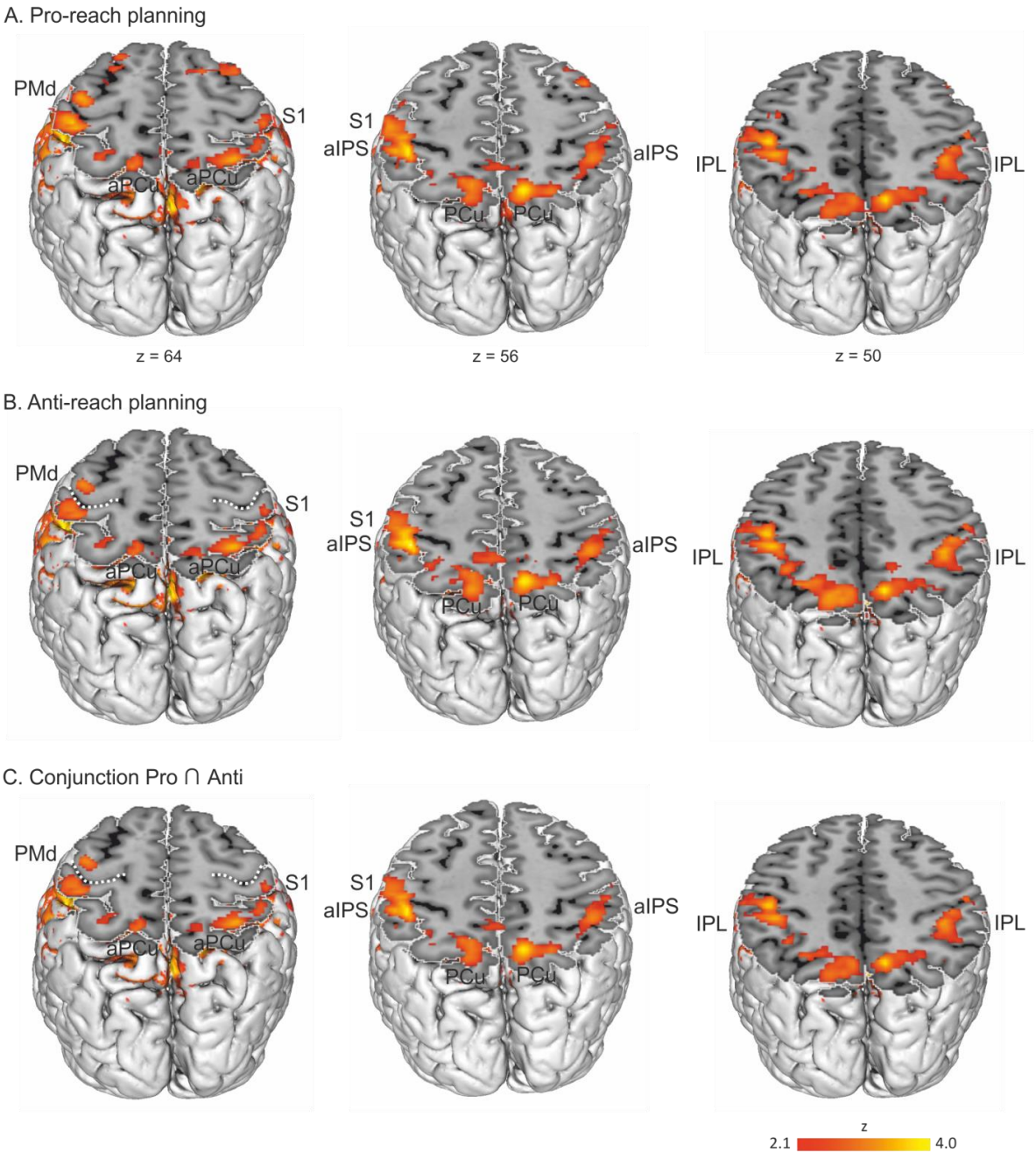

Figure 2.2: Delay phase activation for the specified conditions pro (**A**) and anti (**B**) obtained by calculating the respective baseline contrasts (PRO LEFT + PRO RIGHT) > FIX and (ANTI LEFT + ANTI RIGHT) > FIX. **C.** The overlap of activation in both specified conditions, pro ∩ anti, as revealed by the conjunction analysis of the two contrasts shown in 2A and 2B. White broken lines denote the central sulcus. S1, primary somatosensory cortex; aIPS, anterior intraparietal sulcus; IPL, inferior parietal lobule; PCu, precuneus; PMd, dorsal premotor cortex; aPCu, anterior precuneus.

Figure 2.2B illustrates the results for the specified condition anti contrasted against fixation (ANTI LEFT + ANTI RIGHT) > FIX. The planning of anti-reaches activated a similar frontoparietal network as we found for pro-reaches which contained bilateral activation in the SPL (including the left and right PCu), the IPL, the aIPS, and S1 and a left-lateralized activation in the PMd which also covered the left M1. In addition, the specified condition anti activated the left and right frontal pole with the left activation spreading into the left MFG.

Descriptively, condition pro yields activation in the left and right SFG and the right MFG, while we see no such effect for the specified condition anti. To examine whether activation differences were statistically significant between planning pro- and anti-reaches, we calculated the contrasts (ANTI LEFT + ANTI RIGHT) > (PRO LEFT + PRO RIGHT) and (PRO LEFT + PRO RIGHT) > (ANTI LEFT + ANTI RIGHT). These contrasts revealed no cluster more strongly activated in planning anti-reaches as compared to pro-reaches and vice versa, suggesting that the planning of pro- and anti-reaches recruits similar brain areas. In order to substantiate this result, we conducted a conjunction analysis on the two specified conditions, pro ⋂ anti. Consistent with the results described above, the conjunction analysis revealed an activation overlap in a large frontoparietal network extending from the bilateral SPL (signal peaks in the left hemisphere: z = 3.88, right hemisphere: z = 3.82) to the aIPS, the IPL, and S1, as well as to the left PMd and M1 (Figure 2.2C). These clusters comprised the PCu in both the left and right hemispheres. The activation patterns further overlapped in the left frontal pole (z = 3.76) spreading into the left MFG and the right frontal pole (z = 3.34). In short, in the specified pro- and anti-reach conditions delay phase activation expanded throughout posterior parietal and premotor areas and did not differ between conditions.

Table 2.1: Voxelwise analyses. MNI coordinates of local maxima in clusters showing significantly more activation in specified conditions pro and anti as compared to fixation (cluster corrected, $z > 2.1$). Functional labels are given in brackets.

Anatomic region	Hemi-sphere	*MNI coordinates*				*MNI coordinates*			
		x	*y*	*z*	*z* score	*x*	*y*	*z*	*z* score
		Specified condition pro				*Specified condition anti*			
SPL7P (PCu)	R	10	-72	54	3.82	10	-72	54	3.83
	L	-12	-68	56	3.23	-10	-78	52	3.43
SPL7A (aPCu)	R	30	-62	64	3.4	28	-64	64	3.44
	L	-12	-64	66	3.3	-12	-64	66	3.28
SPL7PC	L	-42	-48	58	3.88	-42	-48	58	4.06
SPL 5M	L					-6	-50	56	2.27
Angular Gyrus	R	52	-54	44	2.46				
	L	-52	-58	44	3.08	-52	-56	42	3.11
Supramarginal Gyrus	R	54	-30	44	3.07	54	-30	44	3.3
	L	-48	-46	54	3.47	-48	-46	54	3.64
aIPS (hIP1)	R	38	-56	46	3.18	38	-56	46	3.4
	L	-38	-50	44	3.56	-36	-52	40	3.6
aIPS (hIP2)	R	40	-46	50	3.27	40	-48	50	3.41
	L	-46	-44	44	3.03	-40	-46	48	3.58
aIPS (hIP3)	R					32	-56	52	2.63
	L	-26	-56	52	2.56				
Postcentral Gyrus (BA 1, S1)	R	46	-38	64	3.02	46	-38	64	2.74
	L	-44	-38	60	3.78	-44	-38	60	3.65
Postcentral Gyrus (BA 2, S1)	L	-46	-36	48	3.73	-46	-42	58	3.72
Precentral Gyrus (BA 4a, M1)	L	-42	-16	48	2.67				
Precentral Gyrus (BA6, PMd)	L	-26	4	68	3.02	-26	-18	74	2.38
SFG	R	22	4	68	3.25				
	L	-24	14	62	3				
MFG	R	48	12	50	2.4				
	L	-46	36	32	2.8	-50	28	30	2.39
Frontal Pole	R	30	56	-4	2.42	32	60	-2	2.56
	L	-40	46	-2	3.83	-40	46	-2	3.76

SPL, superior parietal lobule; PCu, precuneus; aPCu, anterior precuneus; aIPS, anterior intraparietal sulcus; hIP, human intraparietal area; S1, primary somatosensory cortex; M1, primary motor cortex; PMd, dorsal premotor cortex; SFG, Superior Frontal Gyrus; MFG, Middle Frontal Gyrus.

Based on our hypotheses on movement goal encoding within the reaching network, we conducted ROI analyses on the PCu and the PMd, using the MNI coordinates reported by Lindner et al., (2010). As the whole-brain analyses revealed that only the left PMd was activated during reach planning in specified conditions, we restricted our ROI analyses to the left PMd in addition to the left and right PCu. For both specified conditions pro and anti we found a main effect in the three ROIs left PCu (pro: $z = 3.09$, anti: $z = 3.03$), right PCu (pro: $z = 3.17$, anti: $z = 3.43$), and left PMd (pro: $z = 2.29$, anti: $z = 2.8$).

Based on previous findings in monkeys (Gail and Andersen, 2006), we hypothesized that the movement goal rather than the physical position of the visual cue is encoded in the reach-related areas PCu and PMd. Therefore, we conducted a two-way RM ANOVA with the factors condition (2) x visual field (2) on the mean percent signal change (%SC) in the respective areas across participants (Table 2.2). If the visual movement goal is represented, we expected higher signal changes in the left PCu for contralateral (right) visual cues in condition pro. However, in condition anti ipsilateral (left) visual cues should yield higher signal changes, as left visual cues combined with the context rule 'anti' indicated movement goals in the right contralateral visual field. This should result in an interaction of condition and visual field. Indeed, we found a significant condition x visual field interaction indicating that the movement goal rather than the physical position of the visual cue is represented in the left PCu ($F_{(1, 18)} = 9.68$, $p = 0.006$). This finding is illustrated in Figure 2.3 showing higher %SC for the specified condition pro right as compared to pro left, and for the specified condition anti left as compared to anti right.

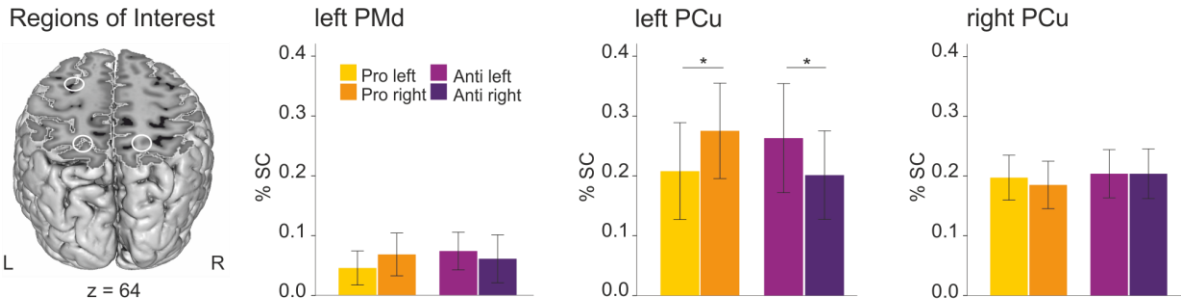

Figure 2.3: Percent signal change (%SC) for specified conditions pro and anti for the Regions of Interest (ROIs): left dorsal premotor cortex (PMd), and left and right precuneus (PCu). In the left PCu, %SC for right visual cues is significantly higher than for left visual cues, while the pattern reverses in condition anti. In both conditions, right movement goals thus lead to higher %SC indicating movement goal encoding. No such interaction effect occurs in the right PCu and the left PMd. Error bars denote the standard error of the mean (* $p < 0.05$, Bonferroni-Holm-corrected; one-sided t test).

Table 2.2: Mean percent signal change (± standard deviations) per ROI and condition.

	pro			*anti*			*Underspecified*		
	left	right	mean	left	right	mean	left	right	mean
PCu L	0.21 (±0.35)	0.28 (±0.35)	0.23 (±0.33)	0.26 (± 0.4)	0.20 (±0.32)	0.23 (±0.35)	0.14 (±0.39)	0.07 (±0.29)	0.10 (±0.31)
PCu R	0.20 (±0.16)	0.19 (±0.17)	0.19 (±0.15)	0.20 (±0.18)	0.20 (±0.18)	0.20 (±0.16)	0.1 (±0.17)	0.06 (±0.16)	0.07 (±0.15)
PMd L	0.04 (±0.12)	0.07 (±0.15)	0.05 (±0.13)	0.07 (±0.14)	0.06 (±0.17)	0.07 (±0.14)			

PCu L, left precuneus; PCu R, right precuneus; PMd, dorsal premotor cortex.

To further test for movement goal encoding within the conditions pro and anti, we performed the respective *post-hoc* paired *t* tests using Bonferroni-Holm adjusted alpha levels ($p < 0.025$ and $p < 0.05$). In condition pro, contralateral right visual cues elicited a significantly higher %SC than ipsilateral left visual cues ($t_{(18)} = 2.53$, $p = 0.0105$, one-sided). In condition anti, the %SC for ipsilateral left visual cues were higher than for contralateral right visual cues ($t_{(18)} = 1.74$, $p = 0.0495$, one-sided). The overall response pattern speaks in favor of movement goal encoding within the left PCu.

For the right PCu and the left PMd, the %SC did not differ between conditions pro and anti or left and right visual cue positions.

ACTIVATION OF REACH-RELATED AREAS IN UNDERSPECIFIED CONDITIONS

In order to investigate whether reach-related brain areas are active during the delay when movement-relevant information is insufficient to prepare the final reach (underspecified situation), we first calculated a baseline contrast for the underspecified condition, (UNDERSPECIFIED LEFT + UNDERSPECIFIED RIGHT) > FIX. As depicted in Figure 2.4A we observed activation in the left parietal cortex, including IPL, aIPS, S1, and, importantly, the left and right PCu and anterior PCu (Table 2.3). Furthermore, the underspecified condition activated the left frontal pole. The results clearly show that posterior parietal areas of the reaching network were active even in situations where the movement goal was underspecified. However, in contrast to the specified conditions, we found no activation in the left PMd in the underspecified condition. Therefore, we performed the ROI analyses on the left and right PCu only.

Next, we identified areas showing higher activation in specified as compared to underspecified conditions by calculating the differential contrasts (PRO LEFT + PRO RIGHT) > (UNDERSPECIFIED LEFT + UNDERSPECIFIED RIGHT) and (ANTI LEFT

+ ANTI RIGHT) > (UNDERSPECIFIED LEFT + UNDERSPECIFIED RIGHT). Comparing the delay phase activations from condition pro to the underspecified condition revealed stronger activation in the specified condition in the left PMd (z = 3.09), and in clusters in the left parietal cortex extending throughout the SPL, the IPL , S1 , along the aIPS, and to the right SPL (Figure 2.4B). Similarly, the specified condition anti yielded higher activation in the left PMd, extending to the left SFG, and in the left and right SPL including the PCu as shown in Figure 2.4C.

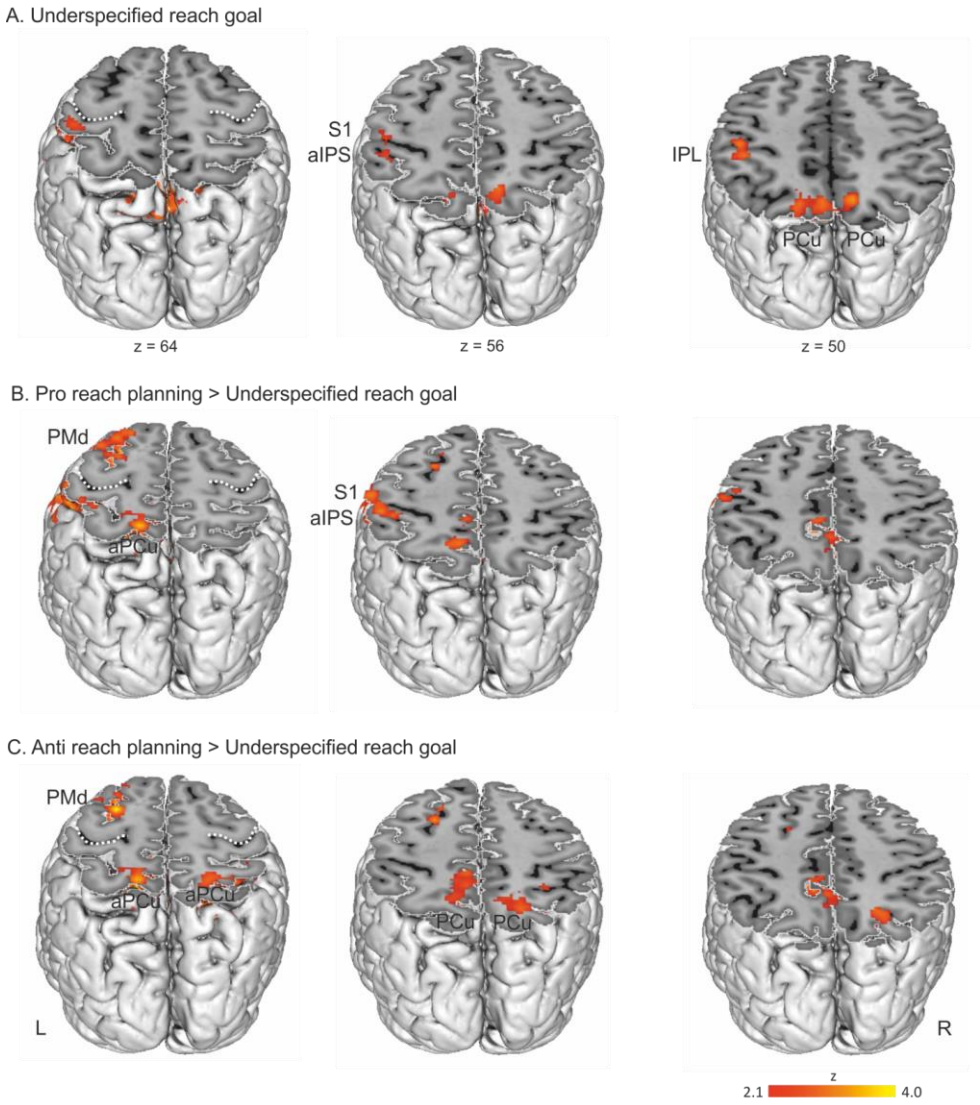

Figure 2.4: A. Delay phase activation in the underspecified condition obtained by the baseline contrast (UNDERSPECIFIED LEFT + UNDERSPECIFIED RIGHT) > FIX. Areas eliciting higher activation in the specified conditions as compared to the underspecified condition are shown in **B** for the differential contrast (PRO LEFT + PRO RIGHT) > (UNDERSPECIFIED LEFT + UNDERSPECIFIED RIGHT) and in **C** for the differential contrast (ANTI LEFT + ANTI RIGHT) > (UNDERSPECIFIED LEFT + UNDERSPECIFIED RIGHT). White broken lines denote the central sulcus. PMd, dorsal premotor cortex; S1, primary somatosensory cortex; aIPS, anterior intraparietal sulcus; PCu, precuneus; aPCu, anterior precuneus; IPL, inferior parietal lobule.

Table 2.3: Voxelwise analyses. MNI Coordinates of local maxima in clusters showing significantly more activation in the underspecified condition as compared to fixation, and in the specified conditions pro and anti as compared to the underspecified condition (all cluster corrected, $z > 2.1$). Functional labels are given in brackets.

		MNI coordinates			
Anatomic region	Hemisphere	*x*	*y*	*z*	*z* score
			Underspecified condition		
SPL7P (PCu)	R	10	-74	50	3.24
	L	-4	-76	50	2.96
Supramarginal Gyrus	L	-48	-48	54	2.34
aIPS (hIP1)	L	-36	-54	42	3.28
Postcentral Gyrus (BA 2, S1)	L	-44	-38	48	3.15
Postcentral Gyrus (BA 1, S1)	L	-46	-36	62	2.89
Frontal Pole	L	-40	46	-2	3.81
			pro > Underspecified		
SPL7A (aPCu)	R	8	-60	44	2.83
	L	-14	-64	64	3.6
Supramarginal Gyrus	L	-56	-30	52	3.08
aIPS (hIP2)	L	-46	-44	56	2.53
Postcentral Gyrus (BA 2, S1)	L	-52	-28	46	2.15
Postcentral Gyrus (BA 1, S1)	L	-50	-24	52	2.56
Precentral Gyrus (BA6, PMd)	L	-30	-8	70	3.09
			anti > Underspecified		
SPL7P (PCu)	R	18	-74	54	3.14
	L	-2	-58	48	2.96
SPL7A (aPCu)	R	30	-60	60	3.25
	L	-14	-64	64	3.45
Precentral Gyrus (BA6, PMd)	L	-26	-6	64	3.84
SFG	L	-20	18	64	2.4

SPL, superior parietal lobule; PCu, precuneus; aPCu, anterior precuneus; aIPS, anterior intraparietal sulcus; hIP, human intraparietal area; S1, primary somatosensory cortex; PMd, dorsal premotor cortex; SFG, Superior Frontal Gyrus.

In addition to the whole brain frontoparietal areas showing higher activation in specified compared to underspecified conditions we examined whether the activation strength differed likewise in the left and right PCu. Moreover, we tested for putative lateralization effects between left and right visual cues that may indicate movement planning or visual memory processes within the ROIs.

Again, we first confirmed the validity of our ROIs based on the results by Lindner et al., (2010) by showing delay phase activation in the left PCu (z = 1.92, p < 0.05, uncorrected) and the right PCu (z = 2.23) in the underspecified condition. Within the left PCu the %SC differed significantly between conditions ($F_{(2, 36)}$ = 17.14, p < 0.001). Post-hoc t tests revealed that %SC were significantly higher in condition pro ($t_{(18)}$ = 4.88, p < 0.017, corrected) and anti ($t_{(18)}$ = 4.75, p < 0.025, corrected) as compared to the underspecified condition, respectively. However, there was no significant difference between the specified conditions ($t_{(18)}$ = 0.25, p = 0.81). Similarly, %SC differed significantly between conditions in the right PCu ($F_{(1.41, 25.40)}$ = 16.11, p < 0.001). Again, we observed higher %SC in the specified conditions pro ($t_{(18)}$ = 3.72, p < 0.025, corrected) and anti ($t_{(18)}$ = 5.03, p < 0.017, corrected) as compared to the underspecified condition, while %SC from the specified conditions did not differ ($t_{(18)}$ = 0.908, p = 0.376). These results extend the findings from the whole-brain contrasts showing that a specified movement goal leads to higher activation as compared to underspecified movement goals in the predefined PCu regions.

In addition, we aimed to explore lateralization preferences in the PCu in the underspecified condition. Left and right visual cues did not elicit significant differences in %SC (Table 2.2) neither in the left PCu ($t_{(18)}$ = 1.69, p = 0.109) nor in the right PCu ($t_{(18)}$ = 1.42, p = 0.173).

2.4 DISCUSSION

In the current study we used a pro-/anti-reach rule-selection task to examine the nature of movement planning processes in conditions with specified and underspecified movement goals. For specified conditions, we identified a reaching network comprising the PPC bilaterally and the left PMd with a large activation overlap between planning pro- and anti-reaches. Within this network, the PCu contralateral to the moving effector elicited directionally selective activation depending on the position of the movement goal and not

on the position of the visual cue. If the movement goal was not specified, areas of the reaching network within the PPC but not the PMd were recruited and showed weaker activation than in the specified conditions.

PRO- AND ANTI-REACH PLANNING IN SPECIFIED CONDITIONS

In the specified conditions which required either a pro- or an anti-reach, we identified a broad frontoparietal network involved in the planning of reaching movements. This network included the bilateral PCu and the left PMd which has also been described in earlier fMRI studies on reach planning and execution (Prado et al., 2005; Beurze et al., 2007; Lindner et al., 2010; Parkinson et al., 2010; Fabbri et al., 2012). Area PCu, labelled 'human PRR' by Connolly et al. (2003), plays a crucial role in planning and executing reaching and pointing movements (Connolly et al., 2003; Fernandez-Ruiz et al., 2007; Bernier et al., 2012) with and without visual feedback from the hand (Filimon et al., 2009) and even engages in imagined and observed reaching (Filimon et al., 2007). The PCu seems to functionally differ from an area in the superior parieto-occipital cortex (SPOC) which is located more posterior and within the parieto-occipital sulcus (Gallivan et al., 2009). SPOC has been shown to be specialized for the transport component of reach and grasp movements (Cavina-Pratesi et al., 2010), but also processes object's reachability (Gallivan et al., 2009), and hand orientation (Monaco et al., 2011) as well as grasp axes (Monaco et al., 2014) for grasping movements. Therefore, SPOC rather than PCu has been discussed as a putative human homologue of monkey area V6A (Gallivan et al., 2009), which does not only contain reach-related neurons but also neurons selective for different grip types (Fattori et al., 2010). However, the exact human homologues of monkey PRR, reach-related area 5, V6A and MIP remain unclear.

Our results showed that pro- and anti-reach movements activated similar brain areas which did not differ in activation strength. This is consistent with findings from Connolly et al. (2003) who also observed no activation differences between pro- and anti-reach movements during the planning phase. We did not find activation in additional brain areas for anti- as compared to pro-reaches, as has been reported in an earlier study by Connolly et al. (2000). However, these results were based on activation during both movement planning and execution and thus are hardly comparable to the present findings where we exclusively focused on activation during movement planning.

MOVEMENT GOAL VS. VISUAL CUE REPRESENTATION IN SPECIFIED CONDITIONS

In order to investigate whether PCu and PMd represent the visual movement goal or maintain the presented visual cue in visual memory during movement planning, we applied an adapted version of the pro-/anti-reach rule-selection task by Westendorff et al. (2010). Here, we focused on the left and right PCu and the left PMd. Based on previous findings from electrophysiological studies in monkeys (Westendorff et al., 2010; Klaes et al., 2011), we hypothesized that the position of the movement goal rather than the position of the visual cue is encoded in PCu and PMd.

In the left PCu, we observed a preference for contralateral visual cues in pro-reach trials where the visual cue coincided with the movement goal. Importantly, this pattern reversed for anti-reach trials showing a preference for ipsilateral visual cues where the visual cue indicated the contralateral movement goal. By showing that human PCu encodes the visual movement goal rather than the position of the visual cue preceding the movement preparation phase we substantially extend the results by Fernandez-Ruiz et al. (2007) who demonstrated a preference for visual over physical movement goals in PCu. Taken together with our findings, it is unlikely that the activation observed in PCu in the study by Fernandez-Ruiz et al. (2007) reflects the visual memorization of the visual cue rather than the visual movement goal.

The present finding is also in line with the results on reach planning in monkeys demonstrating directional selectivity of PRR neurons fixed to the motor goal rather than the visual cue in a similar pro-/anti-reach task (Westendorff et al., 2010). However, caution is needed when comparing fMRI activations in humans with single-unit recordings in monkeys. Kuang et al. (2015) combined a reversing-prism task with an anti-reach task in monkeys and found that the majority of PRR neurons encode the physical movement goal while only a small portion encodes the visual movement goal; a finding incompatible with previous fMRI work (Fernandez-Ruiz et al., 2007) and the present findings in humans. But, when they analyzed the local field potentials (LFPs) instead of single-neuron spiking activity from the same brain areas they found evidence for pure visual movement goal encoding. Furthermore, they demonstrated that the observed movement goal encoding was unrelated to visual memory in line with our fMRI results in humans. This suggests similar spatial coding mechanisms for reaching movement planning in monkey PRR and human PCu.

We found evidence for (visual) movement goal encoding in the left PCu, contralateral to the moving effector (right arm reaches), while no such effect occurred in the right PCu although both the left and right PCu were activated during movement planning. Similarly, Fernandez-Ruiz et al. (2007) also found PCu activation related to movement goal encoding only in the hemisphere contralateral to the moving arm. The movement goal thus seems to be reliably encoded in the contralateral PCu for right arm reaches, while movement goal encoding in the ipsilateral PCu seems to be less robust. One explanation for the lacking effect might be that univariate GLM analyses of fMRI data are not sensitive enough to assess movement goal encoding in the ipsilateral hemisphere. By applying fMRI adaptation, Fabbri et al. (2010) were able to find directional selectivity in the contralateral left and the ipsilateral right PCu for right arm reaches. However, for left arm reaches this effect only occurred for the contralateral right PCu and was absent for the ipsilateral left PCu. Given the fact that the PCu represents both the effector and the movement goal (Beurze et al., 2007) reach movement goals might preferably be encoded in the human PCu contralateral to the moving arm.

During the movement preparation phase only the left PMd contralateral to the reaching hand was activated. Such a contralateral bias was also observed in earlier studies on reach planning (Medendorp, Goltz, Crawford, and Vilis, 2005; Bernier et al., 2012). The activation maximum we observed for planning reaches with specified movement goals was located near an area previously labelled PMd proper due to its movement-specific functions, in contrast to the pre-PMd which has been associated with higher-order processes such as response selection or motor imagery (for a review see Picard and Strick, 2001). The PMd proper has been suggested to transform visuo-spatial information into motor codes by double coding of movement goal and effector signals with a preference for the latter (Medendorp, Goltz, Crawford, and Vilis, 2005; Beurze et al., 2007). Here, we found no directionally selective activation in the left PMd. Our results thus speak in favor of a stronger effector- and weaker target-specificity in PMd compared to PCu in the human brain. Although earlier studies on reach planning indicated that PMd is primarily modulated by the effector-hand (Beurze et al., 2007; Medendorp, Goltz, Crawford, and Vilis, 2005) more recent work using multivariate decoding approaches on fMRI data also demonstrated target-selectivity in PMd (Gallivan, McLean, Smith, et al., 2011; Fabbri et al., 2014).

ACTIVATION OF REACH-RELATED AREAS IN UNDERSPECIFIED CONDITIONS

In conditions with underspecified movement goals, participants knew the position of the visual cue but were uninformed about whether they should perform a pro- or an anti-reach movement after the movement preparation phase. We observed activation in reach-related parietal regions similar to the areas activated in the specified conditions, again comprising the bilateral PCu. Yet, the PCu as well as other parietal areas showed stronger activation in conditions with specified movement goals. Moreover, we found no activation in the PMd in the underspecified conditions, in contrast to the specified conditions. In sum, situations with underspecified movement goals recruit fewer areas which are restricted to the parietal cortex and show weaker activation than in specified conditions.

The lower activation in reach-related areas might be caused by an incomplete stage of sensorimotor integration since only the effector and the visual cue but not the visual movement goal was given. A similar conclusion has been derived from results of a sequential cueing task presenting separate cues for the movement goal and the effector (left vs. right arm) (Beurze et al., 2007). They showed that conditions in which the effector was specified but the visual movement goal was unknown (corresponding to our underspecified condition) yield activation in reach-related areas of the PPC, but activations were stronger and broader when both the effector and the movement goal were specified (after cue 2) compared to situations when only the effector or only the movement goal was given (after cue 1) (Beurze et al., 2007). In a similar study, Bernier et al. (2012) cued the effector (left vs. right arm) either before or simultaneously with the presentation of the movement goal. They tested whether frontoparietal reach regions represent the movement goal for both arms if the effector is unknown, or if the movement goal is only formed after the information about the effector is given. They found evidence for the latter case and concluded that a motor goal is specified only if both the movement goal and the effector information are given. Thus, the specification of both the effector and the movement goal seems to be necessary to reach complete sensorimotor integration in the frontoparietal reaching network. However, the tasks applied by Beurze et al. (2007) and Bernier et al. (2012) differ in various aspects from our pro-/anti-reach rule selection task, e.g. single reaching vs. sequential reaching or reaching to the visual cue vs. the inferred mirrored position, limiting a direct comparison of the findings.

An alternative explanation for the lower activation in reach-related areas could be that in underspecified conditions participants have planned all potential pro- and anti-reach

movements but mutual inhibition of competing movement plans led to lower net activation in reach-planning areas like PCu and PMd. Evidence for this second possibility comes from electrophysiological studies in monkeys demonstrating that neural activity of spatially selective neuronal populations first spans the entire angular range of potential reach directions and after movement goal specification sharpens to reflect the choice (Bastian et al., 1998, 2003). Selection of one movement plan is achieved by mutual inhibition among neuronal populations with different tuning properties (Cisek, 2006) and/or through differential selection in cortico-striatal circuits (Leblois et al., 2006). Simultaneous encoding of multiple movement plans has been identified in frontoparietal areas including PMd and PRR in conditions with underspecified movement goals and even with single cue presentation like in pro-/anti-reach tasks (Cisek and Kalaska, 2002, 2005; Klaes et al., 2011). In humans, evidence for the co-activation of multiple movement plans comes from magnetoencephalographic (Tzagarakis et al., 2010) and electroencephalographic (EEG) studies (Rawle et al., 2012) showing weaker beta-band suppression, and thus attenuated activation, in motor-related frontal areas when multiple potential movement goals were presented before the delay. In accordance, EEG recorded delay phase activity in (pre)motor cortex inversely scaled with the number of possible reach goals presumably caused by mutually suppressive interactions between cell populations encoding different movement directions (Praamstra et al., 2009).

With the present task design, we cannot exclude one of the two aforementioned possibilities. The lack of directional selectivity we observed in the left PCu in the underspecified condition (in contrast to the specified condition) might suggest that human PCu encodes both potential pro- and anti-reach movements in parallel. Future brain imaging studies should investigate in more detail whether reach-related areas in the human brain plan all potential movements in advance and later select the appropriate one or wait until the movement goal is specified and then plan the appropriate movement.

2.5 CONCLUSIONS

Our study aimed to clarify the nature of movement planning processes within the human reaching network in a pro-/anti-reach rule selection task. The present findings demonstrate that the reach-related area PCu encodes the visual movement goal rather than the viewed visual cue if the movement goal is specified and even engages in situations

when only the visual cue but not the movement goal is available. Visual movement goal specificity was only found in the left hemisphere suggesting preferred encoding in the PCu contralateral to the reaching hand.

3. Decoding Movement Goals from the Reach Network

To plan a reaching movement, frontoparietal brain areas need to transform sensory information into a motor code. It is debated whether these areas maintain a sensory representation of a visual cue or a motor representation of the upcoming movement goal during reach planning. Here, we used a delayed pro-/anti-reach task which allowed for dissociating the position of the visual cue from the reach goal. In this task, the visual cue was combined with a context rule (pro vs. anti) to infer the movement goal. Different levels of movement goal specification during the delay were obtained by presenting the context rule either before the delay together with the visual cue (specified movement goal) or after the delay (underspecified movement goal). By applying fMRI multivoxel pattern decoding we demonstrate a strong bias for movement goal encoding in the dorsal premotor cortex (PMd) and posterior parietal cortex (PPC), particularly in the right superior parietal lobule (SPL) when the reach goal is specified. This suggests that fronto-parietal reach regions maintain a prospective motor code during reach planning. When the reach goal is underspecified, only the PMd but not the SPL represents the visual cue position. This suggests an incomplete state of sensorimotor integration.

3.1 INTRODUCTION

The PPC is a core area for planning and guiding reaching movements in both monkeys (Snyder et al., 1997; Batista and Andersen, 2001; Gail and Andersen, 2006; for a review see Andersen and Buneo, 2002) and humans (Connolly et al., 2003; Culham and Valyear, 2006). Previous research in humans has found that areas of the PPC represent the movement effector (Connolly et al., 2003; Medendorp, Goltz, Crawford, and Vilis, 2005; Beurze et al., 2007, 2009; Gallivan, McLean, Smith, et al., 2011; Heed et al., 2011; Leoné et al., 2014), the orientation of hand/wrist (Monaco et al., 2011; Barany et al., 2014), the grip and transport component (Cavina-Pratesi et al., 2010), the availability of visual information (Filimon et al., 2009), the reachability of a target object (Gallivan et al., 2009), and the type of motor act (Fabbri et al., 2010, 2014; Gallivan, McLean, Valyear, et al., 2011; Gallivan et al., 2013).

One key aspect of reach planning and execution is the spatial representation of the movement goal. Movement direction selectivity during reach execution has been demonstrated in the PPC, in particular in the SPL and IPS, as well as in the PMd (Fabbri et al., 2010, 2014; Haar et al., 2015). Likewise, during reach planning SPL and IPS encode the position of a movement goal to be acted upon (Beurze et al., 2007, 2009; Gallivan, McLean, Smith, et al., 2011). In these studies, however, the visual cue spatially corresponded with the movement goal leaving open whether PPC and PMd rely on a retrospective sensory code or a prospective motor code. Using left/right reversing prisms, Fernandez-Ruiz et al. (2007) tried to address this question and reported movement goal rather than visual cue encoding in the SPL contralateral to the effector used for the upcoming reach. While reversing prisms allow for dissociating the visually perceived movement direction toward a spatially corresponding visual cue from the actual (physical) movement direction (i.e. an actual rightward movement to a right visual cue is seen as a leftward movement to a left visual cue), they cannot dissociate the position of the visual cue from the visual movement goal. In a recent study, we applied a pro-/anti-reach task and showed that during reach planning the visual movement goal rather than the visual cue is encoded in the SPL contralateral to the moving effector (Gertz and Fiehler, 2015).

The PPC as well as the PMd have been further associated with sensorimotor integration showing higher activation when information about both the effector and the movement goal is given than when only one piece of information is available (Beurze et al.,

2007, 2009; Bernier et al., 2012). It remains unclear how situations with ambiguous movement goals are represented in reach-related areas.

Here we used multi-voxel pattern analysis (MVPA) of functional magnetic resonance imaging (fMRI) data to investigate the functional specificity of reach-related areas. As MVPA has been shown to detect more subtle characteristics of spatial encoding processes during movement execution (Fabbri et al., 2014; Haar et al., 2015) and thus may reveal different results than univariate analyses, we applied this approach to refine and extend our previous findings (Gertz and Fiehler, 2015). In particular, we examined whether the PPC and PMd represent the visual cue or the movement goal, and, second, different levels of movement goal specification. We applied a pro-/anti-reach task combined with a context cue (pro vs. anti) which was presented before (specified movement goal) or after (underspecified movement goal) a delay. While earlier studies assumed one core PPC region for reaching located in the SPL, the putative human homologue of monkey PRR (Connolly et al., 2003), more recent studies argue for multiple reach-related areas within PPC, possibly following a gradient with different weightings, e.g. of effector- and spatial information (Beurze et al., 2007, 2009; Heed et al., 2011) or different sensory input modalities (Filimon et al., 2009). A broad distinction can be made between two clusters in the SPL7. A posterior SPL7 cluster comprises the posterior PCu and posterior IPS (Prado et al., 2005; Filimon et al., 2009). This cluster often extends to the SPOC (Gallivan et al., 2009; Cavina-Pratesi et al., 2010) just anterior or even posterior of the POS. Based on probabilistic histological maps (Eickhoff et al., 2007) this cluster most often falls into the posterior BA7, thus being labelled as the SPL7P. An anterior SPL7 cluster is also located medially in the SPL, in the aPCu, sometimes extending to the middle portions of medial IPS (Prado et al., 2005; Filimon et al., 2009; Gallivan, McLean, Smith, et al., 2011; Bernier et al., 2012). The corresponding probabilistic histological label for this anterior part of BA 7 is SPL7A. We therefore examined multiple PPC areas with a focus on Brodmann area 7 of the SPL, subdividing it into posterior and anterior ROIs of the SPL7.

In this study, we dissociated for the first time brain regions encoding a sensory representation of a visual stimulus from brain regions encoding a motor representation of the upcoming movement goal by using a multivariate approach. We observed a preference for movement goal encoding in the PMd and PPC with the strongest effects in the right SPL. The PMd, SPL and left aIPS distinguished between specified and underspecified movement goals suggesting an important role in sensorimotor integration.

3.2 MATERIALS AND METHODS

The results of this study are based on the same dataset as in Chapter 2. Therefore, the *Participants*, the *Experimental Design & Conditions*, the *Apparatus & Stimuli*, and the *Trial Timing* are identical to those described in Chapter 2.2 of this thesis. Moreover, the *Behavioral Analyses* and the *Imaging Parameters* were identical to those in Chapter 2.2. All further steps of the preprocessing and analysis of the fMRI data differed between the two studies, and will be described in the following.

PREPROCESSING

Imaging data were preprocessed and analyzed using FSL (version 5.0.2; http://www.fmrib.ox.ac.uk/fsl). The first four volumes (12 s) were discarded due to an incomplete steady state of the magnetic field. After realignment and motion correction using FSL's motion correction tool MCFLIRT (Jenkinson et al., 2002) we used a custom-made fMRI artifact correction tool (Bertram Walter, Bender Institute of Neuroimaging, Giessen, Germany) to detect EPI outlier volumes by calculating the mean squared difference in brightness values to the respective adjacent volumes. These deviation scores were thresholded according to an outlier detection method for skewed data (Hubert and van der Veeken, 2008) globally for the whole data set. Three participants were discarded from further analyses due to large motion artifacts defined by more than 10 % outlier volumes (cf., Hubert and van der Veeken, 2008).

Non-brain tissue was removed from all images using the FSL's brain extraction tool BET (Smith, 2002). Further preprocessing included the following steps: 1) B_0-unwarping using fieldmaps, 2) temporal high-pass filtering with a cutoff of 144 s to remove low frequency drift 3) slice timing correction, and 4) registration of individual functional images to structural images, as well as non-linear registration of individual structural images to the MNI space using FMRIB's Non-linear Image Registration Tool (Smith et al., 2004; Andersson et al., 2010).

In the following, we set up separate GLM analyses for ROI definition and extraction of parameter estimates for MVPA of the six experimental conditions, resulting from a combination of task (pro, anti, underspecified) and position of the visual cue (left, right). To identify group level peaks for ROI definition, we applied a Gaussian kernel of 5 mm full-width-half-maximum (FWHM) for spatial smoothing. To extract the parameter

estimates for MVPA on individual data, data were spatially smoothed with a smaller Gaussian kernel of 2 mm FWHM. Other than that, preprocessing was identical for the two analyses.

ROI DEFINITION

ROIs were defined separately for each participant based on individual univariate statistical maps, combined with anatomical masks from the Juelich anatomical atlas (Eickhoff et al., 2007).

Data analysis was performed using the GLM implemented in FEAT v6.00 (Smith et al., 2004; Jenkinson et al., 2012). FMRIB's Improved Linear Model (FILM) was used to estimate voxel-wise time series autocorrelation for prewhitening of the time series and thereby improve efficiency of the model. We defined the delay phase (3 – 5 s from the offset of the rule cue in specified conditions and of the non-informative cue in the underspecified condition) as the period of interest for putative movement planning. We modeled one separate delay predictor for each experimental condition (specified conditions pro and anti, underspecified condition): PRO, ANTI, UNDERSPECIFIED. Note that here we collapsed data across visual cue positions (left, right). In addition to these delay predictors, we defined the fixation interval (FIX), the presentation of the spatial cue, the presentation of the rule cue, and the movement phase as predictors of no interest. Each predictor was defined as a boxcar function with the magnitude of 1. Predictors were convolved with a double-Gamma hemodynamic response function in order to model the late undershoot. We also added the temporal derivative to our model to achieve a better fit to the data (Friston et al., 1998).

To define the ROIs we first calculated one baseline contrast across the three experimental delay conditions: (PRO + ANTI + UNDERSPECIFIED) > FIX. For individual analyses, *z* statistic images were thresholded at $p < 0.05$, corrected for multiple comparisons using GRF (Worsley et al., 1996). For group-level analyses, parameter estimates were assessed with a mixed effects model, with the random effects component of variance estimated using FSL's FLAME stage 1 procedure (Beckmann et al., 2003; Woolrich et al., 2004). *Z* (Gaussianized T) statistic images were generated using a *z* statistics threshold of 2.3 and a corrected cluster probability threshold of $p = 0.05$ using GRF (Worsley et al., 1996). Subsequently, we used the Juelich probabilistic cytoarchitectonic atlas (Eickhoff et al., 2007) to identify regions exhibiting a signal peak in

the group level analysis. To ensure that the defined ROIs were anatomically precisely located, we multiplied the activations of the group level baseline contrast with an anatomical mask of each (sub-) region. We applied anatomical masks of the Juelich atlas (Eickhoff et al., 2007) which are based on histological processing and cytoarchitectonic analyses of 10 postmortem human brains. The resulting cytoarchitectural areas are probability maps. For ROI definition, we included all voxels that had a probability of at least 50 % as being part of the respective anatomical region. The resulting group-activation-bound anatomical masks in standard MNI space were transformed to individual functional space for each participant separately using FSL's applywarp. In a next step, we detected the individual signal peaks within the activation-bound anatomical masks using FSL featquery, and placed a sphere with a radius of 10mm around the corresponding coordinate. We did so to also account for individual activation patterns. Finally, we masked the individual spheres with the original anatomical Juelich masks (again transformed to individual functional space) to ensure that the individual ROIs only comprised voxels of the respective regions. ROIs comprised at least 10 voxels with a voxel size of 3x3x3 mm (for the mean size of the ROIs see Table 3.1). Note that we therefore had to exclude the right aIPS (4.7 voxels) from further analyses.

MVPA

We used MVPA to examine if and how reach-related areas functionally differ in encoding visual cue or movement goal positions, and movement goals at different levels of specification during the delay of a pro-/anti-reach task. To do so, we first computed parameter estimates for six experimental conditions (pro, anti, underspecified combined with the visual cue position left vs. right).

As we applied a rapid-event related design with interleaved trial structure we artificially split up the experiment into eight runs. To avoid temporal dependencies between the runs we randomized all trials of each of the six conditions (32 per condition) and combined four trials to one predictor per condition for each of the eight runs. Thus, the six predictors of interest per run were: PRO_LEFT, PRO_RIGHT, ANTI_LEFT, ANTI_RIGHT, UNDERSPECIFIED_LEFT, and UNDERSPECIFIED_RIGHT. Predictors were defined with the onset of the delay for a fixed duration of 3 s and a magnitude of 1. In addition, we modeled the fixation phase (FIX), the visual cue presentation, the rule cue presentation, and the reach execution as predictors of no interest as described before (see

ROI definition). In the following, we set up one GLM for each run and participant in FEAT (Smith et al., 2004; Jenkinson et al., 2012) including the FILM prewhitening procedure and contrasted the predictor of each condition to the fixation phase, resulting in six contrasts: PRO_LEFT > FIX, PRO_RIGHT > FIX, ANTI_LEFT > FIX, ANTI_RIGHT > FIX, UNDERSPECIFIED_LEFT > FIX, UNDERSPECIFIED_RIGHT > FIX. We thus obtained 48 PEs for the delay phase per participant (6 conditions x 8 runs) used for MVPA.

MVPA was performed using a linear-discriminant analysis (LDA)-based classifier as implemented in the CoSMoMVPA toolbox (Oosterhof et al., 2016). The following steps were performed for every participant and ROI separately. Classification accuracies were computed using leave-one-run-out cross-validation, so that the classifier was trained using seven runs and tested on the remaining pattern of one run. For each participant this procedure was repeated seven times each time leaving out another run as a test pattern. The resulting classification accuracies were averaged per test.

Using MVPA, we pursued two main goals. First, we examined whether reach-related areas encode the spatial position of the visual cue or the (inferred) movement goal, i.e. the combination of visual cue and context rule, during the delay of the specified conditions. To decode the visual cue position we trained and tested the classifier on the conditions pro left and anti left versus the conditions pro right and anti right. To decode the movement goal position we trained and tested the classifier on planned movements to the left (pro left, anti right) versus movements to the right (pro right, anti left).

Second, we aimed to decode the level of movement goal specification (specified vs. underspecified) and thereby identifying regions potentially involved in sensorimotor integration. The classifier was trained on conditions with underspecified movement goals (underspecified left, underspecified right) versus conditions with specified movement goals (pro left, pro right, anti left, anti right). To account for the different number of specified (4) and underspecified conditions (2), we balanced the number of samples per class by randomly choosing two out of the four specified conditions in each run of the training set.

In addition, we performed two exploratory analyses aiming to decode the type of movement goal (directly cued vs. inferred) and the position of the visual cue in underspecified conditions. We examined if the reach-related ROIs can distinguish between directly cued movement goals (condition pro) and movement goals inferred from the visual cue position (condition anti). Therefore, we trained the classifier on the conditions pro left and pro right versus anti left and anti right.

Next, we tested which ROIs encode the position of the visual cue despite underspecified movement goals. To do so, we separately trained the classifier on the conditions underspecified left versus underspecified right.

We computed a one-tailed one-sample *t* test per ROI against the theoretical chance level of 50% in order to assess statistical significance. Statistical results were FDR corrected for the number of one-sample *t* tests (6 ROIs x 5 classifications = 30 tests; Benjamini and Hochberg, 1995).

To determine whether a region is specialized to encode the visual cue or the movement goal position in specified conditions we ran a two-sample *t* test per ROI testing the accuracy of the visual cue against the accuracy of the movement goal. If a region is specialized for encoding the visual cue position, it should exhibit a decoding accuracy significantly above chance level for the visual cue position, but a non-significant decoding accuracy for the movement goal position as assessed by the *t* tests. In addition, it should also show a significantly higher decoding accuracy for the visual cue position than for the movement goal position. However, if a region is specialized for movement goal encoding decoding accuracy should be significantly above chance for the movement goal and not significantly higher than chance for the visual cue. Moreover, one would expect a significantly higher decoding accuracy for the movement goal than for the visual cue.

3.3 RESULTS

The behavioral results have been reported in Chapter 2.3 in the *Behavioral results* section. The results of the fMRI analyses will be presented in the following section.

UNIVARIATE RESULTS

To define ROIs for subsequent MVPA, we computed a group baseline contrast for the delay phase across all conditions (pro, anti, underspecified). This contrast revealed widespread activation most pronounced in the left and right SPL7, extending to adjacent left and right aIPS, left and right inferior parietal lobule, and left and right primary somatosensory cortex (Figure 3.1). We further detected activation in the right frontal pole extending into the orbitofrontal cortex and the parahippocampal gyrus, and in the left frontal pole extending into the left middle and inferior frontal gyrus. Finally, activation was revealed in the dorsal part of the premotor cortex in BA 6.

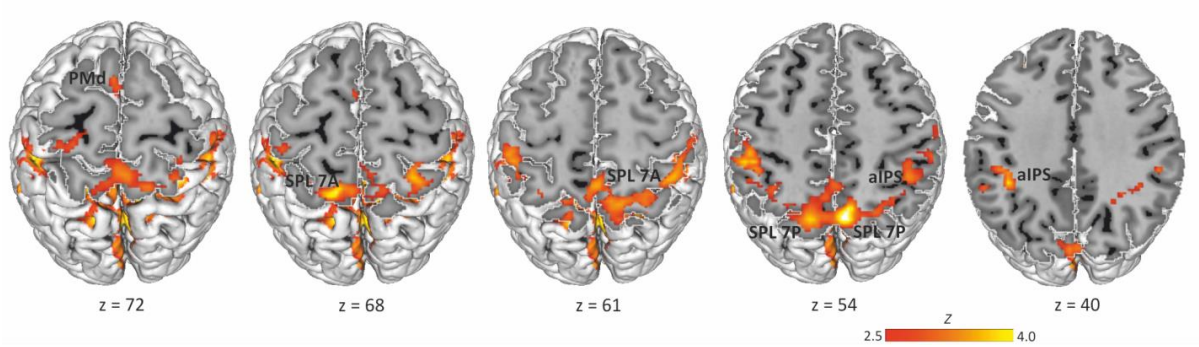

Figure 3.1: Delay phase activation across conditions. Activation maps were obtained by calculating one baseline contrast across the three experimental delay conditions (PRO + ANTI + UNDERSPECIFIED) > FIX (Z > 2.3, corrected cluster probability threshold p = 0.05; N = 19). Labels indicate the location of activation peaks used for ROI definition. PMd, dorsal premotor cortex; SPL7A, anterior portions of Brodmann area 7 in the superior parietal lobule; SPL7P, posterior portions of Brodmann area 7 in the superior parietal lobule; aIPS, anterior intraparietal sulcus.

Previous studies on reach execution identified movement direction encoding in the SPL, adjacent IPS, as well as in the PMd (Fabbri et al., 2010, 2014). Therefore, we focused subsequent analyses on these regions based on our univariate activation cluster and split up SPL activation into two regions per hemisphere to get a more detailed picture of potential functional differences within this area. We defined ROIs for the two SPL regions, SPL7A (peak group MNI coordinates: left -12 -66 68, right 28 -64 64) and SPL7P (peak group MNI coordinates: left -12 -78 54, right 6 -76 54), adjacent left aIPS (peak group MNI coordinates: -38 -52 40), as well as the left PMd (peak group MNI coordinates: -4 -4 72).

MVPA

We used ROI-based MVPA to examine whether the visual cue or the movement goal are encoded in the parieto-frontal reaching network, particularly in SPL regions previously discussed as human parietal reach regions. Second, we aimed to decode the level of movement goal specification, i.e. if the movement goal is specified or underspecified. In addition, we investigated whether reach-related areas represent different types of movement goals (directly cued vs. inferred), and the position of the visual cue in the underspecified conditions.

The spatial position of the visual cue and the movement goal could be decoded in different areas of the SPL for combined specified conditions, pro and anti (Figure 3.2, Table 3.1). We decoded the visual cue position only in one SPL region, the left SPL7A. The left PMd and bilateral SPL regions (left and right 7A, left and right 7P) encoded the

movement goal position. The decoding accuracy was also higher for the movement goal position than for the visual cue position in the right SPL7A and the right SPL7P (Table 3.2). In the left aIPS, the decoding accuracy was not above chance for either the visual cue or the movement goal position.

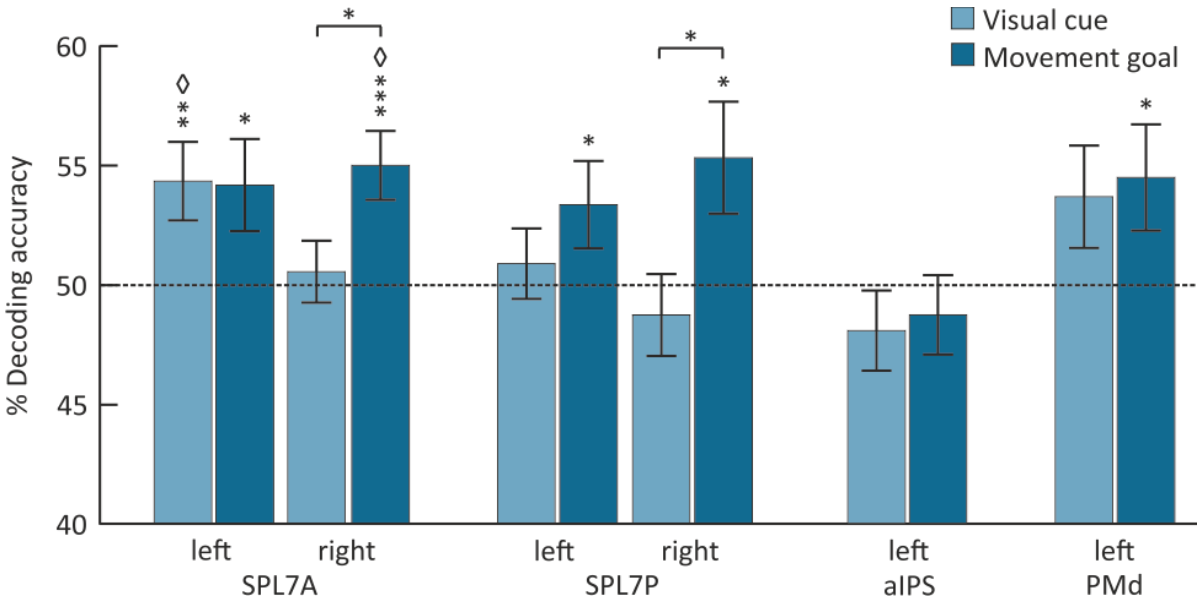

Figure 3.2: Mean classification accuracy for decoding the visual cue position and the movement goal. Error bars indicate SEM, asterisks indicate statistically significant difference from chance (50%) as follows: *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.005$; ◊, FDR corrected for the number of tests. The dotted line represents decoding accuracy at chance (50%). SPL7A, anterior portions of Brodmann area 7 in the superior parietal lobule; SPL7P, posterior portions of Brodmann area 7 in the superior parietal lobule; aIPS, anterior intraparietal sulcus; PMd, dorsal premotor cortex.

Table 3.1: Results of ROI MVPA and *t* tests against chance for visual cue and movement goal decoding.

	Mean size (voxels)	visual cue				movement goal			
		accuracy	SEM	*t*	*p*	accuracy	SEM	*t*	*p*
Left SPL7A	45.8	0.543	0.016	2.60	0.009*	0.541	0.019	2.13	0.023
Right SPL7A	39.9	0.505	0.013	0.38	0.354	0.549	0.014	3.43	0.002*
Left SPL7P	29.1	0.508	0.015	0.56	0.291	0.533	0.018	1.80	0.044
Right SPL7P	41.3	0.487	0.017	-0.77	0.774	0.553	0.023	2.25	0.019
Left aIPS	19.6	0.480	0.017	-1.17	0.873	0.487	0.017	-0.79	0.781
Left PMd	37.3	0.536	0.021	1.69	0.054	0.544	0.022	2.00	0.030

t tests one-tailed, against chance (0.5). * Significant *p* values (FDR corrected for number of tests).

Table 3.2: Results of two-tailed t tests between visual cue and movement goal.

		t	*p*
SPL7A	Left	-0.0777	0.939
	Right	2.6197	0.0174
SPL7P	Left	1.41	0.176
	Right	2.638	0.017
aIPS	Left	0.236	0.816
PMd	Left	0.2538	0.802

We were able to decode underspecified versus specified movement goals from the left PMd. Furthermore, the SPL regions (left and right SPL7A, left and right SPL7P) as well as the left aIPS showed significant decoding accuracies for specified than underspecified conditions (Figure 3.3, Table 3.3).

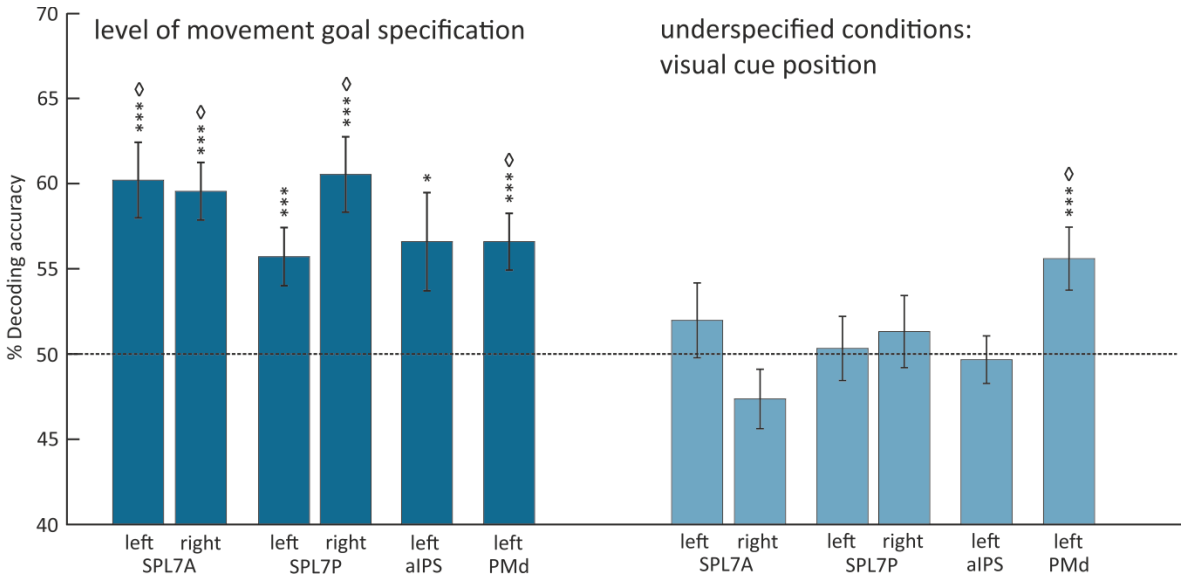

Figure 3.3: Mean classification accuracy for decoding the level of movement goal specification (dark blue) and the visual cue position in underspecified conditions (light blue). Error bars indicate SEM, asterisks indicate statistically significant difference from chance (50%) as follows: *, $p < 0.05$; ***, $p < 0.005$; ◊, FDR corrected for the number of tests. Dotted line represents decoding accuracy at chance (50%). SPL7A, anterior portions of Brodmann area 7 in the superior parietal lobule; SPL7P, posterior portions of Brodmann area 7 in the superior parietal lobule; aIPS, anterior intraparietal sulcus; PMd, dorsal premotor cortex.

Table 3.3: Results of ROI MVPA and *t* tests against chance for decoding the visual cue position in underspecified conditions, and decoding specified vs. underspecified movement goals.

		Levels of movement goal specification				visual cue (underspecified conditions)			
		accuracy	SEM	*t*	*p*	accuracy	SEM	*t*	*p*
SPL7A	Left	0.602	0.022	4.61	0.0001*	0.52	0.022	0.9	0.19
	Right	0.595	0.017	5.65	0.00001*	0.473	0.017	-1.51	0.926
SPL7P	Left	0.557	0.017	3.34	0.0018*	0.503	0.018	0.175	0.432
	Right	0.605	0.022	4.76	0.000078*	0.513	0.021	0.62	0.271
aIPS	Left	0.566	0.029	2.28	0.0174	0.497	0.014	-0.24	0.592
PMd	Left	0.566	0.017	3.95	0.0005*	0.55	0.018	3.03	0.004*

t tests one-tailed, against chance (0.5). * Significant *p* values (FDR corrected for number of tests).

None of the ROIs encoded the difference between directly cued and inferred movement goals, i.e. between conditions pro and anti (Table 3.4).

For underspecified conditions, the position of the visual cue could be decoded from one area, the left PMd (Figure 3.3, Table 3.3).

Table 3.4: Results of ROI MVPA and *t* tests against chance for decoding specified conditions pro vs. anti.

		accuracy	SEM	*t*	*p*
SPL7A	Left	0.515	0.014	1.06	0.152
	Right	0.5	0.020	0	0.5
SPL7P	Left	0.518	0.014	1.26	0.113
	Right	0.484	0.019	-0.86	0.801
aIPS	Left	0.512	0.02	0.58	0.283
PMd	Left	0.487	0.02	-0.67	0.743

t tests one-tailed, against chance (0.5). * Significant *p* values (FDR corrected for number of tests).

The results demonstrate that frontoparietal reach regions do well distinguish between different levels of specification of movement goals (specified vs. underspecified) but not between the type of movement goal (anti - inferred vs. pro - cued). Being provided with all necessary information to form a movement plan seems to bias spatial encoding processes in that network towards the encoding of the respective movement goal rather than the maintenance of the obsolete visual cue position. Especially, right SPL and left PMd play an important role in movement goal encoding. Interestingly, if the movement goal is underspecified the visual cue position is not encoded in the PPC, but only in PMd.

3.4 DISCUSSION

In the present study we aimed to investigate whether areas of the frontoparietal reaching network encode the visual cue position or the movement goal position in a pro-/anti-reach task. Our results demonstrate that SPL and PMd, but not aIPS, encode the position of the movement goal when the movement plan is specified. The right anterior and posterior portions of the SPL elicited highest specificity for movement goal encoding. We also decoded the visual cue position in the SPL, in particular in the left anterior SPL. In line with our previous univariate results (Gertz and Fiehler, 2015), none of the areas

differentiated between directly cued and inferred movement goals, i.e. between pro- and anti-reach planning. For conditions with underspecified movement goals, the visual cue position only showed specificity in the left PMd, but not in parietal regions. Finally, we observed the level of movement goal specification (specified vs. underspecified) to be encoded bilaterally in the posterior and anterior SPL, as well as in the left aIPS and PMd.

SPATIAL ENCODING PROCESSES DURING MOVEMENT PREPARATION

Our findings provide evidence that specifying the movement goal biases the encoding towards the position of the upcoming movement goal and away from the (now obsolete) visual cue position. The latter one seems to be maintained in a brain region which also encodes the movement goal showing that both encoding processes are not necessarily mutually exclusive. This finding may be explained by different neuronal populations within the SPL.

SPL and IPS have been suggested to encode the position of a movement goal to be acted upon (Beurze et al., 2007, 2009; Gallivan, McLean, Smith, et al., 2011). Here we dissociated the positions of the visual target from the movement goal in order to investigate whether frontoparietal areas maintain a visual, a motor representation or both. We found that anterior and posterior regions of the SPL as well as area PMd decode the position of the movement goal. Similar to our results on reach planning, SPL and PMd also show movement direction selectivity during reach execution (Fabbri et al., 2010, 2014; Haar et al., 2015). Our finding highlights the function of the frontoparietal network in encoding motor representations during movement planning. This contributes to the debate how motor-specific areas within the PPC compared to frontal motor regions are and strengthens the view of action representations in the PPC (c.f. Snyder et al., 1997; Andersen and Buneo, 2002; Andersen and Cui, 2009; Filimon, 2010; Lindner et al., 2010; Filimon et al., 2015).

In area aIPS, we were neither able to decode the visual cue position nor the movement goal position. Area aIPS is a grasp-selective region showing higher activation during the execution of grasping than reaching movements in monkeys and humans (Murata et al., 2000; Culham et al., 2003) and decoding of grasp versus reach movement planning as well as of similar grasps on objects with different sizes (Gallivan, McLean, Valyear, et al., 2011). Moreover, aIPS contains overlapping representations of movement direction and grip type and does not show pure directional selectivity (Fabbri et al., 2014).

Therefore, it is not surprising that the position of the movement goal was decoded from preparatory brain activation in reach-selective areas of the SPL and not in area aIPS.

We further demonstrate that none of the examined frontoparietal regions differentiate the type of movement goal, i.e. directly cued versus inferred movement goals for pro- and anti-reaches, respectively. This is in line with the largely overlapping brain activation in the frontoparietal network we found recently during planning of pro- and anti-reach movements (Gertz and Fiehler, 2015). The lack of a differential effect may be due to the fact that decoding was based on a delay phase of 3 s. In monkeys, movement goal tuning in monkey PRR occurs in pro-reach trials after 474 ms while PRR cells are tuned to the movement goal with a delay of 58 ms in anti-reach trials (Gail and Andersen, 2006). Moreover, monkey PRR cells show a preference in a sense of stronger directional selectivity for directly cued pro-reaches compared to anti-reaches, while the opposite effect is present in PMd cells (Gail et al., 2009). In our study, it is likely that participants inferred the movement goal in both specified pro- and anti-reach trials at the very beginning of the delay probably diluting any differences of the type of movement goal across the delay.

HEMISPHERIC ASYMMETRIES IN MOVEMENT GOAL ENCODING

During movement planning only the left PMd contralateral to the reaching hand was activated and encoded the movement goal. Such a contralateral bias was also observed in earlier univariate studies on reach planning (Medendorp, Goltz, Crawford, and Vilis, 2005; Bernier et al., 2012) speaking in favor of a stronger effector- and weaker target-specificity in PMd. For area SPL, on the other hand, we found bilateral activation with highest specificity for movement goal encoding in the right anterior and posterior SPL, thus ipsilateral to the moving effector. Previous studies on spatial encoding processes during reach planning reported movement goal encoding in regions of the SPL contralateral to the moving effector and thus suggested a contralateral bias in SPL (Medendorp, Goltz, Crawford, and Vilis, 2005; Fernandez-Ruiz et al., 2007; Gertz and Fiehler, 2015). However, recent MVPA studies highlight the importance of ipsilateral regions for the encoding of reach direction during reach execution (Fabbri et al., 2014) and for encoding the reach goal during reach planning (Gallivan et al., 2013). Note that uni- and multivariate approaches do not necessarily lead to similar results since amplitude differences of the BOLD response might occur in the absence of differences between activation patterns and vice versa (for a recent example, see Leoné et al., 2014). Yet, it is important to note that we

were also able to decode the position of the movement goal from anterior and posterior regions of the SPL contralateral to the effectoralthough decoding accuracies were lower. While we found movement goal encoding for a left-hemisphere ROI located at the border between SPL7A and SPL7P in our previous univariate study (Gertz and Fiehler, 2015), here we show that the more anteriorly located left SPL7A encodes both the position of the visual cue and the movement goal.

There is also evidence arguing against strict contralateral effector-specificity during reach planning (Gallivan et al., 2013) and execution (Fabbri et al., 2010). During reach execution it has even been shown that right SPL elicits high directional selectivity during both left- and right-hand reaches (Fabbri et al., 2010). Although we did not manipulate the effector for the upcoming movement, our results support and extend this finding to reach planning.

SENSORIMOTOR INTEGRATION IN FRONTOPARIETAL AREAS

Given the fact that participants were only presented with the visual cue in the underspecified condition, one might have predicted decoding of the visual cue position in posterior (more visual) parts of the PPC. Interestingly, only area PMd differentiated left from right visual cue positions. Accordingly, PMd cells of monkeys are tuned to visual target locations (Hoshi and Tanji, 2006) and are preferably involved in spatial aspects of action, such as active maintenance of visuo-spatial coordinates (Cisek, 2006). Moreover, area PMd has been shown to engage in goal selection processes based on competition of multiple alternative movement plans (Cisek 2006; Cisek and Kalaska, 2002). Our result indicates that area PMd can maintain movement-relevant spatial information when the movement goal is ambiguous, while movement goal specification leads to spatial coding also in areas within the SPL. Although we cannot address the time course of sensorimotor integration with the current study, one may speculate that the visual cue position is maintained in PMd until the movement goal is specified. Movement goal selection may then happen in PMd before sending this information via feedback projections to the PPC, as has been previously suggested by studies in monkeys (Pesaran et al., 2008; Westendorff et al., 2010) and also discussed in humans (Bernier et al., 2012).

Posterior parietal and premotor regions also encoded the different levels of movement goal specification, i.e. delay phases in which the movement goal was specified vs. underspecified. This suggests that the frontoparietal network comprising (at least) SPL,

aIPS, and PMd is engaged in integrating sensory and motor information and in setting up a movement plan. Based on differences in activation strength, similar results have been revealed in previous studies arguing for the integration of spatial target and effector information in PPC and PMd (Beurze et al., 2007; Bernier et al., 2012). Likewise, we showed previously that underspecified movement goals yield activation restricted to parietal regions as compared to specified movement goals (Gertz and Fiehler, 2015). Specifically, the medial posterior portions of the SPL were engaged in both specified and underspecified conditions. Our current results thus extend our knowledge about the processes within this region by showing that even if a region shows comparable activation for different levels of movement goal specification the underlying neuronal populations can distinguish between them.

3.5 CONCLUSIONS

We have reported evidence for movement goal encoding in anterior and posterior regions of the SPL as well as in PMd during reach planning. Our results further suggest that a frontoparietal network consisting of the left PMd, left aIPS and bilateral SPL plays a crucial role in sensorimotor integration.

4. THE ENDPOINT

4.1 SUMMARY

In this thesis, I presented results from a pro-/anti-reach task to examine the characteristics of movement planning processes in conditions with specified and underspecified movement goals at the cortical level. In a single experiment, we asked participants to perform a reaching movement either to the position of a visual cue (pro-reach) or to its mirrored position (anti-reach). Doing so, we could dissociate the position of the visual cue from the movement goal. We determined whether participants were to perform a pro- or anti-reach via a context rule cue that was given before the onset of the movement. In the specified condition, the rule cue was given well before the onset of the movement during a delay phase, so participants could infer the position of the movement goal and plan a movement to that position during the delay. In the underspecified condition, the rule cue was given just before movement onset, so the position of the movement goal could not be inferred during the delay. Importantly, we measured the brain activity during the delay phase, allowing us to examine the neural correlates of reach planning when the movement goal was clearly specified and when it is underspecified.

In the first study presented here, we demonstrated that when planning a reaching movement with the position of the movement goal specified, a frontoparietal brain network is recruited which comprises the PPC bilaterally and the left PMd (Figure 2.2). The activation in this network showed a large overlap between planning pro- and anti-reaches. Within this network, the activation in the PCu of the SPL contralateral to the moving arm

was modulated as a function of the position of the movement goal, but not of the position of the visual cue (Figure 2.3). The present findings demonstrate that the reach-related posterior SPL represents the movement goal rather than the visual cue when the movement goal is specified.

If only the visual cue but not the movement goal is available, rendering the reach goal underspecified, areas of the reaching network within the PPC were again recruited, but their activation was substantially weaker compared to the specified conditions (Figure 2.4). The posterior SPL, representing the movement goal in specified conditions, was also engaged in underspecified situations, but did not show any selective activation for the visual cue position or the reach goal position. Interestingly, when the reach goal was underspecified, the PMd was not active.

In the second study, we examined the spatial encoding processes in regions of the frontoparietal reach network in more detail. To detect potential subtle characteristics in spatial encoding during reach planning, we used MVPA which has been shown to be a sensitive approach in determining spatial processing during reach execution (Fabbri et al., 2014; Haar et al., 2015). We did so by decoding the visual cue and the movement goal position from the activation patterns within the frontoparietal regions when the movement goal was specified. Our results demonstrate that SPL and PMd encode the position of the movement goal (Figure 3.2). The highest specificity in the encoding of the movement goal position was found in the right anterior and posterior portions of the SPL, ipsilateral to the moving arm. Yet the anterior SPL also represented the visual cue position even though such information intuitively seems not to be important anymore at this point, since the reach goal was already specified. This may be of particular interest, since one might have expected regions closer to the visual cortex, such as the posterior PPC, to be more involved in the representation of visual information. Moreover, all areas we tested could distinguish well between a specified movement goal and an underspecified movement goal, representing the level of movement goal specification (Figure 3.3).

When the movement goal was underspecified, only the PMd represented the visual cue position. The SPL regions, the regions that encoded the movement goal in the specified conditions, did not represent the visual cue position (Figure 3.3). The encoding of the visual cue position in the PMd may have important implications for the way we understand motor planning in spatially ambiguous situations, and highlight the role of PMd for reach goal selection.

4.2 SPECIFIED REACH GOALS

For the specified conditions we have shown that the frontoparietal reach network was activated and showed a predominant representation of the movement goal position. Areas within the PPC, such as the SPL and IPS, have been shown before to represent the movement goal position in humans (Beurze et al., 2007, 2009; Gallivan, McLean, Smith, et al., 2011). Moreover, it is known that the SPL exhibits a preference for the physical movement direction over the visual cue position (Fernandez-Ruiz et al., 2007). By dissociating the visual cue from the movement goal position, we have extended previous findings by showing that several SPL regions maintain the position of the movement goal rather than the visuo-spatial cue. Thus, even regions such as the posterior SPL that are located early in the reach pathway near the visual cortex seem to maintain a prospective motor plan, rather than a retrospective sensory (visual) representation. Likewise, we extend evidence for a motor representation of the reach goal in the PMd (Beurze et al., 2007; Gallivan, McLean, Smith, et al., 2011). These results are in line with research showing movement goal encoding during reach planning in macaque PMd and PRR (Gail and Andersen, 2006; Gail et al., 2009; Westendorff et al., 2010; Klaes et al., 2011).

HEMISPHERIC ASYMMETRIES IN MOVEMENT GOAL REPRESENTATION

Although left and right SPL7 showed comparable levels of activation during movement planning, our analyses revealed differences between the two hemispheres in movement goal encoding. The results of our first study revealed a preference for a movement goal representation in the left posterior SPL7. In the second study, the position of the movement goal was encoded in both the left and right SPL7. Importantly, however, it was the right posterior and anterior SPL7 that showed the highest specificity.

One reason for these seemingly contradictory results may be the anatomical location of the tested ROI. In the first study, we based the ROI on SPL7 coordinates that have previously been shown to be involved in movement planning (Lindner et al., 2010). In this study we examined the characteristics of this reach related region in more detail. The ROI was located in the the PCu in the medial posterior SPL7. In the second study, we defined ROIs in a more elaborate manner, that is, individually for each participant. The activation across all conditions and participants served as a basis. Activation patterns were then combined with anatomical masks to ensure that the ROIs did not exceed the anatomical

border of a respective region. Thereafter, we identified individual signal peaks within the obtained region, resulting in an individually located ROI per participant for the anterior and posterior SPL7, respectively. As a result, the location of both ROIs differed between participants. Moreover, the location was not restricted to the PCu in the medial parts of the SPL7, as the ROI was in chapter 2. Indeed, slight changes in the anatomical location of a ROI in the SPL have recently been shown to dramatically change results on peripheral versus central reaching (Martin et al., 2014). This may be one reason why we found no spatial preference in the right SPL7 in the first study, while the right SPL7 exhibited strongest movement goal encoding in the second study. More so, in the first study, we tested for effects in the activation strength on the group level specifically related to movement goals in the contralateral field. The MVPA results from the second study, on the other hand, addressed the question if information about the movement goal position is encoded in a particular region in the individual activation patterns. Thus, as pointed out in chapter 1 of this thesis, we addressed substantially different questions with the two types of analyses. Moreover, uni- and multivariate approaches do not necessarily lead to similar results since amplitude differences of the BOLD response might occur in the absence of differences between activation patterns and vice versa (Leoné et al., 2014).

In addition to these methodological considerations, recent MVPA studies highlight the importance of ipsilateral regions for the encoding of reach direction during reach execution (Fabbri et al., 2014) and for encoding the reach goal during reach planning (Gallivan et al., 2013). It has been suggested that frontoparietal reach regions do not only represent planned actions with both the contralateral and ipsilateral hand, but also that these representations are to some extent limb invariant (Gallivan et al., 2013). These findings question the concept of a predominant representation of the contralateral arm and are in line with the results of our MVPA study. However, earlier studies using univariate analyses provide evidence that posterior parietal regions show stronger activation for reaches with the contralateral arm to goals in the contralateral visual field (Medendorp, Goltz, Crawford, and Vilis, 2005; Beurze et al., 2007; Bernier et al., 2012), an effect that we also show for the left PCu in our first study. Future research should investigate in more detail to what extent these contradictory lateralization effects can be explained by different methods of analyzing data or actual functional specializations of hemispheres for movements with the ipsi- or contralateral arm or to goals in the ipsi- or contralateral visual field.

VISUAL CUE REPRESENTATION IN THE ANTERIOR SPL7

In the MVPA study, we demonstrated that the anterior SPL7 not only maintains the visual cue position but also the movement goal position. This finding may suggest that the anterior SPL7 contains neural populations for both visual and motor representations. In this case, we may question why the obsolete visual cue position is still represented in the anterior SPL7, although the reach goal has already been specified.

One may speculate that the visual cue is maintained as a back-up, in case the previously presented rule cue may change unexpectedly and the reach goal thus has to be reconsidered. This would not be surprising as there are behavioral studies on goal-directed reaching and grasping movements showing that humans, when confronted with unexpected displacements of the target during the movement, initially adjust their movements to the direction of the displacement, even though this is not advantageous (Aivar et al., 2008; Day and Lyon, 2000). This has been suggested to occur because an automatic posterior parietal mechanism relies on spatial vision to quickly guide the hand to the target (Pisella et al., 2000). Although such effects are related to the phase of movement execution, one could speculate that the visual cue position remains in these posterior parietal areas during planning, in case this position will be used during movement execution.

Moreover, there is also a temporal component of spatial encoding: the spatial tuning to either the visual cue or the movement goal position is not a fixed property in monkey PMd and PRR, but it rather evolves throughout the process of movement planning (Gail et al., 2009; Westendorff et al., 2010). Our analyses in both studies were based on the delay phase, which varied between 3 and 5 seconds. It may be that the representation of the visual cue position in a subpopulation of the anterior SPL7 was the dominant process throughout the delay, while only later on the encoding of the movement goal became predominant.

Future research should address the temporal processes of spatial encoding to answer the question of how visual and motor representations evolve over time. It remains unclear if the visuo-spatial representation in the anterior SPL7 serves indeed as a “back-up”, and what the role of this potential back-up may be. An interesting aspect to address would thus be how this representation is used, or maybe even how it alters, representations in other regions when the movement goal suddenly changes. If there is more uncertainty about the movement goal, more frontoparietal regions may represent the visual cue in addition to, or instead of, the movement goal.

4.3 AMBIGUOUS REACH GOALS

NON-SPATIAL ACTIVATION IN THE POSTERIOR SPL

For the underspecified conditions, we found activation in the posterior SPL7 bilaterally and in the left aIPS, but crucially without any spatial representations of the visual cue position, as was made evident by both the univariate and multivariate study.

Our results are in line with previous findings of non-spatial preparatory activity in PMd and PPC in conditions where only the movement goal or the effector to move was known (Beurze et al., 2007). The role of such non-spatial activation remains widely unclear, but potential explanations have been put forward for findings in macaques. For instance, when the movement goal is still underspecified, a higher magnitude of non-spatial preparatory firing in the macaque PRR is significantly correlated with shorter reach reaction times (Snyder et al., 2006). Snyder and colleagues (2006) argued that the elevated baseline of PRR activity in underspecified conditions is useful for the rapid development of PRR firing rates that represent the reach goal, once it is specified. The more rapid movement goal representation in PRR may in turn cause a faster transfer of the spatial information over to the arm muscles, and thereby lead to shorter reaction times. Since the reach goal is already represented in PRR during a delay in conditions when the movement goal is specified, the stimulus to wait for is the go cue. In their experiment, this was the offset of the fixation point which is not processed by the PRR populations with peripheral response fields encoding the reach goal (Snyder et al. 2006). That may be why the magnitude of PRR activity and reach reaction times are not correlated in conditions with an early specified reach goal. A similar mechanism may account for our findings. The posterior SPL7 showed non-spatial activation in underspecified conditions, which still occured at a weaker level than in specified conditions. This may guarantee a rapid specification of the reach goal once the context rule (pro or anti) is presented. The posterior SPL7 areas and the aIPS may thus be in a “prepare-to-prepare” state rather than in a “prepare-to-move” state.

However, the role of such non-spatial preparatory activation needs to be clarified further. For instance, it remains to be demonstrated that the link between such preparatory activation and the actual reach behavior in humans is as close as it has been shown in macaques (Snyder et al., 2006).

THE ROLE OF PMD IN REACH GOAL SELECTION

Crucially, only the PMd represented the visual cue when the movement goal was ambiguous. In accordance, PMd cells of monkeys are tuned to visual target positions (Hoshi and Tanji, 2006) and are preferably involved in spatial aspects of action, such as active maintenance of visuo-spatial coordinates (Cisek, 2006). The PPC areas, on the other hand, did not show a spatial representation, while they do maintain the movement goal position in specified conditions. Therefore, it seems reasonable to assume a special function in reach plan specification to the PMd.

For instance, macaque PMd has been shown to be engaged in goal selection processes based on competition of multiple alternative movement plans (Cisek, 2006; Cisek and Kalaska, 2002). Similarly, we show that the PMd encodes both potential movement options (the visual cue position) when the movement goal is ambiguous, but switches to a movement goal representation in the specified condition. One may hypothesize that, as in monkeys, the final movement goal is selected in human PMd.

It is possible that PMd is not only engaged in reach goal selection, but may also trigger the SPL regions to switch from non-spatial activation (underspecified condition) to a representation of the movement goal position (specified conditions). Accordingly, it has been demonstrated that macaque PMd encodes the movement goal before it is later represented in PRR (Pesaran et al., 2008; Westendorff et al., 2010). It is still unclear whether this process is mediated by frontoparietal projections from PMd to PRR or because the movement goal specification in PMd causes a dynamic reorganization of PRR activity (Westendorff et al., 2010).

Human PMd has to this day been studied far less than macaque PMd. If and how PMd also represents reach goals in humans before PPC areas and how the areas functionally interact should therefore be a topic of future research. In particular, the temporal characteristics of functional interactions between frontal and (posterior) parietal areas of the reach network should be addressed. That is, do latency differences also occur between the human PMd and the PPC that could reflect the movement goal being specified earlier in frontal regions? This could be achieved by combining fMRI measurements with measurements allowing for a higher temporal resolution, such as EEG, and would be helpful to clarify how frontoparietal regions communicate during sensorimotor processing. For instance, is the PPC indeed involved in setting up movement goals, or is the motor goal set up in PMd and sent back via feedback connections to the PPC? Future research could

not only address the question of where in the brain sensorimotor transformations happen, but also how they evolve.

PARALLEL SPECIFICATION OF MULTIPLE MOVEMENT PLANS?

Taken together, we showed large differences between conditions with specified and underspecified reach goals. For instance, the planning of pro- and anti-reaches caused significantly higher and more widespread activation compared to underspecified movement goals. In this line, all frontoparietal regions we tested in the MVPA study could distinguish well between specified and underspecified movement goals. Moreover, the non-spatial activation in SPL, as well as the visual cue representation in PMd, demonstrate substantially different processes when the reach goal is underspecified. Overall, our results suggest an incomplete state of sensorimotor integration when the movement goal is ambiguous.

This interpretation contradicts findings from behavioral studies indicating the parallel specification of movement plans until the final reach goal is cued (C. S. Chapman et al., 2010; Stewart et al., 2013; Gallivan et al., 2016). It is important to note that the task we and others (Bernier et al., 2012) applied differs from the behavioral studies in the crucial aspect of when the final reach goal is cued. We cued the final reach goal right before movement onset. Our participants were thus aware that they could wait for the context rule cue and may therefore only then have started planning the movement. In the behavioral studies (C. S. Chapman et al., 2010; Stewart et al., 2013; Gallivan et al., 2016), the reach goal was cued only after movement onset. This manipulation may have biased the results towards what has been called a parallel specification of movement plans.

4.3 CONCLUSIONS

The results presented in this thesis show that a motor code is maintained in frontoparietal regions even before movement onset. This is true even for regions located early in the visuo-motor pathway. However, an ambiguous movement goal is not sufficient to cause the specification of a reach goal, arguing against the parallel specification of reach goals in ambiguous situations. The findings highlight the role of the PMd in representing underspecified reach goals and may suggest an earlier representation of reach goals in PMd, similar to what has been reported for the macaque reach network. The studies presented in this thesis thereby contribute to our understanding of how humans plan goal-directed reaching movements.

5. REFERENCES

Aflalo, T., Kellis, S., Klaes, C., Lee, B., Shi, Y., Pejsa, K., … Andersen, R. A. (2015). Decoding motor imagery from the posterior parietal cortex of a tetraplegic human. *Science*, *348*(6237), 906–910.

Aivar, M. P., Brenner, E., & Smeets, J. B. J. (2008). Avoiding moving obstacles. *Experimental Brain Research*, *190*, 251–264.

Andersen, R. A., & Buneo, C. A. (2002). Intentional maps in posterior parietal cortex. *Annual Review of Neuroscience*, *25*, 189–220.

Andersen, R. A., & Cui, H. (2009). Intention, action planning, and decision making in parietal-frontal circuits. *Neuron*, *63*(5), 568–583.

Andersson, J. L. R., Jenkinson, M., & Smith, S. (2010). Non-linear registration, aka spatial normalisation. FMRIB technical report TR07JA2 from www.fmrib.ox.ac.uk/analysis/techrep

Astafiev, S. V, Shulman, G. L., Stanley, C. M., Snyder, A. Z., Van Essen, D. C., & Corbetta, M. (2003). Functional organization of human intraparietal and frontal cortex for attending, looking, and pointing. *The Journal of Neuroscience*, *23*(11), 4689–4699.

Barany, D. A., Della-Maggiore, V., Viswanathan, S., Cieslak, M., & Grafton, S. T. (2014). Feature interactions enable decoding of sensorimotor transformations for goal-directed movement. *The Journal of Neuroscience*, *34*(20), 6860–6873.

Bastian, A., Riehle, A., Erlhagen, W., & Schöner, G. (1998). Prior information preshapes the population representation of movement direction in motor cortex. *Neuroreport*, *9*(2), 315–320.

Bastian, A., Schoner, G., & Riehle, A. (2003). Preshaping and continuous evolution of motor cortical representations during movement preparation. *European Journal of Neuroscience*, *18*(7), 2047–2058.

Batista, A. P., & Andersen, R. A. (2001). The parietal reach region codes the next planned movement in a sequential reach task. *Journal of Neurophysiology*, *85*, 539–544.

Battaglia-Mayer, A., Ferrari-Toniolo, S., Visco-Comandini, F., Archambault, P. S., Saberi-Moghadam, S., & Caminiti, R. (2013). Impairment of online control of hand and eye movements in a monkey model of optic ataxia. *Cerebral Cortex*, *23*(11), 2644–2656.

Beckmann, C. F., Jenkinson, M., & Smith, S. M. (2003). General multilevel linear modeling for group analysis in FMRI. *NeuroImage*, *20*(2), 1052–1063.

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society. Series B (Methodological)*, *57*(1), 289–300.

Berndt, I., Franz, V. H., Bülthoff, H. H., & Wascher, E. (2002). Effects of pointing direction and direction predictability on event-related lateralizations of the EEG. *Human Movement Science, 21*, 387–410.

Bernier, P.-M., Cieslak, M., & Grafton, S. T. (2012). Effector selection precedes reach planning in the dorsal parietofrontal cortex. *Journal of Neurophysiology, 108*, 57–68.

Beurze, S. M., de Lange, F. P., Toni, I., & Medendorp, W. P. (2007). Integration of target and effector information in the human brain during reach planning. *Journal of Neurophysiology, 97*, 188–199.

Beurze, S. M., de Lange, F. P., Toni, I., & Medendorp, W. P. (2009). Spatial and effector processing in the human parietofrontal network for reaches and saccades. *Journal of Neurophysiology*, *101*(6), 3053–3062.

Blangero, A., Ota, H., Delporte, L., Revol, P., Vindras, P., Rode, G., … Pisella, L. (2007). Optic ataxia is not only "optic": Impaired spatial integration of proprioceptive information. *Human Brain Mapping Journal*, *36*(3), T61–T68.

Blangero, A., Gaveau, V., Luauté, J., Rode, G., Salemme, R., Guinard, M., …Pisella, L. (2008). A hand and a field effect in on-line motor control in unilateral optic ataxia. *Cortex, 44*, 560-568.

Buneo, C. A., Jarvis, M. R., Batista, A. P., & Andersen, R. A. (2002). Direct visuomotor transformations for reaching. *Nature, 416*, 632–636.

Busan, P., Barbera, C., Semenic, M., Monti, F., Pizzolato, G., Pelamatti, G., & Battaglini, P. P. (2009). Effect of transcranial magnetic stimulation (TMS) on parietal and premotor cortex during planning of reaching movements. *PLoS ONE*, *4*(2), e4621.

Calton, J. L., Dickinson, A. R., & Snyder, L. H. (2002). Non-spatial, motor-specific activation in posterior parietal cortex. *Nature Neuroscience*, *5*(6), 580–588.

Caminiti, R., Johnson, P. B., Galli, C., Ferraina, S., & Burnod, Y. (1991). Making arm movements within different parts of space: the premotor and motor cortical representation of a coordinate system for reaching to visual targets. *The Journal of Neuroscience*, *11*(5), 1182–1197.

Cavina-Pratesi, C., Monaco, S., Fattori, P., Galletti, C., McAdam, T. D., Quinlan, D. J., … Culham, J. C. (2010). Functional magnetic resonance imaging reveals the neural substrates of arm transport and grip formation in reach-to-grasp actions in humans. *The Journal of Neuroscience*, *30*(31), 10306–10323.

Chang, S. W. C., Papadimitriou, C., & Snyder, L. H. (2009). Using a compound gain field to compute a reach plan. *Neuron, 64*, 744-755.

Chapman, C. S., Gallivan, J. P., Wood, D. K., Milne, J. L., Culham, J. C., & Goodale, M. A. (2010). Reaching for the unknown: multiple target encoding and real-time decision-making in a rapid reach task. *Cognition*, *116*(2), 168–176.

Chapman, H. L., Eramudugolla, R., Gavrilescu, M., Strudwick, M. W., Loftus, A., Cunnington, R., & Mattingley, J. B. (2010). Neural mechanisms underlying spatial realignment during adaptation to optical wedge prisms. *Neuropsychologia*, *48*, 2595–2601.

Cisek, P. (2006). Integrated neural processes for defining potential actions and deciding between them: a computational model. *The Journal of Neuroscience*, *26*(38), 9761–9770.

Cisek, P. (2007). Cortical mechanisms of action selection: the affordance competition hypothesis. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *362*, 1585–1599.

Cisek, P., & Kalaska, J. F. (2002). Simultaneous encoding of multiple potential reach directions in dorsal premotor cortex. *Journal of Neurophysiology*, *87*, 1149–1154.

Cisek, P., & Kalaska, J. F. (2005). Neural correlates of reaching decisions in dorsal premotor cortex: specification of multiple direction choices and final selection of action. *Neuron*, *45*, 801–814.

Connolly, J. D., Andersen, R. A., & Goodale, M. A. (2003). FMRI evidence for a "parietal reach region" in the human brain. *Experimental Brain Research*, *153*, 140–145.

Connolly, J. D., Goodale, M. A., Desouza, J. F. X., Menon, R. S., & Vilis, T. (2000). A comparison of frontoparietal fMRI activation during anti-saccades and anti-pointing. *Journal of Neurophysiology*, *84*, 1645–1655.

Connolly, J. D., Goodale, M. A., Menon, R. S., & Munoz, D. P. (2002). Human fMRI evidence for the neural correlates of the preparatory set. *Nature Neuroscience*, *5*(12), 1345–1352.

Crammond, D. J., & Kalaska, J. F. (1996). Differential relation of discharge in primary motor cortex and premotor cortex to movements versus actively maintained postures during a reaching task. *Experimental Brain Research*, *108*, 45–61.

Cui, H., & Andersen, R. A. (2007). Posterior parietal cortex encodes autonomously selected motor plans. *Neuron*, *56*(3), 552–559.

Cui, H., & Andersen, R. A. (2011). Different representations of potential and selected motor plans by distinct parietal areas. *The Journal of Neuroscience*, *31*(49), 18130–18136.

Culham, J. C., Cavina-Pratesi, C., & Singhal, A. (2006). The role of parietal cortex in visuomotor control: what have we learned from neuroimaging? *Neuropsychologia*, *44*, 2668–2684.

Culham, J. C., Danckert, S. L., DeSouza, J. F. X., Gati, J. S., Menon, R. S., & Goodale, M. A. (2003). Visually guided grasping produces fMRI activation in dorsal but not ventral stream brain areas. *Experimental Brain Research*, *153*, 180–189.

Culham, J. C., & Kanwisher, N. G. (2001). Neuroimaging of cognitive functions in human parietal cortex. *Current Opinion in Neurobiology*, *11*, 157–163.

Culham, J. C., & Valyear, K. F. (2006). Human parietal cortex in action. *Current Opinion in Neurobiology*, *16*(2), 205–212.

Dassonville, P., Lewis, S. M., Zhu, X.-H., Ugurbil, K., Kim, S.-G., & Ashe, J. (1998). Effects of movement predictability on cortical motor activation. *Neuroscience Research*, *32*, 65–74.

Day, B. L., & Lyon, I. N. (2000). Voluntary modification of automatic arm movements evoked by motion of a visual target. *Experimental Brain Research*, *130*, 159–168.

Dum, R. P., & Strick, P. L. (2005). Frontal lobe inputs to the digit representations of the motor areas on the lateral surface of the hemisphere. *The Journal of Neuroscience*, *25*(6), 1375–1386.

Eickhoff, S. B., Paus, T., Caspers, S., Grosbras, M.-H., Evans, A. C., Zilles, K., & Amunts, K. (2007). Assignment of functional activations to probabilistic cytoarchitectonic areas revisited. *NeuroImage*, *36*(3), 511–521.

Fabbri, S., Caramazza, A., & Lingnau, A. (2010). Tuning curves for movement direction in the human visuomotor system. *The Journal of Neuroscience*, *30*(40), 13488–13498.

Fabbri, S., Caramazza, A., & Lingnau, A. (2012). Distributed sensitivity for movement amplitude in directionally tuned neuronal populations. *Journal of Neurophysiology*, *107*(7), 1845–1856.

Fabbri, S., Strnad, L., Caramazza, A., & Lingnau, A. (2014). Overlapping representations for grip type and reach direction. *NeuroImage*, *94*, 138–146.

Fattori, P., Gamberini, M., Kutz, D. F., & Galletti, C. (2001). "Arm-reaching" neurons in the parietal area V6A of the macaque monkey. *European Journal of Neuroscience*, *13*, 2309–2313.

Fattori, P., Raos, V., Breveglieri, R., Bosco, A., Marzocchi, N., & Galletti, C. (2010). The dorsomedial pathway is not just for reaching: grasping neurons in the medial parieto-occipital cortex of the macaque monkey. *The Journal of Neuroscience*, *30*(1), 342–349.

Fernandez-Ruiz, J., Goltz, H. C., DeSouza, J. F. X., Vilis, T., & Crawford, J. D. (2007). Human parietal "reach region" primarily encodes intrinsic visual direction, not extrinsic movement direction, in a visual motor dissociation task. *Cerebral Cortex*, *17*(10), 2283–2292.

Ferrari-Toniolo, S., Papazachariadis, O., Visco-Comandini, F., Salvati, M., D'Elia, A., Di Berardino, F., … Battaglia-Mayer, A. (2014). A visuomotor disorder in the absence of movement: does optic ataxia generalize to learned isometric hand action? *Neuropsychologia*, *63*, 59–71.

Filimon, F. (2010). Human cortical control of hand movements: parietofrontal networks for reaching, grasping, and pointing. *The Neuroscientist*, *16*(4), 388–407.

Filimon, F., Nelson, J. D., Hagler, D. J., & Sereno, M. I. (2007). Human cortical representations for reaching: mirror neurons for execution, observation, and imagery. *NeuroImage*, *37*(4), 1315–28.

Filimon, F., Nelson, J. D., Huang, R.-S., & Sereno, M. I. (2009). Multiple parietal reach regions in humans: cortical representations for visual and proprioceptive feedback during on-line reaching. *The Journal of Neuroscience*, *29*(9), 2961–2971.

Filimon, F., Rieth, C. A., Sereno, M. I., & Cottrell, G. W. (2015). Observed, executed, and imagined action representations can be decoded from ventral and dorsal areas. *Cerebral Cortex*, *25*(9), 3144–3158.

Friston, K. J., Fletcher, P., Josephs, O., Holmes, A., Rugg, M. D., & Turner, R. (1998). Event-related fMRI: characterizing differential responses. *NeuroImage*, *7*(1), 30–40.

Gail, A., & Andersen, R. A. (2006). Neural dynamics in monkey parietal reach region reflect context-specific sensorimotor transformations. *The Journal of Neuroscience*, *26*(37), 9376–9384.

Gail, A., Klaes, C., & Westendorff, S. (2009). Implementation of spatial transformation rules for goal-directed reaching via gain modulation in monkey parietal and premotor cortex. *The Journal of Neuroscience*, *29*(30), 9490–9499.

Gallivan, J. P., Cavina-Pratesi, C., & Culham, J. C. (2009). Is that within reach? fMRI reveals that the human superior parieto-occipital cortex encodes objects reachable by the hand. *The Journal of Neuroscience*, *29*(14), 4381–4391.

Gallivan, J. P., Logan, L., Wolpert, D. M., & Flanagan, J. R. (2016). Parallel specification of competing sensorimotor control policies for alternative action options. *Nature Neuroscience*. *19*, 320-326.

Gallivan, J. P., McLean, D. A., Flanagan, J. R., & Culham, J. C. (2013). Where one hand meets the other: limb-specific and action-dependent movement plans decoded from preparatory signals in single human frontoparietal brain areas. *The Journal of Neuroscience*, *33*(5), 1991–2008.

Gallivan, J. P., McLean, D. A., Smith, F. W., & Culham, J. C. (2011). Decoding effector-dependent and effector-independent movement intentions from human parieto-frontal brain activity. *The Journal of Neuroscience*, *31*(47), 17149–17168.

Gallivan, J. P., McLean, D. A., Valyear, K. F., Pettypiece, C. E., & Culham, J. C. (2011). Decoding action intentions from preparatory brain activity in human parieto-frontal networks. *The Journal of Neuroscience*, *31*(26), 9599–9610.

Gertz, H., & Fiehler, K. (2015). Human posterior parietal cortex encodes the movement goal in a pro-/anti-reach task. *Journal of Neurophysiology*, *114*(1), 170–183.

Haar, S., Donchin, O., & Dinstein, I. (2015). Dissociating visual and motor directional selectivity using visuomotor adaptation. *The Journal of Neuroscience*, *35*(17), 6813–6821.

Hagler, D. J., Riecke, L., & Sereno, M. I. (2007). Parietal and superior frontal visuospatial maps activated by pointing and saccades. *NeuroImage*, *35*(4), 1562–1577.

Hallett, P. E. (1978). Primary and secondary saccades to goals defined by instructions. *Vision Research*, *18*, 1279–1296.

Haxby, J. V, Gobbini, M. I., Furey, M. L., Ishai, A., Schouten, J. L., & Pietrini, P. (2001). Distributed and overlapping representations of faces and objects in ventral temporal cortex. *Science*, *293*, 2425–2430.

He, S.-Q., Dum, R. P., & Strick, P. L. (1993). Topographic organization of corticospinal projections from the frontal lobe: motor areas on the lateral surface of the hemisphere. *The Journal of Neuroscience*, *13*(3), 952–980.

Heed, T., Beurze, S. M., Toni, I., Röder, B., & Medendorp, W. P. (2011). Functional rather than effector-specific organization of human posterior parietal cortex. *The Journal of Neuroscience*, *31*(8), 3066–3076.

Holmes, C.J., Hoge, R., Collins, L., Woods, R., Toga, A.W., & Evans, A.C. (1998). Enhancement of MR images using registration for signal averaging. *Journal of Computer Assisted Tomography*, *22*, 324–333.

Hoshi, E., & Tanji, J. (2006). Differential involvement of neurons in the dorsal and ventral premotor cortex during processing of visual signals for action planning. *Journal of Neurophysiology*, *95*, 3596–3616.

Hubert, M., & Van der Veeken, S. (2008). Outlier detection for skewed data. *Journal of Chemometrics*, *22*, 235–246.

Hwang, E. J., Hauschild, M., Wilke, M., & Andersen, R. A. (2012). Inactivation of the parietal reach region causes optic ataxia, impairing reaches but not saccades. *Neuron*, *76*(5), 1021–1029.

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *NeuroImage*, *17*(2), 825–841.

Jenkinson, M., Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W., & Smith, S. M. (2012). FSL. *NeuroImage*, *62*, 782–790.

Johnson, P. B., Ferraina, S., Bianchi, L., & Caminiti, R. (1996). Cortical networks for visual reaching: physiological and anatomical organization of frontal and parietal lobe arm regions. *Cerebral Cortex*, *6*, 102–119.

Kalaska, J. F., Scott, S. H., Cisek, P., & Sergio, L. E. (1997). Cortical control of reaching movements. *Current Opinion in Neurobiology*, *7*, 849–859.

Kamitani, Y., & Tong, F. (2005). Decoding the visual and subjective contents of the human brain, *8*(5), 679–685.

Karnath, H.-O., & Perenin, M.-T. (2005). Cortical control of visually guided reaching: evidence from patients with optic ataxia. *Cerebral Cortex*, *15*(10), 1561–1569.

Khan, A. Z., Crawford, J. D., Blohm, G., Urquizar, C., Rossetti, Y., & Pisella, L. (2007). Influence of initial hand and target position on reach errors in optic ataxic and normal subjects. *Journal of Vision*, *7*(8), 1–16.

Klaes, C., Westendorff, S., Chakrabarti, S., & Gail, A. (2011). Choosing goals, not rules: deciding among rule-based action plans. *Neuron*, *70*(3), 536–548.

Kuang, S., Morel, P., & Gail, A. (2015). Planning movements in visual and physical space in monkey posterior parietal cortex. *Cerebral Cortex*, 1–17.

Leblois, A., Boraud, T., Meissner, W., Bergman, H., & Hansel, D. (2006). Competition between feedback loops underlies normal and pathological dynamics in the basal ganglia. *The Journal of Neuroscience*, *26*(13), 3567–3583.

Lehmann, S. J., & Scherberger, H. (2013). Reach and gaze representations in macaque parietal and premotor grasp areas. *The Journal of Neuroscience*, *33*(16), 7038–7049.

Leoné, F. T. M., Heed, T., Toni, I., & Medendorp, W. P. (2014). Understanding effector selectivity in human posterior parietal cortex by combining information patterns and activation measures. *The Journal of Neuroscience*, *34*(21), 7102–7112.

Lindner, A., Iyer, A., Kagan, I., & Andersen, R. A. (2010). Human posterior parietal cortex plans where to reach and what to avoid. *The Journal of Neuroscience*, *30*(35), 11715–11725.

Luauté, J., Schwartz, S., Rossetti, Y., Spiridon, M., Rode, G., Boisson, D., & Vuilleumier, P. (2009). Dynamic changes in brain activity during prism adaptation. *The Journal of Neuroscience*, *29*(1), 169–178.

Martin, J. A., Karnath, H.-O., & Himmelbach, M. (2014). Revisiting the cortical system for peripheral reaching at the parieto-occipital junction. *Cortex*, *64*, 363–379.

Medendorp, W. P., Goltz, H. C., Crawford, J. D., & Vilis, T. (2005). Integration of target and effector information in human posterior parietal cortex for the planning of action. *Journal of Neurophysiology*, *93*, 954–962.

Medendorp, W. P., Goltz, H. C., & Vilis, T. (2005). Remapping the remembered target location for anti-saccades in human posterior parietal cortex. *Journal of Neurophysiology*, *94*(1), 734–740.

Medendorp, W. P., Goltz, H. C., & Vilis, T. (2006). Directional selectivity of BOLD activity in human posterior parietal cortex for memory-guided double-step saccades. *Journal of Neurophysiology*, *95*(3), 1645–1655.

Messier, J., & Kalaska, J. F. (2000). Covariation of primate dorsal premotor cell activity with direction and amplitude during a memorized-delay reaching task. *Journal of Neurophysiology*, *84*, 152–165.

Monaco, S., Cavina-Pratesi, C., Sedda, A., Fattori, P., Galletti, C., & Culham, J. C. (2011). Functional magnetic resonance adaptation reveals the involvement of the dorsomedial stream in hand orientation for grasping. *Journal of Neurophysiology*, *106*(5), 2248–2263.

Monaco, S., Chen, Y., Medendorp, W. P., Crawford, J. D., Fiehler, K., & Henriques, D. Y. P. (2014). Functional magnetic resonance imaging adaptation reveals the cortical networks for processing grasp-relevant object properties. *Cerebral Cortex*, *24*(6), 1540–1554.

Mountcastle, V. B., Lynch, J. C., Georgopoulos, A., Sakata, H., & Acuna, C. (1975). Posterior parietal association cortex of the monkey: command functions for operations within extrapersonal space. *Journal of Neurophysiology*, *38*(4), 871–908.

Murata, A., Gallese, V., Luppino, G., Kaseda, M., & Sakata, H. (2000). Selectivity for the shape, size, and orientation of objects for grasping in neurons of monkey parietal area AIP. *Journal of Neurophysiology*, *83*(5), 2580–2601.

Ogawa, S., Lee, T. M., & Kay, A. R. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences of the United States of America*, *87*, 9868–9872.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*, *9*(1), 97–113.

Oosterhof, N. N., Connolly, A.C., & Haxby, J.V. (2016). CoSMoMVPA: multi-modal multivariate pattern analysis of neuroimaging data in Matlab / GNU Octave. *biorxiv.org*.

Parkinson, A., Condon, L., & Jackson, S. R. (2010). Parietal cortex coding of limb posture: in search of the body-schema. *Neuropsychologia*, *48*(11), 3228–3234.

Passingham, R. (2009). How good is the macaque monkey model of the human brain? *Current Opinion in Neurobiology*, *19*, 6–11.

Pellijeff, A., Bonilha, L., Morgan, P. S., McKenzie, K., & Jackson, S. R. (2006). Parietal updating of limb posture: an event-related fMRI study. *Neuropsychologia*, *44*(13), 2685–2690.

Perenin, M.-T., & Vighetto, A. (1988). Optic ataxia: a specific disruption in visuomotor mechanisms. I. Different aspects of the deficit in reaching for objects. *Brain*, *111*, 643–674.

Pesaran, B., Nelson, M. J., & Andersen, R. A. (2006). Dorsal premotor neurons encode the relative position of the hand, eye, and goal during reach planning. *Neuron*, *51*(1), 125–134.

Pesaran, B., Nelson, M. J., & Andersen, R. A. (2008). Free choice activates a decision circuit between frontal and parietal cortex. *Nature*, *453*, 406–409.

Picard, N., & Strick, P. L. (2001). Imaging the premotor areas. *Current Opinion in Neurobiology*, *11*, 663–672.

Pisella, L., Gréa, H., Tilikete, C., Vighetto, A., Desmurget, M., Rode, G., … Rossetti, Y. (2000). An "automatic pilot" for the hand in human posterior parietal cortex: toward reinterpreting optic ataxia. *Nature Neuroscience*, *3*(7), 729–736.

Pisella, L., Michel, C., Gréa, H., Tilikete, C., Vighetto, A., & Rossetti, Y. (2004). Preserved prism adaptation in bilateral optic ataxia: strategic versus adaptive reaction to prisms. *Experimental Brain Research*, *156*, 399–408.

Praamstra, P., Kourtis, D., & Nazarpour, K. (2009). Simultaneous preparation of multiple potential movements: opposing effects of spatial proximity mediated by premotor and parietal cortex. *Journal of Neurophysiology*, *102*(4), 2084–2095.

Prado, J., Clavagnier, S., Otzenberger, H., Scheiber, C., Kennedy, H., & Perenin, M.-T. (2005). Two cortical systems for reaching in central and peripheral vision. *Neuron*, *48*, 849–858.

Rawle, C. J., Miall, R. C., & Praamstra, P. (2012). Frontoparietal theta activity supports behavioral decisions in movement-target selection. *Frontiers in Human Neuroscience*, *6*(138), 1–11.

Rossetti, Y., Pisella, L., & Vighetto, A. (2003). Optic ataxia revisited: visually guided action versus immediate visuomotor control. *Experimental Brain Research*, *153*, 171–179.

Scott, S. H., Sergio, L. E., & Kalaska, J. F. (1997). Reaching movements with similar hand paths but different arm orientations. II. Activity of individual cells in dorsal premotor cortex and parietal area 5. *Journal of Neurophysiology*, *78*, 2413–2426.

Smith, S. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, *17*(3), 143–155.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., … Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, *23*(Supplement 1), S208–19.

Snyder, L. H., Batista, A. P., & Andersen, R. A. (1997). Coding of intention in the posterior parietal cortex. *Nature*, *386*, 167–70.

Snyder, L. H., Batista, A. P., & Andersen, R. A. (1998). Change in motor plan, without a change in the spatial locus of attention, modulates activity in posterior parietal cortex. *Journal of Neurophysiology*, *79*, 2814–2819.

Snyder, L. H., Dickinson, A. R., & Calton, J. L. (2006). Preparatory delay activity in the monkey parietal reach region predicts reach reaction times. *The Journal of Neuroscience*, *26*(40), 10091–10099.

Stewart, B. M., Baugh, L. A., Gallivan, J. P., & Flanagan, J. R. (2013). Simultaneous encoding of the direction and orientation of potential targets during reach planning: evidence of multiple competing reach plans. *Journal of Neurophysiology*, *110*, 807–816.

Stewart, B. M., Gallivan, J. P., Baugh, L. A., & Flanagan, J. R. (2014). Motor, not visual, encoding of potential reach targets. *Current Biology*, *24*(19), R953–954.

Tanné-Gariépy, J., Rouiller, E. M., & Boussaoud, D. (2002). Parietal inputs to dorsal versus ventral premotor areas in the macaque monkey: evidence for largely segregated visuomotor pathways. *Experimental Brain Research*, *145*, 91–103.

Tomassini, V., Jbabdi, S., Klein, J. C., Behrens, T. E. J., Pozzilli, C., Matthews, P. M., … Johansen-Berg, H. (2007). Diffusion-weighted imaging tractography-based parcellation of the human lateral premotor cortex identifies dorsal and ventral subregions with anatomical and functional specializations. *The Journal of Neuroscience*, *27*(38), 10259–10269.

Toni, I., Shah, N. J., Fink, G. R., Thoenissen, D., Passingham, R. E., & Zilles, K. (2002). Multiple movement representations in the human brain: an event-related fMRI study. *Journal of Cognitive Neuroscience*, *14*(5), 769–784.

Tunik, E., Frey, S. H., & Grafton, S. T. (2005). Virtual lesions of the anterior intraparietal area disrupt goal-dependent on-line adjustments of grasp. *Nature Neuroscience*, *8*(4), 505–511.

Tunik, E., Rice, N. J., Hamilton, A., & Grafton, S. T. (2007). Beyond grasping: representation of action in human anterior intraparietal sulcus. *NeuroImage*, *36*, T77–86.

Tzagarakis, C., Ince, N. F., Leuthold, A. C., & Pellizzer, G. (2010). Beta-band activity during motor planning reflects response uncertainty. *The Journal of Neuroscience*, *30*(34), 11270–11277.

Van Essen, D. C., Lewis, J. W., Drury, H. A., Hadjikhani, N., Tootell, R. B. H., Bakircioglu, M., & Miller, M. I. (2001). Mapping visual cortex in monkeys and humans using surface-based atlases. *Vision Research*, *41*, 1359–1378.

Vesia, M., & Crawford, J. D. (2012). Specialization of reach function in human posterior parietal cortex. *Experimental Brain Research*, *221*, 1–18.

Westendorff, S., & Gail, A. (2011). What is "anti" about anti-reaches? Reference frames selectively affect reaction times and endpoint variability. *Experimental Brain Research*, *208*, 287–296.

Westendorff, S., Klaes, C., & Gail, A. (2010). The cortical timeline for deciding on reach motor goals. *The Journal of Neuroscience*, *30*(15), 5426–5436.

Wise, S. P., Boussaoud, D., Johnson, P. B., & Caminiti, R. (1997). Premotor and parietal cortex: corticocortical connectivity and combinatorial computations. *Annual Review of Neuroscience*, *20*, 25–42.

Woolrich, M. W., Behrens, T. E. J., Beckmann, C. F., Jenkinson, M., & Smith, S. M. (2004). Multilevel linear modelling for FMRI group analysis using Bayesian inference. *NeuroImage*, *21*(4), 1732–1747.

Worsley, K. J., Marrett, S., Neelin, P., Vandal, A. C., Friston, K. J., & Evans, A. C. (1996). A unified statistical approach for determining significant signals in images of cerebral activation. *Human Brain Mapping*, *4*(1), 58–73.

Yttri, E. A., Wang, C., Liu, Y., & Snyder, L. H. (2014). The parietal reach region is limb specific and not involved in eye-hand coordination. *Journal of Neurophysiology*, *111*(3), 520–532.

ERKLÄRUNG

Ich erkläre: Ich habe die vorgelegte Dissertation selbstständig und ohne unerlaubte fremde Hilfe und nur mit den Hilfen angefertigt, die ich in der Dissertation angegeben habe. Alle Textstellen, die wörtlich oder sinngemäß aus veröffentlichten Schriften entnommen sind, und alle Angaben, die auf mündlichen Auskünften beruhen, sind als solche kenntlich gemacht. Bei den von mir durchgeführten und in der Dissertation erwähnten Untersuchungen habe ich die Grundsätze guter wissenschaftlicher Praxis, wie sie in der „Satzung der Justus-Liebig-Universität Gießen zur Sicherung guter wissenschaftlicher Praxis“ niedergelegt sind, eingehalten.

Gießen, 21. April 2016

Hanna Margareta Gertz