Reach and gaze representations in the anterior intraparietal area and the ventral premotor cortex of macaques

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Publication Date:
2013

Permanent Link:
https://doi.org/10.3929/ethz-a-009787079

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REACH AND GAZE REPRESENTATIONS IN THE ANTERIOR INTRAPARIETAL AREA AND THE VENTRAL PREMOTOR CORTEX OF MACAQUES

A dissertation submitted to
ETH ZURICH

for the degree of
Doctor of Sciences

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2013
Acknowledgments

Since this thesis extended over six years and 600 kilometres, a lot of people enriched my scientific and after work life.

Therefore I want to thank:

Hansjörg Scherberger, my supervisor, who gave me the opportunity to realize this project, starting it in Zürich and ending it in Göttingen. His open door policy, combined with useful advice in scientific as well as other questions resulted in a nice and productive work ambience.

Natalie Nazarenus and Tanya Lewis, who helped me recording the data.

All former group members in Zürich for fun times during and after work: Markus Baumann, Erk Subasi, MC Fluet, and Ben Townsend. We were a brilliant “Team B”.

The administration office at the Institute of Neuroinformatics, in particular Kathrin Aguilar for continuously forwarding my post to Germany.

All group members in Göttingen, in particular my office neighbours Stefan Schaffelhofer and Katharina Menz. Further thanks to Ricarda Ahlert and Matthias Dörge, Jacopo Rigosa and Shubo Chakrabarti for fruitful discussions during and after work. In addition I want to thank the caretakers and veterinaries in both Zürich and Göttingen.

Thanks to Prof. Kevan Martin and Prof. Bernhard Hess for their agreement to participate in the examination committee.

Last but not least, I want to thank my parents, who supported me throughout my life, making it possible to follow my interests.
# Table of contents

Acknowledgments ............................................................................................................. 3

Table of contents ............................................................................................................... 4

Summary ............................................................................................................................. 7

Zusammenfassung ............................................................................................................... 9

1. Introduction .................................................................................................................... 13

1.1 Overview ...................................................................................................................... 13

1.2 The cortical motor system .......................................................................................... 14

1.3 Parieto-frontal networks for movement planning and execution ......................... 17

1.3.1 The hand grasping network: AIP and F5 .............................................................. 20

1.3.1.1 The anterior intraparietal cortex (AIP) ......................................................... 20

1.3.1.2 Area F5 ....................................................................................................... 24

1.3.2 The reach network: PRR & PMd ........................................................................ 28

1.3.2.1 Parietal reach region PRR ........................................................................... 28

1.3.2.2 The dorsal premotor cortex (PMd) .............................................................. 30

1.3.3 The saccade network: LIP and FEF .................................................................... 31

1.3.3.1 Lateral intraparietal cortex (LIP, Brodman area 7) ..................................... 31

1.3.3.2 Frontal eye field (FEF) .............................................................................. 32

1.3.4 Primary motor cortex (M1) .................................................................................. 33

1.4 Reference frame transformation during goal-directed actions ............................. 35

1.5 Local field potentials (LFP) ...................................................................................... 37

1.6 Motivation and goal of the thesis .............................................................................. 39

2. Methods ......................................................................................................................... 41

2.1 Experimental setup .................................................................................................... 42
2.2 Task paradigms........................................................................................................49
  2.2.1 Target variation task (TASK I).................................................................50
  2.2.2 Start variation task (TASK II)....................................................................52
2.3 Surgical procedures and MRI scans.................................................................52
2.4 Neuronal recordings..........................................................................................54
  2.4.1 Data analysis of spiking activity...............................................................55
  2.4.2 LFP analysis..................................................................................................60

3. Modulation of spiking activity in AIP and F5.................................................64
  3.1 Introduction.......................................................................................................64
  3.2 Results from target variation task (TASK I)..............................................64
    3.2.1 Tuning analysis.........................................................................................64
      3.2.1.1 Population tuning............................................................................70
      3.2.1.2 Encoding Preferences....................................................................75
      3.2.1.3 Tuning onset....................................................................................77
      3.2.1.4 Anatomical organization of tuned units........................................78
    3.2.2 ROC analysis............................................................................................80
    3.2.3 Coordinate frames - linear modeling ....................................................82
    3.2.4 Decoding simulation................................................................................88
  3.3 Results from start variation task (TASK II)...............................................96
    3.3.1 Single unit examples for different tuning qualities...............................96
    3.3.2 Population Tuning..................................................................................98
  3.4 Discussion.........................................................................................................102
    3.4.1 Representations in the target variation task (TASK I).......................102
    3.4.2 Grip type tuning.....................................................................................104
    3.4.3 Target and gaze representations............................................................105
3.4.4 Representations in the start variation task (TASK II) .........................107
3.4.5 Reference frames ...........................................................................109
3.4.6 Motor planning and coordination ....................................................110

4. Modulation of LFP activity in AIP and F5 .........................................112

4.1 Population activity ..........................................................................112
4.2 Tuning analysis of LFP activity .........................................................115
  4.2.1 Epoch tuning in different frequencies ........................................115
  4.2.2 Epoch tuning for “broader” frequency bands ..............................118
  4.2.3 Tuning onset for different LFP bands ........................................122
  4.2.4 Distribution of preferred conditions .........................................123
4.3 Decoding simulation with LFP activity ..........................................130
4.4 Linear Model ..................................................................................135
4.5 Discussion ......................................................................................140
  4.5.1 Summary ..................................................................................140
  4.5.2 General considerations ............................................................142
  4.5.3 Representation of grip type ......................................................143
  4.5.4 Representation of spatial information ......................................144
  4.5.5 Implications for brain machine interfaces .................................146

5. Conclusions ......................................................................................148

References ..........................................................................................151

List of abbreviations ...........................................................................169

Curriculum Vitae Sebastian J. Lehmann ..............................................170
Summary

Voluntary, goal-directed movements are frequently composed of several actions that are combined to achieve a specific behaviour. For example, prehension involves reaching and grasping actions to transport the hand to a target in order to grasp or manipulate it. For controlling these actions, separate parieto-frontal cortical networks have been described for generating reaching and grasping actions. The network specialized for grasp movements consists of the anterior intraparietal area (AIP) and ventral premotor area (F5), which are strongly and reciprocally connected to each other. Various studies revealed that these visuo-motor areas are involved in the transformation of an object’s intrinsic properties, like size or orientation, into the appropriate finger configuration in order to grasp it. However, as grasping and reaching are behaviorally and functionally so strongly combined, it could be expected, that also spatial, reach related factors influence neuronal grasp activity in the areas AIP and F5. These spatial factors could be the position of the grasp target in space, the position of gaze, or the starting position of the hand. The majority of studies about neuronal representation in the hand grasping areas were focused on either the grasping or the reaching component of reach-to-grasp movements.

For this thesis, we therefore analyzed the influence of systematically varied spatial factors on grasp related neuronal activity in AIP and F5. We developed an environment that allowed the systematic variation of grip type, target position, gaze position, as well as the starting position of the hand. Two macaques were trained to perform a delayed reach-to-grasp task. We then recorded 353 single units in parietal area AIP and 585 single units in premotor area F5. The neuronal populations in both of these areas not only showed grasp representation, but in addition also encoded
spatial information. Whereas the fraction of grip type tuned units increased toward movement execution, the number of cells with spatial representations stayed relatively constant throughout the task, however more prominently in AIP than in F5. Among the spatial representations, we found both target and gaze information to be encoded in each of the areas AIP and F5. Furthermore, the target position was substantially encoded in retinotopic, i.e. eye-centered, coordinates in both areas. In comparison, the initial hand position was not substantially represented in any of the areas.

Moreover, we analyzed the encoding properties of the local field potentials (LFP) during the delayed reach-to-grasp task. Similar to our findings for the single-unit activity, we found the strongest grasp representation during movement execution in both areas, whereas the spatial representations stayed on similar levels across epochs. Also in the LFP, we found a mixture of gaze, target, and retinotopic target representations, and spatial information was generally stronger present in AIP than in F5.

In conclusion, this thesis reveals new insights into visuo-motor processes in the hand grasping areas AIP and F5. It shows the simultaneous presence of grasp-related and spatial information in AIP and F5, in both single unit as well as LFP activity. This suggests an at least supportive role of these spatial signals for the planning of grasp actions. Whether these spatial signals in AIP and F5 also play a causal role for the planning of reach actions would need to be the subject of further investigations.
Zusammenfassung


Für diese Dissertation analysierte ich den Einfluss systematisch varierter räumlicher Faktoren auf die handgreif-spezifische neuronale Aktivität in AIP und F5. Wir entwickelten eine Umgebung, die die systematische Variation von Griff-Art,

Des weiteren untersuchten wir den Einfluss unseres Tasks auf das lokale Feldpotential (LFP). Ähnlich zu unseren Resultaten in der neuronalen Population war die Griff-Art am stärksten während der Bewegungsausführung repräsentiert, wohingegen die räumliche Information stabil in allen Epochen zu finden war. Auch hier handelte es sich um eine Mischung aus Blickrichtung und Objektposition, die wiederum zum Teil retinotop repräsentiert war, und auch hier waren die räumlichen Faktoren meist deutlich stärker in AIP kodiert.

Diese Dissertation gewährt neue Einblicke in visuell-motorische Prozesse, die sich bei der Ausführung von Handgreif- und Armbewegungen in den Arealen AIP und F5 abspielen. Sie zeigt die gleichzeitige Präsenz von griff-spezifischer und räumlicher Information in beiden Arealen auf, die sich sowohl auf neuronaler Ebene, als auch in
1. Introduction

1.1 Overview

Using the hand in order to manipulate objects in the peri-personal environment is a unique key feature in the behaviour of both human and non-human primates. The anatomy of the hand enables a huge variety of different finger configurations and therefore hand movements. These movements range from the highly accurate manipulation of objects with thumb and the opposed fingertips (so called precision grip) to stronger grips with the whole hand (power grip). Typically, grasp movements are visually guided: observed information about target objects is transformed into motor plans, and finally motor output. Grasps are usually embedded in reach movements towards the target that is supposed to be manipulated. A range of spatial factors is of potential importance for these combined reach-to-grasp movements. These include the spatial position of the target relative to the body or the hand position, as well as the position of gaze. Subject of the present thesis is, to which extent these spatial factors are represented in the hand grasping areas of parietal and premotor cortex. This could be of importance for understanding how the brain manages complex sensori-motor processes during goal-directed reach movements in non-human primates.

The introduction gives a short overview of the cortical motor system (Chapter 1.2), followed by a review of literature about the relevant areas in the parieto-frontal networks involved in visuo-motor transformation processes during goal-directed
1. Introduction

actions (Chapter 1.3). The focus is on the key nodes of the hand grasping planning circuit (Chapter 1.3.1) and their human homologues, but also the primate areas for reaching (Chapter 1.3.2) and saccade-generation (Chapter 1.3.3), as well as the primary motor cortex (Chapter 1.3.4.) will be introduced. In addition, I will give a general overview about visuo-motor (or reference frame) transformation processes that the brain performs between the input of visual information and the output of motor signals (Chapter 1.4). Furthermore, I will give a short introduction to local field potentials (LFP) in the hand grasping areas AIP and F5 (Chapter 1.5). The final part of the introduction specifies the research question and goals of the present thesis (Chapter 1.6).

1.2 The cortical motor system

Motor related areas within the frontal cortex

John Hughling Jackson was the first to suggest that sensory-motor functions are located in a somatotopic way in cortical structures, interpreting the progression of epileptic seizures. Early electrical stimulation studies by Fritsch and Hitzig in dogs (1870) and by Ferrier in monkeys (1878) confirmed the motor function of the cortex. Further studies by Beevor and Horsley (1887) revealed more details about the topographic mapping in frontal cortex, with distinct regions representing different limbs and their actions (for a detailed review about the “Discovery of Motor Cortex” see Gross, 2007; Wallis et al., 2001).

Based on electrophysiological, anatomical and architectonical findings the frontal cortex could be divided into at least seven premotor areas which project directly to the
primary (or precentral) motor cortex (M1): ventral and dorsal premotor cortex (PMv, PMd), the supplementary motor area (SMA), and three cingulate motor areas (CMAv, CMAd, CMAr), (for further anatomical details please see Dum and Strick, 2002; Hoshi and Tanji, 2007; Matelli et al., 1985; Wise, 1985). An overview about frontal (and parietal) cortical areas is given in Figure 1.1, taken from Caminiti et al. (2010). Instead of the functional descriptive names for the premotor areas, the architectural definitions F2 to F7 given by Matelli et al. (1991) are used in this figure: F2 corresponds to the caudal part of PMd, F3 to SMA, F4 and F5 to caudal and rostral PMv, F6 to pre-SMA, and F7 to rostral PMd. In addition, the color code indicates the definitions according to Brodmann.

The primary motor cortex is the source of the signals directly controlling muscle activity and therefore movements, whereas in the premotor areas, also sensory and abstract planning activity is represented. Neurons in both PMv and PMd respond to the appearance of visual signals and are active during the planning and execution of visually guided movements (e.g. Hoshi and Tanji, 2007; Rizzolatti and Luppino, 2001; Wise, 1985). Similarly, the frontal eye field (FEF), located in the anterior bank of the arcuate sulcus, is involved in planning and executing saccades.

The premotor areas SMA, pre-SMA and CMA have a supportive and rather abstract character: they are involved in monitoring limb movements (SMA), in the process of acquiring and planning more complex spatio-temporal movement patterns (pre-SMA) and in decision processes (CMA) (Kaas et al., 2012; Rizzolatti and Luppino, 2001; Tanji, 1996) and will not be further discussed here.
1. Introduction

Motor related areas within the parietal cortex

Early studies about posterior parietal cortex (PPC) described its role either in sensory and attentional processes (Colby and Goldberg, 1999; Mishkin et al., 1982; Robinson et al., 1978) or in motor control (Mountcastle et al., 1975; Rizzolatti et al., 1997). It turned out that both processes are combined in PPC, and that its regions play an important role in multisensory integration and sensori-motor transformation (Andersen, 1997). A large component of the activity in the PPC represents intention for different movements (Andersen and Buneo, 2002). In line with this, there is an anatomical segregation into specialized cortical areas for grasping, reaching, or generating saccades (Snyder et al., 2000). Research during the last decades gave deeper insight into the key areas involved in the planning and execution of several motor actions (Cui and Andersen, 2011): in parietal cortex, these are the lateral intraparietal cortex (LIP) for saccades, the parietal reach region (PRR) for reach movements, and the anterior intraparietal cortex (AIP) for hand grasping movements.
1. Introduction

Figure 1.1 Parcellation of frontal and parietal cortex in the macaque monkey.

(A) Lateral view on frontal and parietal cortex of the left hemisphere; the inset on the bottom shows a flattened and more detailed view of areas within the intraparietal sulcus (IPS); (B) mesial view, (C) modified lateral view with the inferior parietal lobule (IPL) removed to show the areas lying in the medial wall of IPS. For abbreviations, please see text and list of abbreviations in the appendix. Figure taken from Caminiti et al. (2010).

1.3 Parieto-frontal networks for movement planning and execution

During the planning and execution of voluntary, visually guided movements, sensory information is transformed into motor information. The afore-mentioned cortical areas form a system of parieto-frontal pathways that is involved in this sensori-motor transformation process (Goodale and Milner, 1992; Milner and Goodale, 2008; Tanne-Gariepy et al., 2002).

In general, visual information about a grasp target, e.g. its form and location, is stepwise processed: it is forwarded from visual areas in the occipital cortex to more integrative areas in parietal cortex, and finally to the frontal motor areas. There, the
appropriate motor command is created (Rizzolatti and Luppino, 2001). This idea is compatible with the suggestion of a dorsal stream (the ‘where’ stream), processing spatial visual information by sending it from the early visual areas to parietal cortex (Mishkin et al., 1982). In addition, a ventral visual stream (the ‘what’ stream) would process information about the nature of an object (e.g. form, colour, texture) and send it to the temporal cortical lobe (Milner et al., 1977; Pohl, 1973; Ungerleider and Brody, 1977). This idea was refined by the work of Milner and Goodale in the 1990s, who suggested to interpret the specializations of the two streams depending on their final use. According to them, the ventral stream transforms visual input into representations of the objects’ characteristics and should therefore better be named ‘vision for perception’ stream. In contrast, the dorsal stream, named ‘vision for action’ stream, is relevant to coordinate goal-directed movements and used for the continuously updated control of sensori-motor processes (Goodale and Milner, 1992; Milner and Goodale, 2008). Of course both processes are closely linked to each other, as object characteristics also influence motor processes, e.g., the size of an object is important for grasp prehension during vision to action (Rizzolatti and Luppino, 2001).

Although being anatomically segregated, both streams share inputs from common areas (Morel and Bullier, 1990).

This thesis is focussing on the areas AIP and F5 of the parieto-frontal network, which are part of the dorsal “vision for action” stream. This dorsal stream can be (anatomically and functionally) further subdivided into a medial dorsal stream for reaching (connections from the superior parietal lobe (SPL) to PMd) and a lateral dorsal stream for grasping (connections from inferior parietal lobe (IPL) to PMv), as
confirmed by several studies (Borra et al., 2008; Gharbawie et al., 2011; Raos et al., 2004; Tanne-Gariepy et al., 2002). Some of these visual pathways are shown as schematic in Figure 1.2.

Figure 1.2 Parietal projections to dorsal and ventral premotor areas in the macaque.
Schematic diagram of the parietal projections to premotor cortex shown as lateral (bottom) and medial (top) views of the left hemisphere. The strength of arrows represents the density of parieto-frontal projections (Tanne-Gariepy et al., 2002). For abbreviations please see text and list of abbreviations in the appendix.

But there are also indications that are questioning this strict separation. First, there is a considerable functional overlap of these areas (please find detailed references in Chapters 1.3.1, 1.3.2, and 1.3.3 below). Furthermore, a functional connectivity fMRI study in humans suggests that contributions of the lateral dorsal and medial dorsal circuits are not due to the effector choice (i.e. arm or hand) but more a function of the
1. Introduction

complexity, i.e. the amount of online control required by the movement (Grol et al., 2007).

In the following I will summarize the key literature about the parieto-frontal networks that are directly involved in the generation of different visually guided motor acts. This includes descriptions about functional and anatomical properties of the relevant areas in the macaque and, in addition, references to the homologue regions in the human brain.

The main focus is on the grasping network (AIP and PMv/F5), but I also regard the networks for reaching (PRR & PMd) and saccade-generation (LIP & FEF). For each of these networks, I will first address the parietal area, followed by the frontal area.

1.3.1 The hand grasping network: AIP and F5

1.3.1.1 The anterior intraparietal cortex (AIP)

The functional role of AIP

Modulation of neural activity in posterior parietal cortex by visually guided reach-to-grasp movements was first described in the 1970ies (Mountcastle et al., 1975). Later, more detailed mapping studies found neuronal populations modulated during grasp movements in the rostral part of the lateral intraparietal sulcus (Taira et al., 1990), in the following referred to as anterior intraparietal cortex (AIP). In subsequent studies, these grasp related neurons showed a clear selectivity for certain grip types, like precision or power grips, and the respective pre-shaping of the hand in the early movement phase (Baumann et al., 2009; Murata et al., 2000; Sakata et al., 1995; Taira...
et al., 1990). In addition, a broad variety of sensori-motor features was found: 1) “motor-dominant” neurons without preference for grasping in the light or the dark; 2) “visuo-motor” neurons with a preference for grasping in the light; 3) “visual-dominant” neurons which were only active during visual guided grasping; 4) “object-type” neurons that were already activated by only presenting objects (Murata et al., 1996; Murata et al., 2000; Sakata et al., 1995). Furthermore, a variety of studies reported selectivity for visual properties like object size (Murata et al., 2000), orientation (Murata et al., 2000; Baumann et al., 2009), and shape in two (Romero et al., 2012) or three dimensions (Theys et al., 2012). AIP’s functional relevance for grasp movements was confirmed by an inactivation study causing severe behavioural deficits of pre-shaping the fingers while approaching grasp targets (Gallese et al., 1994). Grasps were only successfully executed or corrected after tactile feedback. This indicates that AIP plays a crucial role in transforming visual information about characteristics of a graspable object into motor plans.

The location of AIP within parietal cortex as well as the nature of grasps, closely bound to reach movements, hint on a possible involvement of spatial factors like position of gaze or position of the target. However, almost nothing has been published about the influence of these factors. To my knowledge there are no neurophysiological studies in AIP that deal with systematic variation of target and gaze components. In fact, an influence of spatial target position was denied by Taira et al. (1990), who tested, however, only a small number of neurons. No studies about spatial influences have been reported since then. Therefore, addressing this question of spatial representation in a systematic way could be of substantial benefit for understanding the visuo-motor properties of the grasping network.
1. Introduction

Anatomical connectivity

As mentioned earlier, AIP is building a strongly and reciprocally connected parieto-frontal circuit with the premotor hand grasping area F5 (Borra et al., 2008; Gharbawie et al., 2011; Jeannerod et al., 1995; Luppino et al., 1999; Rizzolatti and Luppino, 2001; Tanne-Gariepy et al., 2002). As described later in detail (Chapter 1.3.1.2), F5 is anatomically a step closer to motor output. In addition to the connections with F5, AIP receives input from several other areas, from both the dorsal as well as the ventral visual stream (see Chapter 1.3).

First, considering the dorsal visual stream, AIP receives projections from neighbouring parietal areas like PF, PG, and PFG, which are involved in visual and somatosensory reach and saccade processing (Borra et al., 2008; Fogassi and Luppino, 2005; Mountcastle et al., 1975; Rozzi et al., 2006). In addition, AIP is target of projections from LIP and from the ventral part of FEF, which both might be sources of information about eye position and saccade preparation (Blatt et al., 1990; Borra et al., 2008). AIP also receives input from area V6A (Gamberini et al., 2009) and is a target of projections from CIP, the caudal part of the bank lateral to intraparietal sulcus (Borra et al., 2008; Nakamura et al., 2001). Both areas are known to encode a variety of two- and three-dimensional visual features, e.g. shape or form of objects (Galletti et al., 2003; Taira et al., 2000). In addition, V6A is also modulated by motor features like hand orientation and reach position (Fattori et al., 2009; Fattori et al., 2010, Fattori et al., 2012; Galletti et al., 2003).

Second, considering the ventral visual stream, AIP receives input from the infero-temporal cortex (e.g. TEO, TEa, TEp; see Borra et al., 2008), which might provide
information to recognize objects and to choose the appropriate motor program, e.g. pre-shaping the hand.

Given the importance of proprio-receptive feedback during finger manipulation, it is not surprising that AIP is reciprocally connected to SII, a higher order somatosensory area. SII could be the source of information about tactile feedback, or the goal of information about hand motor signals to integrate haptic coding of objects (Borra et al., 2008). Furthermore, the afore-mentioned projecting areas PF, PG, and PFG in turn receive input from somatosensory areas (Pandya and Seltzer, 1982; Rozzi et al., 2006). Finally, AIP shares connections with the prefrontal areas 46 and 12 (Borra et al., 2008), which are involved in higher order processing like working memory (Wilson et al., 1993) and learning rules (White and Wise, 1999), or more abstract processes like the categorization of pictures (Wallis et al., 2001).

These unique anatomic connections of AIP to various sensory, motor, but also to higher order cognitive areas make it a central node for the sensori-motor transformation of hand grasping movements in the dorsal visual stream (or “vision for action” stream, as proposed by Goodale and Milner (1992).

**Human equivalents**

It was suggested that the functional human homologue of macaque AIP can be found between the anterior portion of intraparietal sulcus and the inferior postcentral sulcus (Culham et al., 2006). This region, called aIPS, is active during visually guided grasping (Binkofski et al., 1998; Culham et al., 2003; Frey et al., 2005; Grol et al., 2007) as well as during hand manipulations without visual feedback (Binkofski et al., 1998; Culham et al., 2006). Human patients with aIPS lesions lack grasping skills
1. Introduction

(Binkofski et al., 1998; Jeannerod et al., 1994). Furthermore, virtual lesions of aIPS by transcranial magnetic stimulation (TMS) disrupt adaptation of hand preshaping according to changes in object orientation (Tunik et al., 2005) and lead to a change in grasp-specific muscle-activity (Davare et al., 2010). Another fMRI study reported that aIPS is activated during grasping but not during reaching (James et al., 2003). Altogether, the human aIPS seems to be the most likely functional equivalent of macaque AIP, even though other human parietal areas seem to be activated during grasp movements as well (Culham et al., 2006).

1.3.1.2 Area F5

The functional role of F5

Area F5 is defined as the rostral part of the ventral premotor cortex, therefore also referred to as PMvr (Luppino et al., 1999; Rizzolatti and Luppino, 2001). Anatomical and functional studies imply further subdivision in F5ab (the arcuate bank posterior to the arcuate sulcus) and F5c (the convexity).

Electrophysiological studies revealed that neurons in F5 are active during the preparation and execution of grasp movements (Godschalk et al., 1981; Kurata and Tanji, 1986). Furthermore, microstimulation experiments confirmed the functional relevance of F5 for grasping and mouth movements (Hepp-Reymond et al., 1994; Rizzolatti et al., 1988). A lot of the neurons found in this area seemed to encode complete motor acts, rather than single parts of grasp movements (Rizzolatti et al., 1988). These neurons are specifically modulated during execution of a certain grip type, therefore it was suggested that F5 contains a “motor vocabulary” of grasping
actions (Rizzolatti et al., 1988; Rizzolatti and Luppino, 2001). In addition, Murata et al. (1997) found not only planning and movement related “motor neurons”, but also “visuo-motor neurons” which already fired during object presentation. Therefore these neurons might encode a potential motor plan, even if they do not perform the subsequent movement itself (Murata et al., 1997; Raos et al., 2006; Rizzolatti and Luppino, 2001). Reversible inactivation of F5 by injecting the GABA$_A$-receptor agonist muscimol led to strong impairment of the contralateral hand, especially the pre-shaping of the hand during the reaching phase (Fogassi et al., 2001). Similar to the inactivation study in AIP mentioned in Chapter 1.3.1.1, successful grasps were mainly achieved by help of tactile feedback.

But F5 also seems to play a role for the performance of reach movements: neurons in PMv were found to be modulated by reach direction (Kakei et al., 2001; Stark et al., 2007). In addition, ablation of PMv resulted in deficits of avoiding obstacles, particularly in changing the reach trajectory (Moll and Kuypers, 1977). Interestingly, when separating the motor action from its visual feedback by use of virtual sensorimotor tasks, the reach direction representation in PMv seemed to match better with the visual feedback than with the actual movement (Ochiai et al., 2005; Schwartz et al., 2004). This further hints at a visual feedback role of PMv during control of reach-to-grasp movements. Furthermore, muscimol inactivation of PMv during a reach perturbation led to deficits in reach adaption, whereas no changes were noticed by inactivation of the reach-related premotor area PMd (Kurata and Hoshi, 1999). The authors of this study therefore suggested an important role of PMv in motor adaption, in particular for the recalibration of visual and motor coordinates during visually guided movements.
1. Introduction

Although F5 seems to play an important role for the visuo-motor transformation of hand grasping movements, the role of gaze position is only rarely touched in the literature. Moreover, these studies are conflicting: some reported neural activity that was not modulated by gaze position (Fogassi et al., 1992; Gentilucci et al., 1983), whereas Boussaoud et al. (1993) reported gaze-dependent activity in a visual response task. In addition, gaze-dependent reach activity was mentioned in a short report with data from one monkey (Mushiake et al., 1997).

Studying the influences of systematic spatial target and gaze variation on neuronal grasp activity in F5 could therefore provide important insights into its role for visuomotor processing.

Neurons in F5, mainly in the convexity (F5c), were also found to have so called mirror properties: they are not only discharging during the execution of a certain grasp, but also while watching the same or similar action being performed by another individual, no matter if this individual is monkey or human (Gallese et al., 1996; Rizzolatti and Luppino, 2001). Mimicked grasps without object, mere presentation of the object, or an inappropriate movement towards the object led to a lower or no modulation of these neurons. In general, mirror properties point to a coupling of action observation and action execution, implying a cellular mechanism for action understanding in F5 (for detailed reviews see Casile et al., 2011; Rizzolatti and Luppino, 2001).
Anatomical connectivity of F5

Besides the strong and reciprocal connections to the parietal grasping area AIP (Luppino et al., 1999), F5 receives strong sensory input from somatosensory area SII and area PF (Gerbella et al., 2011; Gharbawie et al., 2011; Matelli et al., 1986). F5 can be subdivided in the areas F5ab and F5c. Area F5ab is strongly interconnected with parietal area AIP, which is in line with the functional studies showing an involvement of goal directed hand movements (Raos et al., 2006; Umilta et al., 2007). In contrast, the convexity (F5c) is missing these connections (Gerbella et al., 2011).

Generally, given the presence of mirror neurons in F5c, it seems to play a more cognitive role for action understanding (Rizzolatti and Luppino, 2001).

Recently, more detailed anatomical studies suggested a further subdivision of area F5ab in an anterior and a posterior part: F5a and F5p (Belmalih et al., 2009; Gerbella et al., 2011). Whereas all the areas F5a, F5p, and F5c share strong intrinsic connections to each other, F5a in addition gets stronger inputs from SII as well as from prefrontal areas 46v and 12, which are involved in the encoding of higher order goals (Gerbella et al., 2011). The authors suggested this could speak for an additional rostral premotor area F5a, circumscribing it as pre-PMv.

Furthermore, there are strong connections of F5 from and to the finger areas of primary motor cortex (M1), as well as robust reciprocal connections with PMd and SMA (Borra et al., 2010; Dum and Strick, 2005; Gharbawie et al., 2011; Muakkassa and Strick, 1979). Dum & Strick therefore suggested that these areas form an interconnected network for the control of hand grasping movements, with F5 playing also a role in direct motor control. Indeed it was shown, that F5 has direct and indirect (via superior colliculus) descending pathways to the cervical spinal chord (Borra et
1. Introduction

al., 2010), therefore providing direct and indirect access to motoneurons controlling limb muscles. This further suggests an involvement of F5 in the direct control of hand grasping movements in parallel with M1.

Human equivalents

In agreement with the studies in non-human primates, functional imaging studies and transcranial magnetic stimulation (TMS) studies in healthy subjects confirmed the importance of human PMv in grasp execution. It is active during the manipulation of objects and execution of skilled grasp movements (Binkofski et al., 1999; Ehrsson et al., 2000; Grol et al., 2007; Verhagen et al., 2008), and virtual lesion of PMv induced by TMS impaired grasp performance (Davare et al., 2006).

1.3.2 The reach network: PRR & PMd

1.3.2.1 Parietal reach region PRR

Functionally, the posterior area medial to the intraparietal sulcus was considered to be relevant for the processing of visually guided reach movements and therefore named the parietal reach region, PRR (similar to area 5 defined by Brodman) (Hyvarinen and Poranen, 1974; Mountcastle et al., 1975; Snyder et al., 1997). Over the years, anatomical and physiological studies led to a more detailed parcellation of this area into the medial intraparietal area (MIP), visual area 6A (V6A) and parietal area PEc. Most of the reach studies mentioned in the following focussed on MIP (for a review see Andersen and Cui (2009) ), located within the medial bank of the IPS.
1) **MIP**: In addition to its reciprocal connections to the dorsal premotor cortex PMd (Caminiti et al., 1999; Marconi et al., 2001; Tanne-Gariepy et al., 2002), MIP gets main inputs from the parietal visual areas V6 and V6A (Colby et al., 1988; Galletti et al., 1996). MIP encodes the planning and execution of reach movements towards a visual or auditory target, predominantly in eye-centered coordinates (Batista et al., 1999; Battaglia-Mayer et al., 2001; Caminiti et al., 1996; Kalaska et al., 1997). More abstract, it encodes potential reach plans (Klaes et al., 2011) and is involved in decision making processes and reward expectation (Cui and Andersen, 2007; Musallam et al., 2004).

2) **Area V6A** represents mainly visual factors, but also the reach direction in reach-to-grasp movements (Fattori et al., 2001; Fattori et al., 2005; Marzocchi et al., 2008). In addition, it is modulated by hand orientation and different grip types and receives visual information from visual area 6 (V6) as well as from other parietal visual areas types (Fattori et al., 2009; Fattori et al., 2012; Fattori et al., 2010). The combination of V6A and V6 is also referred to as V6-complex, Brodman area 19, or area PO (Caminiti et al., 2010; Galletti et al., 2001; Gamberini et al., 2009, see Figure 1.1).

3) **PEc** receives input from various visuo-motor parietal areas and is connected to the caudal part of dorsal premotor cortex (Marconi et al., 2001). The activity of its cells is modulated by early arm movement direction and hand position, often also influenced by gaze position and saccadic information (Battaglia-Mayer et al., 2001; Ferraina et al., 2001).
1. Introduction

1.3.2.2 The dorsal premotor cortex (PMd)

The dorsal premotor cortex (PMd) is located posterior to the arcuate sulcus, medial from the arcuate spur. Functionally and anatomically it can be subdivided into a more arm related caudal part (PMdc, corresponding to F2) and a more eye related rostral part (PMdr, corresponding to F7; also see Figure 1.1). The subparts of PMd are reciprocally connected to the reach related visuo-motor parietal areas MIP, PEc, and V6A (Battaglia-Mayer et al., 2003; Battaglia-Mayer et al., 2001; Marconi et al., 2001; Matelli et al., 1998; Rizzolatti and Luppino, 2001; Tanne-Gariepy et al., 2002). This is consistent with the results of various studies about the functional role of PMd in the visuo-motor encoding of reach movements, similar to its parietal counterpart MIP (within PRR, see previous Chapter 1.3.2.1). It was first seen as a predominantly motor area, encoding the movement direction during planning and execution of reaches (Caminiti et al., 1991; Crammond and Kalaska, 1996) as well as the amplitude (Messier and Kalaska, 2000) and speed (Churchland et al., 2006). Nevertheless, it was also found to substantially encode sensory information. A study by Ochiai et al. (2002) reported that neural activity during a virtual reaching task predominantly reflected arm-image movement rather than the physical arm movement. This pointed to a use of PMd in visual guidance during the execution of movements. Ochiai et al. found this representation to be strongly dependent on the relative position of the hand to the target. Another study showed the encoding of the relative position of hand, eye, and goal in a complex reaching task, varying start position, target position, and gaze position in PMd activity (Pesaran et al., 2006). Besides spatial representation, also grasp modulation was shown for PMd (Stark et al., 2007). Taken together, the representation of all these factors fits with the anatomy–based hypothesis of Dum and
Strick (2005), that ventral and dorsal premotor cortices (PMv & PMd) form a densely interconnected network involved in the generation and control of reach and hand movements.

1.3.3 The saccade network: LIP and FEF

1.3.3.1 Lateral intraparietal cortex (LIP, Brodman area 7)

LIP is located at the lateral bank of the intraparietal sulcus (IPS). It is strongly and reciprocally connected with its premotor counterpart FEF (Blatt et al., 1990). In addition it receives input from several cortical visual areas, e.g. V2, V3, V4, MT, and PO (Andersen et al., 1990; Felleman and Van Essen, 1991; Snyder et al., 2000), and has connections to other parietal areas (Asanuma et al., 1985; Blatt et al., 1990). It is also strongly connected to superior colliculus, which is involved in saccade generation (Lynch et al., 1985). Neurons in LIP are active during planning and execution of saccade movements and respond to presentation of objects in their receptive fields (Snyder et al., 1997, 1998; Thier and Andersen, 1996, 1998). Microstimulation with low currents in LIP leads to saccadic eye movements without evoking motor responses in limbs (Thier and Andersen, 1996, 1998). Deactivation of this area by injecting the GABA_A-receptor agonist muscimol did not have a direct effect on the execution of saccades, however, decision processes and memorized saccades were impaired (Li et al., 1999). It is unclear if this is due to saccadic intention or to visual attention, which is difficult to clarify, as saccades are usually accompanied by a shift in attention (Colby and Goldberg, 1999). Finally, neurons in
LIP are able to combine visual information and cognitive factors like behavioural context, task difficulty, or reward information (Wardak et al., 2011).

### 1.3.3.2 Frontal eye field (FEF)

The frontal eye field (FEF) is a region of primate prefrontal cortex, located in the anterior bank of the arcuate sulcus. It plays an important role in planning and execution of saccadic eye movements and, similar to other premotor areas, represents both sensory and motor facets (Schiller and Tehovnik, 2005). Therefore FEF is likely to contribute to visuo-motor transformation. Besides the reciprocal connections with LIP (see previous Chapter 1.3.3.1), it shares connections with other frontal areas, e.g. area 46 and the supplementary eye field, which are involved in higher order processing for movement planning. Furthermore, it receives input from the temporal cortex and extrastriate area V4 (Schall, 2002; Wardak et al., 2011). Subcortical projections are mainly directed to the superior colliculus and other brainstem regions (Schiller and Tehovnik, 2005; Wardak et al., 2011). FEF microstimulation with low intensity resulted in saccades with a fixed vector, whose amplitude depended on the stimulation site (Schiller and Tehovnik, 2005). Inactivation of FEF lead to massive saccadic deficits in visually guided and memorized saccades (Wardak et al., 2006), complete ablation of FEF caused a severe impairment of saccades which only partly recovered with time (Schiller and Tehovnik, 2005). In addition there is growing evidence that FEF also plays a role for attentional effects and decision making (Schall, 2002; Schiller and Tehovnik, 2005; Wardak et al., 2006; Wardak et al., 2011).
1.3.4 Primary motor cortex (M1)

The final motor output, the precise movement of hand and finger during grasp, is controlled by the primary motor cortex (M1). M1 shows a rough somatotopic map representing different parts of the body, also known as Penfield’s classic “homunculus” (Schott, 1993). However, the details of cortical encoding for hand and finger movements are more complex than this simple model suggests. For example, neuronal activity directly linked to individual finger movements seems to be widely distributed across M1 (Schieber, 2001; Schieber and Hibbard, 1993). Nevertheless, a hand area which is unique for higher primates, can be defined in the caudal region of M1, containing arm and finger representations (Rathelot and Strick, 2009). A high number of pyramidal tract neurons have been found there; these project along the cortico-spinal tract to the spinal chord and directly synapse onto motoneurons, thereby controlling muscle activity (Lemon, 2008; Rathelot and Strick, 2009). This was confirmed by two retrograde, trans-neural labelling studies using rabies virus, identifying monosynaptic connections from single finger and hand muscles to motor cortex (Rathelot and Strick, 2006, 2009). These studies revealed that hand-muscle related cortical projecting cells are predominantly found in the caudal part of M1. Instead of being somatically ordered according to the anatomy of the hand, the cells were found to be spread across this area. The authors concluded that M1 can be anatomically subdivided into a “new” region with direct finger and hand muscle control, and another “old” region that influences motor control more indirectly (Rathelot and Strick, 2006, 2009).

The caudal region of M1 gets major inputs from ventral and dorsal premotor cortices. Minor inputs come from supplementary (SMA) and cingulate motor areas.
(CMA) as well as from parietal cortex (Dum and Strick, 2005; Gharbawie et al., 2011; Strick et al., 1998). Subcortical input originates from other structures involved in motor control: the basal ganglia, the thalamus, and the cerebellum (Hoover and Strick, 1999).

Behaviourally, neuronal tuning for specific dynamics and kinematics of hand and reach movements can be found, related to muscle force, joint angle, motor load, or directional tuning of reach movements (Georgopoulos et al., 1986; Graziano, 2006; Kakei et al., 1999). But there are indications that these are only single parameters extracted from a multidimensional tuning profile, meaning that motor acts are encoded in a more complex way (Graziano, 2006). Stimulation trains around 500ms (roughly matching with the time needed for goal-directed actions) in M1 lead to complex, multi-joint movements, like reach-to-grasp movements or defence actions (Graziano, 2006). In contrast, short stimulation evokes undirected muscle twitches. Lesions or inactivation of the hand area in M1 lead to force deficits and impairment of individual finger movements (Borra et al., 2010).

In general neural activity in motor cortex is much more directly related to hand muscle activity and therefore direct motor output compared to the other cortical areas involved in motor control (Kakei et al., 2001; Umilta et al., 2007).
1.4 Reference frame transformation during goal-directed actions

As already pointed out in the first part of the introduction, reach-to-grasp actions require a fine spatial and temporal coordination of the proximal (arm) and distal (hand) movement components (Jeannerod et al., 1995). In addition, eye-hand coordination plays a central role, as goal-directed movements are usually visually guided. Not only information about the intrinsic features of the object to be grasped (e.g. shape, size, orientation), but also the spatial information about the object’s position relative to the hand and the gaze position are of high relevance (Crawford et al., 2011; Crawford et al., 2004; Goodale and Milner, 1992; Milner and Goodale, 2008; Rizzolatti and Luppino, 2001).

Several reference or coordinate frames are important for goal-directed movements:

1) The body-centered, extrinsic reference frame, encoding an objects position relative to the subjects position in space.

2) The retinotopic, or gaze-centered, reference frame, depicting objects in our surrounding relative to the position of gaze (and relative to the fovea on the retina).

3) The limb-centered, extrinsic reference frame, encoding the object’s position relative to the effector, in our case the hand.

4) The muscular (or intrinsic) reference frame, encoding the muscle commands for executing a movement.

During the process from visual input to motor output, a transformation of these reference frames has to take place along the parieto-frontal networks: visual information entering the brain is encoded in a retinotopic reference frame and, step by step, transferred into a muscle specific coordinate frame (Chang and Snyder, 2010).
According to this classic idea of discrete stepwise transformation, a reaching goal would first be purely represented in retinotopic coordinates in the occipital and parietal areas. It would then be passed to dorsal premotor cortex, transferred into a limb-centered frame, and finally sent to motor cortex, directly controlling the muscles of the arm (intrinsic, muscle-centered frame) (Crawford et al., 2004). All of the parieto-frontal networks mentioned in the previous chapter (AIP – PMv, PRR – PMd, LIP – FEF) share visuo-motor representations that are, following the dorsal stream from parietal to frontal areas, increasingly dominated by representations of the motor output they are specialized for: grasping, reaching, and saccades.

But this classic view of highly specialized and anatomically separated visuo-motor pathways (e.g. Tanne-Gariepy et al., 2002) has recently been challenged by findings of mixed functional representations and coordinate frames in distinct areas. The “reach” area PRR represents visual reach targets predominantly in retinotopic coordinates (Batista et al., 1999; Pesaran et al., 2006). In contrast, neurons in its frontal counterpart PMd seem to encode spatial factors in several reference frames: 1) the reach target relative to the gaze position (retinotopic), 2) the reach target relative to the hand position (limb-centered), 3) the gaze position relative to the hand, as well as combinations of these encodings (Batista et al., 2007; Pesaran et al., 2006, 2010).

Furthermore, V6A, another area within the medial dorsal stream, is modulated by target position both in limb-centered (Fattori et al., 2001; Fattori et al., 2005) and in retinotopic coordinates (Marzocchi et al., 2008), as well as by hand orientation (Fattori et al., 2009). Mixed functional representations have also been reported for areas in the more grasp-related lateral-dorsal stream: F5 was shown to be modulated by reach movements (Schwartz et al., 2004; Stark et al., 2007) or their visual
representations (Ochiai et al., 2005; Schwartz et al., 2004). In addition, also gaze-dependent activity has been reported here (Boussaoud et al., 1993; Fujii et al., 1998; Gentilucci et al., 1983).

The aforementioned studies, conducted in several visuo-motor areas, indicate that various spatial representations could also exist in the grasping areas AIP and F5. However, a systematic analysis of spatial influences (like reach movement and gaze position) has not been reported yet. Doing so in parietal and premotor areas AIP and F5 could therefore lead to new insights into the process of visuo-motor transformation in the latero-dorsal hand grasping network.

1.5 Local field potentials (LFP)

Together with single unit spiking activity, local field potential (LFP) activity was recorded during our experiments. In opposition to spiking information, which represents the cortical output of single- or multi-units, the local field potential can be seen as a summation signal of inhibitory and excitatory dendritic potentials with a bigger “listening sphere” around the tip of a recording electrode (Andersen et al., 2004; Buzsaki and Draguhn, 2004; Scherberger et al., 2005). Therefore, LFP provides additional information to single neuron activity and might reveal insights of activity within cell assemblies, in particular local processing (Engel et al., 2001). Furthermore, cortical LFP activity is more stable and therefore easier to record over longer time periods compared to single-unit spiking activity, which makes it of potential use as a supportive signal for the development of brain machine interfaces.
1. Introduction

(BMI) and algorithms to control cortical prosthesis over long periods (Andersen et al., 2004; Scherberger et al., 2005).

LFP is also thought to be closely related to the BOLD (blood-oxygen-level-dependent) signal measured during fMRI (Buzsaki and Draguhn, 2004; Logothetis, 2003) and could therefore be used to improve the interpretation of results of this non-invasive brain imaging method.

In different cortical regions, the LFP signal was shown to represent sensory and motor related factors during the planning and execution of visually guided actions. For example, task modulated LFP activity was found in parietal areas like LIP (Pesaran et al., 2002) and PRR (Scherberger et al., 2005) as well as in primary motor cortex (Mehring et al., 2003; Rickert et al., 2005). Some of these studies also report a non-uniform distribution of directional preferences in the LFP signals, making it more difficult to decode movement signals, compared to single unit activity.

Only a few studies have been dealing with LFP signals in the hand grasping areas AIP and F5. In AIP, LFP activity was shown to be modulated by reach direction and object representations (Asher et al., 2007). But the information was mostly represented after movement onset, and therefore not useful to decode movement intentions.

In premotor area F5, selectivity for grasp type was reported in the movement phase of LFP activity (Spinks et al., 2008). In particular, the authors reported a preference for power grips during movement execution. In addition, a study about low frequency components smaller than 4 Hz demonstrated the possibility of robustly using this signal to decode reach and grasp kinematics in M1 and PMv (Bansal et al., 2011).
In conclusion, relatively little is known about the encoding properties of LFP activity in these areas. Therefore, we wanted to see how the LFP activity is modulated by delayed reach-to-grasp movements, in particular during variation of grip type and spatial positions.

1.6 Motivation and goal of the thesis

As reviewed above, voluntary, goal directed movements are composed of several actions that are combined to achieve a specific behavior. For controlling these actions, separate parieto-frontal network have been described for generating reaching and grasping actions. Key nodes for the planning and execution of grasp movements are premotor area F5 and parietal area AIP, two visuo-motor areas located within the latero-dorsal stream. Considering 1) that a lot of cortical visuo-motor areas are reported to represent a combination of several spatial factors, and 2) the behavioral complex interactions of looking, reaching, and grasping, spatial influences could also be expected in the grasping areas.

So far, the majority of the literature about neuronal representations in the grasping areas AIP and F5 focused on either reaching or grasping movements, but not on a combination of both.

In this thesis, I therefore analyzed the influence of systematically varied spatial factors on grasping-related neuronal activity in AIP and F5. We developed an experimental setup for non-human primates that allowed the systematic variation of grip type, target position, gaze position, and the starting position of the hand. Two
1. Introduction

animals were trained to perform a delayed reach-to-grasp task. During task performance, neuronal activity was recorded from parietal area AIP and premotor frontal area F5, using acute recording techniques with single electrodes. Single-unit activity as well as local field potential (LFP) activity was analyzed for the recorded dataset in both areas.
2. Methods

In order to address the questions introduced in the previous chapter, we designed an experiment in which the spatial influences on cortical activity during hand grasping movements could be studied.

This chapter introduces:
- the experimental setup developed for the conducted reach-to-grasp experiment (Chapter 2.1),
- the task paradigm, which the animals were trained to perform (Chapter 2.2),
- the surgical procedures and MRI performed prior to the recordings (Chapter 2.3),
- the general recording techniques (Chapter 2.4), as well as
- the analyses used for both the recorded single unit activity (Chapter 2.4.1) and the local field potential activity (LFP, Chapter 2.4.2).

A condensed part of this chapter is included in a manuscript that has been accepted for publication in the Journal of Neuroscience (Lehmann & Scherberger, in press).
2. Methods

2.1 Experimental setup

Two purpose-bred female rhesus monkeys (*Macaca mulatta*) participated in this study (animals P and S; weight 4.5 kg and 5.5 kg, resp.). They were pair-housed in a spacious and enriched environment. Animal care and all procedures were conducted in accordance with the regulations set by the Veterinary Office of the Canton of Zurich, the guidelines for the care and use of mammals in neuroscience and behavioral research (National Research Council, 2003), and in agreement with German and European laws governing animal care.

The two animals were habituated to comfortably sit upright in an individually adjusted primate chair with the head rigidly fixed to the chair. A grasp target was located in front of the animal at a distance of approximately 24 cm. The target consisted of a handle that could be grasped with two different grip types, either with a precision grip (using index finger and thumb in opposition) or a whole-hand power grip (Baumann et al., 2009; Fluet et al., 2010). To monitor the correct execution of precision grips, two touch sensors were placed in small recessions on both sides of the target (red area in Figure 2.1 A). The sensors had to be pressed with opposed thumb and index finger at the same time. As indicator for correctly performed power grips, the animals had to interrupt a light barrier on the back of the handle (indicated by red line in Fig 2.1 A) and pull the handle until a defined threshold was crossed (measured by an integrated force sensor).
2. Methods

Figure 2.1 Grasp target and different grip types.
A) The grasp target had to be manipulated with the left hand, contra-lateral to the recording sites in both monkeys. The red line indicates a light barrier; the red area on the handle is one of two recessions with force sensors on each side of the handle; B) Execution of precision grip; C) Execution of power grip.

The focus of the thesis was to study spatial influences on cortical activity during grasp movements. Therefore, we constructed an experimental setup that allowed the systematic variation of several spatial factors: target position, gaze position, and starting position of the hand.

Variation of target position

In order to vary the target position, we constructed a setup that allowed it to smoothly move the grasp target vertically and, on a circular pathway, horizontally in front of the animal (Fig. 2.2). Target movement was carried out by controlling two stepper motors independently from each other. Both motors were mounted on a carrying platform, which could be moved along a semi-circular pathway (Fig. 2.2A). One motor controlled the vertical position of the target, moving it up or down with a tooth belt drive along a linear support trail. The second, horizontal motor controlled a cogwheel underneath the carrying platform, moving the whole construction along a drive-belt that was strained to a guide parallel to the semi-circular pathway (see Fig.
2. Methods

2.2B). This combination of independent motors allowed to move the target in various positions in front of the animal. For the experiment presented in this work, the grasp target was moved to five different target positions with a spacing of 11 cm (~25° visual angle): in straight-ahead (or center) position in front of the animals’ chest, as well as to the left, right, top, and bottom of the center position. The change of target position was performed in-between trials in the dark. Therefore, animals had no visual information about the target location before the start of the next trial. However, the sound of the moving motors could potentially provide some acoustic clues to the animal about the upcoming target location prior to the start of the next trial. To illuminate the handle in the dark, two dedicated spotlights were positioned to the left and right of the handle (outside of the animal’s reach).

**Variation of gaze position**

The gaze position was defined by the place, in which fixation and grip type instructions were provided. For this, we used small sets of LEDs. To vary the gaze position in a systematic way, we constructed an aluminium screen that was installed at the front side of the box, which was carrying the grasp target (see Fig. 2.2C). The screen consisted of 5 panels; each of them had a width of 11 cm and a height of 27.5 cm. The panels were mounted together, each tilted 24.5° relative to the neighbouring panel. Thus, the construction of the screen followed the semi-circular track, along which the above-mentioned grasp target was moved. The central panel had a circular notch (diameter 8.5 cm), in which the grasp target was located. In addition, each panel had three small recessions with a distance of 11 cm to each other (red circles in Figure 2.2C). These recessions hosted the locations of the LEDs for fixation and cue
instruction. Thereby, their positions were equivalent to the different gaze positions of the animals in space. By addressing these different LEDs, gaze position could be varied to five different positions (similar than the target positions). The complete setup is shown in Figure 2.2C. Altogether, this construction allowed to vary both target and gaze position in a versatile way, leading to several spatial combinations that are introduced in Chapter 2.2 (Task paradigms).
Variation of hand starting position

In order to control the position of the animal’s hands, four touch sensors (*model EC3016NPAPL; Carlo Gavazzi*) were used to monitor the hand resting position of both hands. They were located in front of the animal’s hips. One sensor was used to control the position of the hand, which the animal had to keep motionless throughout a trial (ipsi-lateral to the cortical hemisphere we recorded from). In addition, there were three sensors for the contra-lateral hand, defining three different possible hand starting positions for the reach-to-grasp task (see schematic drawing in Fig. 2.3). These had a distance of 7.5 cm to each other.

*Figure 2.2 Setup construction.* (opposite page).

A) Overview: the grasp target could be moved along vertical and horizontal (circular) pathways by controlling two motors; B) The plate carrying box and motors was sliding on a skid along the semicircular track. It was moved by the horizontal motor, driving the cog wheel along a tooth belt (orange) that was strained parallel to the track; C) View of the complete setup, including the screen with recessions for the gaze signals (marked by red circles).
2. Methods

Figure 2.3 Hand starting positions.
Grasp target and cue LEDs were located in front of the monkey in central position. The 4 circles at the bottom represent the position of the ipsilateral (right) and three potential starting positions of the contra-lateral hand (left, 1 to 3) at the beginning of a trial. Red circles indicate standard positions of the hands during the target variation task (TASK I, see Chapter 2.2)

Online control of behavior during trial execution

The motors moving the grasp target and all stimulus parameters (fixation and cue LEDs, illumination), as well as all behavioral factors (e.g. movement timing by surveilling the touch sensors) were monitored with LabView Realtime (National Instruments, Austin, TX, USA) with a time resolution of 5 ms using custom-written software. In addition, the animals’ eye position was constantly monitored with an optical eye tracking system (Thomas Recording ET-49B, Giessen, Germany) and sent to the monitoring software. The monitoring program was based on an existing code written for a previous project (Baumann et al., 2009; Fluet et al., 2010) and was further developed to control the motors and various LEDs, as well as to surveil the hand rest sensors.

Altogether, the hardware design of the setup described above made it possible to systematically vary the following factors: 1) the grasp type (either precision or power grip), 2) the target position in space, 3) the gaze position in space, and 4) the starting
position of the contra-lateral hand. This led to two different task paradigms, described in detail in the following section.

2.2 Task paradigms

Monkeys were trained to perform two different grasping tasks: the “target variation task” (TASK I) and the “start variation task” (TASK II).

Both tasks shared the same basic behavioral components of a *delayed reach-to-grasp task*. For this, monkeys were instructed to grasp a target with either a power grip or a precision grip. They initialized each trial by placing both hands on the hand rest sensors and fixating a red LED while sitting in the dark. Each trial (see Figure 2.4A for summary sketch) started with a baseline (fixation) epoch (500–700 ms), during which the animal had to maintain its resting position in the dark. In the following cue epoch (fixed length of usually 800 ms) an additional LED was shown close to the fixation position that informed the animal about the required grasp type (green LED: power grip, orange LED: precision grip). At the same time the grasp target was illuminated to reveal the handle position in space (by two dedicated spotlights, see Chapter 2.1). In the following planning epoch of variable length (800–1200 ms) the cues were turned off again and only the fixation light was visible, so that the animal could plan, but not yet execute the movement. A short blink of the fixation light (‘go’ cue) then instructed the animal to reach and grasp the target (movement epoch) with its left arm (contra-lateral to the recording chamber). Planning and movement epochs were in complete darkness except for the red LED light that the animal had to keep fixating throughout the task (window radius: 11.4°). All trials correctly executed by the animal were rewarded with a fixed amount of juice. After
that the animal could initiate the next trial after a short inter-trial interval. Error trials were immediately aborted without reward. To maintain a high motivation for obtaining fluid rewards, animals were restricted from access to water prior to training and recording sessions. Besides these common features, the two tasks also featured different spatial variations as described in the following.

2.2.1 Target variation task (TASK I)

In the target variation task (TASK I), both target position and gaze position were systematically varied during the inter-trial interval, which led to a grouping of spatial conditions in three different subtasks:

1. **Combined gaze-and-reach variation (CV):** target and gaze position are varied together, both are at the center or at the left, right, top, or bottom position (Fig. 2.4B, left).

2. **Target variation (TV):** gaze position is located at the center of the workspace while target position is either at the center or at the left, right, top, or bottom position (Fig. 2.4B, middle).

3. **Gaze variation (GV):** target position is located at the center of the workspace while gaze position is varied between the center, left, right, top, and bottom position (Fig. 2.4B, right).

In combination with the two different grip types, this led to a set of 26 task conditions that were presented pseudo-randomly interleaved, resulting in typically 10 trials per condition.
2. Methods

Figure 2.4 Task paradigm.

A) Delayed reach-to-grasp task with the epochs: fixation, cue, planning, and movement. Monkeys initiated trials by placing both hands on rest sensors and fixating a red LED in the dark. After a delay of 500–700ms (fixation epoch), target position was revealed together with the instruction (color of a 2\textsuperscript{nd} LED), which grip type to apply (cue epoch). After a variable delay of 800 – 1200ms (planning epoch), a short blink of the fixation light instructed the animal to reach and grasp the target in darkness while maintaining gaze.

B) Schematic view of conditions for the “target variation task”: Target (T) and gaze (e) were systematically varied, resulting in the subtasks “combined variation” (CV, left) with target and gaze presented in five joint positions, “target variation” (TV, middle) with gaze position in the center, and “gaze variation” (GV, right) with target position in the center.
2. Methods

2.2.2 Start variation task (TASK II)

In the start variation task (TASK II), target and gaze position were always in center position, but the required starting position of the left hand changed during the inter-trial interval. To initiate a trial, the monkeys had to find the correct of the three possible starting positions. When placing the left hand on the corresponding hand rest sensor (see Figure 2.3), the trial started with fixation onset (see Fig. 2.4A). In combination with the two different grip types, this led to a set of 6 different task conditions that were also presented pseudo-randomly interleaved, with typically 10 trials per condition.

In an ideal experiment, the conditions of these two different tasks would have been tested and recorded in combination within in a single task. However, this would have resulted in a huge number of 78 different conditions (including 3 starting positions, 13 target and gaze positions, and 2 grip types). Given the number of trials necessary for statistical reliability and the limitation of the used acute recording techniques, it was almost impossible to achieve the required amount of trials in a combined task. Therefore, the task was split in two blocks (TASK I & TASK II) that were recorded sequentially.

2.3 Surgical procedures and MRI scans

Details of the surgical procedures and MRI scans have been published previously (Baumann et al., 2009; Fluet et al., 2010).

Structural magnetic resonance image (MRI) scans of the brain and skull were obtained from each animal prior to the surgical procedures to help guiding the chamber placement. For this procedure, animals were sedated (Robinul 0.001mg/kg,
Ketamine 10mg/kg, Atropine 0.05 mg/kg, and Xylazine 0.5 mg/kg), supplemented with O₂ (1l/min). Heart rate, O₂-saturation and CO₂-level were continuously monitored. After placing the animal in a prone position in the scanner (*GE Healthcare 1.5T at the University Clinics Zürich; Siemens 3.0T at Biomed NMR Göttingen*), T1-weighted volumetric images of the brain and skull were obtained and realigned offline in stereotaxic coordinates using the software *AFNI 3.0*. Stereotaxic zero was defined as the intersection of the inter-aural line and the lower rims of both orbits (Scherberger et al., 2003). The stereotaxic locations of the intraparietal sulcus and the knee of the arcuate spur of the right hemisphere were then obtained for both animals (see Table 2.1). These coordinates were later used to guide the placement of the recording chamber over both AIP and F5.

<table>
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<td>20.0</td>
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</tbody>
</table>

*Table 2.1 Stereotaxic locations of cortical landmarks used to guide chamber placement.*

*Numbers give the distance (in mm) to stereotaxic zero (IP = intraparietal sulcus, AS = arcuate spur).*

Afterward, a dental acrylic head cap (*Rebofacin, Biomet Orthopaedics, USA*) was mounted on the animal’s head, stabilized by a number of titanium (*Synthes, Switzerland*) and ceramic bone screws (*Thomas Recording, Germany*). A titanium head post was embedded in the acrylic cap in anterior position above the midline. This was required to keep the animal’s head fixated in a constant position (necessary
2. Methods

for eye tracking) during training and neural recordings. In addition, an oval-shaped recording chamber (outer dimensions $40 \times 25 \text{ mm}^2$, inner dimensions $35 \times 20 \text{ mm}^2$), made out of PEEK ("polyether ether ketone") was implanted over the right hemisphere according to the results of the MRI carried out before (see Figure 2.5).

After chamber implantation and further behavioral training of the monkey, a second MRI scan was obtained to register the cortical structures to the exact coordinates of the chamber. This allowed us to target the areas of interest precisely for the following craniotomy surgery (see Fig. 2.5). In this second surgery the skull bone underneath the chamber was removed to allow access to the areas AIP and F5. In subsequent recording sessions, recording microelectrodes where inserted by penetrating the dura mater without discomfort to the animal.

2.4 Neuronal recordings

Neuronal activity was recorded using quartz-glass coated platinum/tungsten electrodes (Thomas Recording, Germany). The electrodes had an impedance of 1-2 MOhm at 1 kHz, allowing to record both spiking activity and local field potentials (LFP). They were positioned simultaneously in AIP and F5 by two 5-channel micromanipulators (Mini-Matrix, Thomas Recording, Germany). Figure 2.5 B,C shows details about the penetration sites in the two areas.

Neural signals were amplified (x400), digitized with 16-bit resolution at 30kS/s using a Cerebus Neural Signal Processor (Blackrock Microsystems, Salt Lake City, UT, USA). Signals were stored on hard drive together with the behavioral data. From
the raw data, both single-unit activity and LFP were extracted and analyzed offline as described below.

A) Coronal view of MRI from animal P, with chamber placed over right hemisphere; B) MR image of right hemisphere of monkey P in plane of recording chamber. Blue dots represent the recording sites in AIP and F5: AS = arcuate sulcus, CS = central sulcus, IPS = intraparietal sulcus, PS = principal sulcus; C) MR image of recordings sites in animal S.

2.4.1 Data analysis of spiking activity

Neural signals were high-pass-filtered with a cut-off-frequency of 500 Hz and single units were isolated and sorted manually, using principal component analysis techniques (Offline Sorter v2.8.8, Plexon Inc, Dallas, TX, USA). We included all units in our database that had an average firing rate of at least 5 Hz in one of the task conditions and that were stably recorded in typically 9-11 trials per condition.

Peristimulus time histograms (PSTH) were generated using a gamma distribution as a causal kernel (parameters: shape $\alpha=1.5$, rate $\beta=30$, see: Baumann et al., 2009). However, all following statistical tests were based on exact spike counts.

The preferred and non-preferred grip type as well as the preferred and non-preferred spatial position in the CV, TV, and GV task were determined for each neuron as follows. The mean activity of a given neuron in the time interval from
fixation onset to movement end was averaged across all trials of the same grip type or spatial position, respectively. The grip type with the higher (or lower) mean firing rate was defined as the preferred (or non-preferred) grip type. Similarly, the spatial position with the highest (or lowest) mean firing rate for a given subtask was defined as the preferred (or non-preferred) position.

**Tuning for grip type and spatial position**

To test the significance of tuning for grip type and for spatial position in the target variation task (TASK I) in each task epoch, we calculated the mean firing rate in every trial (spike count / length of epoch). Based on the firing rates, we performed a two-way ANOVA (factors grip type and spatial position; p < 0.01) separately for each of the epochs fixation, cue, planning, and movement.

The same tuning analysis was performed for the spiking activity of the start variation task (TASK II, two-way ANOVA, factors grip type and start position, p < 0.01) for each of the epochs.

Tuning onset of each cell in the target variation task (TASK I) was determined with a sliding window ANOVA analysis for grip type and spatial position. Here, a two-way ANOVA (with a fixed p-value of 0.01) was repeated for a series of windows of 200 ms length that were shifted in time steps of 50 ms. Tuning onset was then defined as the first occurrence of (at least) five consecutive windows with a significant ANOVA. This definition prevented a possible bias due to multiple testing. The analysis was performed for three different alignments of spiking activity: to fixation onset, cue offset, and onset of movement epoch (‘go’-cue).
2. Methods

ROC analysis

To estimate how well individual neurons represent grip type and spatial positions, we quantified the discriminability of different conditions with the receiver operator characteristics (ROC) score (Townsend et al., 2011). For this, we compared the trials of the two grip types and from the preferred and non-preferred position in each task: CV, TV, and GV. For each grip type or spatially tuned unit, the ROC score was calculated in a sliding window of 200 ms width, shifted in steps of 20 ms. The population average of the resulting ROC curves over time were then compared for grip type and the various spatial conditions in the CV, TV, and GV task (one-way ANOVA, p < 0.01).

Stepwise linear model

To further investigate the tuning of individual neurons, we modeled the firing rates \( f \) of each neuron (in specific task epochs) in a stepwise linear model including the factors grip type (GT), target position (T), and gaze position (G) and a constant (a). This resulted in the coefficients \( gt, t, \text{ and } g \) as a measure of modulation by the respective factor.

\[
f = a + gt \times GT + t \times T + g \times G \quad (Equation \ 1)
\]

Since the spatial factors (T and G) each have a horizontal (x) and a vertical (y) component, a more detailed description of the model is:
2. Methods

\[ f = a + gt \cdot GT + t_x \cdot T_x + t_y \cdot T_y + g_x \cdot G_x + g_y \cdot G_y \]

*(Equation 2)*

By starting with the constant model: \( f = a \), additional components were added in a stepwise fashion until no further significant improvements could be obtained (Matlab function: stepwisefit; \( p < 0.05 \)). This allowed categorizing each neuron according to its significant modulations. A neuron was considered modulated by a spatial factor, if the model contained either a significant horizontal or vertical component. This resulted in a spatial categorization of neurons that were modulated by target position, by gaze position, by neither or by both factors.

In addition, the coefficients of this linear regression analysis were further processed by calculating the angular difference between the vectors \( t = \begin{pmatrix} t_x \\ t_y \end{pmatrix} \) and \( g = \begin{pmatrix} g_x \\ g_y \end{pmatrix} \) as well as the length contrast (LC) between both vectors:

\[ LC = \frac{\| t \| - \| g \|}{\| t \| + \| g \|}, \quad \text{(Equation 3)} \]

where \( \| t \| \) and \( \| g \| \) describe the length of vectors \( t \) and \( g \), respectively. Neurons were considered to encode spatial information retinotopically, if:

a) they were both significantly modulated by target and gaze position (as revealed by the stepwise fit),
b) if they showed similar vector lengths for \( t \) and \( g \) (\(-0.33 < LC < +0.33\); i.e., vector lengths differed by less than factor 2), and
c) if the angular difference between $t$ and $g$ was at least 135°, corresponding to $t$ and $g$ pointing approximately in opposite directions.

These assumptions are reasonable, since for retinotopic coding $t = -g$ and hence

$$f = a + gt \cdot GT + t \cdot (T - G).$$

**Decoding simulation**

For neural decoding, we used a maximum likelihood estimation approach (for details see: Scherberger et al., 2005; Townsend et al., 2011). This method allows estimating unknown parameters based on known outcomes (in this case the activity of a population of neurons for given task conditions).

We simulated the decoding of grip type, individual spatial conditions, as well as the spatial target position, retinotopic target position, and gaze position from neural activity during the different task epochs. The decoding simulation was performed based on the sequentially recorded populations of neurons in AIP and F5. For the analysis they were assumed to be recorded simultaneously, hence the term: decoding simulation. Decoding was performed with all units that were significantly modulated for the conditions to be analyzed in the respective task epoch (one-way ANOVA, $p < 0.05$). We calculated the percentage of correctly decoded conditions from 100 simulated repetitions. This process was iterated 200 times to obtain a mean performance and a standard deviation, from which 95% confidence limits were inferred by assuming a normal distribution. To illustrate the decoding results, we plotted the frequency of instructed and decoded condition pairs in a color-coded confusion matrix. In this matrix, correctly classified trials line up on the diagonal.
2. Methods

These results represent the maximal performance of such a decoding. Besides this, it is also interesting to know how many tuned units are needed to reach a satisfying decoding performance for a given factor. This could be of interest for the control of a brain-machine-interface (BMI). Therefore, a neuron dropping analysis was performed, in which an increasing number of randomly chosen neurons from the pruned database was used to simulate the decoding. As a result, the decoding performance could be displayed as a function of the number of neurons that were taken into account for simulation.

2.4.2 LFP analysis

For LFP analysis, we mostly used similar methods as previously presented for the spiking activity. But instead of using the firing rates of neurons, the analyses were based on the spectral activity for different frequency bands of a recording site. This allowed us to compare the information content of LFP activity with spiking activity.

In the literature, certain ranges of LFP frequencies are usually pooled together in different frequency bands: the delta band (1-4 Hz), the theta band (4-8 Hz), the alpha band (8-13 Hz), the beta band (13-30 Hz), and the gamma band (30-100 Hz) (Buzsaki and Draguhn, 2004). The gamma band can be further subdivided into a low gamma (30-60 Hz) and a high gamma range (60-100 Hz). As the frequency bands from 1 to 13 Hz are usually quite similar in their activity, in combination they are also referred to as slow band (1-13 Hz).

LFP signal was recorded in parallel with spiking data. To further process the LFP activity, it was extracted from the raw signal using a low-pass filter (1-200 Hz), sampled down to 1000 Hz, and further cut into behavioural trials, aligned to the onset
of the planning epoch. The resulting signal is a mixture of different frequencies, therefore a frequency decomposition had to be performed in order to analyse the LFP signal in a systematic way. In order to reveal the spectral power of different frequencies, a widely used signal processing toolbox for Matlab was used for multi-taper spectral analysis ("Chronux" Toolbox, see Mitra & Bokil, 2008). Compared to "conventional" Fourier analysis for frequency decomposition, multi-taper analysis reduces the variance for small datasets. The multi-taper analysis was done in a sliding window (window size 300 ms, steps of 50 ms, 5 tapers, frequency resolution of 1.95 Hz).

Results from the multi-taper spectral analysis were then visualized as follows: the spectrograms for each given recording site were averaged over all trials and, for each frequency, normalized by the averaged activity of a window (-2 s to -1.5 s) prior to fixation onset. The spectrograms were averaged over all sites of a given area, resulting in a population spectrogram, revealing the population activity over time for different frequencies.

In order to analyse the tuning properties of each LFP recording site, a two-way ANOVA (factors grip type and position, p < 0.05) was performed in frequency steps of 1.95 Hz, averaging the spectral power of a given frequency band during the epochs fixation, cue, planning, and movement.

As the results of this detailed tuning analysis generally justified the subdivision into the “classic” LFP bands (as shown in results section of LFP analysis, Chapter 4.2.1), the rest of the analyses presented in the following were performed for the
2. Methods

following four broader bands: the slow band (1-13 Hz), the beta band (13-30 Hz), the low (30-60 Hz), and the high gamma band (60-100 Hz).

First, a two-way ANOVA (factors grip type and position; p < 0.05) was performed with the averaged activity for each of the bands in the four different epochs.

Second, the tuning onset for each band was defined by performing the same analysis (two-way ANOVA with factors grip type and position, p < 0.05) for a sliding window (size 250 ms, steps 50 ms). As in the corresponding spiking data analysis, tuning onset for each band was defined as the first occurrence of at least five significantly tuned windows in a row.

Third, the sites and bands tuned for grip type or position were further analysed with respect to their tuning properties. For this, the spectral power was averaged over all trials for the two different grip types, or the 13 different spatial conditions. The condition with the highest activity was considered the preferred grip type, or the preferred position, respectively.

Fourth, a decoding simulation was performed, using a maximum likelihood estimation approach (as for the spiking data). We simulated the decoding of grip type and individual spatial conditions, using the averaged spectral activity of a given band in the relevant epoch. The decoding was performed with a “pruned” database of all recorded sites, for which the given band was significantly modulated by the given factor (grip type or position) in the respective band (for further details about the method, consider Chapter 2.4.1 about decoding spiking activity).

Finally, to investigate the components of the positional tuning, we modelled the averaged LFP power $P$ for a given band and epoch for each recording site in a
stepwise linear model with the factors grip type (GT), target position (T), gaze position (G), and the retinotopic target position (R), similar to the analysis of spiking data (Chapter 2.4.1, section “Stepwise linear model”).

\[ P = a + gt \cdot GT + t \cdot T + g \cdot G + r \cdot R \quad (Equation 4) \]

Since the spatial factors (T, G, and R) each have a horizontal (x) and a vertical (y) component, a more detailed description of the model would be:

\[ P = a + gt \cdot GT + t_x \cdot T_x + t_y \cdot T_y + g_x \cdot G_x + g_y \cdot G_y + r_x \cdot R_x + r_y \cdot R_y \quad (Equation 5) \]

A site was considered to be tuned for a spatial factor, if it showed significant modulation by at least one of the horizontal or vertical components of this factor. This allowed us to further categorize each band of a recording site according to its significant modulation by one of these factors.

In comparison to the model for the spiking activity, retinotopic factors and their coefficients were included separately, and not, as for the spiking activity, defined by a following analysis of modulation strength and tuning direction of target and gaze vectors.
3. Modulation of spiking activity in AIP and F5

3.1 Introduction

A condensed part of this chapter is included in a manuscript that has been accepted for publication in the Journal of Neuroscience (Lehmann & Scherberger 2013, in press).

We recorded neural activity from two animals for two versions of a delayed reach-to-grasp task: a target variation task (TASK I) and a start variation task (TASK II). Animals usually made about 600-1000 correct trials per recording session and performed the task with high accuracy: errors due to grip type confusion were below 3 %.

3.2 Results from target variation task (TASK I)

3.2.1 Tuning analysis

For the target variation task (TASK I), we recorded a total of 353 single units in AIP (animal P: 207 units, animal S: 146 units) and 585 units in F5 (P: 284 units; S: 301 units). The locations of the recording sites for both areas are displayed in Figure 2.5 of the methods section. Task behavior was consistent across the different task conditions with a mean reaction time of 270 ms (SD: 40 ms) for animal P and 250 ms (SD: 40 ms) for animal S, independent of grip type. Movement times were slower for precision grips (animal P: 350 ms (SD: 160 ms); animal S: 450 ms (SD: 120 ms)) than power grips (P: 300 ms (SD: 70 ms); S: 330 ms (SD: 70 ms)) and were slightly faster
for targets closer to the hand starting position (left and down targets). However, there was no systematic difference between central and peripheral, or foveated and non-foveated targets. Also, even though we did not measure hand kinematics explicitly, we observed no differences of finger aperture or forearm rotation as a function of target location.

A large fraction of the recorded cells was modulated by the reach-to-grasp task, either exclusively for grip type, target, or gaze position, or in combination. In the following, single unit examples from both areas are presented.

**Examples for different tuning qualities**

Figure 3.1 shows spike raster plots and averaged firing rates of a representative neuron from F5 in animal P that was strongly tuned for the instructed grip types as well as for spatial position. For precision grips, spiking activity was clearly higher during the planning epoch and towards movement execution (Figure 3.1A-C) than for power grips (Figure 3.1D-F). In addition, the activity of this neuron was strongly modulated by the spatial target and gaze position, in particular during precision grip trials (Figure 3.1A-C). In the CV task, activity differences were only moderate, with the strongest modulation between the top and bottom positions (Figure 3.1A). Position modulation was stronger in the TV and GV task, when target and gaze positions were spatially separated (Figure 3.1B-C). Here, modulation by target and gaze position was not independent. In fact, it was consistent with a retinotopic representation of the grasp target, as activity during the cue and planning epoch was highest for target positions to the left and down of the eye fixation (gaze) position.
This was independent of whether the target position was varied and gaze kept constant (TV task; Figure 3.1B) or gaze position was varied and the target position fixed (GV task; Figure 3.1C). Together, this single unit was strongly modulated by grip type and retinotopic target position.

Figure 3.1 Example neuron from F5. (opposite page)

Activity of this neuron from F5 in animal P was modulated by both grip type and spatial factors. In each panel, solid vertical lines indicate the on- and offset of the task epochs: fixation, cue, planning, and movement; dotted lines indicate movement start. All trials were three-fold aligned to fixation onset, cue offset, and the ‘go’ cue (indicated by black triangles). Spike rasters (on top) and averaged firing rates (at bottom) are shown in different colors for each condition, as indicated by the inset. (A - C) Neural activity for performing precision grip trials in the CV, TV, and GV conditions. (D – F) Same for performing power grips. On-center condition (eT) is identical and reappears in the CV, TV, and GV task. Note that colors code either target and gaze position (A, D), only target position (B, E), or only gaze position (C, F).
3. Modulation of spiking activity in AIP and F5

![Graph](image-url)
A second example neuron (from AIP) is shown in Figure 3.2. It was grip-type tuned during the movement epoch with a preference for power grip (Figure 3.2D-F). In addition it was modulated by spatial factors, especially during the execution of power grips in the CV conditions (Figure 3.2D). Furthermore, it was spatially modulated during the cue, planning, and movement epochs of various conditions (Figure 3.2B,C,E,F), but it did not depend linearly on these spatial factors. Hence, in contrast to the first example, this neuron showed a much more complex tuning of spatial representation that was more difficult to categorize.

Figure 3.2. Example neuron from AIP. (opposite page)
This neuron from AIP in animal S was modulated by both grip type and spatial factors. (A - C) Neural activity for performing precision grip trials for CV, TV, and GV conditions. (D – F) Same for performing power grips. Figure conventions are identical to Figure 3.1.
3. Modulation of spiking activity in AIP and F5

![Graphs illustrating modulation of spiking activity in AIP and F5 for different grip types: power grip and precision grip. The graphs show firing rate (Hz) over time, with different markers indicating fixed (Fix), cue (Cue), plan (Plan), and movement (Mov) phases.](image)
3. Modulation of spiking activity in AIP and F5

3.2.1.1 Population tuning

To better understand the nature of the tuning for grip type and spatial position (of target and gaze) in the neuronal populations of AIP and F5, we performed a two-way ANOVA (p < 0.01) with factors grip type (precision or power grip) and spatial position (the 13 combinations of target and gaze positions from the subtasks CV, TV, and GV). This was done separately for each neuron and each of the task epochs: fixation, cue, plan, and movement.

In general, a considerable number of units in both areas was significantly modulated by the task, i.e. tuned for at least one of the factors grip type or position (AIP: fixation 37%, cue 57%, plan 50%, movement 63%, (N=353); F5: fixation 13%, cue 23%, plan 28%, movement 50%, (N=585)).

More detailed, 43% of all AIP neurons were significantly tuned for grip type in at least one of the epochs, whereas a higher fraction, namely 73%, were modulated by spatial position (Figure 3.3A). In contrast, more units in F5 were tuned for grip type in any of the epochs (54%), while only 28% were modulated by position (Figure 3.3B).
3. Modulation of spiking activity in AIP and F5

Figure 3.3. Tuning for grip type and position across epochs.

A) Fraction of single units in AIP (N = 353) tuned for grip type (blue) and position (red) in at least one of the epochs fixation, cue, planning, or movement; B) Fractions of tuned cells in F5 (N = 585). Results from two-way ANOVA (p < 0.01).

These findings persisted when comparing the tuning for the specific task epochs; the detailed tuning classifications for both areas and all epochs are listed in Table 3.1. It shows the presence or absence of significant tuning for grip type or spatial position in each of the different task epochs, revealing a broad variety of tuning combinations for both areas.

As it could be expected, almost no cells were tuned for grip type during the fixation epoch, as the relevant cue was not given yet (Figure 3.4). The fractions of tuned cells increased significantly during cue epoch (AIP: 12%; F5: 17%), when the cue information was available. Proportions remained on a similar level during
planning epoch (AIP: 11%; F5: 21%), and finally strongly peaked during movement execution (AIP: 32%; F5: 46%, Figure 3.4A,B, blue bars).

Figure 3.4. Spatial and grip type tuning for different epochs.
Fraction of cells with tuning (two-way ANOVA, p < 0.01) for the factors grip type (blue), position (red), or both: grip type and position (black horizontal lines) during the different task epochs for AIP (A) and F5 (B).

In contrast to these findings, the number of position-tuned cells remained rather constant across epochs (Figure 3.4, red bars). An average of ~45% of all cells in AIP were spatially modulated across all task epochs (fix: 36%, cue: 53%, plan: 46%, mov: 52%). In contrast, these numbers were much lower in F5: on average ~15% of units across epochs were tuned for position (fix: 13%, cue: 14%, plan: 14%, mov: 16%).

These findings demonstrated that grip type and positional information were represented in both areas, but on different levels. Grip type tuning was a prominent
feature of F5, whereas position tuning was more strongly represented in AIP across all epochs.

This was also found when analysing the tuning characteristics of units in the population over time more detailed (Table 3.1). A large fraction of AIP cells stayed tuned for position during the whole task (19% of the total population, N = 353) or from cue onward (10%; Table 3.1, a,b) while 9% of the units were tuned exclusively in the movement period (Table 3.1, c). In contrast, by far the biggest fraction of grip-type tuned units in AIP was tuned only during movement execution (23%; Table 3.1, d).

Of the small fraction of neurons tuned for position in F5, the biggest groups were the cells tuned throughout the task (4%) or only in the movement epoch (6%) (Table 3.1, e,f). In contrast, grip-type tuned cells were tuned mainly from cue onward (10%; Table 3.1, g) or exclusively during movement execution (27%; Table 3.1, h).

Interestingly, a substantial fraction of cells in both areas was simultaneously modulated by grip type and spatial position (AIP: cue 8%, plan 7%, mov 20%; F5: cue 7%, plan 8%, mov 12%; displayed by horizontal lines in Figure 3.4). This indicated that grip type and spatial tuning was not separated, but often co-represented (intermingled) in the cells of AIP and F5.
3. Modulation of spiking activity in AIP and F5

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<td>2.5</td>
</tr>
<tr>
<td>-</td>
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<td>+</td>
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</tr>
<tr>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>57.2</td>
<td>26.6</td>
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</tbody>
</table>

**Table 3.1. Cell classification by tuning in task epoch.**

List of cell classes according to the presence (+) or absence (-) of significant tuning for grip type (GT) or position (Pos) in the task epochs fixation, cue, planning, and movement (two-way ANOVA, p < 0.01; see Methods). Percentages indicate the fractional size in the AIP (N=353) and F5 (N=585) population, respectively; i.e., percentages add up to 100% within each column. Marked entries (a-h, shaded cells) are referenced in the text.
3.2.1.2 Encoding Preferences

In order to reveal potential grip type preferences in the population, we analyzed the encoding preferences of the grip type tuned cells. This was done for all epochs besides the fixation epoch (in which the grasp instruction was not available yet, see Figure 3.5). In AIP, 67% of the cells with grip type tuning during the cue epoch showed a preference for precision grip, switching to a preference of power grip (59%) during the planning epoch and a balanced ratio during movement epoch (Figure 3.5A).

In F5, the ratio of precision and power grip tuned cells was approximately balanced throughout the task, with small preferences for precision grip during cue (53%) and movement epoch (54%) or for power grip during planning epoch (52%; Figure 3.5C). As mentioned before, a substantial number of cells was modulated by both grip type and position (Figure 3.4, displayed by horizontal line for each epoch). Potentially, this could be due to a linkage of spatial tuning to a certain grip type (e.g. precision grips had to be performed with higher accuracy to manipulate the target in the dark, and could therefore represent more spatial factors). To exclude this possibility of a spatial tuning dependency on a certain grip type, we compared the fractions of spatially modulated cells for the two different grip types.

In AIP, 66% of the cells tuned for precision grip showed a spatial tuning during the cue epoch; this was similar to tuned cells for power grip, of which 71% revealed spatial tuning. Similar sized fractions were found during the planning (69% / 57%) and movement epoch (67% / 62%, Figure 3.5B).

Also in F5 we found similar spatially tuned fractions for the grip type tuned cells during the cue (45% / 40%), planning (40% / 35%), and movement epoch (23% /
28%, Figure 3.5B). The fraction sizes were decreasing towards the end, because the amount of grip type tuning was increasing towards movement execution, whereas position tuning stayed on a relatively low level in F5 (see Figure 3.5). In conclusion, the prevalence of spatial tuning in both areas did not depend on a particular grip type.

**Figure 3.5** Encoding preferences of grip type tuned cells.

(A,C) Ratio of grip type tuned cells preferring precision grip (blue) or power grip (red) for areas AIP (A) and F5 (C) during the different epochs. (B, D) Fraction of spatially tuned cells in the population of precision (blue) and power grip (red) tuned cells (in %).
3. Modulation of spiking activity in AIP and F5

3.2.1.3 Tuning onset

As mentioned before, we found a variety of tuning combination for units across different epochs (see Table 3.1). To better analyze the chronological properties of tuning for grip type and position, the two-way ANOVA was repeated in a sliding window analysis for each cell. Doing so, we were able to highlight the tuning onset of individual cells, and to reorder them accordingly (Figure 3.6; for details see methods chapter 2.4.1).

Confirming our results from the epoch analysis, the dominant effect in AIP was a tuning for position (Figure 3.6A, red horizontal lines). Most of the position-tuned cells became selective during the fixation and cue epoch. Fewer cells were tuned for grip type, and their tuning onset occurred predominantly during movement execution (Figure 3.6A, blue horizontal lines).

In the F5 population, we found similar distributions for the onset of position and grip type tuning: position tuning started predominantly in the fixation and cue epoch, while most cells became grip type tuned during movement execution and less so during cue presentation (Figure 3.6B).

In both areas, some cells showed tuning onset for position shortly before the fixation epoch started. This can be explained by acoustic information from the motors that were moving the target before trial onset. If the animals did recognize the target position because of the sounds, also the gaze position could be guessed due to our task design. In cases in which the target position was not the central one (in the CV and TV subtasks), the possible location of the gaze position was automatically limited to two possible positions. However, the presence of such spatial hints shortly before the fixation epoch does not affect the general interpretation of our data.
3. Modulation of spiking activity in AIP and F5

Figure 3.6 Sliding window analysis for tuning onset.
A sliding window analysis (window size 200ms, step size 50ms) for each neuron (y-axis) and time-step (x-axis) revealed the times with significant tuning for AIP (A) and F5 (B). Horizontal bars indicate time windows with significant tuning for grip type (blue) or position (red) and are three-fold aligned to fixation onset, cue offset, and the ‘go’ cue. Neurons are ordered by tuning onset (defined by the appearance of at least five consecutive significant steps). Vertical lines indicate onset of fixation, cue, planning, and movement epoch.

3.2.1.4 Anatomical organization of tuned units
In order to see if there was any correlation between the functional classification of units and the location where they were recorded, we analyzed the spatial distribution of tuned cells in AIP and F5. For this, we projected the position of a recorded unit on an axis that was approximately parallel to the intraparietal sulcus (units from AIP) or the relevant section of the arcuate sulcus (units from F5), respectively. For both animals, the populations were split in eight equal sized bins along these axes. For each of these bins, the fraction of cells tuned for grip type or position in at least one of
the task epochs (results of the two-way ANOVA, p < 0.01) was determined. The distributions of tuned units along the corresponding sulcus are displayed in Figure 3.7.

![Figure 3.7. Distribution of tuned cells along sulci.](image)

Distribution of cells tuned for grip type (blue) or position (red) along the intraparietal sulcus (IP) for area AIP (A) and along arcuate sulcus for area F5 (B). Tuning classifications according to the results depicted in Figure 3.4.

In both AIP and F5, the cells tuned for grip type and the cells tuned for position did not show any clustering along the sulcus, being distributed approximately uniform. In particular, the distribution of tuned cells did not seem to be different from each other, again suggesting that grip-type and spatially tuned neurons are anatomically intermingled in AIP and F5 (compare with Figure 3.4).

In summary, we found grip-type as well as position tuned cells in AIP and F5. Position tuning was present in all task epochs at roughly constant levels, whereas the
number of grip-type-tuned cells was strongly increasing during the task with a peak at movement execution. Position information was more prominent in AIP than in F5, while F5 contained a much higher fraction of grip-typed tuned cells compared to AIP.

3.2.2 ROC analysis

To estimate how well individual neurons represent grip type and spatial positions, we computed a receiver operator characteristic (ROC) score for each neuron that was tuned in at least one of the epochs (compare with Figure 3.3). This ROC score was calculated by comparing spiking activity of the preferred vs. non-preferred grip type (across all tasks) in grip type tuned units, and of the preferred vs. non-preferred target/gaze position (separately for the CV, TV, and GV task) of the units tuned for position. Figure 3.8 shows the averaged ROC score of all tuned neurons for grip type as well as for target (TV), gaze (GV), and combined (CV) spatial position (sliding window analysis).

In AIP, the ROC score for grip type showed a small increase after cue onset and a stronger one around movement execution. In contrast, ROC values for all three position tasks (CV, TV, and GV) increased earlier and stronger compared to grip type, and stayed on that high level throughout the task (Figure 3.8A). In F5, ROC scores had approximately the same temporal profile as in AIP, but were higher for grip type and lower for spatial positions (Figure 3.8B).

However, there were two differences: First, ROC scores for target and gaze position declined strongly during movement execution in F5 while remaining high in AIP, indicating a weaker representation of spatial positions in F5 during movement
execution. Second, the ROC score was larger for grip type than for spatial positions during movement execution in F5.

These ROC results showed that both the stronger representation of grip type in F5 and the more prominent representation of spatial information in AIP hold true not only in terms of the fraction of tuned neurons (compare Figure 3.4A), but also with respect to their tuning strength. Spatial ROC values for CV, TV, and GV were significantly above chance level in both areas (one-way ANOVA, p < 0.01) and were similar within each area. These findings were consistent with the notion that AIP and F5 might encode relative spatial positions, like the retinotopic target position (as observed in the example neuron in Figure 3.1), in addition to spatial and other, more complex gaze-dependent representations (Figure 3.2).

**Figure 3.8** Averaged receiver operator characteristics (ROC) for the tuned units. Colored lines show the ROC score of sliding windows analysis in AIP (A) and F5 (B) for distinguishing the two grip types (blue) as well as the preferred and non-preferred condition in the CV task (yellow), TV task (orange) and GV task (red). Curves are three-fold aligned to fixation onset, cue offset, and the 'go' cue; gaps in the curves mark realignment.
3. Modulation of spiking activity in AIP and F5

3.2.3 Coordinate frames - linear modeling

To further investigate the tuning of individual cells, we modeled the firing rates of each neuron (in specific task epochs) in a stepwise linear model including the factors grip type (GT), target position (T), and gaze position (G). (Figure 3.9A; see also Methods chapter 2.4.1). This allowed categorizing each cell depending on its significantly modulating factors.

In both areas, a large fraction of cells was significantly modulated by one or several of these factors. In AIP, an average of 68% of all cells across epochs was modulated by at least one factor (fixation: 214 of 353 neurons (61%), cue: 239 (68%), plan: 238 (67%), movement: 275 (78%)). In F5, an average of 48% of all cells was modulated by at least one factor (fixation: 181 of 585 neurons (31%), cue: 266 (45%), plan: 287 (49%), movement: 390 (67%)). This occurrence of large fractions of cells with significant coefficients in the stepwise fit was similar to our previously performed tuning results and supported the reliability of our classification.

Following these results, we categorized each neuron according to its significant modulation by grip type (GT) as well as by target position (T), gaze position (G), or a combination of both (T&G). Figure 3.9B,C displays the fractions of cells modulated by these factors for the various epochs and areas.

Consistent with our previous analysis (ANOVA, ROC), the fraction of cells with a significant factor grip type (GT) strongly increased from the fixation (< 5%) to the movement epoch (AIP: 40%; F5: 58%). In contrast, the fraction of cells with significant spatial modulation (T, G, or T&G) was approximately constant in all task epochs: around 60% for AIP (fixation: 59%, cue: 63%, plan: 61%, movement: 68%), and around 30% for F5 (fixation: 29%, cue: 32%, plan: 31%, movement: 32%).
Concerning the underlying coordinate frame for the coding of target and gaze position, similar fractions of cells were classified as modulated by spatial target position (T), gaze position (G), or both (T&G). Across epochs, values averaged around 21% for AIP (T: 15%, G: 26%, T&G: 22%; Figure 3.9B) and 10% for F5 (T: 11%, G: 12%, T&G: 9%; Figure 3.9C).

Spatial position and grip type modulation were also found to be intermingled: in AIP, spatially tuned groups (T, G, and T&G) exhibited a similar percentage of grip type tuning as found in the entire population (Figure 3.9D). In F5, the same was true for the target (T) and gaze (G) modulated cells (Fig. 3.9E), whereas the T&G group represented grip type even more frequently (cue: 60%, plan: 64%, movement: 83%) than in the entire population (cue: 26%, plan: 32%, movement: 58%). This again suggested that grip type and spatial information is processed in a combined fashion in AIP and F5.
3. Modulation of spiking activity in AIP and F5

Figure 3.9 Results from the linear model in AIP an F5.

(A) Combined linear model fitted to the data. The fit predicted the firing rate of an individual neuron by the factors grip type (GT, dark blue underscore), target position (T, green), and gaze position (G, light blue). (B) Percentage of cells in AIP that are tuned for each of the factors or for a combination of the two spatial factors (solid red line). Their retinotopic fraction (see paragraph “Retinotopy”) is shown as dashed red line. (C) Same analysis for F5. (D) Fraction of grip type tuned cells in the spatially tuned populations (T, G, T&G) and in the entire population. (E) Same analysis for F5.
To further analyze the modulation of the spatially tuned neurons with respect to target and gaze position and their underlying coordinate frame, we compared the estimated coefficient vectors for target and gaze modulation. For each neuron, we computed a length contrast (LC) index, comparing the length of both gradient vectors, as well as the angular orientation difference between these vectors. Figure 3.10 shows scatter plots of these measures for data during all epochs: fixation (A,B), cue (C,D), planning (E,F) and movement (G,H). Purely target or gaze coding neurons had a LC close to +1 or -1, respectively.

**Retinotopy**

Neurons were considered to be retinotopic, i.e. coding the target position in retinal coordinates (like exemplarily seen for the unit presented in Figure 3.1), if their target and gaze coefficient vectors had approximately equal length (LC close to zero: -0.33 < LC < +0.33) and opposite directions (angular difference larger than 135º). Neurons classified as retinotopic are framed by black rectangles in all plots in Figure 3.10. While angular difference was broadly distributed for target- (green dots) and gaze-modulated neurons (light blue dots), a majority of T&G neurons (red dots) was retinotopic. The percentage of retinotopic neurons was quite similar across task epochs, as reported in Figure 3.9B,C (dashed red line): they comprised about 68% (AIP) and 73% (F5) of all T&G cells, which corresponds to a fraction of 15% (AIP) and 6% (F5) of the entire population (Figure 3.9B,C, dashed line), about equal in size to the fraction of target-tuned cells (green line). Furthermore, the amount of grip type tuning in retinotopic neurons was similar to that of the T&G group in AIP and F5 (Figure 3.9D,E). These results clearly demonstrated a large variety of target, gaze, and
3. Modulation of spiking activity in AIP and F5

retinotopic target coding that was strongly intermingled with grip type coding in AIP and F5.

Figure 3.10 Retinotopic character of spatially tuned neurons in AIP and F5. (opposite page)
Scatter plot of spatially tuned neurons in AIP (left column) and F5 (right column) for the different epochs, illustrating angular orientation difference (y-axis) between the target position (t) and gaze position vectors (g, as in Figure 3.9A) against the length contrast (LC) of these vectors (x-axis). Neurons with target and gaze tuning were considered retinotopic if the coefficient vectors (t and g) were of comparable length (|LC|<0.33) and oriented in nearly opposite directions (angular difference >135deg). The fraction of neurons meeting these criteria (inside black rectangles) are drawn as red dashed lines in Fig. 3.9B-E.
3. Modulation of spiking activity in AIP and F5

AIP

- **fixation**
  - Scatter plot showing relationship between angular difference and length contrast.

- **cue**
  - Scatter plot showing relationship between angular difference and length contrast.

- **plan**
  - Scatter plot showing relationship between angular difference and length contrast.

- **mov**
  - Scatter plot showing relationship between angular difference and length contrast.

F5

- **fixation**
  - Scatter plot showing relationship between angular difference and length contrast.

- **cue**
  - Scatter plot showing relationship between angular difference and length contrast.

- **plan**
  - Scatter plot showing relationship between angular difference and length contrast.

- **mov**
  - Scatter plot showing relationship between angular difference and length contrast.

Legend:
- Red dots: Target & Gaze
- Green dots: Target
- Blue dots: Gaze
3. Modulation of spiking activity in AIP and F5

3.2.4 Decoding simulation

To further investigate the coding scheme and the employed coordinate frames in AIP and F5, we performed an offline decoding analysis to predict grip type and positional information from the population of sequentially recorded neurons (see Methods). In short, the decoding was performed based on all units that were significantly modulated for the conditions to be analyzed (one-way-ANOVA for grasp type or position, p < 0.05) and repeatedly simulated. To illustrate the results, the percentage of “planned” and decoded condition pairs was plotted in a color-coded confusion matrix. Correctly classified conditions line up on the diagonal.

Figure 3.11 displays the confusion matrices for the simulated position decoding in both areas and all epochs for animal P. For each instructed spatial condition (y-axis, numbered from 1 to 13, for details see Figure 3.11I), they display the percentage with which the conditions had been decoded in our analysis (x-axis).

The average decoding performance for each epoch and area was calculated by averaging the correct decoding occurrences for all 13 conditions (diagonal entries in the confusion matrices, Figure 3.11).

Figure 3.11 Simulated decoding performances for position in animal P. (opposite page)
Confusion matrices show the percentage (color coded) with which a particular instructed condition (y-axis) had been decoded for each condition (x-axis). Percentages in each row add up to 100%. Confusion matrices are shown for all epochs in the areas AIP (A-D) and F5 (E-H) in animal. Numbers from 1-13 correspond to the conditions of the subtasks CV (1-5), TV (6-9), GV (10-13). Position 3 is the redundant central (target and gaze) position shared by all subtasks. I) Numerical index for the different spatial conditions used in A-H.
3. Modulation of spiking activity in AIP and F5
3. Modulation of spiking activity in AIP and F5

For position decoding (13 conditions, chance level of 7.8%) in area AIP of animal P, we found high decoding performances throughout the task (see Figure 3.11A-D). Average performance was at 78% during the fixation epoch, reaching 91% (cue) and 92% (planning) after complete cue instruction was given, and finally dropped during movement execution (85%). Compared to these results, the average performance of position decoding was weaker for area F5 of the same animal (fixation: 55%, cue: 54%, planning: 48%, movement: 42%, see Figure 3.11E-H), but still clearly above chance level.

The averaged simulated decoding results for animal P are displayed in Figure 3.12A (AIP in dark blue, F5 in red). The error bars indicate 95% confidence limits after decoding 200 times with 100 simulated repetitions. As can be seen here, the average decoding performances for the different epochs we showed above were on a similar level for the second monkey (animal S, decoding results for AIP in cyan, F5 orange).

For spatial position decoding in AIP, we found average performances (across cue, planning, and movement epochs) of 89% for animal P and 80% for animal S (Figure 3.12A, blue and cyan lines). For F5 these values were considerably lower (animal P: 48%; animal S: 38%, red and orange lines). This is in correspondence with the results of our previous analyses (ANOVA, ROC, and the linear model), revealing stronger representation of spatial factors in AIP, compared to F5.
When performing the offline simulation for grasp type decoding, we also found similar results across animals. As soon as grasp information was present (with the beginning of the cue epoch), decoding performance for grip type in AIP was in both animals above 75% correct in cue and planning epochs, finally reaching almost 100% during movement epoch (Figure 3.12B, blue and cyan curves, chance level 50%). In agreement with our findings of other analysis (ANOVA, ROC, linear fit), decoding performance was clearly better in F5: already from cue onset on, performance was nearly perfect (>95%) for both animals (Figure 3.12B, red and orange curves).

These results confirmed that the modulated spiking activity of tuned units can be used to decode positional and grip type information in an offline simulation well above chance level.
Neuron dropping analysis

The decoding performances presented above were based on “pruned databases” containing a pre-selection of units that were significantly tuned for the relevant factor, e.g. grasp type or position (one-way ANOVA, p < 0.05). The information of all of these units was then used to simulate the decoding. The practical use of this method could be to decode movement plans online for the development of brain machine interfaces, using data from multiple electrodes. Therefore it would be interesting, how many (tuned) units are needed to reach a satisfying decoding performance for a specific factor.

This question was addressed by randomly choosing a subset of neurons from the pruned database, starting with one single unit and proceeding till the complete number of cells in the database was reached. For every given subset of neurons, the decoding simulation was performed as introduced before. This neuron dropping analysis was performed for grip type and position in each epoch. The results are displayed in Figure 3.13. The decoding performance with the maximal number of cells, equivalent to the full set of tuned units for an epoch, corresponds to the maximal decoding performance reported before (Figure 3.12).
3. Modulation of spiking activity in AIP and F5

Figure 3.13 Neuron dropping analysis.

Decoding performance for each epoch as a function of the numbers of cells (randomly chosen from tuned units) used for the decoding simulation of grip type (A-D) and position (E-H) for AIP and F5. Colors indicate the different areas in the two animals (blue: AIP, animal P; cyan: AIP, animal S; red: F5, animal P; orange: F5, animal S). The horizontal dashed line indicates chance level (50% for grip type decoding, 7.8% for position decoding).

The results of the neuron dropping analyses were similar across animals (see Figure 3.13). In case grip type instruction was available (i.e. in the cue, planning, and movement epoch), the decoding performance in F5 quickly increased with numbers of cells and saturated on a high level of nearly 100% (Figure 3.13B-D, red and orange curves). In AIP, the decoding performance for grip type was not as good in the cue and planning epoch (in both animals), but during movement epoch the trend was similar to the increase of decoding performance observed for F5 (Figure 3.13D). In agreement with the previous analyses, this implied that grip type information was generally stronger and earlier represented in F5 than in AIP (less cells were needed...
for correct decoding), whereas grip type information in AIP was strongest represented during the movement epoch.

Also for the simulation of position decoding, results were similar across animals. Positional information was similarly present in AIP and F5 in the fixation epoch (Figure 3.13E). In contrast, there was a clear difference in performance between the two areas as soon as the set of positional information was fully available in the cue epoch (by illuminating the target position). Decoding performance increased much faster in AIP than in F5 (i.e. needing less units for the same performance, see Figure 3.13F-H). In addition, the maximal performance for position decoding was much higher in AIP as well, as already shown before (Figure 3.12A).

**Decoding spatial components of the different positions**

To further investigate the underlying coordinate frames for the coding of the spatial positions (compare with linear fit analysis, Chapter 3.1.3), we also decoded the spatial target position, the gaze position, and the retinotopic target position separately from each other (Figure 3.14A-C).

From cue onset on (when all spatial information was available), decoding performances for the spatial factors were generally higher in AIP than in F5 (Figure 3.14A-C). This was the case for both animals and all spatial factors, no matter if the spatial target position or the gaze position were decoded alone (Figure 3.14A,C) or as a combination of both factors (the retinotopic target position, Figure 3.14B).

Comparing the decoding performances in AIP averaged across the epochs cue, planning, and movement, the best performance was achieved for predicting the retinotopic target position (average performance across these epochs: animal P, 92%;
animal S, 95%; see Figure 3.14C,D). In contrast, decoding performance in AIP was significantly lower (one-way ANOVA, and post-hoc t-test; p < 0.01) for predicting the spatial target position (P: 85%; S: 74%; Figure 3.14A,D) or gaze position alone (P: 88%; S: 79%; Figure 3.14B,D). Similar results were obtained from area F5, however, with an overall lower performance (Figure 3.14A-D).

In summary, the decoding of retinotopic target position was significantly better than decoding of target position or gaze position (Figure 3.14D). This was the case for both areas and animals.

![Figure 3.14 Decoding simulation for different spatial factors.](image)

Results of decoding simulation for the factors “spatial target position” (A), “retinotopic target position” (B), and “gaze position” (C). Colors indicate the different areas in the two animals (blue: AIP, animal P; cyan: AIP, animal S; red: F5, animal P; orange: F5, animal S). Horizontal dashed lines indicate the chance level (20 %). (D) Average performance for decoding target, gaze, and retinotopic target position across the cue, planning, and movement epoch for each animal and area. Error bars indicate 95% confidence interval.
3. Modulation of spiking activity in AIP and F5

Taken together, the decoding results demonstrated that AIP and F5 both represented the grip type as well as the reach target and gaze position during the different epochs of the delayed grasping task, and that target position was encoded in both spatial and, even better to decode, retinotopic representations.

3.3 Results from start variation task (TASK II)

As mentioned in the introduction, another spatial factor that could be of potential influence in reach-to-grasp movements is the starting position of the hand. In the start variation task, we systematically varied the initial position of the contra-lateral hand in three different positions (see Methods, Chapter 2.2.2).

For this task, we recorded 327 units from AIP (animal P: 189 units; animal S: 138 units) and 535 units from F5 (animal P: 278 units; animal S: 257 units). As we recorded these units directly after the main task as described above (Chapter 2.2.2), the total numbers were relatively similar to those we reported previously for TASK I (~90% in both areas). Similar to the main task, many units were modulated by the reach-to-grasp task.

3.3.1 Single unit examples for different tuning qualities

Figure 3.15 shows an example for a grip type tuned unit, recorded in F5 of animal S. It was clearly tuned for precision grip from cue onset on (red lines in Figure 3.17A-
C). Comparing the different starting positions, we did not see any significant tuning throughout the epochs.

![Figure 3.15 Example unit from F5.](image)

Activity of this neuron was modulated by grip type, but not by initial hand position. In each panel, solid vertical lines indicate the on- and offset of the task epochs: fixation, cue, planning, and movement. All trials are aligned to cue offset. Spike rasters (on top) and averaged firing rates (at bottom) are shown in different colors for each condition in A,B,C. Plots in the first row show neural activity for performing precision (red) and power grips (blue) starting from the left (A), middle (B) and right position (C). (D–E) Averaged activity for different grip types (D) and starting positions (E; yellow: left starting position, black: central, green: right).

A second example unit is shown in Figure 3.16. It was recorded in AIP (animal P) and showed a tuning for grip type (with a preference for precision grip) during the planning epoch. In addition it was tuned for starting position: there was a clear
preference for the right starting position throughout the cue, planning, and movement epoch (Figure 3.16C,E).

**Figure 3.16 Example unit from AIP.**

Activity of this neuron from animal P was modulated by both grip type and initial hand position. (A - C) Neural activity for performing precision grip trials for left, middle, and right starting position. (D, E) Averaged activity for different grip types (D) and starting positions (E). Figure conventions are identical to Figure 3.15.

### 3.3.2 Population Tuning

In order to see how strongly the factors grip type and starting position were represented in the recorded populations in AIP and F5, we performed a two-way ANOVA for these two factors (p < 0.01). The results for both areas are displayed in Figure 3.17.
3. Modulation of spiking activity in AIP and F5

Figure 3.17 Population tuning result for grip type and start position.

Fraction of cells with tuning for the factors grip type (blue) or start position (green) during the different task epochs (two-way ANOVA, $p < 0.01$) for AIP (A) and F5 (B).

The fraction sizes of grip type tuned units in the start variation task (TASK II) were similar to the previously presented results for the target variation task (TASK I, Figure 3.4) in both AIP and F5. Grip type information became present after cue onset (13% each in AIP & F5), stayed on a similar level (AIP: 13%) or slightly increased (F5: 21%) during planning epoch, and finally peaked during movement execution (AIP: 23%, F5: 36%, see Figure 3.17). Table 3.2 compares the fractions of grip type tuned cells for the two different tasks, confirming the general trend of increased grip type tuning towards movement execution.
3. Modulation of spiking activity in AIP and F5

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<td>21.4</td>
<td>46.3</td>
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</table>

Table 3.2 Comparison of grip type tuning in TASK I and TASK II

The table compares the fraction size of units (in %) that were significantly tuned for grip type (two-way ANOVA, \( p < 0.01 \)), showing the results from the two tasks previously presented in Figure 3.4 and Figure 3.17. Fractions sizes are listed for the two recording sites, AIP and F5, and for different epochs (fixation, cue, planning, movement).

In contrast to the increasing fractions of grip type tuned units towards movement execution, the fractions of units significantly modulated by starting position in TASK II were on a very low level both in AIP (average 2.9%; fixation 2.8%, cue 3.1%, plan 2.1%, movement 3.7%) and in F5 (average 2.1%; fixation 2.4%, cue 2.6%, plan 2.8%, movement 0.7%, see Figure 3.17).

As explained in the methods part (see Chapter 2.2.2), due to methodical limitations it was not possible to test the influence of all spatial factors (target position, gaze position, and starting position) together with grip type in one task. However, we usually recorded TASK I and TASK II in subsequent blocks of trials during the same recording sessions. This resulted in roughly equal-sized populations with similar fractions of cells tuned for grip type. So at least some comparisons could be drawn on the contribution of all spatial factors, including the initial hand position.
In AIP, an average fraction of ~45% (across task epochs) showed spatial modulation by position (target and gaze) during the target variation task (TASK I). This was much higher than the average fraction of 3% that was modulated by initial hand position during the start variation task (TASK II), as listed in Table 3.3. In F5, the differences of spatial representation were not as distinct, but an average of ~15% units tuned for position in the target variation task compared to 2% for start position task meant also big difference in tuning properties.

<table>
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<tr>
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<th>Fix</th>
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<td>position</td>
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Table 3.3 Comparison of spatial tuning in TASK I and TASK II

The table compares the fraction size of units that were significantly tuned for spatial factors (two-way ANOVA, p < 0.01), showing the tuning results for the two tasks that were previously presented in Figure 3.4 and Figure 3.17 (i.e. tuning for position (target or gaze) in TASK I, and tuning for the starting position of the hand in TASK II). Fractions with spatial tuning are listed for the recording sites, AIP and F5, and for different epochs (fixation, cue, planning, movement).

In conclusion, units that were modulated by the initial hand position could be found in both hand grasping areas AIP and F5, but their number was vanishingly low.
3. Modulation of spiking activity in AIP and F5

Even if it was only possible to compare the results at the population level, it appeared that the position of target and gaze was represented much stronger in AIP and F5, as compared to the initial position of the hand.

3.4 Discussion

We analyzed neural activity in two hand-grasping areas, parietal area AIP and premotor area F5, during a target variation task with systematic variation of grip type and of target and gaze position in extrinsic space (TASK I, Chapter 3.2). In addition, during a start variation task (TASK II, Chapter 3.3), the initial position of the hand was varied in three different positions before onset of the trials.

3.4.1 Representations in the target variation task (TASK I)

In the target variation task, we found grip type and positional information represented in the neuronal populations of both AIP and F5 (Figures 3.3 & 3.4). While the number of grip type tuned neurons increased during the task, with the biggest fractions found in the movement epoch for both AIP and F5, this was different for position tuning. The fraction of cells with spatial tuning stayed approximately constant across epochs, on a level around 40% in AIP, and on a lower level around 15% in F5 (Figure 3.4A,B). A substantial number of cells in both areas were significantly modulated by grip type as well as position. This was not due to the binding of spatial tuning to a certain grip type: units tuned for precision grip or power
grip revealed similar fractions of cells that were in addition tuned for position (Figure 3.5).

The analysis for tuning onset confirmed that position tuning was dominant in AIP, whereas grip type was stronger represented in F5. We also showed that most of the position tuned cells became selective relatively early (fixation and cue epoch) in both areas, whereas onset of grip type tuning could be noticed after cue onset and, more strongly, during movement execution (Figure 3.6).

Anatomically, we found both grip type and position tuned cells to be distributed approximately uniform along the intraparietal sulcus (AIP) and arcuate sulcus (F5), without any obvious clustering (Figure 3.7). This implied that neurons tuned for grip type or position were anatomically intermingled in both areas.

A ROC analysis was performed to estimate how well tuned neurons represent grip type and spatial positions. This revealed a stronger encoding of spatial positions in AIP and F5 than of grip type, except for F5 during movement execution (Figure 3.8).

We further analyzed the nature of these surprisingly strongly encoded spatial signals by applying a stepwise linear model. This analysis revealed that individual neurons represented the spatial information in various reference frames, ranging from purely spatial encodings of gaze position to prominent representations of target position. Furthermore, target information was encoded in spatial as well as in gaze-centered (retinotopic) coordinates. The fractions of these spatial representations stayed approximately constant throughout the task (Figure 3.9B,C), in both AIP and, on a lower level, in F5. Interestingly, the majority of units that were significantly modulated by both target and gaze position were found to encode the spatial
information in a retinotopic reference frame: 68% across epochs in AIP, and 73% across epochs in F5.

Finally, consistent with the tuning results, decoding simulations resulted in better predictions of grip type from F5 than from AIP activity, whereas spatial conditions could be more accurately decoded from AIP (Figure 3.12). When comparing the decoding performance for the different spatial factors, the retinotopic target position was consistently predicted best, or at least as good as the spatial target or the gaze position (Figure 3.14).

These results demonstrate that AIP and F5 provide a heterogeneous network, in which individual neurons represent grip type together with spatial signals, including gaze position as well as retinotopic and spatial target positions. Such a network could integrate gaze and reach target information during grasp movements planning and execution (Jeannerod et al., 1995).

### 3.4.2 Grip type tuning

We found an increase of grip type tuned neurons after the cue instruction, with the biggest fraction during movement execution, in both AIP and F5. In general, similar results were shown for these areas before (Baumann et al., 2009; Fluet et al., 2010), based on a similar task design for grip type variation. But in comparison to these studies, we found smaller fractions of grip type tuned cells in all epochs of AIP. Similarly, in F5 we found smaller fractions of grip type tuned in the cue and planning, but not in the movement epoch. These aberrant tuning properties in both areas compared to the previous studies could be due to the different task design of the work presented here. Neurons tuned exclusively for gaze or target position, which
comprised a substantial fraction of our dataset, could have easily been missed in the previous studies, where spatial factors were not varied. Including these in the database has very likely changed the fraction of tuned neurons.

### 3.4.3 Target and gaze representations

To our knowledge, substantial representations of reach target and gaze position in AIP have not been described before. In fact, an influence of spatial target position was denied by Taira et al. (1990). However, in this study, only a very small number of neurons was tested in an unsystematic way. Since then, no studies about spatial influences or representations have been reported.

In our dataset, a majority of AIP neurons (73%) contained spatial information in at least one of the four task epochs, whereas grip type was encoded only by 43% of all neurons (Figure 3.3A & Table 3.1) and was strongest during movement execution. Also the tuning strength in AIP measured by the ROC score (Figure 3.8A) was on average stronger for target and gaze position than for grip type. This was surprising, given that AIP is causally linked to the planning and execution of hand grasping movements but not to reaching movements (Gallese et al., 1994; Taira et al., 1990).

Potentially, grasping for different target positions in space could result in small differences in wrist orientation. A previous study reported a tuning for wrist orientation in 55% of neurons recorded from AIP (Baumann et al., 2009). In our experiment, differences in wrist orientation for different target positions were not observed (by visual inspection), but could not be completely ruled out. However, minimal differences in wrist orientation could not explain the prominent encoding of spatial factors (gaze, target, and retinotopic position), which were even stronger than grasp type tuning in AIP. Furthermore, spatial tuning could not be explained by
3. Modulation of spiking activity in AIP and F5

perceived changes in target orientation, e.g. due to non-foveal retinotopic presentations (Crawford et al., 2011), since these were minimal in our task (less than a few degrees). This renders them an order of magnitude smaller than the wrist orientation effects that were previously investigated (Baumann et al., 2009; Fluet et al., 2010).

In F5 of the same animals, we found target and gaze representations with similar tuning strength compared to those found in AIP (see results of ROC analysis, Figure 3.8B). However, the fractions of spatially tuned cells were only around 15 % in each of the epochs (Figure 3.4B), and only 29 % of all recorded cells were significantly tuned in at least one of the epochs (Figure 3.3B). Previously, reach target representations have been reported in PMv for different virtual motor tasks (Ochiai et al., 2005; Schwartz et al., 2004), which were rather dominated by the visual feedback than by the actual motor output. In addition, Stark et al. (2007) found strong reach and grasp representations in PMv and PMd. The stronger reach representation in PMv, as compared to our work, could result from different recording locations, since we have investigated more specifically area F5. Gaze dependent activity has also been reported for F5 in visual response tasks (Boussaoud et al., 1993; Gentilucci et al., 1983).

Neurons with grip type tuning and neurons with position tuning were found to be anatomically intermingled in AIP and F5 (Figure 3.7). Interestingly, considerable fractions of neurons in both areas represented both spatial and grip type factors (Figure 3.4A,B; Figure 3.9D,E). This leads to the question, why target and gaze signals are co-represented in hand grasping areas. Clearly, AIP and F5 are directly
and reciprocally connected and participate in the parieto-frontal network for grasp planning and execution (Borra et al., 2008; Luppino et al., 1999; Rizzolatti and Luppino, 2001). Furthermore, intracortical microstimulation in F5 elicited mostly distal upper limb movements (Hepp-Reymond et al., 1994; Rizzolatti et al., 1988; Stark et al., 2007), and chemical inactivation studies of AIP (Gallese et al., 1994) and F5 (Fogassi et al., 2001) resulted in deficits in hand preshaping and grasping, without impairment of reaching. Interestingly, deficits in reach adaption during a perturbation task were reported after PMv inactivation, but not after PMd inactivation (Kurata and Hoshi, 1999). Therefore, F5 could play a role in motor adaption during visually guided reach-to-grasp movements.

In summary, the target and gaze position signals we found in AIP and F5 are perhaps not causally linked to the generation of reach movements. Rather, they might function as a reference signal (or efference copy) for selecting or generating appropriate grasp movements. Since the spatial representations were present well before the start of the movement, they also cannot represent simple sensory feedback during movement execution (Mountcastle et al., 1975).

### 3.4.4 Representations in the start variation task (TASK II)

As the recording for the start variation task was performed directly after the target variation task, trying to keep the isolated single units stable for this second task. The total number of recorded units was lower than for the target variation task. But in both areas, the populations recorded within this task contained still more than 90% of the total number recorded in the target variation task (AIP: 327 units in TASK II
3. Modulation of spiking activity in AIP and F5

compared to 353 units in TASK I; F5: 535 units in TASK II compared to 585 units in TASK I).

As mentioned before, it would have been preferable to check the tuning for each of the factors grip type, target, gaze, and starting position in a combined approach, but the execution of this experiment was not possible under the given circumstances. But given the fact, that the neurons for the start variation task were recorded directly after the target variation task and comprised more than 90% of the recorded numbers for the target variation task, we can assume to have a considerable overlap of units in both populations. In addition, the fractions of grip type tuned neurons in AIP and F5 were relatively similar in both tasks, especially during the cue and planning epoch. Only during the movement epochs, both areas yielded clearly smaller fractions of grip type tuned units.

In both AIP and F5 we found units that were tuned for the starting position; an example from AIP is shown in Figure 3.16. But within the populations recorded from the areas, only a very low number of cells like this was found (Figure 3.17). Across epochs, around 3% of the AIP units were tuned for starting position. Similarly, only 2% of the units in F5 showed a tuning for the initial position of the hand.

To our knowledge, no reports have been published about possible effects of the initial hand position in AIP and F5. The low representation of starting position we found in both areas implies, that the initial hand position does not play an important role for reach-to-grasp movements; particularly in comparison to the other spatial factors. It could be argued, that the distances of the starting positions to each other (7.5 cm), defined by the positions of the hand rests sensors, were to small to see an effect in our results. But increasing the distance would have resulted in un-natural arm
and body postures. In addition, the two outer start positions had a distance of 15 cm to each other, which should have been large enough to see an effect, if present.

3.4.5 Reference frames

In both areas, a considerable fraction of neurons was modulated by a combination of the spatial target and gaze position in TASK I; a majority of these neurons encoded the target in retinotopic coordinates (Figure 3.9A,B; Figure 3.10). To our knowledge, these findings are novel for AIP. For F5 only a brief report exists describing gaze-dependent reaching signals in a single animal (Mushiake et al., 1997), whereas gaze-dependent activity has been observed in a visual response task (Boussaoud et al., 1993). In contrast, Fogassi et al. (1992) and Gentilucci et al. (1983) reported gaze-independent response fields in F5. Our results of retinotopic and spatial reach representations in F5 (Figure 3.9C,E; Figure 3.10, right column) extend these studies by demonstrating that reaching and grasping signals are co-represented by the same neurons (Figure 3.4B), suggesting that signals are computationally combined.

Retinotopic reach representations have been observed in other posterior parietal areas related to arm reaching, including area V6A (Marzocchi et al., 2008), the parietal reach region (PRR) (Batista et al., 1999; Buneo et al., 2002; Chang et al., 2009; Chang and Snyder, 2010; Pesaran et al., 2006), and parietal area 5 (Bremner and Andersen, 2012; Buneo et al., 2002), but also in dorsal premotor cortex (PMd) (Batista et al., 2007; Boussaoud and Bremmer, 1999; Pesaran et al., 2006, 2010). Most of these studies found reach representations in various reference frames, ranging from spatial to mixed and purely retinocentric coordinates. In addition, gaze-dependent reach target representations have also been observed in human parietofrontal cortex (Beurze et al., 2010).
Our results therefore support the idea that a set of spatial and gaze-dependent reference frames (including retinotopic ones) can provide a unified framework for spatial information processing that is able to facilitate multisensory integration and coordinate frame transformation (Andersen and Buneo, 2002; Buneo and Andersen, 2006; Crawford et al., 2011). Nevertheless, retinotopic reference frames can coexist with other, partly overlapping, representations, and furthermore with other signals not tested here, like the head position in space (Bremner and Andersen, 2012; Chang and Snyder, 2010; Pesaran et al., 2006).

Finally, our finding that the spatial coding schemes in AIP and F5 are approximately identical, although less represented in F5, is compatible with the hypothesis that reaching information in F5 originates form AIP, as supported by direct anatomical connections (Borra et al., 2008; Luppino et al., 1999). Alternatively, it could originate from PMd (Gharbawie et al., 2011; Matelli et al., 1986). AIP, on the other hand, could receive reaching information from PRR, V6A, or parietal area 5 (Borra et al., 2008; Gamberini et al., 2009).

### 3.4.6 Motor planning and coordination

We found that AIP and F5 contain not only signals directly related to their specific output (grasping code), but also reach target and gaze related information. These signals were quite strong in AIP and F5, so strong that the spatial and retinotopic reach target and the gaze position could be decoded from them (Figure 3.12). Even if not causally involved in generating motor output, they may be used for the coordination of reaching and grasping movements (Stark et al., 2007). The fact that we found reach-related signals in AIP and F5 points to a distributed nature of motor planning, which cannot be clearly separated into a grasping (dorsolateral) and
reaching system (dorsomedial network). Similar co-representations of reaching and grasping signals have also been described in the dorsomedial network both in monkeys (parietal area V6A) (Fattori et al., 2012; Fattori et al., 2010; Galletti et al., 2003) and humans (Grol et al., 2007; Verhagen et al., 2008). Inter-areal computation between parietal and premotor areas to generate reach-coordinated grasping movements might seem unlikely. However, similar coordination takes place between parietal and premotor cortex in order to integrate external (e.g., sensory) and internal (e.g., volitional or intentional) signals for reach and grasp movement planning (Andersen and Cui, 2009; Rizzolatti and Luppino, 2001).

We conclude that the classical subdivision into reaching and grasping areas is certainly lost from a representational point of view. From a causal perspective, however, future research is needed to investigate the effective connectivity of these areas with respect to grasp, reach, and gaze movements. At least, the sheer presence of a motor signal does not imply a causal effect for movement execution.
4. Modulation of LFP activity in AIP and F5

In total, we recorded 246 LFP sites in AIP (animal P: 147 sites, animal S: 99 sites) and 307 sites in F5 (animal P: 163 sites, animal S: 144 sites). The results presented in this chapter are based on LFP activity recorded simultaneously with the spiking data in the target variation task (TASK I) that was introduced in chapter 3.1 of this thesis. In both animals we found task related modulations of LFP activity, but in contrast to the spiking analysis we found substantial differences in the results across animals. Therefore, the results will not be presented pooled together across animals as in the previous chapter, but separately for the two animals and areas.

In short, we performed a frequency decomposition of the recorded raw data, a so-called multi-taper spectral analysis, calculating the spectral power of different frequencies (for further details, see Methods Chapter 2.4.2). Performing this decomposition repeatedly for different time windows in each trial revealed the modulation of different frequencies over time and can be depicted as a spectrogram. The obtained spectral activity was used for further analysis described in the following.

4.1 Population activity

Figure 4.1 shows LFP population spectrograms for both animals and areas. Spectrograms were normalized to the baseline epoch (before onset of the fixation signal) and averaged over all recording sites in the respective area.
4. Modulation of LFP activity in AIP and F5

Figure 4.1 LFP spectrograms for AIP and F5 in both animals.

LFP spectrograms for both animals, normalized to the baseline epoch before onset of the fixation signal, and averaged over all recording sites in AIP (A: animal P, 147 recording sites; B: animal S, 99 sites) and F5 (C: animal P, 163 sites; D: animal S, 144 sites). Activity is aligned to the onset of the planning epoch; vertical white lines indicate start and end of the epochs fixation, cue, planning, and movement.

In general, we found a modulation in LFP activity during task performance for both animals and areas. The highest spectral power was present around movement execution in the slow band (1 – 13 Hz) as well as in the gamma band (30 – 100 Hz), in both AIP and F5 (Figure 4.1).

In AIP (Figure 4.1A,B), the clearest modulations preceding movement execution were present in the beta band (13 – 30 Hz), with decreasing spectral power after
beginning of the task (fixation and cue epoch), an increase in activity during the planning epoch, again followed by an activity decrease during movement execution.

In the slow band and the gamma band, a general decrease in activity was found from the fixation to the planning epoch, followed by an activity increase in the movement epoch.

In F5, the modulations of averaged activity during the task seemed to be less prominent (Figure 4.1C,D). Across frequencies, there was an activity decrease after fixation onset, being relatively stable during the cue and planning epochs, followed by an increase of activity around movement execution. This modulation was strongest in the slow frequency ranges for both animals, and additionally in animal S around 20 – 40 Hz.
4.2 Tuning analysis of LFP activity

4.2.1 Epoch tuning in different frequencies

As a first step to analyze the tuning properties of LFP across different frequencies, a two-way ANOVA was performed. For this, the spectral power in different frequency bands (in steps of 1.95 Hz between 1 - 120 Hz) was computed for each trial, and the average power was calculated for each of the epochs (fixation, cue, planning, and movement). For each frequency band and epoch, this data was used to perform a two-way ANOVA (factors grip type and position, p < 0.05) to check for significant modulation by one of the factors during the relevant epoch. This was done for each recorded site; the results are shown in Figure 4.2.

The percentages of significantly tuned sites (p < 0.05) for a given frequency are shown as blue (grip type tuning) and red lines (position tuning) for each epoch (four columns) and animal (rows). The background colors indicate the different frequency ranges (green: slow frequencies, 1-13 Hz; blue: beta band, 13-30 Hz; yellow: low gamma band, 30-60 Hz; red: high gamma band, 60-100 Hz). This color code for the different frequency bands is maintained in all plots throughout this LFP chapter.

In AIP, the biggest fraction of sites tuned for position (red lines) was found in the beta band (13-30 Hz, Figure 4.2A-H, blue background). This was most prominent in the cue and planning epochs for both animals (Figures 4.2B,C & 4.2F,G). Notably, during movement epoch, the fraction of tuned sites in the beta band decreased, in combination with a tuning increase in the other frequency ranges (Figure 4.2D,H).
In comparison, the tuning for grip type was less consistent across animals. In animal P, there was an increase in tuned sites during grip type instruction in the cue epoch for all frequencies, but most prominently in the beta band (Figure 4.2B). The percentage of grip type tuned sites then decreased during the planning epoch (Figure 4.2C) and increased to a top level during the movement epoch (Figure 4.2D), always across all frequencies. In animal S, there was a small increase across most frequencies in the cue and planning epoch (Figure 4.2F,G), but less prominently in the beta band, compared to animal P. During the movement epoch, grip type tuning was represented across all frequencies, on a level of 30 to 40% of the channels (Figure 4.2H).

**Figure 4.2 Tuning for grip type and position in LFP activity (opposite page).**

Percentage of sites (y-axis) that are tuned for factors grip type (blue line) and position (red line) across different frequency bands. A two-way ANOVA was performed for the spectral activity (p < 0.05; frequency steps of 1.95 Hz) in AIP (A-H) and F5 (I-P), for both animals and the four epochs: fixation (1.), cue (2.), plan (3.), and movement (4.). Background colors indicate the division into the following frequency bands: 1-13 Hz (green background), 13-30 Hz (blue), 30-60 Hz (yellow), and 60-100 Hz (red).
4. Modulation of LFP activity in AIP and F5

F5

Percentage of Tuned Sites

AIP

Percentage of Tuned Sites

animal S

animal P

Fix

Cue

Plan

Mov

A

B

C

D

N = 44

N = 163

N = 69

N = 147

1-13 Hz (slow)

13-30 Hz (beta)

30-60 Hz (low gamma)

60-100 Hz (high gamma)
4. Modulation of LFP activity in AIP and F5

In area F5, we found a distributed tuning for grip type and position across all frequencies during the movement epoch in both animals (Figure 4.2L,P). Furthermore, grip type was represented stronger across all frequencies (around 40% in animals P and S (blue line), compared to position tuning (red lines) with percentages around 30%).

Besides this, there were clear differences in tuning properties between the animals. Whereas animal S showed highest tuning for position in the frequency range between 20 and 50 Hz (i.e. the beta and the low gamma range) from fixation till planning epoch (red line, Figure 4.2M-O), the tuning was much less prominent in animal P (Figure 4.2I-L). Similarly, the increased tuning representation for grip type in ranges between approximately 25 and 50 Hz in monkey S (Figure 4.2N,O, mostly in the low gamma range) was only found rudimentarily in animal P (Figure 4.2J,K).

Taken together, we found a strong representation of positional information in frequencies between 10 and 30 Hz throughout the task and across animals in AIP, whereas grip type information was mainly present during movement execution. In F5, tuning was less consistent in the pre-movement epochs. We found strong representations of grip type and position in frequencies between 10 and 50 Hz for animal S, whereas tuning for these factors was on a much lower level in animal P.

4.2.2 Epoch tuning for “broader” frequency bands

After having quantified the tuning properties for frequency bands in small frequency steps in the previous analysis, further analysis were performed using the typical broader classifications of frequencies: slow range (1-13 Hz), beta range (13-30 Hz), low gamma range (30-60 Hz), and high gamma range (60-100 Hz). This allowed
Figure 4.3 Tuning for grip type and position in different frequency bands.

Fraction of sites with tuning (two-way ANOVA, \( p < 0.05 \)) for the factors grip type (A,C,E,G) and position (B,D,F,H) in different bands and task epochs for AIP (A-D) and F5 (E-H). Colors indicate different frequency bands: green 1-13 Hz, blue 13-30 Hz, yellow 30-60 Hz, red 60-100 Hz.
us to compare the results of the following LFP analyses with the results of the spiking analyses.

A tuning analysis with averaged spectral activity over these broader bands (two-way ANOVA with factors grip type and position, p < 0.05) confirmed the previous observations for the narrow bands (Figure 4.3).

In AIP, there was only a small increase of grip type tuning after cue onset in most bands (besides the beta band in animal P, cyan bar in Figure 4.3A). In both animals, the biggest tuning effects in all bands were found during the movement epoch, being relatively consistent across all bands (30 to 37% in animal S, Figure 4.3C) or most of the bands (above 40% in beta and both gamma bands in animal P, Figure 4.3A).

Compared to the increase of grip type representation, position representation in AIP was more stable across all epochs. This was relatively consistent for all bands in both animal P (Figure 4.3B) and animal S (Figure 4.3D). The highest percentage of sites tuned for position was found in the beta band, with a tuning above 40% (animal P) and 50% (animal S) of recording sites during cue and planning epochs. Interestingly, both the slow band and the high gamma band showed less tuning for position during the planning epoch, compared to the other epochs.

The results of the tuning analysis for F5 were less consistent across animals (Figure 4.3E-H), as already observed above (Chapter 4.2.1).

In general, tuning for grip type was predominantly found during the movement epoch in both animals (Figure 4.3E,G). The percentage of tuned sites in the preceding epochs was relatively small across bands in animal P (Figure 4.3E), whereas for the second animal, there was a much higher amount of grip type tuned sites in the low
gamma band during the cue (44%) and planning epoch (28%). In addition, a small increase in grip type tuning during the cue epoch was also found in the beta band.

Position tuning was present on similar levels (around 30%) during the movement epoch in both animals. Besides this, there was a clearly higher percentage of tuned sites in the beta and low gamma bands in animal S (Figure 4.3H) in the epochs preceding movement, represented relatively constant throughout the task. In comparison, position in animal P (Figure 4.3F) was represented on a lower level in all bands, finally strongly increasing during the movement epoch.

Comparing the tuning results from the LFP activity to these of the spiking analysis generally revealed similar representation of grip type and spatial representations in the two signals. In particular in AIP, the constant representation of position information in AIP across epochs and bands (most prominent in the beta band), as well as the increased tuning for grip type during movement epoch was consistent with the results from the spiking analysis (see Chapter 3.1.1, Figure 3.4).

As the LFP results were less consistent for the two animals in F5, they are also more difficult to compare with the spiking analysis (compare Figure 3.4). In general, there was an increase in grip type representation towards movement execution in both LFP and spiking data, as well as a stable representation of positional information on a lower (animal P) or higher level (beta and gamma band in animal S) across epochs.
4. Modulation of LFP activity in AIP and F5

4.2.3 Tuning onset for different LFP bands

To gain a better understanding of the temporal progress of grip type and positional tuning, a two-way ANOVA was performed in a sliding window (size 250 ms, steps of 50 ms) for each band in both areas AIP and F5 (see Figure 4.4).

![Figure 4.4 Sliding window analysis for tuning onset.](image)

A sliding window analysis (window size 250 ms, step size 50 ms) for each site (y-axis) and time-step (x-axis) revealed the times with significant tuning for AIP (A-H) and F5 (I-P) in the different frequency bands for both animals. Horizontal bars indicate time windows with significant tuning for grip type (blue) or position (red) and are aligned to onset of the planning epoch. Sites are ordered by tuning onset (defined by the appearance of five consecutive significant steps). Vertical black lines indicate onset of fixation, cue, planning, and movement epoch.
In general, the results for the tuning onset analysis for the LFP data were similar to the results in the spiking activity (Figure 3.6 in Chapter 3.2.1.3). Whereas grip type information (blue horizontal lines) usually came up in the cue epoch and peaked again during the movement epoch, the onset of position tuning (red horizontal lines) started earlier (during or even before the fixation epoch). This was the case for all bands and epochs, in both area AIP (Figure 4.4A-H) and F5 (Figure 4.4I-P).

In AIP, the results were again quite consistent across animals, with the positional tuning (red) being most prominent in the beta band (Figure 4.4 B,F). This was in correspondence with the results of the epoch tuning analysis (for comparison see Figure 4.3B,D).

In F5, spatial information was represented less prominently, but in the cue and planning epoch stronger for animal S (Figure 4.4N,O). Depending on the frequency band, grip type tuning occurred after cue onset, but predominantly started after the go signal was given (movement epoch). The relatively strong tuning onset for grip type in the cue epoch for the low gamma band in animal S (Figure 4.4O) corresponded to the big fraction of grip type tuned sites during cue epoch as reported in the previous analysis (Figure 4.3G).

4.2.4 Distribution of preferred conditions

For each LFP site with significant tuning for grip type or position, the preferred conditions were defined. This was done by comparing the averaged spectral power of a given band for each epoch between all conditions (precision and power grip, as well as the 13 different positions). The condition with the highest power was defined as the preferred one.
Figures 4.5 to 4.8 display the distribution of preferred conditions for the tuned sites reported in the previous analysis (Figure 4.3, Chapter 4.2.2). Pie charts depict the preference for precision or power grips for the grip type tuned sites, whereas the histograms show the distribution of preferred positions for the spatially tuned sites. Numbers from 1 to 13 correspond to the conditions of the subtasks CV (1-5), TV (6-9), and GV (10-13).

In AIP, as already reported, most grip type tuning was found during the movement epoch in both animals (compare to Figure 4.3A,C). Interestingly, there was a clear preference for one grip type in both animals across bands in the movement epoch, but not for the same type. Whereas in animal P higher activity in the movement epoch was found for power grip in all bands (84 to 95%, see Figure 4.5, pie plots in the right column), in animal S precision grip was higher represented (60 to 90%, Figure 4.6) in the tuned units.

In comparison, the distribution of preferred positions was more complex. As mentioned before, the fraction of sites tuned for position was quite stable over task epochs for the different bands in AIP, with the biggest fractions in the beta band for both animals (Figure 4.3B,D). Looking at the position tuned sites in the beta band in animal P (Figure 4.5B), the preferences were changing for the different epochs (fix: most preferences for position 10, cue: 9 and 10, plan: 13, mov: 7). Across frequency bands, the preferred positions were varying as well. Only during the movement epoch, the preference for position 7 (gaze position centered with target position on top) seemed to be persistent for the beta, low gamma and high gamma ranges.
4. Modulation of LFP activity in AIP and F5

**Figure 4.5 Tuning preferences for AIP in animal P.**

Distribution of preferred conditions for the sites tuned for grip type (displayed in pie charts) and position (displayed in histograms) for AIP in animal P. Colors in pie charts indicate a tuning for precision grip (black) or power grip (grey). Columns show results for the 4 different epochs (fixation, cue, plan, movement). Background colors indicate from which frequency band the activity was used (green: 1-13 Hz; blue: 13-30 Hz; yellow: 30-60 Hz; red: 60-100 Hz).
Figure 4.6 Tuning preferences for AIP in animal S.

Distribution of preferred conditions for the sites in AIP (animal S) tuned for grip type (pie charts) or position (histograms) in the different epochs. Figure conventions are identical to Figure 4.5.
Figure 4.7 Tuning preferences for F5 in animal P.

Distribution of preferred conditions for the sites in F5 (animal P) tuned for grip type (pie charts) or position (histograms) in the different epochs. Figure conventions are identical to Figure 4.5.
Figure 4.8 Tuning preferences for F5 in animal S.

Distribution of preferred conditions for the sites in F5 (animal S) tuned for grip type (pie charts) or position (histograms) in the different epochs. Figure conventions are identical to Figure 4.5.
For animal S, we found this non-uniform distribution of position preferences in all bands of AIP activity as well (Figure 4.6). In the beta band, fractions bigger than 40% showed preference for single positions (Figure 4.6B; fix: 2, cue: 9, plan: 9, mov: 13). Interestingly, the same preferences were found in the slow gamma band from cue epoch on and during the planning epoch in the high gamma band.

LFP sites in area F5, where grip type tuning was mostly found during the movement epoch (compare Figure 4.3E,G), exhibited a general preference for power grip. During the movement epoch, both animals showed bigger fractions of sites tuned for power grip (animal P: beta: 62%, low gamma: 57%, high gamma: 63%; animal S: slow: 73%, beta: 65%, low gamma: 59%, high gamma: 57%; see Figures 4.7 and 4.8, pie plots in right column). Also the bigger fractions with grip type tuning in the cue and planning epoch in the low gamma band of animal S (compare Figure 4.3G) were tuned for power grip. Only the slow band in animal P showed a preference for precision grip.

The preferences of sites tuned for position in F5 were distributed in a non-uniform way, similar to the findings in AIP. Interestingly, sometimes this seemed to be more persistent over epochs (e.g. animal S showed a preference for position 9 in the fixation, cue, and planning epochs in the beta band; Figure 4.8B) and over frequency bands (animal P showed preference for position 7 during movement epoch in the beta band as well as in the low and high gamma band; Figure 4.7).

In summary, the grip type preferences during movement epoch were consistent across LFP bands for both animals in AIP (general preference of power grip in animal P and of precision grip in animal S) and even across animals in F5 (with a preference for power grip in both animals and most of the bands).
In contrast, the preferences of sites tuned for position were distributed highly non-uniform. In addition, the preferred positions where strongly varying between epochs and LFP bands in both areas and animals, therefore the results were difficult to interpret.

4.3 Decoding simulation with LFP activity

To further investigate the coding scheme in AIP and F5, we performed an offline decoding analysis in order to predict grip type and position from different frequency bands of LFP activity. For this, as previously demonstrated for the spiking activity (Chapter 3.1.4), we used a maximum likelihood approach to simulate the decoding by feeding in the averaged spectral power for different frequency bands and epochs. The results are shown in Figure 4.9. For both animals, the performances for grip type and position decoding in AIP (Figure 4.9A-D) and F5 (Figure 4.9E-H) were plotted for the four epochs. Results for the different bands are shown in consistency with the color code used in the previous figures. The error bars indicate 95% confidence limits after 200 decoding repetitions.
4. Modulation of LFP activity in AIP and F5

Figure 4.9 Decoding simulation with LFP activity.
Results of simulated decoding of grip type and position from LFP activity in AIP (A-D) and F5 (E-H). Line plots depict the maximal decoding performance for different frequency bands in the different epochs for grip type decoding (first column, A,C,E,G) and spatial position (second column, B,D,F,H). Horizontal dashed lines indicate the corresponding chance levels (50% for grip type decoding, 7.8% for position decoding). Error bars indicate 95% confidence limits after 200 repetitions.
Grip type decoding in AIP

Given the fractions of grip type tuned sites in AIP revealed from the previous analysis, it was not surprising that the best decoding performances were achieved for the movement epoch in both animals. Performances ranged around 90% for the beta and the low gamma band in animal P (Figure 4.9A), and above 80% for the low gamma band in animal S (Figure 4.9C). Even though the fractions of tuned sites were similar across frequency bands (see Figure 4.3A,C), most information useful for a decoding seemed to be available in the low gamma band in both animals, and in addition in the beta band in animal P, revealing the best decoding performances.

Besides this, decoding performances were only around 60% in the fixation and planning epoch in both animals, with a small increase during the cue epoch in between (beta and both gamma bands in animal P (Figure 4.9A); low and high gamma band in animal S (Figure 4.9C)).

Position decoding in AIP

In addition to the visualized results in Figure 4.9, the averaged performances for position decoding across epochs are listed for each band, area, and animal in Table 4.1.

The best performances of position decoding in AIP were achieved in the beta band in both animals (see Figure 4.9B,D). This was in line with the tuning analysis reported before (Chapter 4.2.2; Figure 4.3B,D), in which the biggest fractions of sites tuned for position were found in the beta band. Across epochs, the average decoding performances were on similar levels for the beta band (34%) and the high gamma band (33%) in animal P (see Figure 4.9B and Table 4.1), but looking at the cue and planning epoch, performance revealed to be more consistent for the beta band.
Similarly, average position decoding performance for animal S was clearly highest for the beta band (37%, see Figure 4.9D and Table 4.1).

**Grip type decoding in F5**

The decoding results for grip type in F5 were more heterogeneous across animals compared to AIP, corresponding to the heterogeneous tuning properties we observed before in F5. In animal P, the best decoding results for all frequency bands were achieved in the movement epoch (with performances between 70% to 80%). Performances in cue and planning period were similarly low as in the fixation period, in which no grip type information was given yet (Figure 4.9E). This was different in animal S, in which the decoding performance for the low gamma band was on a high level from cue onset on (cue: 88%, plan: 86%). This was consistent with the relatively big fraction of grip type tuned sites in the low gamma band in the previous analysis (compare Figure 4.3G). Besides this, the best decoding performances for animal S were found during the movement epoch: above 90% in all bands besides the slow band. Please note, that no decoding was performed for the slow band in the fixation epoch in animal S (Figure 4.9G), as the preceding one-way ANOVA did not result in any tuned site for the pruned database.

**Position decoding in F5**

Position decoding performances were relatively stable across epochs in both animals, but on a very low level (see Figure 4.9F,H). Average performances for all bands across epochs ranged around 20% or lower in both animals (see Table 4.1; chance level: 7.8%).
4. Modulation of LFP activity in AIP and F5

<table>
<thead>
<tr>
<th>band</th>
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<th>animal S</th>
<th>animal P</th>
<th>animal S</th>
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<td>60 – 100 Hz (high gamma)</td>
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</table>

*Table 4.1. Position decoding performances (across epochs).*

Position decoding performances averaged across all epochs (fixation to movement) for different LFP bands in AIP and F5.
4. Modulation of LFP activity in AIP and F5

4.4 Linear model

To further analyze the tuning properties of individual LFP sites and frequencies, we modeled the spectral activity of each band and recording site (for specific task epochs). Similar to our model for spiking data analysis (see Chapter 3.1.3), we used a stepwise linear model with the factors grip type, target position, gaze position, and retinotopic target position (for details see Chapter 2.4.2). This allowed us to categorize every recording site according to its significant modulation by the considered factors. Therefore we could see which of the factors contributed most to the spatial representations we found in the previous LFP analyses. The factor “retinotopic target position” (i.e. the target position relative to the gaze position) was included in order to investigate if the substantial retinotopic representations found in the spiking data in both areas (see Chapter 3.1.3) were also reflected in the LFP activity.
4. Modulation of LFP activity in AIP and F5
4. Modulation of LFP activity in AIP and F5

**Figure 4.10 Linear model for LFP activity.** (opposite page)

Combined linear model fitted to the LFP activity in different frequency bands (as indicated by background colors; green 1-13 Hz, blue 13-30 Hz, yellow 30-60 Hz, red: 60-100 Hz). The fit predicted the activity of a given frequency band from an individual recording site by the factors grip type (dark blue line), target position (green), gaze position (red), and retinotopic target position (cyan) in the different epochs. Results are displayed as the percentage of sites that are modulated by the respective factor.

Figure 4.10 shows the fraction of sites in AIP and F5 that were modulated by the following factors: 1. grip type (displayed in dark blue), 2. target position (green), 3. gaze position (red), and 4. retinotopic target position (cyan). The results are displayed for each epoch and the different frequency bands.

**Results of the linear model for sites in AIP**

In all frequency bands in AIP, the representation of grip type (Figure 4.10A-H, blue line) was consistent with the results of the tuning analysis (Figure 4.3A,C): the fraction sizes of grip type tuned sites were generally reflected in the fraction of grip type modulated sites in the model. In addition, we found fractions of sites representing target position (green), as well as fractions representing gaze position (red). Usually, the fractions of sites representing gaze position were the biggest during fixation epoch, compared to the other spatial factors. Given that the fixation signal (and therefore the gaze position) was the dominant factor during this epoch, this is not surprising.

In animal P, gaze position was on average stronger represented than target position in all frequency bands. The size of fractions averaged over all four epochs are listed in Table 4.2. In animal S, both factors were represented on a similar level in all bands.
Interestingly, the retinotopic factor (cyan) was generally represented on a similar level as target and gaze position in both animals, and sometimes even exceeded those (e.g. in the low and high gamma bands in animal S (see Figure 4.10G,H and Table 4.2)).

<table>
<thead>
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<td>G</td>
<td>R</td>
<td>T</td>
</tr>
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<table>
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<td>18</td>
<td>11</td>
<td>12</td>
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Table 4.2 Fractions of sites modulated by spatial factors (across epochs).

Fraction of sites (in %) modulated by the spatial factors target position (T), gaze position (G), and retinotopic target position (R), averaged across all epochs (fixation to movement epoch).

Results of linear model for sites in F5

As in AIP, the fractions of sites modulated by grip type in F5 were consistent with the representations reported for the tuning analysis, including the high amount of
tuned sites in the low gamma band for animal S (compare Figure 4.10O with results from tuning analysis, Figure 4.3E,G).

In both animals, target and gaze position were represented in similar strength, sometimes with a small bias towards target position (e.g. low gamma band in animal S, see Figure 4.10O) or gaze position (e.g. high gamma band in animal P, see Figure 4.10L). The fraction sizes averaged over epochs are listed in Table 4.2. In addition, the representation of target position usually increased during movement epoch in both animals and most frequency bands (besides the low gamma band in animal S). Similar to AIP, retinotopic target position was also substantially encoded in F5 in both animals, generally on a similar level than the target or gaze position representations (Figure 4.10I-P, Table 4.2).

In summary, the results of the linear fit analysis in both areas revealed representations of all spatial factors: target position, gaze position, and in combination, the retinotopic target position. This is consistent with the results obtained from the spiking data analysis reported previously (Chapter 3.1.3, Figure 3.9).
4. Modulation of LFP activity in AIP and F5

4.5 Discussion

We recorded LFP activity in the cortical areas AIP and F5 during a delayed reach-to-grasp task with systematic variation of grip type, target position, and gaze position (TASK I, Chapter 2.2.1). In order to compare the tuning properties of LFP activity to the properties reported for the single unit activity in Chapter 3, we used in general similar methods as described before.

4.5.1 Summary

We found modulations in LFP activity during task performance in AIP and F5 in both animals. In contrary to the results for spiking activity, the results were not consistent across animals for some aspects.

The highest spectral power in the population spectrograms was generally found around movement execution, for both areas and animals. In addition, most spectral modulations over time were present between 10 and 40 Hz (Figure 4.1). When analyzing the tuning properties of narrow frequency bands, tuning for grip type and position was generally increased across most frequencies during movement epochs, compared to the preceding epochs. Besides this, the strongest tuning effects in the cue and planning epochs, in particular for position but also for grip type tuning, were found in frequency ranges from 15 to 40 Hz, approximately corresponding to the beta band and parts of the low gamma band (Figure 4.2). In addition, we found clear differences in tuning properties between the two animals, which was most obvious in F5.

These results were confirmed for broader frequency bands. In AIP, spatial information was represented relatively stable throughout the task, with similar
percentages of sites tuned for position across different epochs (for a given frequency
band, Figure 4.3B,D). Highest representation of position information was found in the
beta band. In contrast, grip type tuning was represented strongest during the
movement epoch, in general across bands. This was the case for AIP, but also for F5
in animal P. However, animal S showed in addition strong grip type representations in
the low gamma band during the cue and planning epochs (Figure 4.3G). For the same
animal, we found relatively constant position tuning representations in F5, in
particular in the beta and low gamma band. In contrast, position information in animal
P was strongest represented during movement epoch (across bands).

Tuning onset analysis for different epochs and frequency bands (Figure 4.4)
revealed in general an early onset of position tuning (predominantly around fixation
and cue epochs). In comparison, onset of grip type tuning was mostly found during
the movement epoch or directly after cue instruction. This was the case across
frequency bands and animals, in both of the areas AIP and F5.

The analysis of tuning preferences during the movement epoch in AIP (Figures 4.5
& 4.6) revealed clear preferences across bands for power grip (animal P) or for
precision grip (animal S). In comparison, a general preference for power grip was
found in F5 in both animals during movement epoch (Figures 4.7 & 4.8). In contrast
to these findings, preferences for spatial conditions were distributed highly non-
uniformly in both areas and animals and rarely revealed a consistent pattern across
different epochs or across bands (Figures 4.5 to 4.8).

Decoding simulation of grip type usually revealed best performances during the
movement epoch, in both areas and across bands. In addition, the low gamma band of
F5 (only in animal S) showed high decoding performances after cue onset (Figure
4.9G). Decoding performances for position were in general better in AIP compared to
4. Modulation of LFP activity in AIP and F5

F5. In AIP, best results for position decoding were achieved for the beta band (for both animals; Figure 4.9B,D).

In order to quantify the contributions of grip type and different spatial factors, a linear model was fitted to the LFP activity (Figure 4.10). The model found grip type representations in accord with the tuning analysis, across bands in both AIP and F5. In addition, comparing the spatial factors target, gaze, and retinotopic target position (averaged across epochs for the different bands) revealed similar sized representations of factors in most bands in both animals (Figure 4.10, Table 4.2). Only AIP in animal P showed a clearly stronger representation of gaze position in all bands.

4.5.2 General considerations

The reported differences for the two animals, in particular for the representation of grip type and position in F5, made it difficult to interpret the results. In previous experiments of our workgroup, the encoding properties of LFP activity in AIP were also found to be quite inconsistent for different animals, in particular in the beta band (Baumann, 2009). While grip type and handle orientation were clearly represented in the beta band of one animal, no orientation representation was found in the other animal. They mainly explained this with strong leg and body movements of this animal during task performance. These strong movements might have influenced LFP activity.

However, this explanation did not seem to be the reason for the differences observed in our case. First, both animals were sitting calm in the chair throughout the task, not moving their body or legs. Second, we did find representations for grip type and position in both animals and areas, but on different levels in the epoch. In
particular in the cue and planning epoch of F5, grip type and position information were clearly encoded in animal S, but only on a very low level in animal P.

The few studies published about LFP activity in AIP and F5 reported their findings to be consistent across animals. However, given the differences between animals we found in our experiment and which were also observed in previous work in this lab (Baumann et al., 2009), it could well be that LFP activity in these areas is of specific nature, potentially varying for each animal.

4.5.3 Representation of grip type

In both animals and areas, we found strongest grip type representation during the movement epoch. This was the case across all frequency bands and confirmed findings from previous studies. Asher et al. (2007) reported significant object selectivity in AIP during a reach-to-grasp task with two different objects (grasped with a precision and a power grip). Similar to our results, object selectivity was found across different frequency bands, always strongest during the movement and hold epochs of their task. In addition, Asher et al. reported different grip type preferences for the frequency bands. While they found a preference for power grip in the slow band and in the beta band, the high gamma band showed a preference for precision grip (Asher et al., 2007). This was different to our results, which revealed consistent grip type preferences across bands, but for a different grip type between animals (bands in animal S showed a preference for precision grip, in animal P for power grip).

Also for F5, strong grip type tuning in LFP activity was reported during movement and hold epochs (Spinks et al., 2008). Similar to our results, the authors found grip type related representations across LFP frequencies in F5, but clearly strongest in
ranges of the beta band. Interestingly, they report a general selectivity for power grips in the tuned sites of the beta band, which was similar to our findings for grip type preference (in both of the animals and almost all bands).

Together, our findings about grip type representation in the LFP during the movement epoch are in accordance with the mentioned literature for the areas AIP and F5. Similarly, studies in primary motor cortex also reported LFP modulation during the execution of movements (Mehring et al., 2003; Rickert et al., 2005). Interestingly, in addition to general grip type encoding during the movement epoch, one animal also showed strong planning activity for grip type. This was the case in the low gamma band in F5 of animal S, in both the cue and planning epoch (Figure 4.3G). This was also reflected in all analysis performed for this band. Even though some studies demonstrated that LFP activity can also encode movement intention (Asher et al., 2007; Scherberger et al., 2005), this was the case for reach direction and not for grip type. Given the discrepancy in our results between animals in F5, it is impossible to state if LFP activity in this area could be used for the decoding of grasping plans (e.g. within an algorithm of a brain machine interface). This could be subject for further studies.

4.5.4 Representation of spatial information

Our findings, that spatial information was represented relatively constantly across epochs in both AIP and F5 (i.e. on a similar level for the respective frequency band) were similar to the results from the spiking data. Also the fact, that the spatial information was stronger represented in AIP than in F5 is in line with these results. In
both animals, we found the strongest representations of spatial positions in AIP in the beta band, which was also reflected in the best decoding performance across epochs (and in particular during the cue and planning epoch). These findings are in accordance with the results published by Asher et al. (2007), who reported representations of reach direction in AIP for a reach-to-grasp task. But in contrast to our findings, their position information was mainly present during (or shortly before) movement execution. In contrast, our results showed a stable representation of position throughout the task.

This might be due to the different task designs used for the experiments. While for our task, animals had to reach to different locations with horizontal and vertical variations in front of them, in the experiment by Asher et al. the animals had to perform a center-out-reach task on a horizontal plane, leading to reach movements towards the body or away from the body.

In addition, we systematically varied the gaze position during the task, which was not the case in their study. As AIP is a visuomotor area, this could of course result in strong differences in spatial representations in the LFP activity. Therefore, it might be that they found representations of reach movement direction, whereas we found a combination of spatial factors.

When analysing the contributions of different spatial factors to the position information in the LFP signal, we found that each of the factors target position, gaze position, and retinotopic target position were represented on similar levels in AIP. This showed that not only the reach information (or target position) is encoded across bands in all epochs, but also visual information. The finding of retinotopic representations throughout the task implies, that also the combination target and gaze signal is of importance, as similarly found for target representations in the spiking
analysis. Similarly in F5, all spatial factors contributed to the position information, but altogether on a much lower level.

For both areas, we found the preferred position of tuned sites to be distributed highly non-uniformly. This was the case in all LFP bands and epochs. Similar non-uniformly distributed preferences have been reported for parietal areas. Scherberger et al. (2007) found non-uniform distributions for different reach directions in PRR. For AIP, Asher et al. (2007) reported non-uniform distributions of preferred directions during a reach-to-grasp task. Similar to our results in AIP and F5, these distributions were different for the analyzed task epochs. This seems to be a general feature of LFP activity.

4.5.5 Implications for brain machine interfaces

LFP signals are often discussed to potentially contribute to the development of brain machine interfaces (BMI), helping to improve the decoding performances of movement intentions (Andersen et al., 2004). Representation of reach directions as reported for parietal areas (Asher et al., 2007; Pesaran et al., 2002; Scherberger et al., 2005) and motor cortex (Mehring et al., 2003; Rickert et al., 2005) support this idea, but a lot of these show the highest representations only during the movement itself and not during movement planning, which would be of special interest. Similarly, grip type information in our work was strongest represented during movement execution. In contrast, we found spatial representation throughout the task in the LFP activity, in particular in the cue and planning epochs. If the decoding of these factors could be optimized, e.g. by selecting smaller frequency bands depending on the best tuning ranges, LFP signals could be a source of supportive information in the online decoding of spatial parameters and movement intention.
But as demonstrated in this work, spatial and grip type information were still much more present in the spiking activity. This was also reflected in results for decoding simulations. In addition, the fact that LFP signals seemed to be less reliable across animals, in combination with the highly non-uniform distribution of preferred directions, make the signals more difficult to include into algorithms for clinical application. However, in particular the spatial information that was represent in AIP could be of supportive character in combination with the interpretation of spiking data. Therefore, different parameters could be drawn from different signal sources during online decoding.
5. Conclusions

In the previous chapters, we demonstrated that the visuo-motor areas AIP and F5, which in the past were shown to play an important role for the planning and execution of grasp movements, in addition also feature clearly reach related properties. In particular, we found various spatial representations in addition to grasp type representations, both in single unit and LFP activity.

Whereas grasp type representations were increasing towards movement execution, spatial factors were represented at constant levels across task epochs. These spatial representations were clearly stronger in AIP than in F5. Furthermore we showed that these representations were functionally and anatomically intermingled. The linear fit analysis revealed, that the spatial information was encoded in various reference frames, including gaze coordinates, target coordinates, and, in combination, the target position in retinotopic coordinates. These representations with mixed reference frames are similar to findings from reach related parietal areas (Buneo et al., 2002; Chang and Snyder, 2010) and in the dorsal premotor cortex (Batista et al., 2007; Pesaran et al., 2006). The mixed representations we found in AIP and F5 therefore imply a role of this hand grasping areas in reference frame transformation during visually guided reach to grasp movements.

We were able to decode both grip type and spatial position with a simulated Bayesian decoding approach, showing that the information provided in this hand grasping areas could be used for the development of brain machine interfaces. Interestingly, decoding performances were best for decoding the retinotopic target position, compared to decoding one of the factors target position or gaze position.
alone. Besides the similarity in results for single unit and LFP results, the representations and decoding performances for grip type and position were on a much lower level in the LFP signals. It would be of further interest, whether the combination of single unit and LFP information could lead to better decoding performances in total.

Our findings of reach representations in the dorso-lateral parietal stream for grasp movements nicely add to the findings of hand representations in the dorso-medial parietal stream for reach movements (Buneo et al., 2002; Fattori et al., 2009; Pesaran et al., 2006). Therefore, the strict separation of reach and grasp networks is clearly challenged from a representational point of view.

Whether the reach representations in hand grasping areas also play a causal role for the planning of these movements would need to be subject of further investigations. Even though inactivation studies showed that AIP and F5 are not directly causally involved in the generation of reach movements, the representation could indicate a role in online monitoring closely related reach-to-grasp movements. Besides others, an anatomical study by Dum & Strick (2005) revealed strong interconnections in a frontal lobe network for hand movements, including PMv, PMd, SMA, and primary motor cortex. Parietal areas, including AIP, seem to be similarly interconnected (Borra et al., 2008). Furthermore, a lot of these areas are interconnected in parieto-frontal networks (see Introduction, Chapter 1.3). Given these anatomical basics for information exchange between the different visuo-motor areas, a distributed representation of spatial factors is not surprising. Interestingly, studies with motor tasks performed in virtual environments (Ochiai et al., 2005; Schwartz et al., 2004) reported reach representations in PMv, which were rather linked to visual feedback than to motor output.
Therefore it could well be, that spatial information is constantly represented in various reference frames in several visuo-motor areas in premotor and parietal areas. This could allow easier and quicker access to information needed for constantly monitoring complex visually-guided movements. Within the visuo-motor network, the hand grasping areas AIP and F5 might play a role in online error correction of goal-directed reach movements. This hypothesis is supported by a perturbation study of Kurata & Hoshi (1999), who reported that inactivation of PMv during a reach perturbation task led to deficits in reach adaption, whereas no changes were noticed for inactivation of the reach-related premotor area PMd. Our finding that the initial hand position was not represented in the hand grasping areas could support this idea: not the reach movement is represented, but rather the reference frames of target and gaze position, which would allow to quickly react to a mismatch of motor plan and actual movement.

Whether this hypothesis is true could not be answered with our experiment. Future research could include concepts of visual perturbation or movement adaption during visually guided reach to grasp tasks.

Revealing the actual relevance of the spatial representations in the hand grasping areas could mean a further step for understanding the visuo-motor transformation processes that are constantly occurring in our everyday life. Furthermore, this knowledge might contribute to the development of more sophisticated brain-machine interfaces that can not only decode movement intentions, but also contribute to the real-time control for complex reach-to-grasp movements.
References


References


References


References


References


References


References


References


List of abbreviations

AIP: anterior intraparietal area  
aiPS: (human) anterior intraparietal sulcus  
AS: arcuate sulcus  
BMI: brain machine interface  
CIP: caudal intraparietal area  
CMAd: dorsal cingulate motor area  
CMAr: rostral cingulate motor area  
CMAv: ventral cingulate motor area  
CS: central sulcus  
F2: caudal part of dorsal premotor area (PMdc)  
F3: supplementary motor area (SMA)  
F4: caudal part of ventral premotor area (PMvc)  
F5: rostral part of ventral premotor area (PMvr)  
F5ab: rostral part of F5 (arcuate bank)  
F5c: caudal part of F5 (convexity)  
F5vr: ventro-rostral part of F5  
F6: pre-supplementary motor area (pre-SMA)  
F7: rostral part of dorsal premotor area (PMdr)  
FEF: frontal eye field  
fMRI: functional magnetic resonance imaging  
GABA \(_A\): gamma-aminobutyric acid  
IPL: inferior parietal lobule  
IPS: intraparietal sulcus  
LFP: local field potential  
LIP: lateral intraparietal area  
M1: primary motor cortex  
MIP: medial intraparietal area  
MT: middle temporal area  
PEC: parietal area PE  
PEip: medial bank of the IP  
PF: parietal area PF  
PFG: parietal area PFG  
PG: parietal area PG  
PMd: dorsal premotor cortex  
PMdc: caudal part of PMd (F2)  
PMdr: rostral part of PMd (F7)  
PMv: ventral premotor cortex  
PMvc: caudal part of PMv (F4)  
PMvr: rostral part of PMv (F5)  
PO: parieto-occipital cortex (V6/V6A)  
PPC: posterior parietal cortex  
PRR: parietal reach region  
PS: principal sulcus  
SC: superior colliculus  
SII: secondary somatosensory cortex  
SMA: supplementary motor area (F3)  
SPL: superior parietal lobule  
TEa: anterior part of temporal area TE  
TEO: temporal area TEO  
TEp: posterior part of temporal area TE  
TMS: transcranial magnetic stimulation  
V2: visual area 2  
V3: visual area 3  
V4: visual area 4  
V6/V6A: visual areas 6 & 6A  
VIP: ventral intraparietal area
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