

Force information integration in the primate fronto-parietal reach network

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For my family.

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Chapter 1:

General Introduction

Primates interact with their environment predominantly by reaching and grasping with their arms and hands. To do so, the primate brain needs to generate an internal representation of the external environment. Representations (perception) are generated by integrating sensory information from specialized sensory organs (sensation) such as: the ear (audition), the nose (olfaction), the tongue (gustation), the skin (somatosensation) and the eye (vision). Such representations can be used to guide voluntary actions like foraging for food. Imagine a monkey visually searching for food, for example a fruit that fell from a tree. After a successful search the monkey reaches out to grasp the fruit and eat it. Therefore, primates depend predominantly on their vision and their sense of touch. Both senses are strongly represented in the brain and their multisensory integration is indispensable to perform visually guided voluntary actions. Now imagine the monkey is climbing up the tree, trying to reach the remaining fruits that are hanging in the treetop. While climbing it does not only have to consider which branches it should reach and grasp, but also the force required for both movements to be able to pull itself upwards into the treetop and avoid a fatal fall. This leads to the question how the force, associated with an action, is integrated during visually guided voluntary actions. This question shall be addressed in this thesis. First, I review how the brain integrates visual information to guide voluntary actions. Secondly, I review the fronto-parietal grasp network and how it integrates force information during grasp movements. Thirdly, I review the fronto-parietal reach network and answer how it integrates force information during reach movements.

1.1. From vision to visually guided voluntary actions

In non-human primates the visual information enters through the eyes and is projected on the retina. From the retina the visual information propagates via the optical nerve to the lateral geniculate nucleus and on via the optical tract to the primary visual cortex. There the visual information enters two pathways, the ventral and the dorsal pathway (Goodale & Milner, 1992; Maunsell & Newsome, 1987; Mishkin et al., 1983). The ventral pathway is known as the "what" path, due to its involvement in processing object properties such as their shape, size and color. The dorsal pathway is known as the "where" path because it is involved in processing spatial properties of objects such as their location and spatial relations to other surrounding objects. This pathway is important when it comes to performing visually guided voluntary movements, where spatial information needs to be integrated and transformed to generate optimal movement trajectories from the motor effector (eye, arm, hand) to the motor goal (Goodale, 2014).

The difference between both pathways becomes apparent when one of the pathways is impaired (for example, irreversible impairments due to a lesion or reversible impairments due to pharmacological inactivation). In Goodale et al. (1994), patients with either lesions in the ventrolateral occipital region ("what" path perturbed) or lesions in the occipitoparietal region ("where" path perturbed), performed both, a visual shape discrimination task and a grasping task. The patient with an impaired "what"-path could grasp the objects without difficulty, yet was not able to discriminate the distinctly shaped objects from another. The patient with an impaired "where"-path on the other hand was able to discriminate between different object shapes but was not able to use the visual information to grasp the objects. This affirmed the theory that the visual information in these pathways is used differently instead of the visual information itself being different (Goodale & Milner, 1992). Visual information that enters the dorsal pathway propagates to the posterior parietal

cortex. The posterior parietal cortex receives sensory information from several sensory modalities and is supposed to be involved in sensorimotor transformations to visually guide voluntary movements (Andersen & Cui, 2009). It is interconnected with many other regions in the prefrontal cortex, forming a large network, the so called fronto-parietal network.

The fronto-parietal network can be divided into subnetworks which are distinguished by the action modality (eye, hand, and arm movements) they are foremost associated with, as I will describe in this section. The subnetwork that controls ocular movements is formed by the lateral intraparietal area, located in the posterior parietal cortex and the frontal eye field in the prefrontal cortex (Ferraina et al., 2002). The subnetwork that controls hand movements, the so-called grasp network, contains the anterior intraparietal area (AIP), located in the inferior parietal lobe, the ventral premotor cortex (PMv; area F5) and the hand area of the primary motor cortex (M1; Jeannerod et al., 1995). The hand area of M1 projects to the basal ganglia, thalamus, the brainstem and the spinal cord, that innervate motoneurons and interneurons that control muscle contractions in the hand and fingers (Armand et al., 1997; Borra et al., 2010; He et al., 1993; Maier et al., 2002). The reach network, the subnetwork that controls arm movements, consists of the parietal reach region (PRR), a region positioned in the superior parietal lobe, the dorsal premotor cortex (PMd) and the arm area of M1 (Andersen & Cui, 2009). Neurons from the arm area of M1 project to subcortical structures such as the basal ganglia, thalamus, the brainstem and the spinal cord, where they connect to motoneurons and interneurons that control the contractions of muscles in the shoulder and arm (Dum & Strick, 1991).

In the following sections of this chapter, I will describe the areas that from the primate fronto-parietal grasp network (Section 1.2) and reach network (Section 1.4) and how these areas contribute to the control of visually guided voluntary hand and arm movements. Moreover, I will describe how the areas of the grasp network

(Section 1.3) and reach network (Section 1.5) contribute to the control of grip force and reach force.

1.2. The primate fronto-parietal grasp network

The fronto-parietal grasp network comprises the cerebral cortical areas: AIP, PMv and the hand region of the M1. Neurons in AIP encode the type of a grip before (intended grip type) and, to a lesser degree, after (executed grip type) it is being executed (Baumann et al., 2009; Lehmann & Scherberger, 2013). The encoded intended grip type is highly predictive of the executed grip type (Menz et al., 2015; Schaffelhofer et al., 2015; Townsend et al., 2011). The functional role of AIP was shown in a study where AIP was pharmacologically inactivated in a macaque monkey that was trained to grasp objects of different shapes, sizes and orientations (Gallese et al., 1994). Results of the study show, that following AIP inactivation, finger movements of the contralateral hand were impaired because the monkey was not able to use the visual information to preshape the finger posture to the object. Only after feeling the shape, size and orientation of the object, the finger posture adjusted resulting in an accurate grasp. Additional studies show that AIP encodes, along with a variety of grasp types, a large amount of object types and the object location (Chen et al., 2009; Murata et al., 1997, 2000; Schaffelhofer et al., 2015). This confirms the crucial role of AIP in integrating visual information during visually guided hand movements.

Neurons in AIP are reciprocally connected to neurons in PMv (Borra et al., 2008; Luppino et al., 1999; Matelli & Luppino, 2001). PMv and AIP share similarities and encode the intended and executed grip type (Lehmann & Scherberger, 2013, 2015; Rizzolatti et al., 1988; Rizzolatti & Luppino, 2001). As in AIP, pharmacological inactivation of PMv causes an impairment of the contralateral hand's ability to

preshape its fingers, leading to a series of adjustments until an accurate grip was achieved (Fogassi et al., 2001).

Neurons in PMv form direct corticospinal projections to the spinal cord and reciprocal corticocortical connections to neurons in the hand region of M1 (Borra et al., 2010; Dum & Strick, 2002; Godschalk et al., 1984; Muakkassa & Strick, 1979). Neurons in the hand region of M1 encode the executed grip type and, contrary to AIP and PMv, only to a minor degree the intended grip type.

A comparative study that investigated how well the neural activity in AIP, PMv and the hand region of M1 can predict grip type and object type showed that prediction accuracy for grip type and object type during movement preparation was high in AIP and PMv, yet low in the hand region of M1. Contrary when predicting both parameters during movement execution the prediction accuracy was highest in the hand region of M1, followed by PMv (Schaffelhofer et al., 2015). Thus, it can be assumed that grasp network is hierarchically structured with AIP and PMv being involved during the preparation of grasping movements, whereas the hand area of M1 is involved during movement execution.

The hierarchy of the grasp network can be examined by systematic activation and inactivation of nodes of the network. Electrical microsimulation of the primary motor cortex and the premotor cortex evoked movements (Graziano, Taylor, & Moore, 2002; Graziano, Taylor, Moore, et al., 2002). A study by Stepniewska and colleagues (2014) that applied systematic activation and inactivation of the primary motor cortex, the premotor cortex and the posterior parietal cortex showed that electrical stimulation of the posterior parietal cortex primarily evoked movements if neither the premotor cortex nor the primary motor cortex were inactivated. Electrical stimulation of the premotor cortex primarily evoked movements if the primary motor cortex was not inactivated. While inactivation of the primary motor cortex

significantly reduced movements evoked by electrical stimulation of the premotor and parietal cortex, inactivation of the posterior parietal cortex and the premotor cortex did not reduce movements evoked by electrical stimulation of the primary motor cortex (Schmidlin et al., 2008; Stepniewska et al., 2014).

In Section 1.2, I described which cortical areas form the fronto-parietal grasp network and how these areas contribute to the control of visually guided voluntary hand movements. The grasp network is able to integrate the visual information associated with an object, for example the object size, to preshape the fingers of the hand before grasping the object. Object size is generally related to the objects weight as heavier objects are usually larger compared to lighter objects. The following section depicts which areas of the fronto-parietal grasp network contribute to the control of grip force and when they are contributing to the control of grip force, to compensate for example for changes in an object's weight.

1.3. Force encoding in the fronto-parietal grasp network

Early theories about the motor cortex suggested that the motor cortex represents muscles or muscle groups (Brown & Sherrington, 1912; Leyton & Sherrington, 1917). As force is generated by muscle activity, the first force-related studies were performed in the motor cortex. Evarts (1968) investigated the encoding of force in pyramidal tract neurons in the wrist area of M1 during voluntary wrist. He examined if pyramidal tract neurons encode the direction of force or the direction of displacement of the flexor and extensor muscle, while three macaque monkeys performed flexion-extension movements with their wrist with different force loads. A majority of pyramidal tract neurons encoded the direction of force and only a minority encoded direction of displacement. The importance of these pyramidal tract neurons for force generation was additionally shown in a study, where the pyramidal

tract was impaired by repetitively induced pyramidotomies (Hepp-Reymond & Wiesendanger, 1972). The results showed impairments of the contralateral hand while monkeys were completing a conditioned grip task with varying force loads. Although the impairments improved over time, even in monkeys with a total or nearly total lesion of the pyramidal tract, a delay in the generation of the grip force remained.

Building on Evarts (1968), Thach (1978) designed a study where different movement-related parameters (force, direction and position) could be dissociated. He found three categories of neurons in the primary motor cortex, which encoded the force, position and direction. The conclusion that can be drawn from these early studies is that the activity of neurons in the primary motor cortex is associated with movement force.

1.3.1. Force encoding in the hand area of the primary motor cortex

The hand region of M1 forms monosynaptic connections to motoneurons that control muscle contractions in the hand and fingers (Bennett & Lemon, 1994; Cheney & Fetz, 1980; Lemon et al., 1986; Rathelot & Strick, 2006). Therefore, this area is well suited to study the relationship between neural activity and force resulting from muscle activity. In one of the first studies that investigated the exerted grip force in the hand area of M1 (Smith et al., 1975), monkeys performed precision grips against different instructed force loads. Here, a majority of neurons showed increased activity during the dynamic phase when the force was steadily ramping up, compared to the static phase when the force was stable. Only a minority of neurons showed an increased activity when the force was stable. How the hand area of M1 contributes to the control of grasp force can be studied when the area is inactivated. Pharmacological inactivation of the hand area of M1 reduced the monkeys' ability to perform finger movements and decreased the grip force generated by the hand and finger muscles, when monkeys performed a precision grip (Brochier et al., 1999).

These and other studies (Hepp-Reymond et al., 1978; Intveld et al., 2018; Keisker et al., 2009; Maier et al., 1993) demonstrate that the hand area of M1 encodes the executed grip force, during movement execution.

Some studies that investigated the direct relationship between the neural activity in the hand region of M1 and executed grip force in more detail showed a positive correlation between the neural activity and executed grip force (Hepp-Reymond et al., 1978; Maier et al., 1993; Wannier et al., 1991). The strength of this positive correlation seemed to depend on the force level, with higher correlations for changes in force at smaller force levels (Evarts et al., 1983; M. C. Hepp-Reymond et al., 1978; Maier et al., 1993; Wannier et al., 1991) compared to larger force levels (Cheney & Fetz, 1980; Hoffman & Luschei, 1980; Thach, 1978). Thus, the positive correlation might only be present for a certain force range. The theory that the relationship between exerted grip force and the neural activity in the hand region of M1 is linear is therefore debatable. Particularly, some neurons show a nonlinear relation between their firing rate and the grip force, indicating that the relationship between the executed grip force and neural activity in the hand region of M1 could be more complex and might vary from cell to cell, depending on the muscles or muscle groups they project to (Maier et al., 1993). The aforementioned studies additionally indicate that there is a direct relationship between the hand area of M1 and exerted grip force, and that this relationship is complex and not necessarily linear.

1.3.2. Force encoding in the ventral premotor cortex

Another area well suited to study the relationship between neural activity and grip force is PMv. As mentioned, PMv, similarly to the hand area of M1, projects to subcortical structures like the brainstem and the spinal cord (Borra et al., 2010). A study performed by Hepp-Reymond et al. (1994) found neurons, similar to neurons in the hand area of M1, for which the neural activity was positively or negatively

correlated with exerted grip force. The overall force sensitivity was on average higher in trials where the monkeys had to perform force-loaded precision grips with two compared to three consecutive force levels during a visuomotor step-tracking task. This finding again indicates that linear correlations might only be present for a certain force range (see also Hepp-Reymond et al., 1999). Additional studies also found neurons in PMv that encode exerted grip force, though to a smaller percentage compared to the hand area of M1 (Hendrix et al., 2009). However not all studies were able to find neurons with such properties (Boudreau et al., 2001), still leaving room for debate.

1.3.3. Force encoding in the anterior intraparietal area

An area of the grasp network whose relationship between grip force and neural activity has been barely studied is AIP. Only one study (Intveld et al., 2018) investigated if the neural population activity in AIP encodes grip force. This study investigated, contrary to past studies, not only the encoding of grip force during the movement (executed grip force), but also the encoding of grip force during the movement preparation (intended grip force) in the hand area of M1, as well as PMv and AIP. Intveld and colleagues (2018) trained two macaque monkeys to perform a delayed grasping task where grip type and grip force were instructed, while neural population activity was recorded in parallel from AIP, PMv and the hand area of M1. Neural populations in all three areas encoded the exerted grip force, while intended grip force was encoded in PMv, and to an extent AIP.

Section 1.3 discussed in detail which areas of the fronto-parietal grasp network encode grip force and if they do so during the movement preparation or movement. Since the fronto-parietal networks involved during grasping and reaching share similarities, we were interested if the encoding of force can be generalized across fronto-parietal networks. We were therefore interested to investigate if areas of the

fronto-parietal reach network encode reach force during the movement preparation or movement.

1.4. The primate fronto-parietal reach network

The fronto-parietal reach network is composed of three cortical areas: the parietal reach region (PRR), the dorsal premotor cortex (PMd) and the arm region of the primary motor cortex (M1). PRR is a cluster containing multiple areas in the posterior parietal cortex. This cluster contains: the medial intraparietal area, parts of the parieto-occipital area, the medial dorsal parietal area and V6a (Galletti et al., 1997, 2003; Snyder et al., 1997, 2000). Neurons in PRR preferably encode the direction of an intended arm movement by encoding the direction of a reach goal before the reach is executed (Batista et al., 1999; Buneo et al., 2002; Snyder et al., 1997). Thus, PRR is predominantly involved during the preparation of arm movements.

The functional role of PRR during visually guided arm movements becomes apparent when this area is pharmacologically inactivated (Hwang et al., 2012, 2014). Such studies showed that the inactivation of PRR led to optic ataxia, which impaired reaches but not saccades. Patients with optic ataxia have impaired coordination of the hand and arm during visually guided reaches. They do perceive peripheral reach goals yet have difficulties to use that visual information to guide their arm to those reach goals. This shows, similar to AIP in visually guided hand movements, how important PRR is in the integration of visual information during visually guided arm movements. In addition, the neural activity in PRR does not only increase when a reach goal is visually presented. Some PRR neurons increase their activity when the instruction is given to prepare a reach even when the reach goal has not been visually presented (Calton et al., 2002; Gail & Andersen, 2006), indicating that the neural activity in PRR might also be correlated with the intention to move.

A study conducted in human patients (Desmurget et al., 2009) showed that electrical stimulation of parietal regions, homologue to PRR, did not cause the contralateral arm to move but resulted in a strong intention and impulse to move the arm. After intensified electrical stimulation, the patients even reported they had performed an arm movement, when electromyographically measured muscle activity proved otherwise. In comparison electrical stimulation of premotor regions, homologue to PMd, caused the contralateral arm to move, yet patients denied that they had moved. In summary, these results show that neural activity in PRR and not PMd is related to movement intention and awareness (Quiroga et al., 2006; Snyder et al., 2000).

PRR is reciprocally connected with PMd (Andersen et al., 1990). Neurons in PMd and PRR share some physiological properties. Like PRR, PMd encodes the direction of a reach goal before the reach is executed and thus is involved in movement preparation (Crammond & Kalaska, 2000; Gail et al., 2009; Snyder et al., 1997; Weinrich & Wise, 1982; Westendorff et al., 2010).

The functional role of PMd in the preparation of visually guided arm movements can be shown by pharmacologically inactivating PMd. In a study by Kurata and Hoffman (1994), macaque monkeys performed two wrist flexion-extension tasks, where they were instructed either by directional cues or contextual color cues to perform a wrist flexion or extension. The contextual color cues in itself did not carry any spatial information about the direction of the upcoming wrist movement; instead, the monkeys learned to associate the movement type with different color cues. After pharmacological inactivation of PMd, the number of direction errors increased, foremost in the condition in which the contextual color cues was presented, suggesting that PMd seems to be important for integrating contextual information. Following up on these finding, Kurata (2010) evaluated if the integrated contextual information in PMd was arm-specific or independent of the arm used. In this study, monkeys were instructed to perform reaching movements towards a reach goal

during unilateral inactivation of PMd. with either the ipsi- or the contralateral arm (relative to the side of the inactivation). The monkeys made significant more movement selection errors when instructed to reach with their contralateral arm by erroneously using the arm not indicated by the instruction. Thus, PMd integrates contextual information predominantly in an arm-specific way, showing how importantly PMd is involved in movement initiation during visually guided hand movements.

PMd is reciprocally connected to the arm area of M1 (Johnson et al., 1996). Neurons in the arm area of M1 encode the executed reach directed, rather than the intended reach direction (Crammond & Kalaska, 2000; Georgopoulos et al., 1982; Kalaska & Crammond, 1992), indicating that M1 is predominantly involved in movement execution but not movement preparation. Temporary thermal inactivation of the primary motor cortex of macaque monkeys that performed reach-to-grasp movements, evoked drastic movement deficits, thus demonstrating the functional role of M1 during movement execution (Goldring et al., 2022). Moreover, neural population activity in M1 is closely associated to muscle activity. Neural population activity in M1 predicts the muscle activity of associated muscle groups (Heming et al., 2016).

1.5. Force encoding in the primate fronto-parietal reach network

As described in Section 1.3, studies that investigated the encoding of grasp force in the fronto-parietal grasp network showed evidence that the hand area of M1, PMv and AIP encode the executed grasp force, while PMv, and to an extent AIP, encode the intended grasp force. Due to similarities between grasping and reaching, it could be assumed that forces are not only encoded in the grasp network but also in the reach network. However, comparatively fewer studies have investigated the

encoding of the executed reach force in the reach network. The following section reviews the encoding of the executed reach force in the fronto-parietal reach network.

1.5.1. Force encoding in the arm area of the primary motor cortex

Studies that studied the encoding of forces in the arm area of M1 showed that external loads applied to the arm had major effects on the neural activity (Kalaska et al., 1990; Kalaska & Hyde, 1985). The neural activity in the arm area of M1 is not only affected by external loads, but also by spatial hand position, force direction, and the interaction of hand position and force direction, as shown in experiments where monkeys produced isometric forces by pushing against a handle that was placed at different distinct locations in different directions (Sergio & Kalaska, 1997, 2003).

In a study were monkeys had to perform arm movements with a heavy movable handle, the neural activity and neural population activity in the arm area of M1 reflected the temporal patterns of the muscle activation (Sergio et al., 2005). Furthermore, it has been shown that M1 neurons had directional preferences similar to their corresponding muscle group and that neural population activity in M1 predicted the spatiotemporal patterns of their corresponding muscle groups (Heming et al., 2016). In addition, a small subpopulation of M1 neurons had directional preferences that were opposite to that observed for its corresponding muscle group, suggesting a selective control mechanism when the muscles act as antagonists during reach movement. All those studies suggest that the neural activity in the arm area of M1 is associated with arm muscle activity and that M1 encodes the executed reach force. Yet, no studies, to my knowledge, have been published that investigated the encoding of intended reach force in the arm area of M1, therefore it remains uncertain if the arm area of M1 encodes the intended reach force.

1.5.2. Force encoding in the dorsal premotor cortex

Fewer studies investigated the encoding of force applied during reach movements in the dorsal premotor cortex. In two studies conducted in humans, participants lifted objects with varying weights by applying forces that matched the expected weight of the object (Chouinard et al., 2005; Nowak et al., 2009).

In a given trial, participants either inferred the information about the object's weight from the preceding lift or were informed about the weight via a weight-indicating contextual color cue. Repetitive transcranial magnetic stimulation over M1 disrupted the weight-appropriate scaling of the applied forces based on information from the previous lift, whereas repetitive stimulation over PMd disrupted the scaling of forces based on contextual color cues. This suggests that M1 and PMd might have different roles during the predictive scaling of forces and that PMd may be crucial when force information has to be inferred from visual information. Studies showed that properties of an objects are better estimated, when visual and proprioceptive information are combined (Ernst & Banks, 2002; Helbig & Ernst, 2007). When visual information is absent, force scaling is impaired, compared to when both, visual and proprioceptive information are present (Buckingham & Goodale, 2010). Desynchronization of visual and proprioceptive information, introduced by a visual delay, impairs force scaling, leading participants to perceive objects as heavier with than without visual delay (van Polanen et al., 2019). Therefore, it can be assumed that force predictions depend on visual information or proprioceptive information or both to be generated. All those studies seem to indicate that the dorsal premotor cortex does encode the executed reach force. Still, it remains uncertain, if the dorsal premotor cortex encodes the intended reach force.

1.5.3. Force encoding in the parietal reach region

Even fewer studies have been published that investigate the encoding of force in the parietal cortex during reach movements. Two studies showed that external loads applied on the arm had a minor effect on the neural activity in the parietal cortex (area 5) compared to the neural activity in the motor cortex (area 4) (Kalaska et al., 1990; Kalaska & Hyde, 1985). In comparison, the neural activity in the parietal cortex was less related to the magnitude and pattern of the exerted force. These studies hypothesize that the parietal cortex encodes movement kinematics rather than kinetics. A more recent study conducted in the same research group showed that neural population activity in parietal cortex (area 5) does not reflect the time course of the exerted force or muscle activity, while monkeys perform reaches against inertial loads (Hamel-Pâquet et al., 2006). All those studies are in accordance with the hypothesis that the parietal cortex encodes movement kinematics rather than kinetics. However, recent studies conducted in the fronto-parietal grasp network question this hypothesis (Davare et al., 2007; Ehrsson et al., 2003; Ferrari-Toniolo et al., 2015; Intveld et al., 2018; Keisker et al., 2010; Neely et al., 2011). But, to my knowledge, no studies have been published that investigated the encoding of intended and executed reach force in the parietal reach region.

1.6. Mechanisms of effort-guided action selection

Decisions are often made among actions. Thus, it would make sense to assume that decision processes are not separate from sensorimotor processes, as presumed in classical theories of cognitive psychology (Sternberg, 1969). A hypothesis that supports such an assumption is the affordance competition hypothesis (Cisek, 2007). According to the affordance competition hypothesis, when confronted with choosing among actions, the fronto-parietal network creates competing neural representations of these actions. Neurophysiological studies that support the affordance competition

hypothesis show that, when presented with two reach goals, the neural population activity in PMd generated parallel representations of these reach goals (Cisek & Kalaska, 2002, 2005; reviewed in Cisek & Kalaska, 2010; Klaes et al., 2011; Suriya-Arunroj et al., 2019). These parallel representations competed with one another until a reach goal was chosen, upon which the representation of the chosen reach goal predominated and the PMd population activity reliably predicted the choice. Parallel reach goal representations were also reported for other areas of the fronto-parietal reach network, such as PRR (Christopoulos et al., 2015; Klaes et al., 2011, 2012; Scherberger & Andersen, 2007; Suriya-Arunroj & Gail, 2019). While all these studies were conducted in the fronto-parietal reach network, studies performed in other fronto-parietal networks showed similar results (e.g., Christopoulos et al., 2018).

The competition between parallel reach goal representations can be biased by factors that affect the desirability of an action, such as benefits and costs associated to actions. Some studies showed that the fronto-parietal reach network encodes benefit-related decisions variables (de Lafuente et al., 2015; Kubanek & Snyder, 2015; Pastor-Bernier & Cisek, 2011; Ramkumar et al., 2016). Reward, associated to one of two available reach goals, modulated the neural population activity in PMd during action selection, before an action was selected. But such modulations were missing outside an action selection process, i.e., when only one reach goal was available (Pastor-Bernier & Cisek, 2011).

While most studies investigated the encoding of benefit-related decisions variables in the fronto-parietal reach network, it remains uncertain if cost-related decision variables are also encoded. An exemplary cost-related decision variable is the physical effort, which is associated to an action. A study conducted in humans performing a reach selection task showed that force increases the physical effort of a reach movement, referred to as reach effort (Morel et al., 2017). To investigate if the

fronto-parietal reach network encodes cost-related decision variable, reach effort could be studied during a reach selection task.

1.7. Aims of this thesis

A substantial amount of studies, conducted in human and non-human primates, have investigated how the sensorimotor system integrates force information when executing a motor command. However, it remains debatable, if the sensorimotor system integrates force information before a motor command is executed. A recent study examined the encoding of grasp force in the primate fronto-parietal grasp network during the movement preparation and the movement (Intveld et al., 2018). The authors reported that PMv, and to an extent AIP, encode the intended grasp force, while the hand area of M1, PMd and AIP encoded the executed grasp force. This would indicate that the sensorimotor system integrates force information before a motor command is executed. If this should be the case, we might find similar findings in the reach network. This thesis investigates if the primate fronto-parietal reach network integrates force information before a motor command is executed. First, we investigated force information integration when the sensorimotor system prepared one motor command. Second, we investigated force information integration when the sensorimotor system had to prepare two motor commands in parallel, in an action selection context.

1.8. Overview of thesis chapters

This thesis contains two original manuscripts (Chapters 2 - 3).

Chapter 2 (*Decoding of intended and executed reach force in the macaque fronto-parietal reach network*) describes a study that investigated if the fronto-parietal reach network encodes the reach force, during the movement preparation (intended reach force). We trained two macaque monkeys to perform a reaching task, where reaches

had to be conducted against randomly alternating resistive forces. In parallel, we recorded the neural population activity from three areas of the fronto-parietal reach network: the arm area of M1, PMd and PRR. The results from our first study indicate that the fronto-parietal reach network does not integrate force when preparing a reach movement for which the force had to be inferred from the force of the previous reach.

Chapter 3 (*Decoding intended and executed reach effort during effort-guided action selection*) describes a study that investigated if the primate fronto-parietal reach network encodes the reach effort, during the movement selection and preparation (intended reach effort). We trained one macaque monkey to perform an effort-guided reach selection task. We again recorded the neural population activity from three areas of the fronto-parietal reach network: the arm area of M1, PMd and PRR. The results from our second study suggest that the fronto-parietal reach network does integrate effort when preparing and selecting between reach movements, when the effort of a present trial had to be inferred from the effort of the previous reach.

Chapter 4 summarizes and discusses the findings previously described in Chapters 2 and 3.

Chapter 2:

Decoding intended and executed reach force in the macaque fronto-parietal reach network

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JN, PM and AG designed the study; JN collected the data; JN and PM analyzed the data; JN visualized the results and wrote the original draft; JN, PM and AG revised the manuscript.

2.1. Abstract

The sensorimotor system takes the required muscle activation into account when a motor command is executed. However, it remains unclear if the sensorimotor system does take the required strength of the muscle activation already into account when preparing a motor command. Studies that investigate the integration of grasp force in the fronto-parietal grasping network show that the hand area of the primary motor cortex (M1), the ventral premotor cortex (PMv) and the anterior intraparietal area (AIP) were sensitive to grasp force during the movement, while PMv, and to an extent AIP, were sensitive to grasp force when the movement was prepared. Due to the similarities between grasping and reaching, it can be assumed that force sensitivity is not only present in the fronto-parietal grasp network but also in the fronto-parietal reach network. This study investigates if the fronto-parietal reach network is sensitive to reach force during the movement preparation and the movement. We trained two macaque monkeys (*Macaca mulatta*) to perform a center-out reaching task against alternating resistive forces. We recorded the neural population activity from three areas of the reach network: the arm area of M1, the dorsal premotor cortex (PMd) and the parietal reach region (PRR). We found neurons that were sensitive to reach force during the movement preparation and the movement. We used a multi-class support vector machine decoder to decode the reach force during movement preparation and movement execution in M1, PMd and PRR. We were able to decode the reach force in all three areas during the movement, but surprisingly in none of the areas during movement preparation. Our results show similarities and dissimilarities to previous studies that strengthen the argument that force selectivity depends on how force predictions are achieved, either by visual or haptic assessment.

2.2. Introduction

Imagine you are opening the fridge, to pour yourself a glass of milk. When lifting the milk package, you realize how heavy it is and you do not manage to lift the package in the first attempted. This example shows how much the sensorimotor systems relies on force predictions, when executing a motor command with a certain force. But it remains unclear if the sensorimotor system uses these force predictions to prepare a motor command according to the force the command will be executed with. Studies that investigated the selectivity for grasp force in the primate fronto-parietal grasp network showed that the motor cortex is selective for the executed grip force (M. C. Hepp-Reymond et al., 1978; Intveld et al., 2018; Keisker et al., 2009; Maier et al., 1993), so is the ventral and lateral premotor cortex (M. C. Hepp-Reymond et al., 1994; M.-C. Hepp-Reymond et al., 1999; Keisker et al., 2009) and the intraparietal cortex (Ehrsson et al., 2003). This shows that the fronto-parietal reach network is selective for grasp force during the movement (executed grasp force).

A more recent study investigated if the fronto-parietal grasp network is selective for grasp force during movement preparation (intended grasp force). Neurons in three cortical areas, the hand area of the primary motor cortex (M1), the ventral premotor cortex (PMv) and the anterior intraparietal area (AIP) showed selectivity for the executed grasp force (Intveld et al., 2018). Additionally, the authors showed that PMv, and to a certain extent AIP also encode the intended grasp force. This study suggests that the sensorimotor system is selective for force during the movement preparation and movement, when using visual information to predict forces. Neurons in PMv and AIP are selective for visual information (Janssen & Scherberger, 2015), therefore it could be assumed that these areas could play an important role when force predictions rely on visual information. When visual information associated with an object, for example the object's size, was used to infer object weight,

transcranial magnetic stimulation over PMv, but not M1 or AIP, interfered with predictive force scaling of grip force (Dafotakis et al., 2008). Furthermore, stimulation over AIP, but not M1 or PMd, interfered with reactive force scaling, when force scaling was based on sensorimotor memory. However, a recent study showed that transcranial magnetic stimulation over the anterior intraparietal cortex had a transient role during predictive force scaling, when force scaling was based on visual information (van Polanen et al., 2022). All these studies further suggest that visual information can be used to predict forces and that the sensorimotor system is selective for force during the movement preparation and movement, when using visual information to predict forces.

But what if there is no visual information available that can be used to predict forces, as in our example? Is the sensorimotor system selective for force during the movement preparation and movement, in the absence of visual information when only haptic information is available? We aim to answer these questions by investigating reach force selectivity during movement preparation and execution in reach movement. Neurons in areas of the fronto-parietal reach network such as the dorsal premotor cortex (PMd; Cisek et al., 2003; Cisek & Kalaska, 2002, 2005; Crammond & Kalaska, 1994, 2000; Kalaska & Crammond, 1995) and the parietal reach region (PRR; Batista et al., 1999; Buneo et al., 2002; Klaes et al., 2011; Snyder et al., 1997) are selective for the intended reach direction during the movement preparation. In contrast, neurons in the arm area of M1 are selective for the executed reach direction during the movement (Crammond & Kalaska, 2000; Georgopoulos et al., 1982; Kalaska & Crammond, 1992). Considering that all three areas of the fronto-parietal reach network are selective for either the intended or executed reach direction and that reach force has a direction-related component, it could be assumed that neurons in these areas might be selective for reach force. Especially when their counterparts in the fronto-parietal grasp network are grasp force selective. We hypothesize, if the

results regarding grasp force selectivity in the fronto-parietal grasp network from Intveld and colleagues (2018) were independent from the visual information used to predict forces, we would assume to find similar results regarding reach force selectivity in the fronto-parietal reach network. We would expect to see selectivity for the executed reach force in the arm area of M1, PMd and PRR. In addition, we would expect to see selectivity for the intended reach force in PMd, and to a certain extent PRR. We further hypothesize, if the results from Intveld and colleagues (2018) dependent on the visual information used to predict forces, we would expect to find dissimilarities in our results, because in our study only haptic information, obtained in the previous reach, was used to predict forces of the present reach.

This study investigated if the fronto-parietal reach network is selective for the intended and executed reach force and if this selectivity would depend on the information source used to generate force prediction. To do so, we trained to macaque monkeys to perform a center-out reaching task where reaches had to be conducted against resistive force levels (low, medium, high) that alternated in a block-wise fashion. Within a block, the force of a previous trial was predictive for the force of the present trial. While the monkeys performed the reaching task, we recorded simultaneously single- and multi-unit activity from areas: M1, PMd and PRR. Our study shows that neural populations in the arm area of M1, PMd and PRR were selective for the executed reach force, but neither area was selective for the intended reach force.

2.3. Methods

2.3.1. Subjects

We trained two macaque monkeys (*Macaca mulatta*; monkey K age: 16 years; monkey Y age: 13 years) to complete a memory-guided center-out reach task. Reaches had to be conducted with a haptic manipulandum against resistive forces (Figure 1A). Both animals were trained using positive reinforcement to sit in a primate chair and perform the reaching task while being head fixated. Before entering the study, both monkeys participated in previous research studies and were experienced in center-out reaching tasks but had no prior experience performing reaches against resistive forces.

Both monkeys were implanted with a chronic transcutaneous titanium head holder that has been custom-fit to the skull surface of each animal to allow head fixation. Furthermore, we chronically implanted monkey K with 256 intracortical electrodes using eight floating microwire arrays (32-electrodes, 250 μ or 400 μ electrode-to-electrode separation, electrode impedance 0.4-0.6 M Ω , array size: 2.95 mm x 1.6 mm or 4 mm x 1.8 mm; Microprobes for Life Science, Gaithersburg, Maryland, USA) in the right hemisphere of the cerebral cortex. Two arrays were inserted in the hand area of M1 and three arrays were inserted each in PMd and PRR. Monkey Y was implanted with 192 electrodes using six arrays (32-electrodes, 400 μ electrode-to-electrode separation, electrode impedance 0.4-0.6 M Ω , array size: 4 mm x 1.8 mm) in the left hemisphere with two arrays inserted in each of the three cortical areas. The connectors of the arrays were placed in a custom-designed and custom-fit implants to protect the connectors. Custom-fit implants were designed using the software Rhinoceros 6 (Robert McNeel and Associates, Seattle, Washington, USA) and 3-printed (Shapeways, New York City, New York, USA). The procedure to design implants (Ahmed et al., 2022) and the implantation procedures (Berger et al.,

2020) have been previously described. All surgical procedures were conducted in a sterile surgery suite under general anesthesia and analgesia. Post-surgical analgesia was administered for a few days after the surgery according to the need of the animal. All imaging procedures performed to obtain the CT and MRI scans, used to plan implantation procedures, were conducted under general anesthesia and analgesia.

All experimental procedures have been approved by the responsible regional government office [Niedersächsisches Landesamt für Verbraucherschutz und Lebensmittelsicherheit (LAVES)] under the permit number 33.19-42502-04-18/2823 and comply with the German Law and the Directive 2010/63/EU of the European Parliament and Council that regulates the use of and protects animals used for scientific purpose.

2.3.2. Experimental setup

The study was conducted using a 2D-haptic reach setup (Figure 1B) as previously described (Morel et al., 2016). Animals were performing reaches by moving the handle of a haptic manipulandum (Delta.3, Force Dimension, Nyon, Switzerland) with their dominant hand. Movements of the manipulandum handle were restricted within a fronto-parietal (x-y) plane through forces applied by the manipulandum (Morel et al., 2016). The displacement of the handle controlled in real-time the displacement of a cursor, which was displayed on a monitor placed above the haptic manipulandum (latencies of the haptic manipulandum and monitor were compensated for by forward prediction; Morel et al., 2016). The movements of the manipulandum handle were sampled at 2 kHz, while eye position was detected by a video-based eye tracker with a sampling rate of 1 kHz (EyeLink 1000 Plus, SR Research, Ottawa, Canada). The manipulandum was connected to a computer running custom software (C++, OpenGL) that controlled the generation and presentation of visual stimuli on the monitor, task event recording, eye position and

hand position recording and force generation. The force generated by the manipulandum had a constant magnitude and opposed the movement direction, similar to a kinetic friction force (Morel et al., 2017). The magnitude of this kinetic friction force was modified to generate different resistive force levels (low: 0 N, medium: 3 N, high: 6 N) in addition to forces used to constrain movements to the fronto-parallel plane. The manipulandum and computer communicated bidirectionally, with the manipulandum sending the position of the handle and the computer requesting forces to be applied at the handle for each iteration of this 0.5ms haptic cycle. Movement position, movement velocity (by differentiating the movement position) and applied force were recorded and sampled at 2 kHz.

2.3.3. Experimental design: A memory-guided center-out reach task with force-loaded reaches

Monkeys initiated a trial by moving the manipulandum handle, represented as a yellow circular cursor ($\varnothing = 5.1$ mm) with their dominant hand, into the circular grey hand fixation area ($\varnothing = 37.4$ mm; 3.2° visual angle) with a fixation tolerance diameter of 3.2° visual angle. After the cursor was placed in the hand fixation area, the eye fixation was obtained by directing the gaze to the rectangular eye fixation area ($\varnothing = 8.5$ mm; 0.7° visual angle; fixation tolerance diameter 5.9° visual angle). Once hand and eye fixation were both obtained and held for 600ms, a circular spatial cue ($\varnothing = 59.5$ mm; 5.2° visual angle), was displayed at one of four directions (0° , 90° , 180° , 270° ; eccentricity from monitor center = 60 mm) for 300 ms. The target direction had to be memorized for 600 ms – 1800 ms (uniform distribution). Animals were instructed to initiate the reach movement to the previously presented spatial cue, by the disappearance of the hand fixation point (go cue). To encourage the monkeys to plan the upcoming reach movement prior to movement execution, the animals had to initiate the movement between 150 and 450 ms after the go cue. Movement initiation was defined by either the cursor speed exceeding a threshold of

0.02 m/s or the cursor leaving the position of the hand fixation area. The 150 ms delay after the go cue was introduced to discourage the monkeys from anticipating the go cue and initiating the reach movement prematurely. After initiating the movement, the monkeys were allowed to end the eye fixation and had 700 ms to execute the movement by moving the cursor into the spatial cue (spatial cue tolerance diameter: 5.2° visual angle, i.e., size of previous presented spatial cue) at the memorized position. In addition, the cursor speed had to fall below a threshold of 0.2 m/s to insure animals stopped within the spatial cue. After the cursor was successfully placed and stopped in the spatial cue tolerance, visual feedback was provided to indicate that the reach was correctly performed. The cursor had to remain within the spatial cue tolerance for 300 ms. Successful trials were indicated by additional acoustic feedback (high pitched tone) and the monkeys received juice diluted with water or water as a reward, according to their individual preferences. Unsuccessful trials were indicated by a low pitch tone and the monkeys did not receive a reward. Trials were aborted and declared unsuccessful when the monkeys failed to obtain the hand or eye fixation or ended fixation prematurely, failed to initiate the movement in time or failed to complete the movement in time.

Movements had to be conducted against resistive forces that opposed the movement direction with a constant magnitude of 0 N, 3 N or 6 N. The resistive forces were applied only during the movement. Force levels were constant for blocks of 32 successful trials before switching. The combinations of movement directions and movement forces resulted in 4 (direction: 0° , 90° , 180° , 270°) \times 3 (force: 0 N, 3 N, 6 N) = 12 task conditions, which had to be successfully completed at least 24 times per session. Movement directions were drawn pseudo-randomly from trial to trial, i.e., the task condition of an unsuccessful trial was not repeated immediately but added back to the pool of conditions drawn randomly from. Movement forces were drawn pseudo-randomly from block to block (Figure 1C). Within a block, the force of a

previous trial was predictive for the force of the present trial. Exceptions were trials between blocks, where the force of a previous trial was not predictive for the force of the present trial.

2.3.4. Behavioral data analysis

The behavioral and neural data analyses were carried out using MATLAB 2018a with the data visualization toolbox *gramm* (Morel, 2018).

We quantified general performance, as percentage of unsuccessful trials and the percentage of unsuccessful reaches. The first indicates how often errors occurred across trials and trial epochs. The second indicates how often errors occurred across trials during the movement epoch.

To analyze if monkeys could use the force of the previous trial to predict the force of a present trial, we compared movement velocities of trials between blocks, where the force of a previous trial was not predictive for the force of the present trial, with movement velocities of trials within blocks, where force of a previous trial was predictive for the force of the present trial (Figure 2; Supplementary figure 1). We took all transitions from one force condition to another, which resulted in five force difference conditions (-6 N, -3 N, 0 N, 3 N, 6N), into consideration in this analysis. For each trial, we extracted movement velocity 150 ms after movement onset. This early velocity should reflect mostly feedback-independent movement production and hence serve as proxy for monkeys' motor planning. We used a Poisson-family generalized linear model (`fitglm()`; MATLAB 2018a) to test if the force difference modulated early movement velocities of the first and the fifth trial, after the force alternated (Model 1). The model included movement velocity as response variable and the predictor force difference (continuous variable).

(Model 1) $\text{Velocity} \sim 1 + \text{Force difference}$

If the results of the generalized linear model indicated that force difference was a significant predictor of velocity, we performed additional post-hoc tests (Wilcoxon rank sum test, $\alpha = 0.05$).

2.3.5. Neural recordings

We conducted extracellular neural recordings while the monkeys were performing the reaching task against resistive forces. Neural recordings were obtained for monkey K from all eight microelectrode arrays and for monkey Y from all six arrays simultaneously. We recorded the signals from each array with 32-channel CerePlex M headstages (hardware filter: 0.3 Hz – 7.5 kHz, sampling rate: 30 kHz, resolution: 16 bits ADC; Blackrock Microsystems LLC, Salt Lake City, Utah, USA), which filtered and digitized the neural signal. The digitized neural signal was sent to the Cerebus Neural Processing System (Blackrock Microsystems LLC, Salt Lake City, Utah, USA). The Cerebus System allowed to extract the extracellular spikes (neural events) from the raw neural signal by high-pass filtering the signal (filter: 250 Hz Butterworth filter, 4th order) and setting a negative detection threshold (threshold: $-4.5 \times \text{RMS}$), where extracellular spikes were defined as threshold crossings. Extracellular spikes were manually sorted using Offline Sorter V4 (Plexon Inc, Dallas, Texas, USA). Whenever a channel contained spike waveform clusters, which could not be isolated from the noise cluster we defined the channel as unsorted. Channels that contained spike waveform clusters that could be isolated from the noise cluster were defined as sorted. If spike waveform clusters, in sorted channels, were well differentiable from one another we defined them as single-units, while non-differentiable clusters were defined as multi-units. Single-units and multi-units were treated identically in our analysis and referred to as “units”. We derived the spike density function from the spikes of each unit by convoluting the spike trains (spike event times) with a Gaussian kernel ($\sigma = 50$ ms). Spike counts and spike

density functions (sampled at 200 Hz) were temporally aligned to the onset or offset, respectively, of visual stimuli and analyzed in corresponding time windows.

2.3.6. Neural data analysis

First, we analyzed if units were selective for direction or force or both (Figure 3; Supplementary figure 3). To do so we modeled spike counts using Poisson-family generalized linear models with a stepwise regression (`stepwiseglm()`; MATLAB2018a). Starting from a constant model with spike counts as response variable, the categorical predictors (direction, force) were added and removed by forward or backward stepwise regression to determine the final model. At each step, the function searched for predictors to add or remove from the model. Predictors were added when the F-statistic p-value < 0.01 and removed when F-statistic p-value > 0.05 . Final models could look as following using Wilkinson-Rogers formula notation:

(Model 2.1) Spike count ~ 1

(Model 2.1) Spike count $\sim 1 + \text{Direction}$

(Model 2.2) Spike count $\sim 1 + \text{Force}$

(Model 2.3) Spike count $\sim 1 + \text{Direction} * \text{Force}$

Spike counts were aligned for the following time windows: baseline (-300 ms – 0 ms, aligned to spatial cue onset), early movement planning (earlymem; 0 ms to 300 ms, aligned to spatial cue offset), late movement planning (latemem; -300 ms – 0 ms, aligned to go cue onset), movement (mov; 0 ms – 500 ms, aligned to go cue offset).

Second, we analyzed if the neural populations in the fronto-parietal reach network showed systematic linear selectivity of the intended or executed reach force (Supplementary figure 4; Supplementary figure 5). To do so we identified the

maximum response direction (PD_{\max}) of each unit and averaged the spike density functions of all units of each brain area in accordance with the units PD_{\max} , generating the population spike density function. This was done separately for the force conditions. To test at every time point for differences between the force conditions, we used a cluster-based permutation test (Maris & Oostenveld, 2007; as described in Dann et al., 2016). All units that were significantly encoding both the direction and force or the force were included in the neural population analysis.

Third, we analyzed whether the intended and executed reach direction and reach force could be decoded from the neural population using a multi-class support vector machine decoder (`fitcecoc()`; MATLAB2018a) (Figure 4; Supplementary figure 6). Spike counts of all sorted and unsorted channels were extracted for the following time windows: movement planning (-500 ms – 1000 ms, aligned to spatial cue onset) and movement (-500 ms – 1000 ms, aligned to go cue onset). The following procedure was repeated ten times per area. We selected pseudo-randomly twenty trials per condition for each channel of an area. Pseudo-randomly selected trials were different across channels, but the number of trials per condition was not. The spike counts of these trials were binned in time bins of 150 ms (with 50 ms overlap). This resulted per time bin in a matrix that contained the concatenated spike counts of all channels, with twenty repetitions per conditions. Half of these repetitions per condition were used to train and the other half to test the decoder, with the concatenated spike counts of all channels as input. The decoder was trained using the following predictors: direction, force or both. Predicted conditions (`predict()`; MATLAB2018a) were compared with the actual conditions to calculate the decoding performance. This was repeated for all time bins. As mentioned, the whole procedure was repeated ten times per area, resulting in ten decoding performances per bin per area. The same procedure was used when calculating permuted decoding performance, except that the spike counts were permuted. To test for each time bin

for significant differences between the decoding performance and the permuted decoding performance, we used the cluster-based permutation test (Maris & Oostenveld, 2007; as described in Dann et al., 2016). To test for significant difference between areas, we calculated the time when differences between the decoding performance and the permuted decoding performance became significant and the maximum decoding performance and used the Wilcoxon rank sum test ($\alpha = 0.05$).

2.4. Results

2.4.1. Movement velocities adjust fast to force changes, indicating that monkeys are accurately anticipating the force

To investigate if the fronto-parietal reach network encodes the intended and executed reach force, we trained two macaque monkeys to perform a reaching task against three levels of resistive force (0 N, 3 N, 6 N). The task design encouraged planning of the required force and allowed to evaluate the degree to which animals did so. The force-level was varied in a block-wise fashion, after 32 successful trials.

Within a block, the force of a previous trial was predictive for the force of the present trial and, hence, forces could be taken into account by the animal when preparing the reach movements. A short movement initiation time enforced preparing the reach movements in advance. Movement time constrains encouraged to take the force into account before the movements, to be able to perform movements successfully under the given time constrains (see Methods section). Both monkeys performed the reaching task well with an average of 84% correct reaches for monkey K (74 % correct trials) and 94% correct reaches for monkey Y (83 % correct trials) (Table 1). The high performance provided a first indication that the force information of previous trials was used by the animals to predict the force of a present trial.

Transitions between blocks, instead, introduced non-predictable force-loads on the first trial(s) of a new block. Adjustments of reach kinematics over the course of early trials within a block are indicative of the degree to which the animals actually did take into account the force when preparing movements. We analyzed the effect of altering force blocks on the initial, feedback-independent movement velocity across trials to identify putative over- and under-expectation of force levels in preparation of the reach. In the first trial after the force changed, one of two effects could be observed (Figure 2A and 2B). When the force decreased, the movement velocity increased and movement trajectories tended to overshoot. When the force increased, movement velocity decreased and movement trajectories tended to undershoot. Dependence of velocity from force change was confirmed by a Poisson-family generalized linear model (monkey Y: t-statistic = -4.057, $p < 0.001$; monkey K: t-statistic = -2.796, $p < 0.01$). By the fifth trial after the force changed velocities no longer depended on the force level difference (monkey Y: t-statistic = -0.775, $p = 0.437$; monkey K: t-statistic = -1.063, $p = 0.287$) (Figure 2C). The fact that movement velocity already adjusted after one or two trials (Figure 2D) indicates that by that time the new force level was known and the monkeys prepared the force of the upcoming reach movement. When the force remained unchanged after a block of 32 successful trials, i.e., the condition in which force change equals zero, the velocity profile was indistinguishable from within-block trials. While reach kinematics quickly adjusted in both animals after a force transition, the reported effects seemed stronger in monkey Y (Figure 2) than in monkey K (Supplementary figure 1).

2.4.2. Neurons in the fronto-parietal reach network are sensitive for intended and executed reach force

We collected five sessions for monkey Y (total number of single- and multi-units: 219) and four sessions for monkey K (total number of single- and multi-units: 241). During each of the sessions we recorded simultaneously single- and multi-unit

activity from areas: M1 (total units: 155; monkey Y: 103; monkey K: 52), PMd (total units: 199; monkey Y: 82; monkey K: 117) and PRR (total units: 106; monkey Y: 34; monkey K: 72).

First, we investigated if the units of the fronto-parietal reach network were sensitive to the intended or executed reach force. For this, we used a step-wise generalized linear model to analyze the tuning of the individual units during different trial periods. Similar to previous studies, we found units in M1, PMd and PRR that were sensitive to movement direction in both the movement planning epoch and the movement epoch. Furthermore, we found units that were sensitive to force either exclusively, or in combination with movement direction (Figure 3). Units with combined tuning showed either an independent sensitivity to both movement parameters (spike count \sim direction + force) or a showed a statistical interaction (spike count \sim direction + force + direction * force). During movement planning, most tuned units in all recorded areas were only sensitive to planned movement direction (monkey Y: M1 47-50%, PMd 73-81%, PRR 41-66%; monkey K: M1 48-52%, PMd 70-85%, PRR 67-83%), with very few units showing exclusive or additional force sensitivity (monkey Y: M1 8-9%, PMd 6-11%, PRR 4-8%; monkey K: M1 12%, PMd 11-19%, PRR 1-8%). During the movement period, PMd and M1 saw a large and PRR a moderate increase in the proportion of units with combined sensitivity (monkey Y: M1 63%, PMd 54%, PRR 20%; monkey K: M1 72%, PMd 35%, PRR 19%). In the baseline period, before the spatial cue, few units were notably force tuned in all areas. During this period, the movement direction is not yet known to the animal, but the force is due to the block design for force. Summarizing, we found single- and multi-units in M1, PMd and PRR that were selective for the intended and executed reach force. Units, selective for the intended and executed reach force, did not show systematic selectivity, where higher neural activity was not correlated higher forces. This indicates that force selectivity seems to be more

complex. The percentage of units that were selective for the intended reach force was highest in PMd. The percentage of units that was selective for the executed reach force was highest in M1 and lowest in PRR. In comparison the percentage of units that was selective for the intended reach force was lower than the number of units that encoded the executed reach force (Figure 3C).

2.4.3. Neural populations the fronto-parietal reach network do not show systematic sensitivity to the intended or executed reach force

Second, we investigated if the average neural population activity in areas of the fronto-parietal reach network was sensitive to the intended or executed reach force. We included in the neural population analysis all directional-, combined and force-tuned units. The population analysis tests if a common sensitivity pattern to force was present in the population (e.g. high force = high firing rate). For this, we tested whether the population average of the spike density functions differed between the force conditions using a cluster-based permutation test (Maris & Oostenveld, 2007; Inveltd et al., 2018). We found that the average neural population activity in M1, PMd and PRR was not significantly sensitive to the intended or executed reach force (Figure 4), even though some units of the fronto-parietal reach network were. Hence, we added another analysis that does not require a common sensitivity pattern to extract a general sensitivity at the area-level.

2.4.4. Executed reach force can be decoded from neural populations in the fronto-parietal reach network

Third, we used a machine-learning approach to decode the intended and executed reach direction and reach force from recorded neural activity in areas of the fronto-parietal reach network. We were able to significantly decode the intended and executed reach direction from areas: PRR, PMd and M1 (Figure 5A top). The maximum decoding performance of the intended reach direction was highest in PMd, followed by PRR and M1. The time of significant decoding performance was shortest

in PRR, followed by PMd and M1 (Figure 5B top left). Maximum decoding performance of the executed reach direction was high in all three areas, and all areas were significantly decoding the direction from the beginning of this period (Figure 5B top right). In addition, we were able to significantly decode the executed reach force from areas: M1, PMd and PRR (Figure 5A bottom). There were some irregular signs of significant decoding of the intended reach force. The maximum decoding performance of the executed reach force was highest in M1, followed by PMd and PRR (Figure 5B bottom right). The time of significant decoding performance was shortest in M1, followed by PMd and PRR. Summarizing, we could decode the executed reach force from M1, PMd and PRR. The differences in the maximum decoding performance, indicated that the neural activity in M1 was most and neural activity in PRR least predictive of the force. Differences in the time of significant decoding performance, indicated that neural activity in M1 predicted the force the fastest, while neural activity in PRR was slowest.

2.5. Discussion

2.5.1. Summary of results

We found neurons in all three areas of the fronto-parietal reach network that were selective for the intended and executed reach force. While neurons that were selective for the executed reach force were found repeatedly in all three areas, selectivity for the intended reach force was rare, both in parietal cortex as well as in prefrontal cortical areas. Correspondingly, we were only able to decode the executed reach force from neural populations in all three areas during movement, while decoding of upcoming force during movement planning was not reliably possible in either area. Importantly, our task design did not use visual information that could be used to predict forces. Instead our task design used haptic information, which could be used from the previous trial to predict the force of the present trial. Furthermore,

we encouraged the use of the haptic information to plan the force of an upcoming reach movement. Behavioral analyses provide evidence that both animals indeed did plan the force of the upcoming movement within a few trials after a change in force level. Our neural analyses provided additional evidence that the fronto-parietal reach network is selective for the executed reach force, but not the intended reach force, when no visual information was provided that could be used to predict forces.

2.5.2. Force selectivity in the primary motor cortex, premotor cortex and parietal cortex

This study investigated if the sensorimotor system uses force predictions to prepare a motor command according to the force the motor command will be executed with. Force predictions were generated by using haptic information, instead of visual information. In detail, we examined whether force selectivity in the fronto-parietal reach network during movement preparation and movement depended on the source of information used to generate force predictions. Studies that investigated the selectivity for grasp force in the fronto-parietal grasp network showed that the motor cortex is selective for the executed grasp force (Hepp-Reymond et al., 1978; Intveld et al., 2018). Since then, selectivity for the executed grasp force was reported for other regions of the fronto-parietal grasp network, as the premotor cortex (Hepp-Reymond et al., 1994; Hepp-Reymond et al., 1999; Intveld et al., 2018) and the parietal cortex (Ehrsson et al., 2003; Intveld et al., 2018).

A recent study showed that neurons in the hand area of M1, PMv and AIP were selective for the executed grasp force, while PMv, and to an extent AIP, were selective for the intended grasp force (Intveld et al., 2018). This recent study indicates that the sensorimotor system is selective for force during the movement preparation and movement, when visual information was used to predict forces. Even though grasping and reaching involve separate fronto-parietal networks: the grasp network and the reach network, grasping and reaching are closely associated with

one another, as seen in reach-to-grasp movements. Therefore, it would seem plausible if both networks would show some similarities in their selectivity. Indeed, studies conducted in reach-to-grasp movements show that M1 and PMd were selective for the executed grasp force, with a stronger selectivity for grasp force in M1 (Hendrix et al., 2009). A recent study reports that neural population activity in M1, PMd and PMv were selective for the executed grasp force during an isometric grasp force task (Atique & Francis, 2021). Moreover, studies that studied directly the selectivity for static or dynamic isometric forces in reaching movements showed that neural activity in M1 was selective for the hand location, direction of the force and their interaction (Sergio & Kalaska, 1997, 2003).

Our results share similarities to results from previous studies. We were able to decode the executed reach force from all three areas of the fronto-parietal reach network, indicating the fronto-parietal reach network is selective for the executed reach force. But our results show some dissimilarities compared to results from Intveld and colleagues (2018). In comparison of we found neither of the areas of the fronto-parietal reach network was selective for the intended reach force, which would be indicating that the fronto-parietal reach network is selective for the executed reach force. This would indicate that the sensorimotor system is selective for force during the movement but not movement preparation, when haptic information was used to predict forces. We hypothesize that the force selectivity in the sensorimotor system during movement preparation, seems to depend on whether visual or haptic information could be used to predict the force of an upcoming movement.

A study that favors this hypothesis was conducted by Chouinard and colleagues, and suggests that M1 and PMd play different roles in anticipatory force scaling (Chouinard et al., 2005). They showed that repetitive transcranial magnetic stimulation of the primary motor cortex disrupted the scaling of forces based on

haptic information inferred from a previous trial, while repetitive stimulation of the dorsal premotor cortex disrupted the scaling of forces based on visual information. Another study that favors this hypothesis, show that when visual information of the object size was used to infer object weight, transcranial magnetic stimulation over PMv, but not M1 or AIP, interfered with predictive force scaling of grip force (Dafotakis et al., 2008). Moreover, transcranial magnetic stimulation over the anterior intraparietal cortex showed that it had a transient role during predictive force scaling, when force scaling was based on visual information (van Polanen et al., 2022). Summarizing these studies, it seems that PMd and PMv, and to an extent AIP seem to play an important role during force scaling based on visual information. M1 seems, contrary, seem to play an important role during force scaling based on haptic information inferred from a previous trial.

We therefore postulate that the sensorimotor system uses visual information to predict forces and this force prediction is used to plan the force of an upcoming movement. In the absence of visual information to predict forces, the sensorimotor system relies on haptic information acquired during the movement to predict forces. In this case the force prediction is not used to plan the force of an upcoming movement.

2.6. Figures and tables

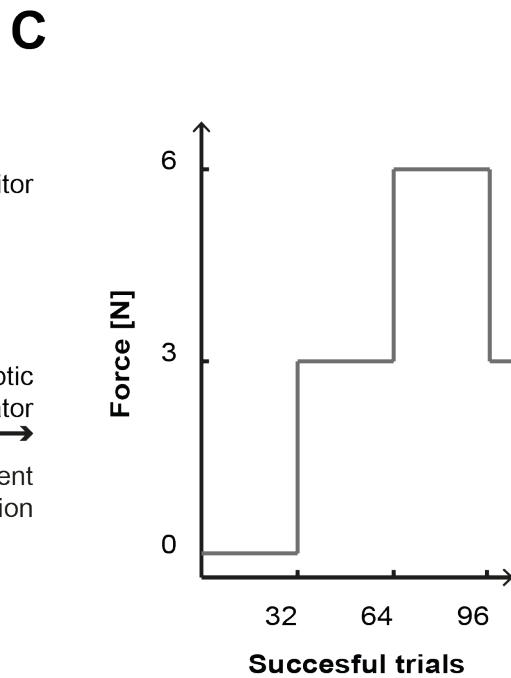
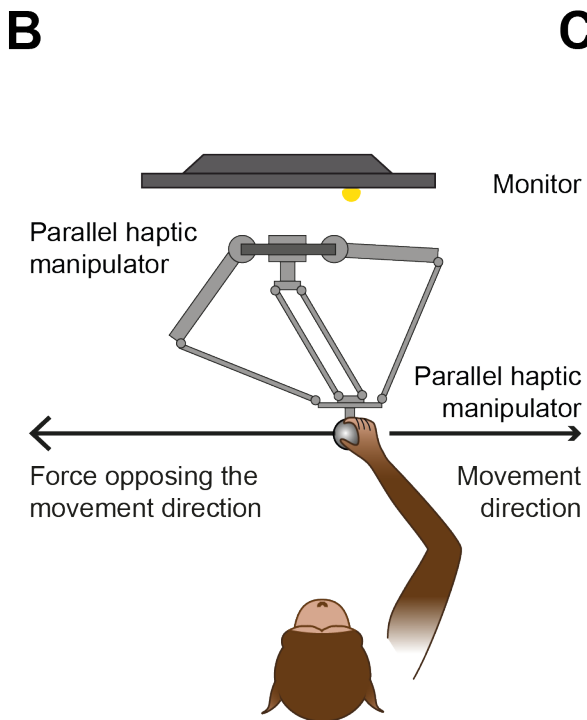
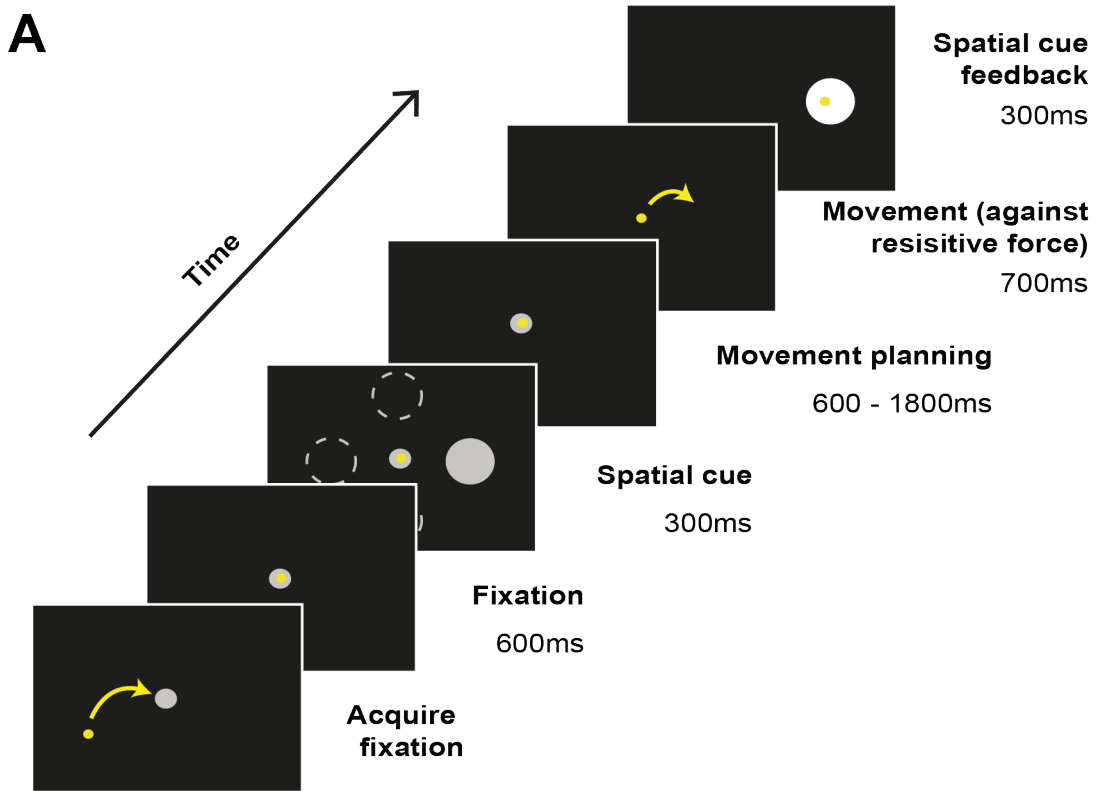


Figure 1 (*see previous page*). **Force-loaded reach task.** A: Overview of the task timeline and spatial layout of the memory-guided center-out reaching task. B: Overview of the setup with haptic manipulandum for loading reaches with different force-levels. C: Block-design of varying force conditions across trials. The force condition changed in a block-wise manner every thirty-two successful trials. Subjects were not explicitly instructed which force they would encounter during the upcoming movement but had to infer the force from the movement in the previous trial.

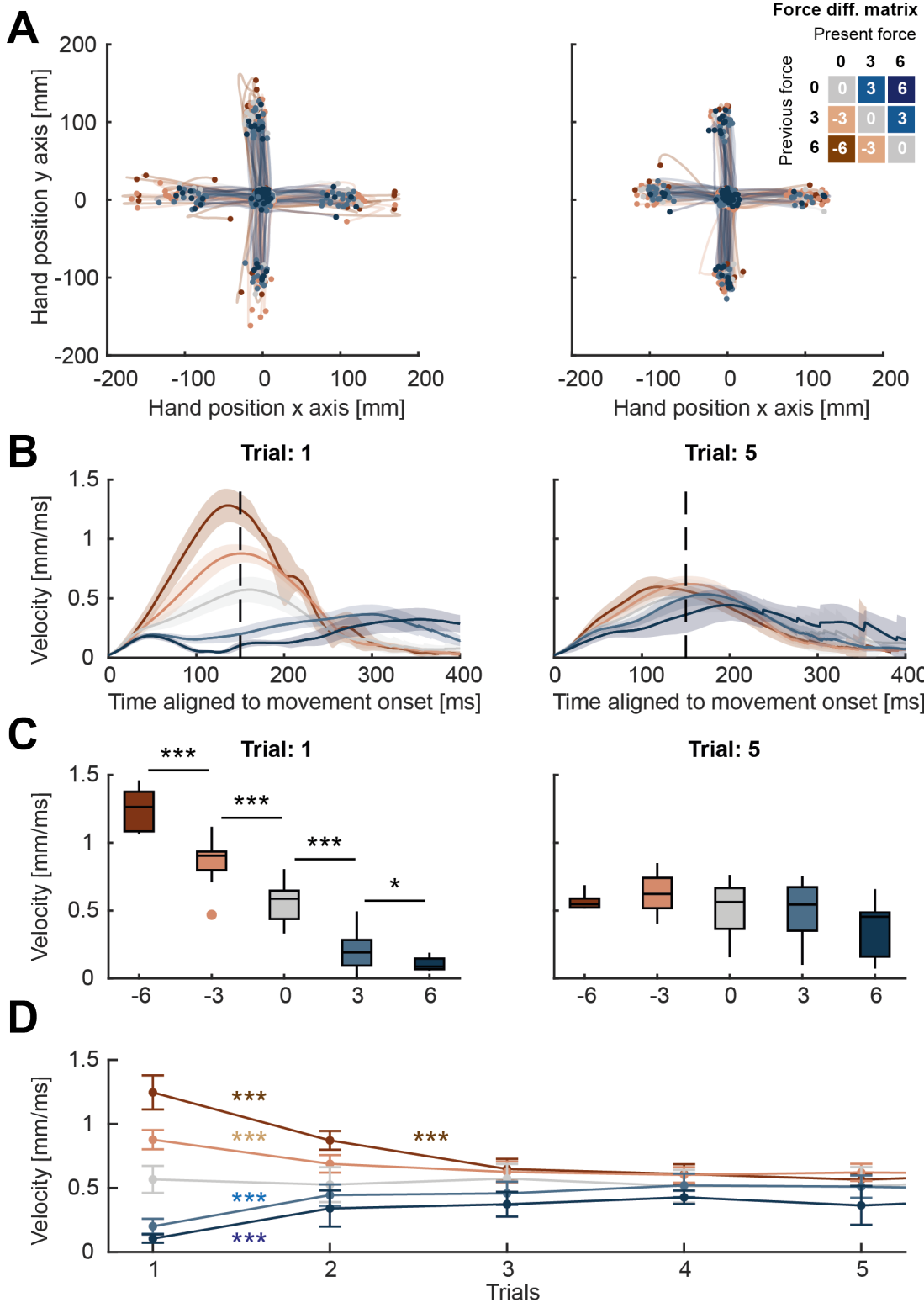


Figure 2 (see previous page). **Movement trajectories and movement velocities reflect if monkey Y anticipated the force.** A: Single trial movement trajectories from the first three trials (*left*) and the last three trials (*right*) of a force-block for the five possible relative changes in absolute force (color matrix). Movement start and movement end are depicted as points along the trajectory. Early trials tend to overshoot after force reductions. B: Mean movement velocities of the first trial (*left*) and fifth trial after the force changed (*right*). The shaded area depicts the 95% confidence interval (CI) of the mean. The dashed vertical line indicates the time 150ms after movement onset around which velocities tend to peak. C: Within-trial comparison of mean movement velocities extracted 150ms after movement onset at the first trial (*left*) and fifth trial after the force changed (*right*). The asterisks indicate significant difference between compared force conditions within trials ($*p < a$ at 5 %, $**p < a$ at 1 %; $***p < a$ at 0.1 %; post-hoc Wilcoxon signed rank test). D: Between-trial comparison of mean movement velocities extracted 150ms after movement onset for the first five trials of a block. The asterisks indicate significant difference within force conditions between trials ($*p < a$ at 5 %, $**p < a$ at 1 %; $***p < a$ at 0.1 %; Wilcoxon signed rank test).

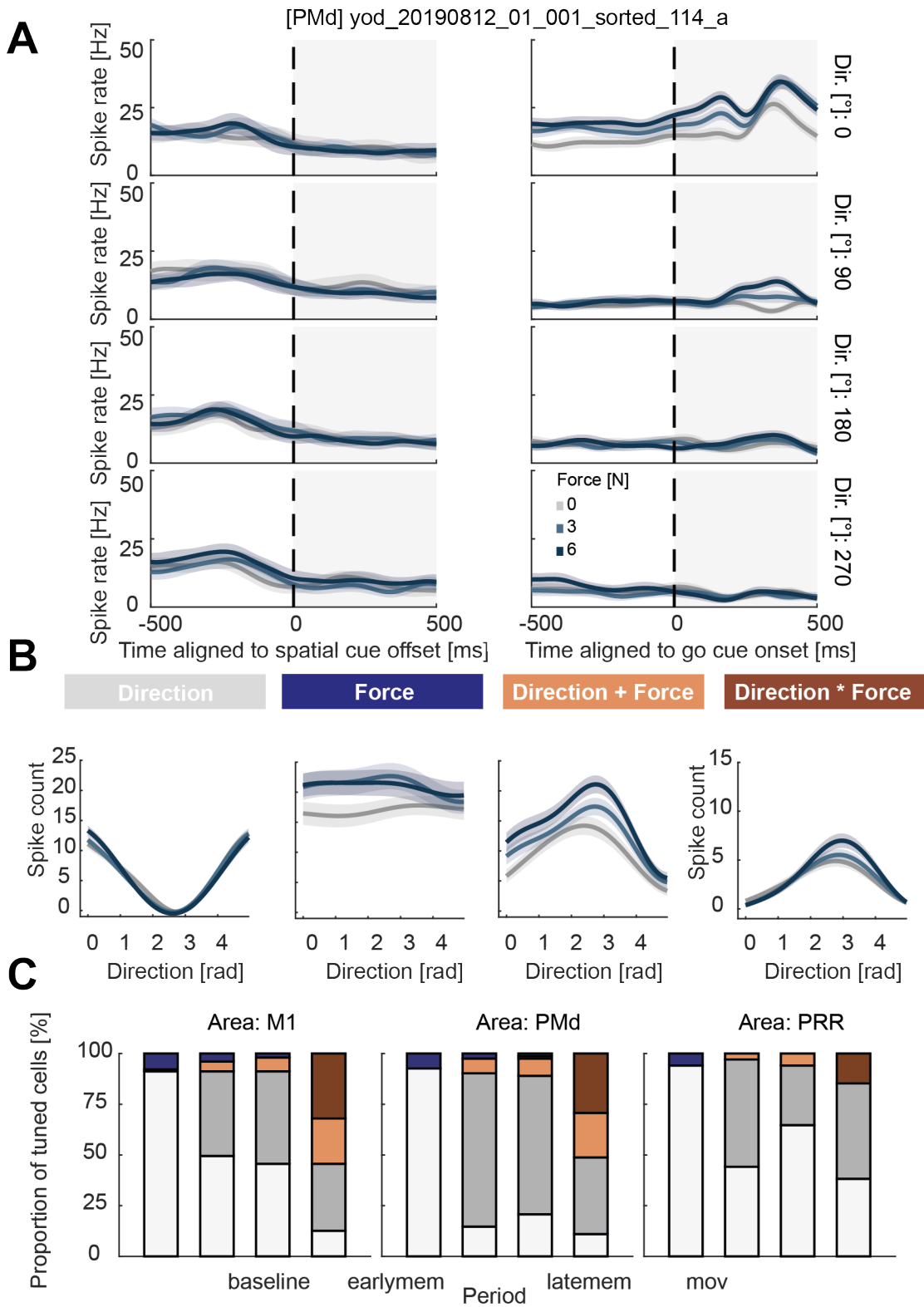


Figure 3 (*see previous page*). **Direction and force selectivity in the fronto-parietal reach network of monkey Y.** A: Example neuron that was selective for the intended (late movement planning) and executed reach force. The shaded area depicts the 95% confidence interval (CI) of the mean. B: Tuning classes with either pure direction, pure force, combined direction and force selectivity, or an interaction of both, according to the tuning analysis. C: Proportion of tuning classes across task periods as fraction of all units. Colors as in (B); White are non-selective units.

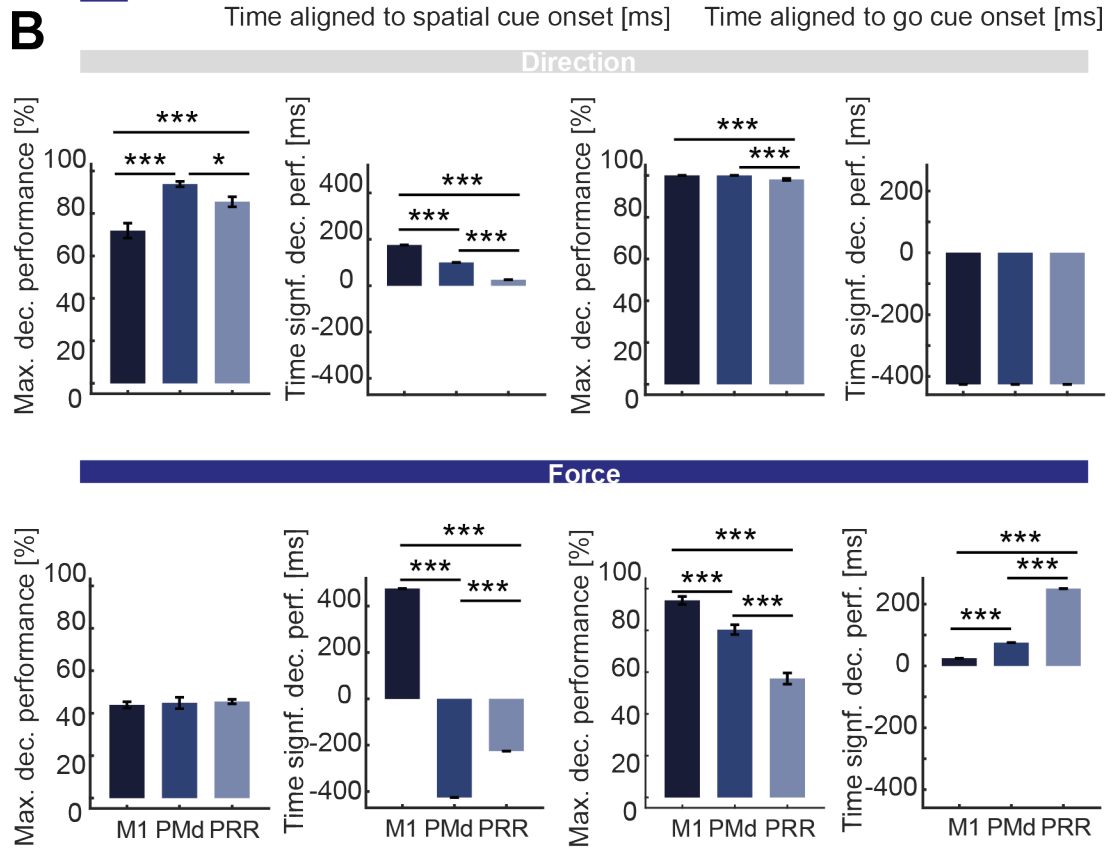
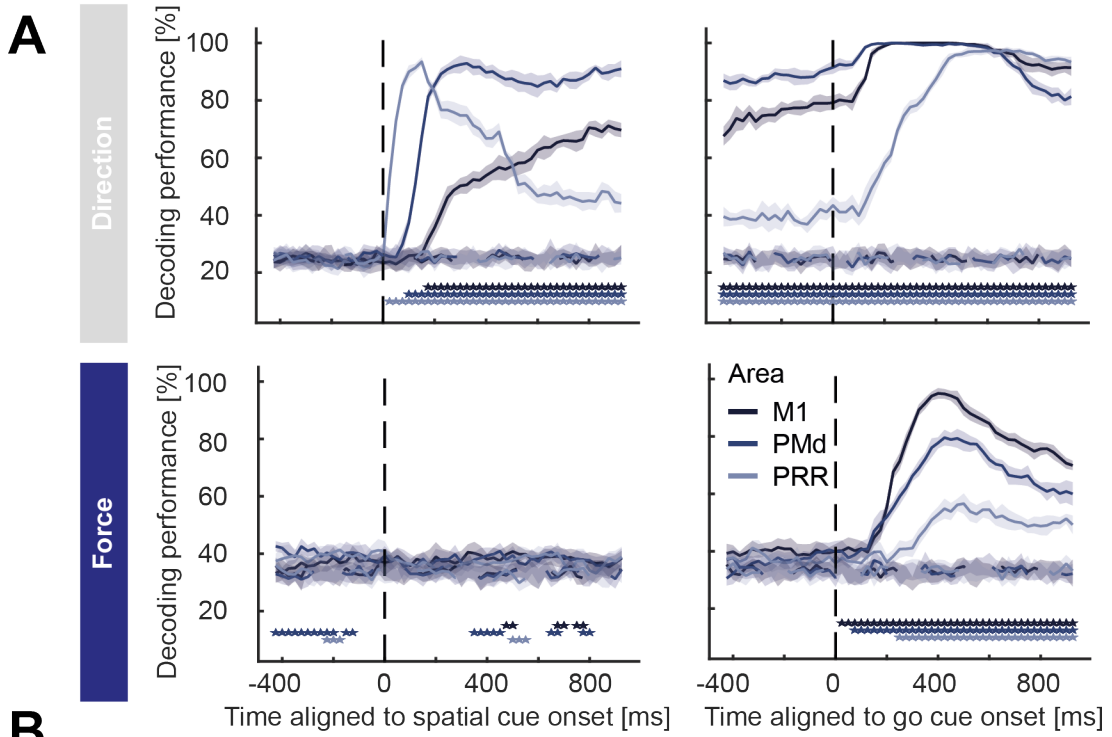
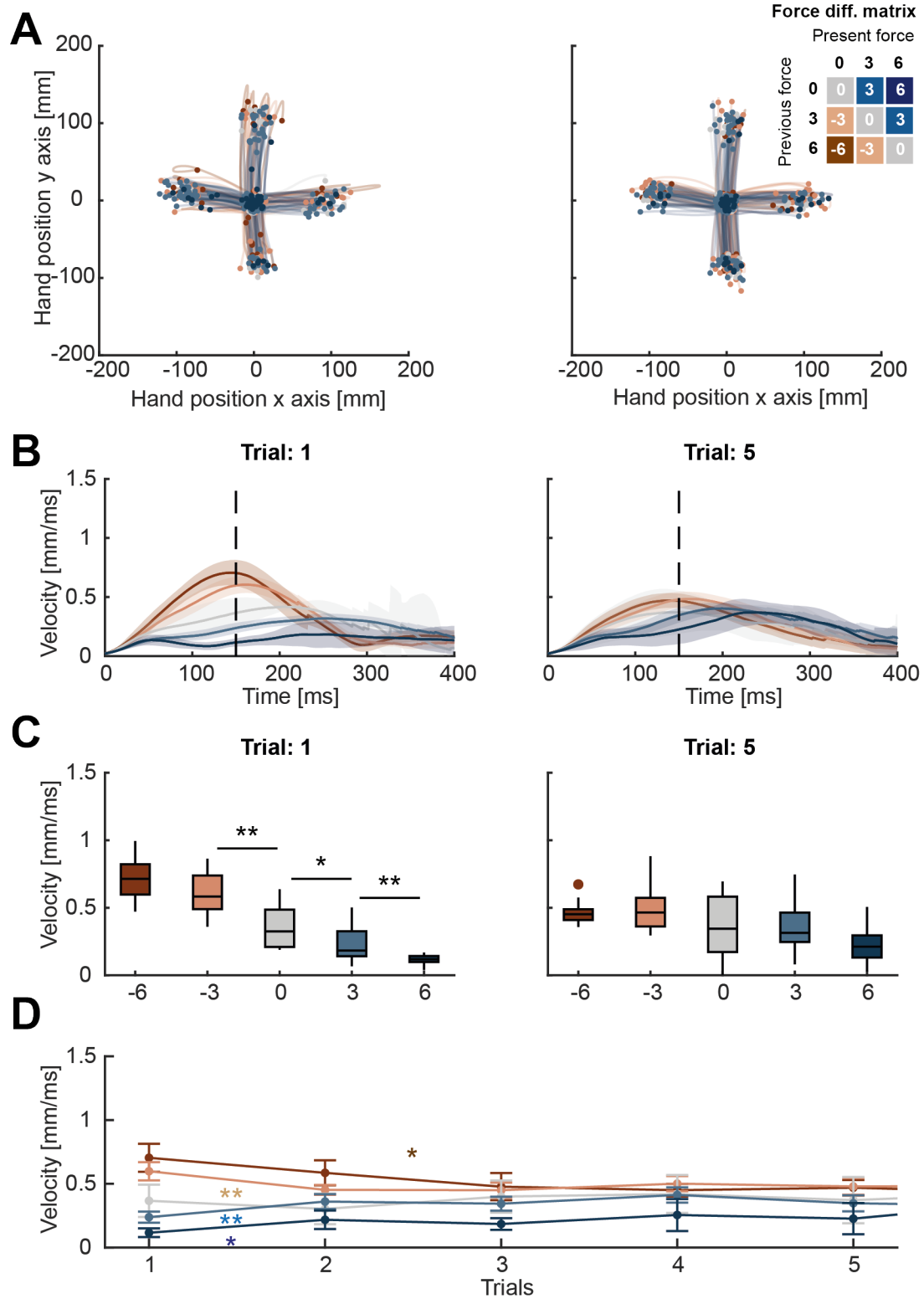
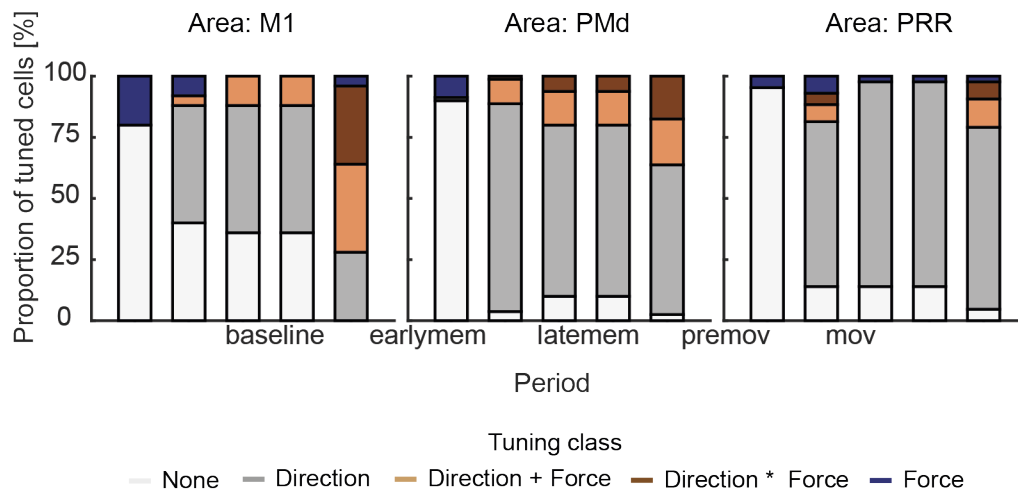


Figure 4 (see previous page). Decoding of force from neural populations in areas M1, PMd and PRR of the fronto-parietal reach network in monkey Y. A: Decoding performance for areas M1, PMd and PRR for decoded variables direction (*top*) and force (*bottom*). The dashed vertical line indicates the time of alignment. Full lines indicate decoding performance, while dashed lines indicate decoding performance of permuted data. The dashed vertical line indicates the time of alignment. The asterisks indicate significant difference between decoding performance and permuted decoding performance for each area ($*p < a$ at 5 %; Cluster-based permutation test). B: Maximum decoding performance and time of significant decoding performance both for movement planning and movement. The asterisks indicate significant difference between compared areas ($*p < a$ at 5 %, $**p < a$ at 1 %; $***p < a$ at 0.1 %; Wilcoxon signed rank test).

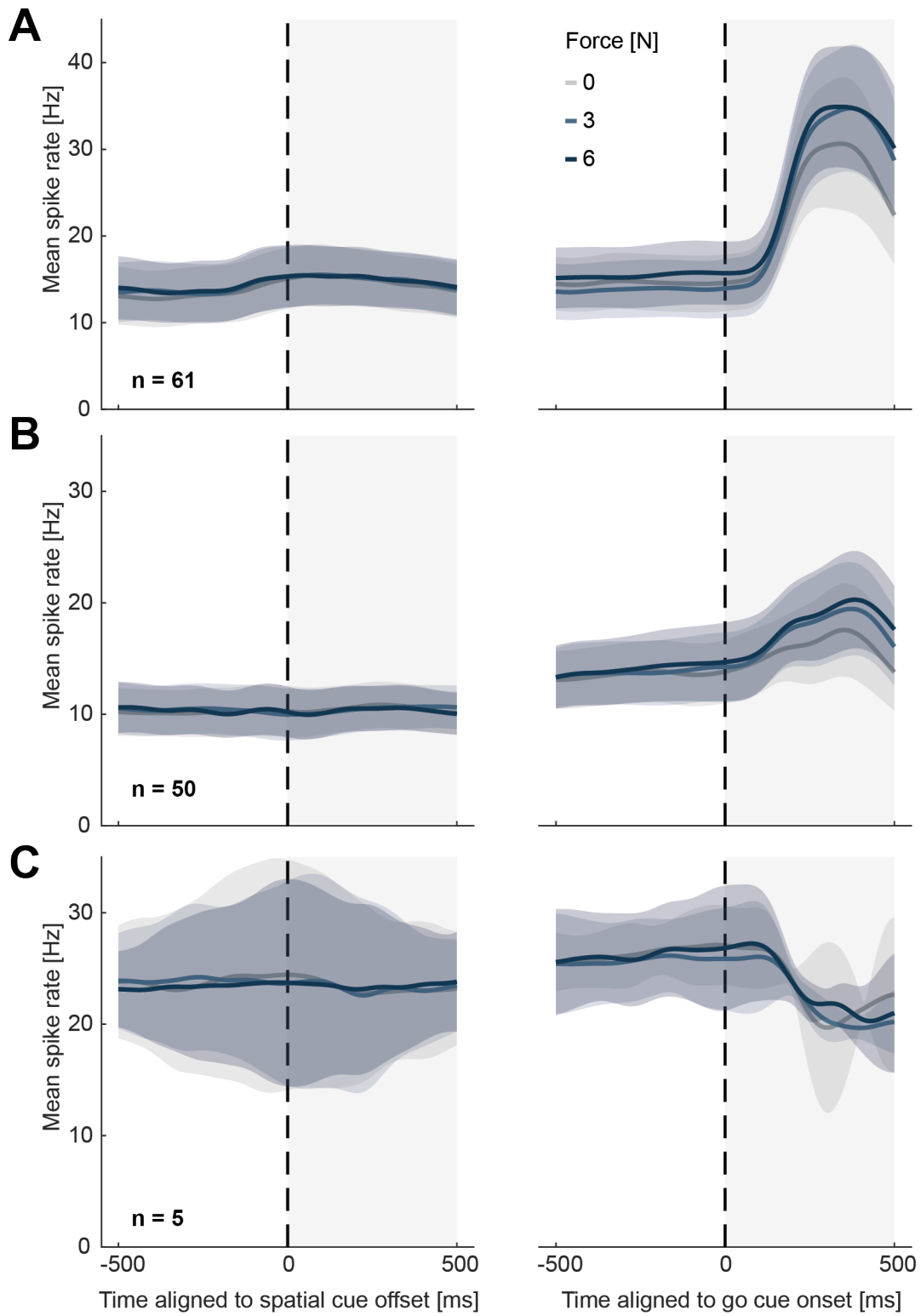


Supplementary Figure 1 (see previous page). Movement trajectories and movement velocities reflect if monkey K anticipated the force. A: Single trial movement trajectories from the first three trials (*left*) and the last three trials (*right*) of a force-block for the five possible relative changes in absolute force (color matrix). B: Mean movement velocities of the first trial (*left*) and fifth trial after the force changed (*right*). The shaded area depicts the 95% confidence interval (CI) of the mean. The dashed vertical line indicates the time 150ms after movement onset around which velocities tend to peak. C: Within-trial comparison of mean movement velocities extracted 150ms after movement onset at the first trial (*left*) and fifth trial after the force changed (*right*). The asterisks indicate significant difference between compared force conditions within trials ($*p < a$ at 5 %, $**p < a$ at 1 %; $***p < a$ at 0.1 %; post-hoc Wilcoxon signed rank test). D: Between-trial comparison of mean movement velocities extracted 150ms after movement onset for the first five trials of a block. The asterisks indicate significant difference within force conditions between trials ($*p < a$ at 5 %, $**p < a$ at 1 %; $***p < a$ at 0.1 %; Wilcoxon signed rank test).

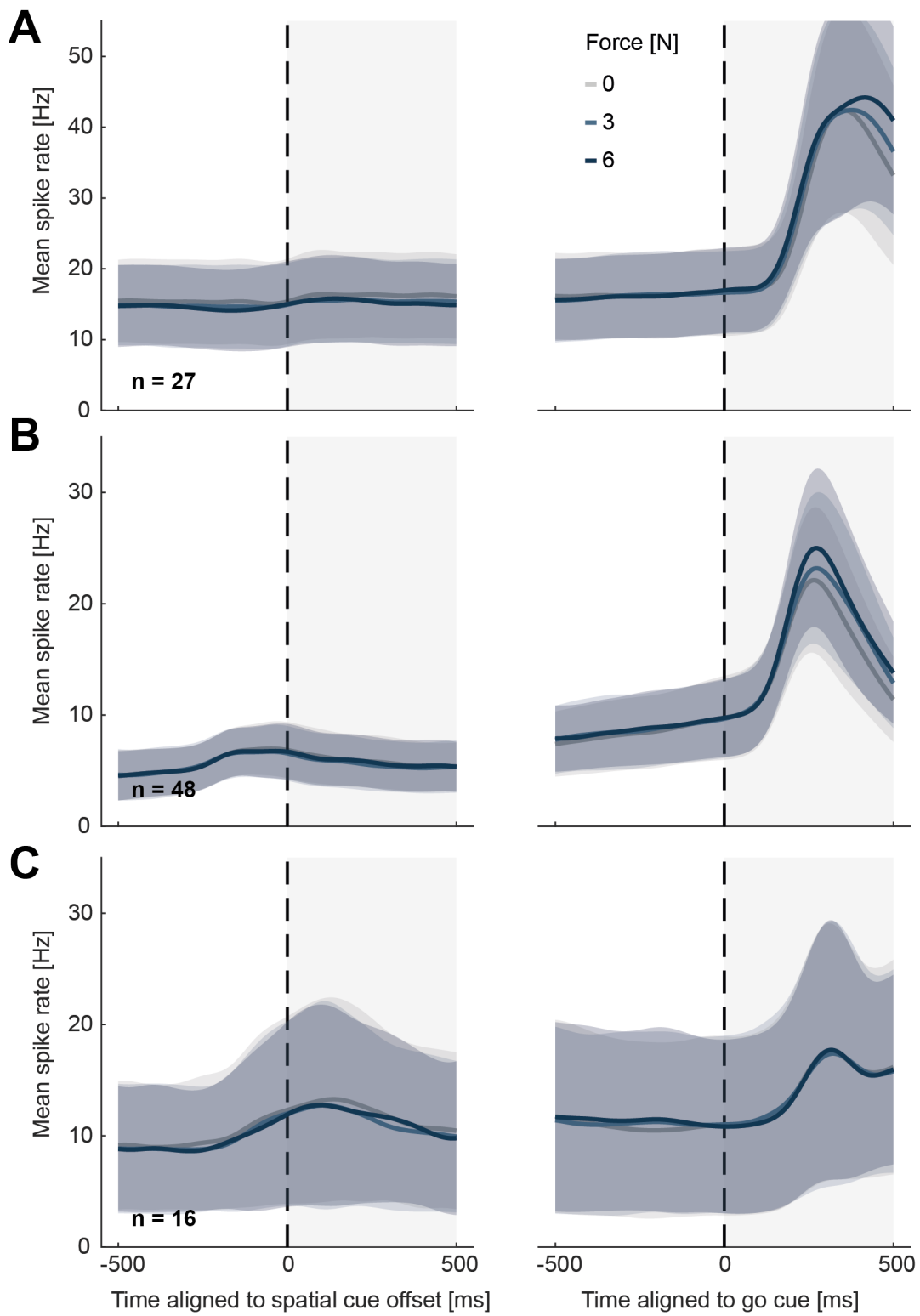


Supplementary Figure 2. Direction and force selectivity in the fronto-parietal reach network of monkey K. Proportion of tuning classes across task periods as fraction of all units. Colored units are selective for direction, force or both. White units are non-selective.

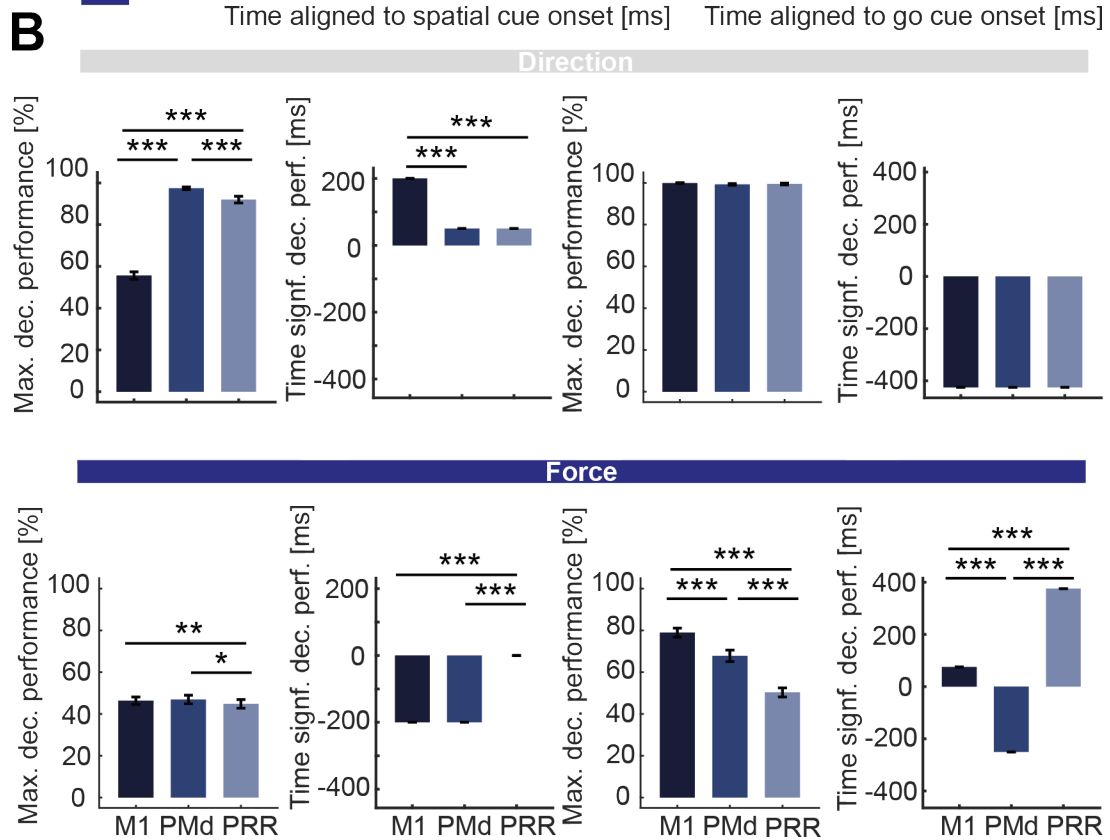
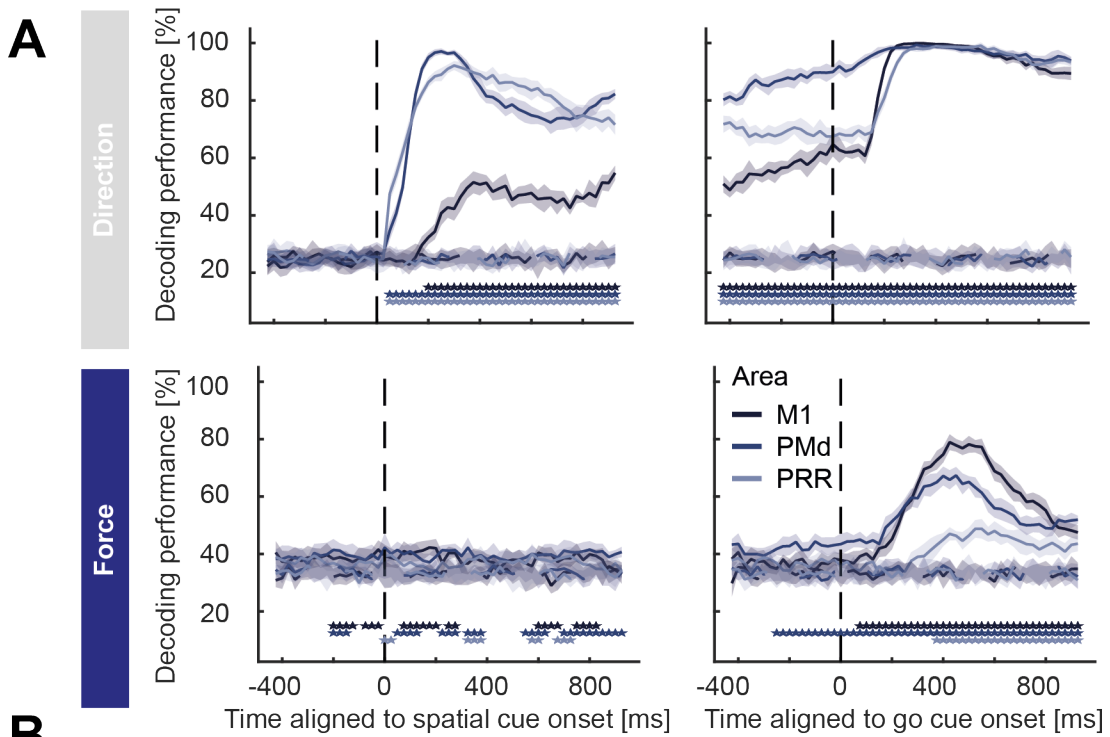
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Supplementary Figure 3 (*see previous page*). Neural populations in areas M1, PMd and PRR of the fronto-parietal reach network show no systematic linear selectivity for force in monkey Y. A: Population average of spike density functions in M1. Population average of spike density functions during movement planning (*left*) are aligned, as indicated by the dashed vertical line, to spatial cue offset. Population average of spike density functions during movement (*right*) are aligned to go cue onset. B: Population average of spike density function in PMd. C: Population average of spike density function in PRR.



Supplementary Figure 4 (*see previous page*). **Neural populations in areas M1, PMd and PRR of the fronto-parietal reach network show no systematic linear selectivity for force in monkey K.** A: Population average of spike density functions in M1. Population average of spike density functions during movement planning (*left*) are aligned, as indicated by the dashed vertical line, to spatial cue offset. Population average of spike density functions during movement (*right*) are aligned to go cue onset. B: Population average of spike density function in PMd. C: Population average of spike density function in PRR.



Supplementary Figure 5 (see previous page). **Decoding of force from neural populations in areas M1, PMd and PRR of the fronto-parietal reach network in monkey K.** A: Decoding performance for areas M1, PMd and PRR for decoded variables direction (*top*) and force (*bottom*). The dashed vertical line indicates the time of alignment. Full lines indicate decoding performance, while dashed lines indicate decoding performance of permuted data. The dashed vertical line indicates the time of alignment. The asterisks indicate significant difference between decoding performance and permuted decoding performance for each area ($*p < a$ at 5 %; Cluster-based permutation test). B: Maximum decoding performance and time of significant decoding performance both for movement planning and movement. The asterisks indicate significant difference between compared areas ($*p < a$ at 5 %, $**p < a$ at 1 %; $***p < a$ at 0.1 %; Wilcoxon signed rank test).

Table 1. Overview of overall performance of both subjects.

Subject	Sessions	Avg. number of trials	Avg. number of successful trials	Avg. percentage of successful trials	Avg. percentage of successful reaches
Monkey Y	5	530	440	83 %	94 %
Monkey K	4	892	660	74 %	84 %

Table 2. Overview of number and percentage of tuned units in M1.

M1 (Monkey Y)	Baseline	Movement planning (early)	Movement planning (late)	Movement
Direction	1 (1%)	38 (47%)	40 (50%)	22 (27%)
Direction + force	-	3 (3%)	6 (7%)	20 (25%)
Direction * force	-	-	-	31 (38%)
Force	7 (8%)	4 (5%)	2 (2%)	-

Table 3. Overview of number and percentage of tuned units in PMd.

PMd (Monkey Y)	Baseline	Movement planning (early)	Movement planning (late)	Movement
Direction	-	56 (81%)	51 (73%)	27 (39%)
Direction + force	-	4 (5%)	7 (10%)	15 (21%)
Direction * force	-	-	1 (1%)	23 (33%)
Force	6 (8%)	1 (1%)	-	-

Table 4. Overview of number and percentage of tuned units in PRR.

PRR (Monkey Y)	Baseline	Movement planning (early)	Movement planning (late)	Movement
Direction	-	16 (66%)	10 (41%)	14 (58%)
Direction + force	-	1 (4%)	2 (8%)	-
Direction * force	-	-	-	5 (20%)
Force	2 (8%)	-	-	-

Table 5. Overview of number and percentage of tuned units in M1.

M1 (Monkey K)	Baseline	Movement planning (early)	Movement planning (late)	Movement
Direction	-	12 (48%)	13 (52%)	-
Direction + force	-	1 (4%)	3 (12%)	9 (36%)
Direction * force	-	-	-	8 (32%)
Force	5 (20%)	2(8%)	-	1 (4%)

Table 6. Overview of number and percentage of tuned units in PMd.

PMd (Monkey K)	Baseline	Movement planning (early)	Movement planning (late)	Movement
Direction	1 (1%)	68 (85%)	56 (70%)	49 (61%)
Direction + force	-	8 (10%)	11 (13%)	15 (18%)
Direction * force	-	1 (1%)	5 (6%)	14 (17%)
Force	7 (8%)	-	-	-

Table 7. Overview of number and percentage of tuned units in PRR.

PRR (Monkey K)	Baseline	Movement planning (early)	Movement planning (late)	Movement
Direction	-	29 (67%)	36 (83%)	32 (74%)
Direction + force	-	3 (6%)	-	5 (11%)
Direction * force	-	2 (4%)	-	3 (6%)
Force	2 (4%)	3 (6%)	1 (2%)	1 (2%)

Chapter 3:

Decoding intended and executed reach effort during effort-guided reach selection

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JN, PM and AG designed the study; JN collected the data; JN and PM analyzed the data; JN visualized the results and wrote the original draft; JN and PM revised the manuscript.

3.1. Abstract

Decisions are often decisions among actions. Current theories, postulate that decision processes are not separated from sensorimotor processes. Congruently, benefit-related decision variables, e.g. reward associated to actions, are represented in the sensorimotor system. But it remains unclear if cost-related decision variables are also represented in the sensorimotor system. In reach movements, a cost-related decision variable is physical effort (reach effort). One of the parameters that increases the physical effort of a reach movement, is force. This study investigates if the fronto-parietal reach network represents reach effort when deciding between two reach goals, by using forces to increase reach effort. We trained a macaque monkey (*Macaca mulatta*) to perform an effort-guided reach selection task. The monkey was trained to associate reaches toward one of the reach goals to be more effortful, compared to the other, less effortful reach goal. We recorded the neural population activity from three areas of the fronto-parietal reach network: the arm area of the primary motor cortex (M1), the dorsal premotor cortex (PMd) and the parietal reach region (PRR). Preliminary results show that a minority of neurons in the fronto-parietal reach network represent reach effort before and after deciding between reach goals (intended reach effort), while a majority of neurons represented reach effort when the decision was executed (executed reach effort). Furthermore, we were able to decode reach effort from the neural population activity in the fronto-parietal reach network. We were able to decode, to a degree, reach effort from areas PMd and M1 before a decision and from all three areas after the decision and when the decision was executed. After the decision, the maximum decoding performance was highest in PMd, followed by M1 and PRR, while when the decision was executed it was highest in M1, followed by PMd and PRR. Our results suggest that the fronto-parietal reach network represents reach effort, indicating that the sensorimotor system represents cost-related decision variables.

3.2. Introduction

Imagine you want to pour yourself a glass of milk. You open the cupboard and can choose to grab a glass of the lower or upper shelf, and choose a glass from the lower shelf of the cupboard. This demonstrates that many decisions we make are decisions among actions. Past hypotheses in cognitive psychology claimed that decision processes are separated from sensorimotor processes (Sternberg, 1969). However a present hypothesis, the affordance competition hypothesis, claims that decision and sensorimotor processes are not separated. According to the affordance competition hypothesis, when confronted with a choice among actions, the fronto-parietal network creates competing neural representations of these actions (Cisek, 2007). Studies conducted by Cisek and Kalaska support the affordance competition hypothesis by showing that, when presented with two reach goals, the neural population activity in PMd produced parallel representations of these two reach goals. Once one of the reach goals was chosen, the representation of the chosen reach goal predominated and the PMd population activity reliably predicted the choice (Cisek & Kalaska, 2002, 2005; reviewed in Cisek & Kalaska, 2010). Similar observations in PMd were also made in other studies (Coallier et al., 2015; Klaes et al., 2011). Furthermore, parallel representations of reach goals, during action selection, could be shown for other areas of the fronto-parietal reach network, such as PRR (Klaes et al., 2011, 2012; Scherberger & Andersen, 2007). It could therefore be argued that, if decision processes and sensorimotor processes are actually separated and do not happen simultaneously, the sensorimotor system should only represented the chosen action and not all actions that can be chosen. In addition, the sensorimotor system should not represent decision variables, for example action-related benefits or costs, which bias competing action representations.

Additional support of the affordance competition hypothesis comes from studies that show that the fronto-parietal reach network (Christopoulos et al., 2015; de Lafuente

et al., 2015; Kubanek & Snyder, 2015; Pastor-Bernier & Cisek, 2011; Ramkumar et al., 2016; Suriya-Arunroj & Gail, 2019) and other fronto-parietal networks (e.g., Christopoulos et al., 2018; for review, see also Cisek & Kalaska, 2010; Glimcher, 2003; Gold & Shadlen, 2007) represent decision variables. Many studies showed that the fronto-parietal reach network represents benefit-related decision variables (de Lafuente et al., 2015; Kubanek & Snyder, 2015; Pastor-Bernier & Cisek, 2011; Ramkumar et al., 2016). Pastor-Bernier and Cisek (2011) showed that reward, associated to a reach goals, modulates fronto-parietal activity while choosing one of two reach goals. This modulation was present during action selection, but absent without action selection when only one reach goal was available. While those studies focused on the representation and biasing-effects of benefit-related decision variables in areas of the fronto-parietal reach network it remains unknown, if cost-related decision variables are represented in those areas. In this study we ask if cost-related decision variables are represented and contribute to the biased competition in areas of the fronto-parietal reach network.

The physical effort associated with an action is a crucial cost-related decision variable that influences action selection. One parameter that increases the physical effort of a reach movement (reach effort), is force (Morel et al., 2017). Thus, force can be used to increase reach effort. This study investigates if the fronto-parietal reach network represents reach effort when deciding between two reach goals, by using forces to increase effort. To do so, we trained a macaque monkey to perform an effort-guided reach selection task. The monkey was trained to associate reaches toward one of the reach goals to be physically more effortful, compared to the other physically less effortful reach goal. By randomly mixing choice and instructed trials, we discourage premature choices and instead encouraged sustained and ambiguous preparation of both reach movements. Choice trials allowed us to assess the actual behavioral bias induced by reach effort. We recorded the neural population activity

from three areas of the fronto-parietal reach network: the arm area of the primary motor cortex (M1), the dorsal premotor cortex (PMd) and the parietal reach region (PRR).

Our preliminary results show that a minority of neurons in the fronto-parietal reach network represent reach effort before and after deciding between reach goals (intended reach effort), while a majority of neurons represented reach effort when the decision was executed (executed reach effort). Moreover, we were able to decode reach effort from the neural population activity in the fronto-parietal reach network. We were able to decode, to a degree, reach effort from areas PMd and M1 before a decision and from all three areas after the decision and when the decision was executed. Our results suggest that the fronto-parietal reach network represents reach effort, indicating that the sensorimotor system represents cost-related decision variables.

3.3. Materials and methods

3.3.1. Animal preparation

A macaque monkey (*Macaca mulatta*; monkey Y, age: 14 years) was trained to perform an effort-guided reach selection task. Positive reinforcement was used to train the animal to sit in a primate chair and perform the reach selection task, while being head fixated. The animal was experienced in performing reaches in a conventional chair seated setting (Chapter 2)¹.

The monkey was chronically implanted with a custom-fit transcutaneous titanium head holder, which allowed the head fixation of the animal. Additionally, the animal was chronically implanted with 192 intracortical electrodes using six floating microwire arrays (32-electrodes, 400 μ electrode-to-electrode separation, electrode

¹ This reference refers to Chapter 2 of this thesis.

impedance 0.4-0.6 M Ω , array size: 4 mm x 1.8 mm; Microprobes for Life Science, Gaithersburg, Maryland, USA) in the left hemisphere with two arrays inserted in each of the three cortical areas (X). The array connectors (Omnetics Connector Corporation, Minneapolis, Minnesota, USA) were each incorporated in a titanium housing pedestal. The six pedestals were mounted on a custom-designed and custom-fit 3D-printed holder (Shapeways, New York City, New York, USA) which allowed aligning the connectors with defined spacing and covering them with an additional protective cap. The holder was embedded in dental cement anchored to the skull with cortical screws. Implants were designed with the software Rhinoceros 6 (Robert McNeel and Associates, Seattle, Washington, USA). The procedure to design implants (Ahmed et al., 2022) and the implantation procedure (Berger et al., 2020) have been previously described. Surgical procedures were performed in a sterile surgery suite under general anesthesia and analgesia. Post-surgical analgesia was administered, according to the need of the animal, usually for several days after the surgery. All imaging procedures performed to obtain the CT and MRI scans, used to plan implantation procedures, were conducted under general anesthesia and analgesia.

All experimental procedures have been approved by the responsible regional government office [Niedersäsisches Landesamt für Verbraucherschutz und Lebensmittelsicherheit (LAVES)] under the permit number 33.19-42502-04-18/2823. This study and the procedures involving non-human primates were conducted according to the relevant national and international laws and guidelines, including the German Animal Protection Law, the European Union Directive 2010/63/EU on the Protection of Animals used for Scientific Purposes and the Society for Neuroscience Policies on the Use of Animals and Humans in Neuroscience Research.

3.3.2. Experimental setup

We conducted the study in a 2D-haptic reach setup (Figure 1B; see also Morel et al., 2016). The animal performed the reaches by moving the handle of a haptic manipulandum (Delta.3, Force Dimension, Nyon, Switzerland). Through forces applied by the manipulandum the movements of the manipulandum were restricted in the fronto-parietal (x-y) plane (Morel et al., 2016). Handle displacement controlled real-time displacement of a cursor that was displayed on a monitor (BenQ XL2720T, screen size 590 x 338 mm, 60 Hz refresh rate, distance 65cm) above the haptic manipulandum (forward prediction compensated latencies of the haptic manipulandum and monitor; Morel et al., 2016). The position of the manipulandum handle, was sampled with a rate of 2 kHz. The eye position was sampled with a sampling rate of 1 kHz with a video-based eye tracker (EyeLink 1000 Plus, SR Research, Ottawa, Canada). The haptic manipulandum and the eye-tracker were connected to a computer running custom software (C++, OpenGL) that controlled the generation and presentation of visual stimuli, task event recording, eye position and hand position recording, and force generation. The manipulandum generated forces with a constant magnitude, similar to a kinetic friction force, which opposed the movement direction (Morel et al., 2017). The magnitude of the kinetic friction force was modified to generate different resistive force levels (low / not effortful: 0 N, high / effortful: 6 N) in addition to forces used to constrain movements to the fronto-parallel plane. The manipulandum and computer communicated bidirectionally, with the manipulandum sending the position of the handle and the computer requesting forces to be applied at the handle for each iteration of this 0.5ms haptic cycle. The movement position, movement velocity (by differentiating the movement position) and applied force were recorded and sampled at 2 kHz.

3.3.3. Effort-guided reach selection task

This study investigates if the fronto-parietal reach network represents reach effort when monkeys were deciding between reach goals in an effort-guided reach selection task (Figure 1A). The task design allowed, by alternating to instruct effortful or not effortful reaches, to investigate within the same trial if reach effort would be represented before or after the decision (imposed by the instruction) or when the decision was executed. Furthermore, by allowing the monkey intermittently to choose a reach goal according to his preference, we were able to examine if reach effort induces a behavioral bias.

A trial was initiated, when the monkey moved the manipulandum handle, displayed as a yellow circular cursor ($\varnothing = 5.1$ mm), with the dominant hand into the circular grey hand fixation area ($\varnothing = 37.4$ mm; 3.2° visual angle). The fixation area had a fixation tolerance diameter matching its size of 3.2° visual angle, i.e., during the time of fixation the cursor had to stay within this area. Additional to the hand fixation, eye fixation had to be obtained by directing the gaze to the square red eye fixation area (side length 8.5 mm; 0.7° visual angle; fixation tolerance 5.9° visual angle). After hand and eye fixation were both obtained and held for 600ms, two circular spatial cues ($\varnothing = 59.5$ mm; 5.2° visual angle; target tolerance 5.2° visual angle), were displayed. This period was used to investigate if reach effort would be represented before a decision was made. The spatial cues had contrasting colors (yellow, blue) and were shown at opposite directions. The spatial cues were pseudo-randomly displayed in one of two configurations (circular direction relative from central fixation 45° and 225° , or 135° and 315° ; eccentricity of both cues from monitor center = 60 mm). Spatial cues remained visible throughout the trial. After 600 ms to 900 ms (uniform distribution), an additional square contextual color cue (yellow, blue, white) was displayed surrounding the fixation point and remained visible throughout the trial. This period was used to investigate if reach effort would be

represented after a decision (imposed by instruction or choice) was made. The color of the contextual cue (yellow, blue) instructed the animal to perform reaches to the reach target with the matching color (percentage of instructed trials: 66 %). If the color of contextual cue was white, the animal was allowed to choose between the reach targets (percentage of choice trials: 33 %). The animal had to maintain hand and eye fixation until the hand fixation point disappeared (go cue) after 900 ms to 1200 ms (uniform distribution). After the go cue, the reach had to be initiated. To encourage the animal to plan the upcoming reach movement prior to movement execution, the animal had to initiate the movement between 150 and 450 ms after the go cue. The 150 ms delay was after the go cue was introduced to discourage the monkeys from anticipating the go cue and initiating the reach movement prematurely. Movement initiation was defined as the cursor speed exceeding a threshold of 0.02 m/s or the cursor leaving the position of the hand fixation area. Once the movement was initiated, the movement had to be executed within 700ms by moving the cursor into the spatial target. To successfully execute the movement, the cursor had to be moved into the instructed or chosen spatial target and the cursor speed had to fall below a threshold of 0.2 m/s. This ensured that the animal stopped within the spatial target. After the reach target was correctly obtained the reach target was displayed and the animal had to remain for 300ms within the reach target tolerance area. Successful trials were indicated by additional acoustic feedback (high pitched tone) and the monkey received water as a reward, according to his preferences. Unsuccessful trials were indicated by a low pitch tone and the monkeys did not receive a reward. Trials were aborted and declared unsuccessful when the monkey failed to obtain the hand or eye fixation or ended the fixation prematurely, failed to initiate the movement in time or failed to complete the movement to the instructed (instructed trials) or chosen (choice trials) reach target in time.

Movements had to be conducted against resistive forces levels, used to modulate reach effort, which opposed the movement direction with a constant magnitude of 0 N or 6 N. The resistive forces were applied during the movement. Resistive force levels, associated with the left and right side of the fronto-parallel plane, were constant for blocks of 36 successful trials before switching between sides. The combinations of reach directions, contextual color cues and reach effort resulted in 4 (direction: 45°, 225°, 135°, 315°) x 3 (contextual cue colors: yellow, blue, white) x 2 (effort: left, right) = 24 task conditions that had to be completed at least 15 times per sessions. Reach directions and contextual color cues conditions were randomized trial-by-trial. This means, even though the force-load was constant for 36 consecutive trials in terms of side of the workspace, the load varied from trial to trial depending on the instructed target or the freely chosen target. Task conditions of unsuccessful trials were not repeated instantly but added back to the pool of task conditions pseudo-randomly drawn from. Reach effort conditions were drawn pseudo-randomly from block to block (Figure 1C). Within a block, the reach effort of a previous trial was predictive of the reach effort of the present trial. Trials between blocks were an exception, here the effort of a previous trial was not predictive for the effort condition of the present trial.

3.3.4. Behavioral data analysis

The behavioral and neural data analyses were carried out using MATLAB 2018a (Mathworks Inc., Natick, Massachusetts, USA) with the data visualization toolbox *gramm* (Morel, 2018).

We quantified the general performance as percentage of successful reaches. In addition, we tested if reach effort biased the choices of the animal by computing the percentage of successful choice trial where the less effortful reach goal was chosen.

We analyzed if the monkey used the reach effort of the previous trial to predict the effort of a present trial. To do so, we compared movement velocities of trials between blocks, where the effort of a previous trial did not predict the effort of the present trial, with movement velocities of trials within blocks, where the effort of a previous trial predicted the effort of the present trial (Figure 2). For each trial, we extracted the movement velocity at the time point 150 ms after movement onset, i.e., in the early phase of movement before feedback-induced velocity corrections would become apparent. A Poisson-family generalized linear model (`fitglm()`; MATLAB 2018a) was used to test if the effort associated with the reach movement modulated the movement velocity. We repeated this analysis for different number of trials after a block switched, e.g., comparing the first and the fifth trial after a switch (Model 1). By doing so we were able to quantify if a switch of the block led to under- or overshooting due to a mismatch of the predicted effort and how quickly the monkey adjusted its effort prediction across trials. The model included movement velocity as response variable and the effort (binomial variable) as predictor.

(Model 1) $\text{Velocity} \sim 1 + \text{Effort}$

If the generalized linear model indicated that effort significantly predicted velocity, we performed additional post-hoc tests (Wilcoxon rank sum test, $\alpha = 0.05$)

3.3.5. Neural recordings and data analysis

While the animal performed the effort-guided reach selection task, we conducted extracellular neural recording from the following three areas of the fronto-parietal reach network: the arm area of M1, PMd and PRR. Neural recordings were obtained from all six arrays simultaneously. Neural recording procedure was previously described (Chapter 2).

We sorted the extracellular spikes using Offline Sorter V4 (Plexon Inc, Dallas, Texas, USA). Channels that contained spike waveform clusters that could not be isolated from the noise cluster were termed as “unsorted”. Channels containing clusters that could be isolated from the noise cluster were termed as “sorted”. Differentiable spike waveform clusters, in “sorted” channels, were defined as single-units, while non-differentiable clusters were defined as multi-units. Single-units and multi-units were treated identically in our analysis and referred to as “units”. The spike density function was derived by smoothing the spike trains of each unit in each trial with a Gaussian kernel ($\sigma = 50$ ms). Spike counts and spike density functions (sampled at 200 Hz) were temporally aligned to the onset or offset, respectively, of visual stimuli and analyzed in corresponding time windows.

In the first step, we analyzed if the individual units represent direction and effort (Figure 3). We used a Poisson-family generalized linear model with a stepwise regression (`stepwiseglm()`; MATLAB2018a) as previously described (Chapter 2). Starting from a constant model, with spike counts as response variable, the predictors (direction, effort) were added and removed by forward or backward stepwise regression to determine the final model. Predictors were added when the p-value of the F-statistic was < 0.01 and removed when the p-value of the F-statistic was > 0.05 . Final models could look as following using Wilkinson-Rogers formula notation:

(Model 2.1) Spike count \sim 1

(Model 2.2) Spike count \sim 1 + Direction

(Model 2.3) Spike count \sim 1 + Effort

(Model 2.4) Spike count \sim 1 + Direction * Effort

The spike counts were aligned and averaged in the following time windows: baseline (-300 ms to 0 ms, aligned to spatial cue onset), early cue period (0 ms to 300 ms, aligned to spatial cue onset), late cue period (-300 ms to 0 ms, aligned to context cue onset), early context cue period (0 ms to 300 ms, aligned to context cue onset), late context cue period (-300 ms to 0 ms, aligned to go cue onset) and movement (0 ms to 500 ms, aligned to go cue onset).

In the second step, we analyzed if direction and effort could be decoded from the neural population activity of areas of the fronto-parietal reach network (Figure 4). To do so we used a multi-class support vector machine decoder (`fitcecoc()`; MATLAB2018a). The detailed procedure on how the time-continuous decoding performance and the time-continuous decoding performance of the permuted data was computed was previously described (Chapter 2). We computed the time-continuous decoding performance and the decoding performance of the permuted data, by using spike counts as decoder input, for the decoded variables: direction, effort or both. We did so for the following time windows: spatial cue (-600 ms to 600 ms, aligned to spatial cue onset), context cue (-600 ms to 600 ms, aligned to context cue onset), movement (-600 ms to 600 ms, aligned to go cue onset). Time windows were binned in 150 ms time bins (with 50 ms overlap). To test for each time bin for significant differences between the decoding performance and the permuted decoding performance, we used the cluster-based permutation test (Maris & Oostenveld, 2007; implementation based on Dann et al., 2016). To test for significant difference between areas, we calculated the time when differences between the decoding performance and the permuted decoding performance became significant and the maximum decoding performance and used the Wilcoxon rank sum test ($\alpha = 0.05$).

3.4. Results

3.4.1. Physical effort biases reach selection

To examine if the fronto-parietal reach network represents reach effort, we trained a macaque monkey to perform an effort-guided reach selection task. Reaches toward one of the reach goals were physically more effortful compared to the other reach goal. Reach goals were associated with different physical efforts by force-loading one of two alternative reaches, i.e., by applying a resistive force against the required movement. Effort here refers to expected cost of executing a reach in the context choice between different reach options. To examine whether reach effort would bias the monkeys reach selection, we calculated the percentage of choice trials where the less effortful reach goal was chosen.

The monkey performed the effort-guided reach selection task with an average percentage of 95% correct reaches (Supplementary Figure 1; Table 1). We investigated if the fronto-parietal reach network represents the intended and executed reach effort, thereby indicating that action costs contribute to biased competition in these areas. To infer from the behavioral data if reach effort biased competition in the fronto-parietal reach network, we quantified the biasing effect reach effort had on monkeys' choices during action selection. In choice trials, the monkey was allowed to choose the reach goal according to its own preference. The monkey chose the physically less effortful reach goal with an average percentage of 71%, showing that reach effort biased reach selection (Supplementary Figure 2). We insured that the effort bias we observed was not induced by associations that were not related to reach effort (for example: a direction bias, a color bias), by varying the effort associations between reach goals.

For the effort to bias reach selection, the monkey needs to anticipate the reach effort accurately. To quantify whether the monkey predicted the effort of a present trial, by

using the effort information of the previous trial, we examined how quickly the animal adjust to a switch of the effort association. Note that even though the effort association switched, instructions whether effortful or not effortful reaches should be performed was instructed from trial to trial. We analyzed the effect of switching effort associations on the movement velocity within and across blocks trials. In the first trial, after the effort association switched, one of two effects could be observed (Figure 2A). For instance, if reaches to the right were previously effortful and were now not effortful, the movement velocity was increased, causing the movement trajectories to overshoot. If reaches to the right were previously not effortful and were now effortful, for instance, the movement trajectories tend to undershoot, caused by a decrease of the movement velocity. To test if movement velocities was significantly affected by effort we used a Poisson-family generalized linear model (t-statistic = -3.438, $p < 0.001$). This effect was less and not significant anymore at the time of the fifth trial (t-statistic = -1.881, $p = 0.059$) (Figure 2B and 2C), suggesting that the movement velocity adjusted to the switching effort association within those trials. Additional analysis of trials showed that the movement velocity adjusted within two trials (Figure 2D). After those two trials the movement velocity stabilized yet remained separate across trial.

3.4.2. Neurons in the fronto-parietal reach network encode reach effort

Five sessions were collected, where we recorded single- and multi-unit activity from three areas of the fronto-parietal reach network in parallel. We recorded across these five sessions a total of 198 single- and multi-units from areas: M1 (number of units: 95), PMd (number of units: 57) and PRR (number of units: 46). We did not differentiate between single- and multi-units in our analysis.

First, we analyzed if the units represented reach direction or reach effort in instructed trials during the following trial periods: baseline, cue period, context cue period, movement. Using a step-wise generalized linear model, we found units in all three

areas of the fronto-parietal reach network that represented direction. The number of direction-representing units differed between time periods of a trial. Generally, only a minor number of units represented direction in all three areas during the spatial cue period (when the reach goals were first presented) compared to the context cue period (when the reach goal was instructed). Once the instruction was given, and the monkey was informed toward which reach goals he was supposed to reach (by instruction) the number of units that represented direction increased (Figure 3B). Comparing the number of direction-representing units across areas, we found that the number of direction-representing units in PMd and PRR was highest during the context cue period, while in M1 the number was highest during the movement period.

Aside from direction-representing units, we found units that were direction- and effort-representing (Figure 3A) or only effort-representing in the three areas of the fronto-parietal reach network. Similarly, to units representing direction, the number effort-representing units differed between trial periods (Figure 3B). In general, the overall number of all effort-representing units in M1, PMd and PRR was highest during the movement period. In more detail, we found in M1 (Figure 3B, Table 2) one unit that was direction- and effort-representing and nine effort-representing units during the early cue period and three effort-representing units during the early context cue period. During the movement period we found thirty direction- and effort-representing units. In PMd (Figure 3B, Table 3) we found six units that were effort-representing during the early cue period and one direction- and effort-representing units during the early context cue period. During the movement period we found twelve direction- and effort-representing units. In PRR (Figure 3B, Table 4) we found five effort-representing units during the early cue period and two effort-representing units during the early context cue period. During the movement period we found eleven direction- and effort-representing units.

3.4.3. Reach effort can be decoded from neural population activity in the fronto-parietal reach network

Second, we used a support vector machine decoder to decode the reach direction and reach effort from areas M1, PMd and PRR of the fronto-parietal reach network. We could significantly decode the direction and effort from all three areas of the fronto-parietal reach network yet observed differences in the decoding performance across trial periods and brain areas (Figure 4).

During the spatial cue period, we could only significantly decode the direction (2-way classifier) from the neural population activity in areas PRR and PMd, with a higher decoding performance in PRR. Furthermore, direction was significantly earlier decoded in PRR. During the context cue period, the direction (4-way classifier) could be significantly decoded from the neural population activity in all three areas, with higher decoding performance in PMd compared to M1 and PRR. As in the previous period the direction was significantly faster decoded in PRR followed by PMd and M1. During the movement period, we could significantly decode the direction (4-way classifier) from all three areas. Decoding performance was highest in M1 and PMd, compared to PRR.

Our findings indicate that the fronto-parietal reach network represents the spatial location of reach goals. Before one of two potential reach goals is instructed, this is the case only to a minor degree. Once instructed, the reach goal representations in the fronto-parietal reach network increased majorly, reaching its peak after the movement is initiated. From all areas of the fronto-parietal reach network PRR represented the direction the earliest, followed by PMd and M1.

In addition to decoding the intended and executed reach direction, we could decode the intended and executed reach effort from the neural population activity in all three areas of the fronto-parietal reach network. During the spatial cue period, we could

only significantly decode the reach effort (2-way classifier; effort conditions: left/right) from the neural population activity in PMd and M1, with a higher decoding performance in PMd compared to M1. During the context cue period, we could significantly decode the reach effort (2-way classifier: effort conditions: effortful/not effortful) from all three areas. The decoding performance was highest in PMd, followed by M1 and PRR. Additionally, the effort was faster significantly decoded in PMd, followed by M1 and PRR. During the movement period, we could significantly decode the effort (2-way classifier: effort conditions: effortful/not effortful) from the neural population activity in all three areas. The decoding performance was highest in M1 and PMd, compared to PRR. Once the movement was initiated, the time of significant effort decoding performance during the movement period was similarly fast in M1 and PMd, and slower in PRR. From our findings, we can infer that the fronto-parietal reach network represents reach effort, to a limited extent, while both reach goals are competing. Once the competition ends and a reach goal is chosen, the reach effort representation strengthens in PMd and M1. The strongest reach effort representation is observed during the movement period in M1 followed by PMd and PRR.

3.5. Discussion

This study investigated if the primate fronto-parietal reach network represents reach effort before and after deciding between reach goals (intended reach effort) and when the decision was executed (executed reach effort). Such a representation would indicate that action costs contribute to biased competition in these brain areas.

Summarizing the results from our study, we found neurons that represent reach effort in following areas of the fronto-parietal reach network: PMd, M1 and PRR. A minority of neurons significantly represented the intended reach effort before and after a decision has been made, while a majority of neurons represented the executed

reach effort when the movement associated with a decision was executed. Moreover, we were able to significantly decode the intended reach effort from the neural population activity in PMd and M1 before and in all three areas after the after a decision has been made. This was particularly prominent when the chosen reach movement was executed. Interestingly, we found that after the decision has been made but before the movement was executed the decoding performance was highest in PMd, followed by M1 and PRR. Once the decision was executed by initiating a reach toward the chosen reach goal, the decoding performance was highest in M1, followed by PMd and PRR.

3.5.1. Representations of intended and executed reach effort in the fronto-parietal reach network

Previous studies showed that the fronto-parietal reach network represents decision-related variables that are associated to action benefits (de Lafuente et al., 2015; Kubanek & Snyder, 2015; Pastor-Bernier & Cisek, 2011; Ramkumar et al., 2016). When we assume that the fronto-parietal reach network represents all decision-related variables that could influence action selection, then decision-related variables that are associated to action costs, such as physically effort, should be represented. Knowing that force can increase physical effort (Morel et al., 2017), we used forces to study reach effort representations. Our results show that the intended reach effort could be decoded, to a smaller degree, before and, to a larger degree, after deciding between two reach goals. Thereby indicating that action costs contribute to biased competition in the fronto-parietal reach network.

We assume that the small degree to which we were able to decode the intended reach effort before the decisions was due to the fact that preparation of both reaches was not enforced enough in the time when the monkey was deciding between both reach goals. Not enforcing preparation of both reaches, could have resulted in postponing the preparation until the monkey received the contextual color information. It this

case the monkey would wait for the contextual color information to start to prepare for the reach, without preparing both reaches. But since we were able to decode the reach direction from neural populations in PRR and PMd, before the monkey decided between the reach goals, this might still suggest that the intended effort, we were able to decode at the same time, could have been contributed to biased competition in both areas. Interestingly, we were able to decode to a larger degree the intended reach effort after the decisions between the two reach goals had been made.

A recent study conducted in our research group showed that areas M1, PMd and PRR of the fronto-parietal reach network represents reach force, during the movement (executed reach force) but not during movement preparation (intended reach force; see Chapter 2). In this study, similar to the current study, the force of a present trial, had to be inferred from the force information obtained in the previous force. Since the intended reach force is not represented in the fronto-parietal reach network according to Nowak and colleagues (see Chapter 2), we should be able to exclude that the representation of intended reach effort we observed were related to intended reach force rather than intended reach effort. However, we did use contextual color cues to instruct which reach goal should be selected.

Intveld and colleagues (2018) reported that areas M1 (hand area), PMv and AIP in the fronto-parietal grasp network represent the executed grasp force, while PMv, and to an extent AIP, represent the intended grasp force. In this study contextual color cues were used, which monkeys associated with grasp forces to instruct grasp force levels. This makes it more difficult to exclude that the representation of intended reach effort we observed in PMd and PRR were related to intended reach force. But it should be noted that the contextual color cues that were used in our study were not used to instruct reach effort rather the reach direction, which was associated with a certain effort condition. Moreover, our results cannot be explained by this argument

either, since we were able to decode the presumably intended effort from areas, PMd, M1 and PRR and not just PMd and PRR, who are the counterparts of PMv and AIP during reaching movements. Therefore, we do argue that the fronto-parietal reach network represents reach effort, though we cannot exclude completely that intended reach effort and intended reach force might be co-represented.

Furthermore, our results show that the executed reach effort could be decoded from areas M1, PMd and PRR in the fronto-parietal reach network, indicating that it represents executed reach effort. We do not exclude that the executed reach force was co-represented.

3.5.2. Representations of reach direction in the fronto-parietal reach network

While we could significantly decode the direction from neural populations in all three areas after the decision between the two reach goals has been made and was executed, the decoding performance before the decision was made was low. This was surprising, since we expected to find higher decoding performance in PRR and PMd. We assume that this could have been because the animal did not start the movement preparation once the two reach goals have been shown but rather waited for the contextual cue to prepare the movement.

3.6. Figures and tables

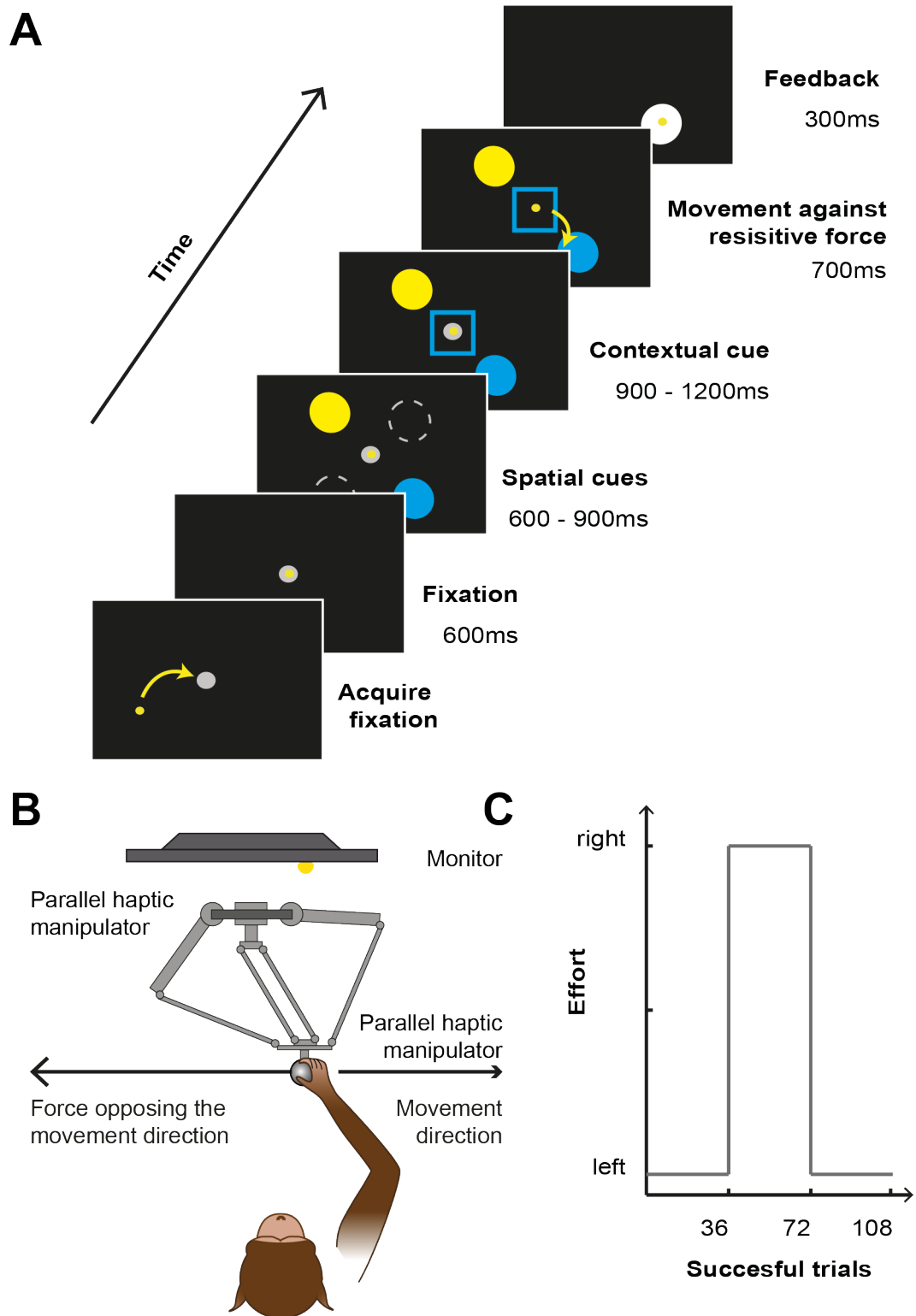


Figure 1 (*see previous page*). **Effort-guided reach selection task.** A: Overview of the task timeline of the effort-guided reach selection task. B: Overview of the setup. C: Schematic of the switching effort associations across trials. Effort associations switched in a block-wise manner every thirty-six successful trials. The effort associations switched between the left and right side of the workspace. Subjects were not explicitly instructed which effort they would encounter during the upcoming movement but had to infer the effort from the movement in the previous trial.

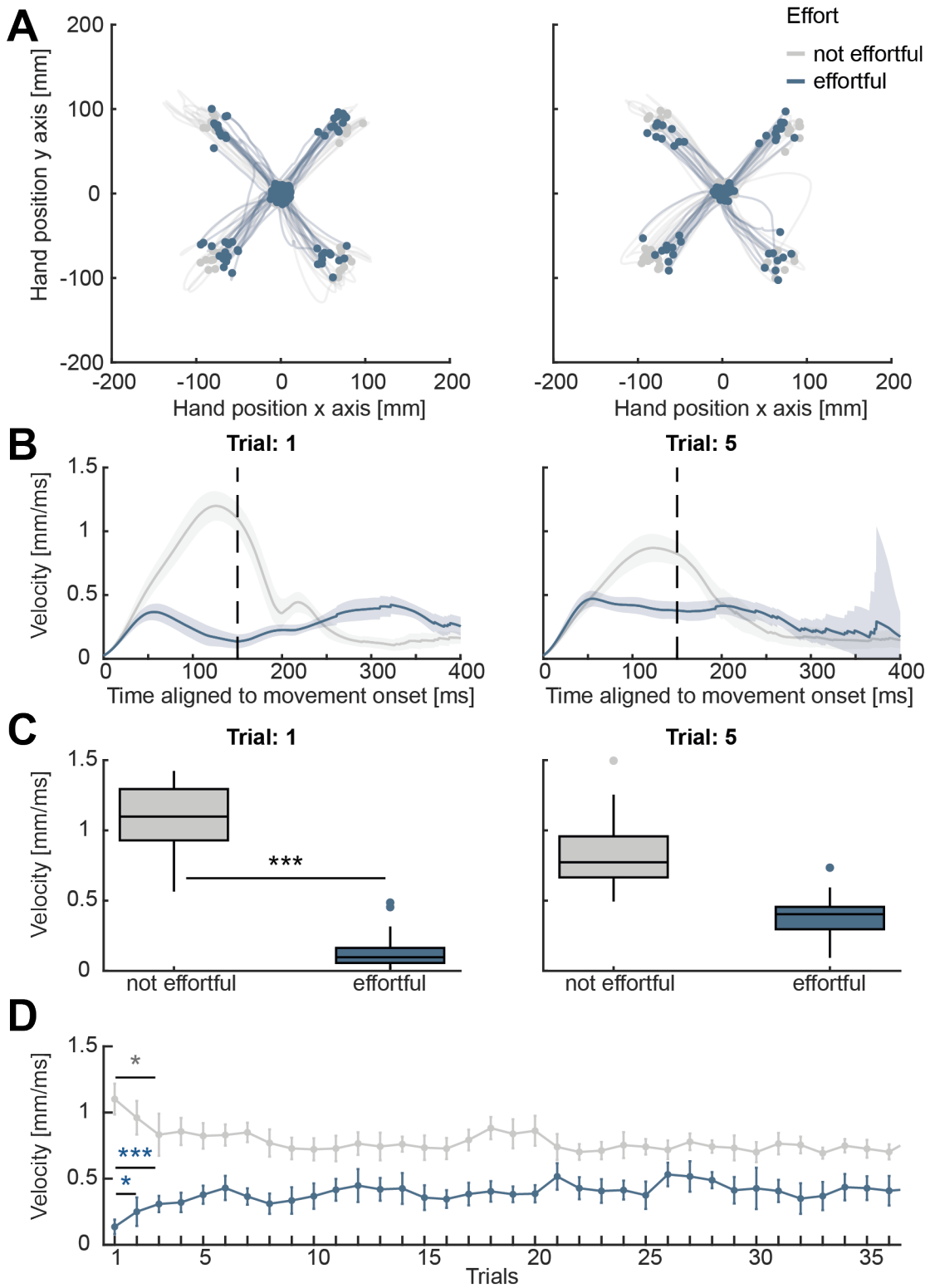
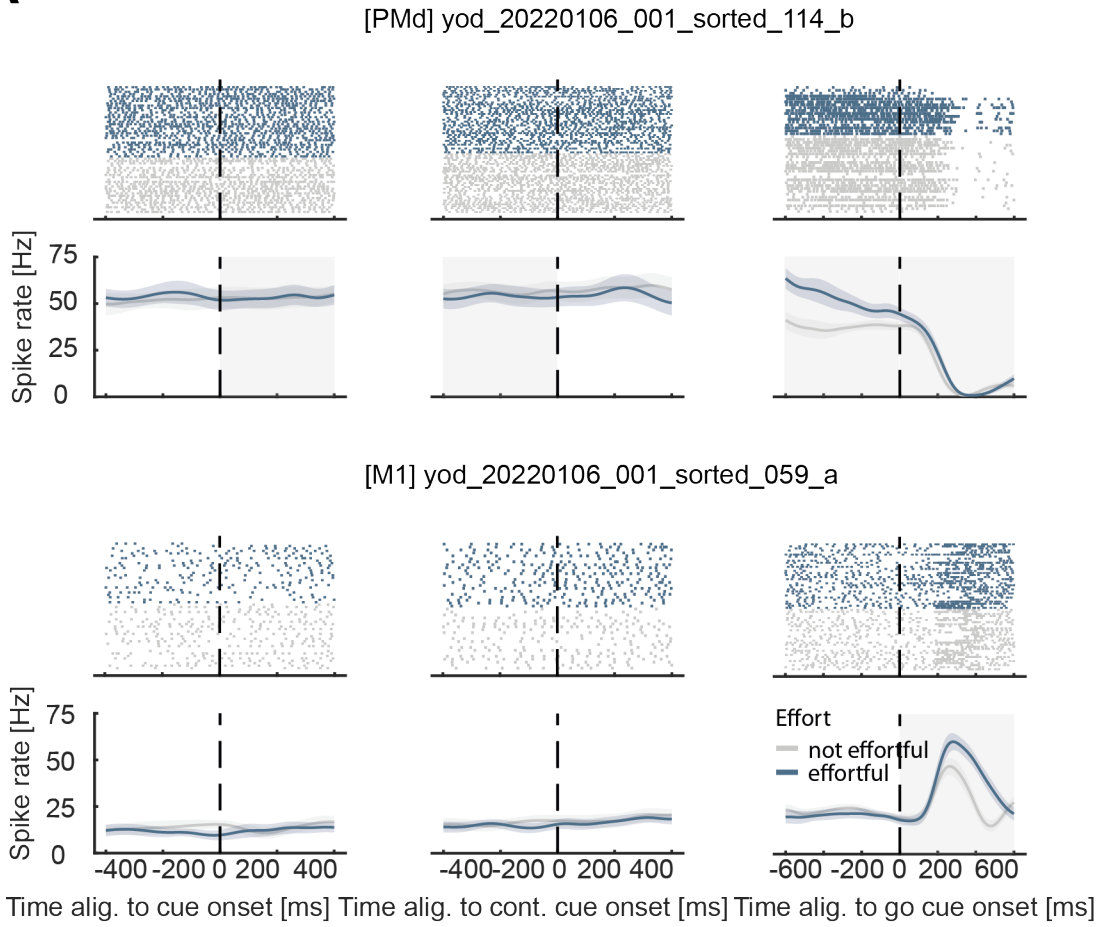


Figure 2 (see previous page). **Movement trajectories and movement velocities reflect that the monkey anticipated the physical effort.** A: Single trial trajectories from the first three trial (*left*) and the last three trials (*right*) after the effort associations switched. The movement start and end are pictured as points along the single trial trajectories. In the first three trials after the effort association switched movement trajectories were overshooting. In the last three trials overshoots were rarely observed B: Mean movement velocity of the first trial (*left*) and fifth trial after the effort associations changed (*right*). The 95% confidence interval (CI) of the mean is pictured as shaded area. The dashed vertical line depicts the time 150ms after movement onset. C: Within-trial comparison of mean movement velocities extracted 150ms after movement onset at the first trial (*left*) and fifth trial after the effort association changed (*right*). D: Between-trial comparison of mean movement velocities extracted 150ms after movement onset between trials. The asterisks indicate significant difference between compared force conditions (* $p < a$ at 5 %, ** $p < a$ at 1 %; *** $p < a$ at 0.1 %; Wilcoxon signed rank test).

A



B

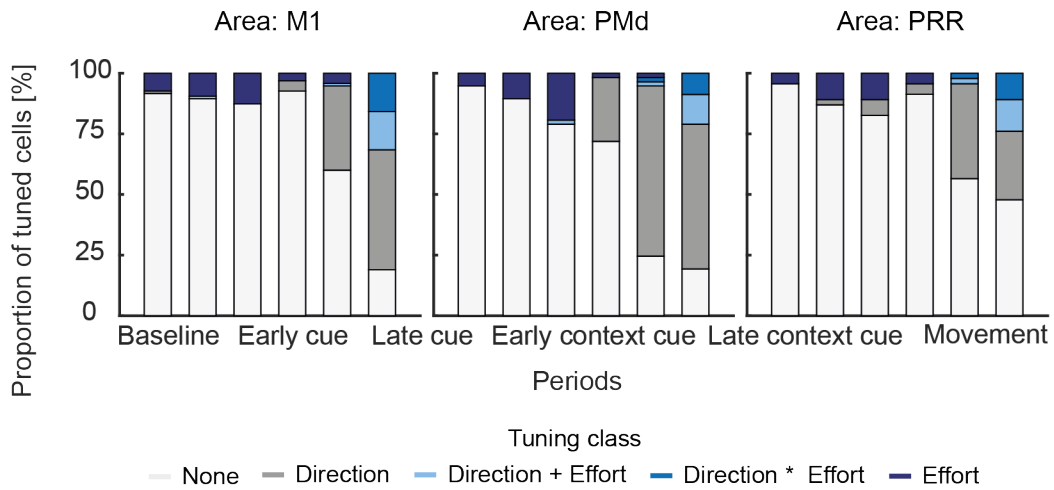


Figure 3 (see previous page). **Direction and effort representations in areas: M1, PMd and PRR of the fronto-parietal reach network.** A: Example units that represents effort during different task periods. The top panel shows an example unit that significantly represents effort during the early and late spatial cue period, during the late context cue period and during the movement period. The bottom panel shows an example unit that significantly represents effort during the movement period. Grey shaded areas indicate the time when the example units were significantly representing effort. For each example unit raster plots and mean spike densities of the example units' maximum response direction (PD_{max}) are pictured. Pictured are the following task periods: cue period, context cue period, movement period. Raster plots and mean spike densities are aligned to spatial cue onset (left), context cue onset (middle), go cue onset (right). The dashed vertical line depicts the time point of alignment. The 95% confidence interval (CI) of the mean is pictured as shaded area.

B: Proportion of tuning classes that represent effort or direction or both across task periods.

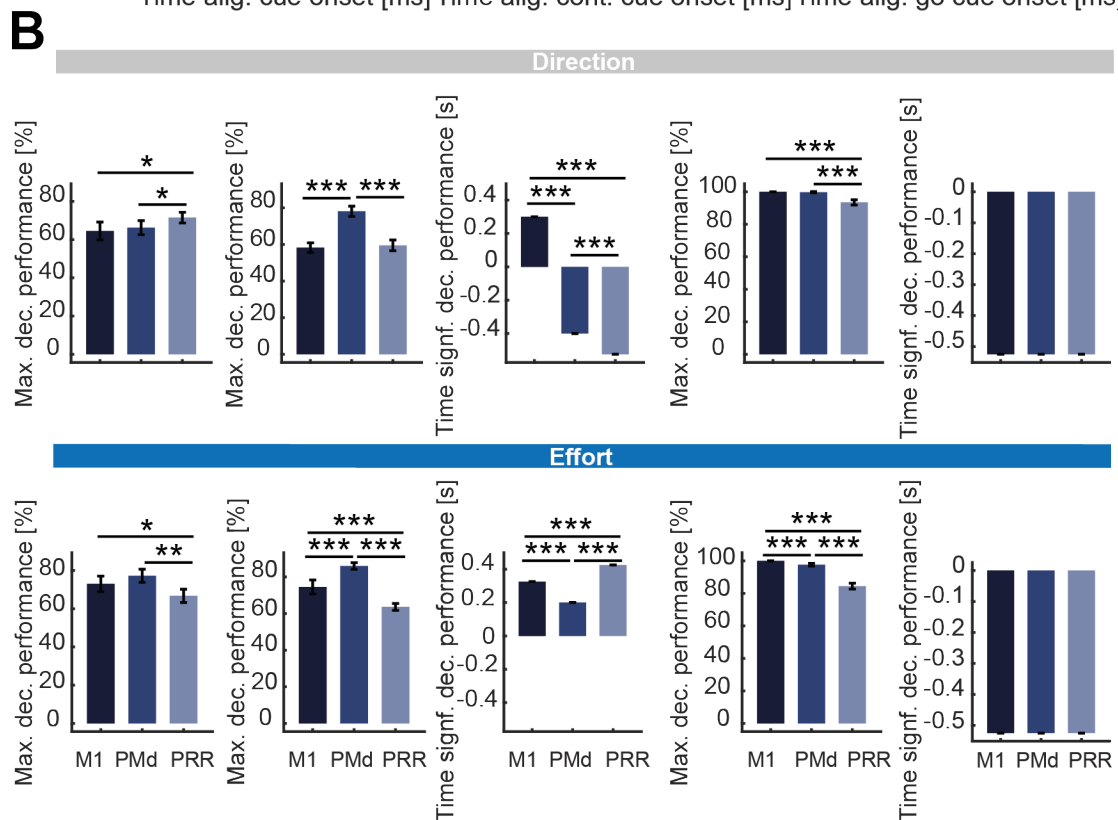
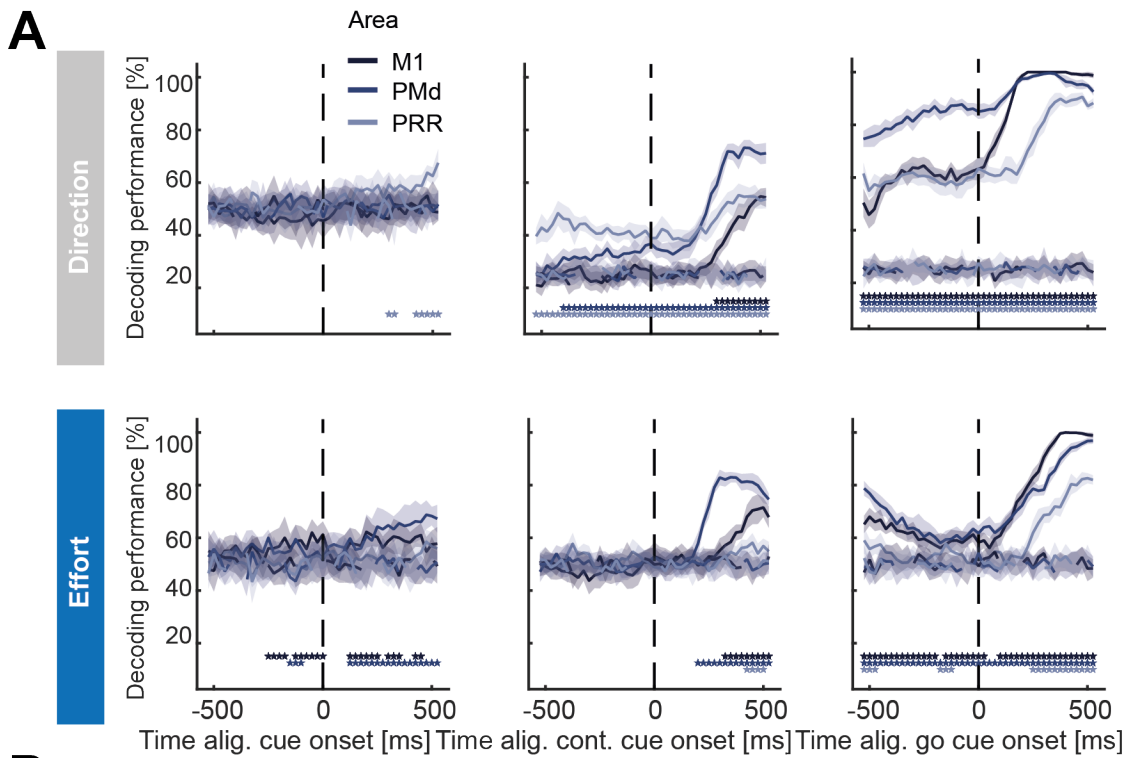
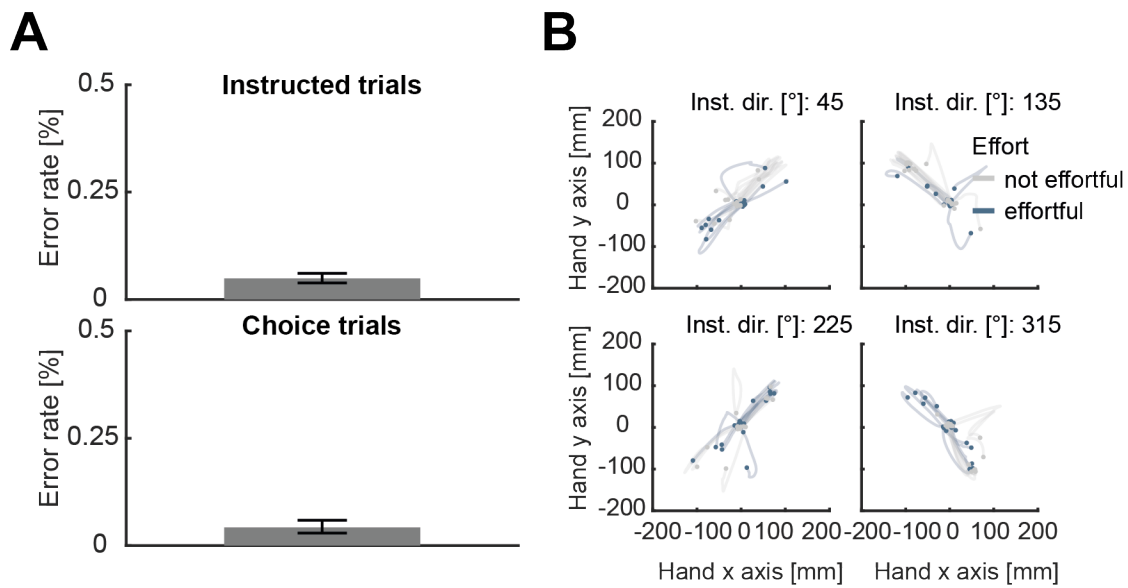
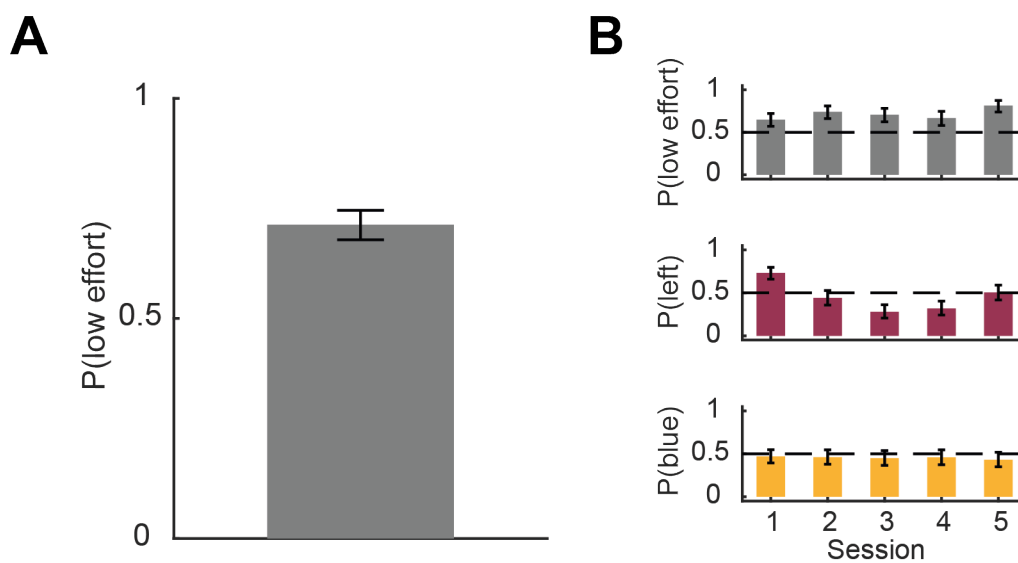


Figure 4 (see previous page). **Decoding of effort in areas M1, PMd and PRR of the fronto-parietal reach network.** A: Decoding performance for areas M1, PMd and PRR for decoded variables: direction (*top*) and force (*bottom*). Decoding performance is depicted for three different task period: spatial cue period, context cue period, movement period. The dashed vertical line indicates the time of alignment: aligned to spatial cue onset (left), aligned to context cue onset (middle), aligned to go cue onset (right). Full lines indicate decoding performance, while dashed lines indicate decoding performance of the permuted data (indicates decoding performance at chance level). The asterisks highlight significant difference between decoding performance and decoding performance of the permuted data for each area ($*p < a$ at 5 %; Cluster-based permutation test). B: Maximum decoding performance of cue period (left), maximum decoding performance and time until the decoding performance significantly deviated from the permuted decoding performance for context cue period (middle) and movement period (right). The asterisks highlight significant difference between compared areas ($*p < a$ at 5 %, $**p < a$ at 1 %; $***p < a$ at 0.1 %; Wilcoxon signed rank test).



Supplementary Figure 1. Error rates during instructed trials and choice trials.

A: Percentage of errors made during the movement in instructed trials (top) and choice trials (bottom). B: Movement trajectories of trials where errors were made during the movement (instructed trials). Shown are errors made in accordance with the instructed direction. In trials where the monkey was instructed to perform effortful reaches (blue movement trajectories), we observed regularly that the monkey ignored the instruction and performed not effortful reaches instead, even though these were not rewarded.



Supplementary Figure 2. Choice probabilities during choice trials. A: Percentage of choice trials were the less effortful reach goal was chosen by the monkey. B: Potential biases of the monkey performing the effort-guided reach selection task across sessions. Percentage of choice trials were the less effortful reach goals (effort bias; top), the left reach goals (spatial bias; middle) and blue reach goals (color; bottom) were chosen.

Table 1. Overview of overall performance of the subject.

Subject	Sessions	Avg. number of trials	Avg. number of successful trials	Avg. percentage of successful trials	Avg. percentage of successful reaches
Monkey Y	5	491.8	434.2	87 %	95 %

Table 2. Overview of number and percentage of tuned units in M1.

M1	Baseline	Early cue	Late cue	Early context cue	Late context cue	Movement
Direction	1 (1%)	-	-	4 (4%)	33 (34%)	47 (49%)
Direction + force	-	1 (1%)	-	-	1 (1%)	15 (15%)
Direction * force	-	-	-	-	-	15 (15%)
Force	7 (7%)	9 (9%)	12 (12%)	3 (3%)	4 (4%)	-

Table 3. Overview of number and percentage of tuned units in PMd.

PMd	Baseline	Early cue	Late cue	Early context cue	Late context cue	Movement
Direction	-	-	-	15 (26%)	40 (70%)	34 (59%)
Direction + force	-	-	1 (1%)	-	1 (1%)	7 (12%)
Direction * force	-	-	-	-	1 (1%)	5 (8%)
Force	3 (5%)	6 (10%)	11 (19%)	1 (1%)	1 (1%)	-

Table 4. Overview of number and percentage of tuned units in PRR.

PRR	Baseline	Early cue	Late cue	Early context cue	Late context cue	Movement
Direction	-	1 (2%)	3 (6%)	2 (4%)	18 (39%)	13 (28%)
Direction + force	-	-	-	-	1 (2%)	6 (13%)
Direction * force	-	-	-	-	1 (2%)	5 (10%)
Force	2 (4%)	5 (10%)	5 (10%)	2 (4%)	-	-

Chapter 4:

General Discussion

This thesis investigated if the sensorimotor system integrates force information before a motor command is executed. First, we studied force information integration, when the sensorimotor system prepared and executed one motor command. Secondly, we studied force information integration when the sensorimotor system prepared and selected between two motor goals, before executing the motor command.

The thesis is divided into two chapters containing two studies. The first study (Chapter 2) investigated if the primate fronto-parietal reach network encodes the reach force during the movement preparation (intended reach force) or movement (executed reach force). To do so, we trained two macaque monkeys to perform a reaching task against alternating forces. We recorded the neural population activity in parallel from three areas of the reach network: the arm area of the primary motor cortex (M1), the dorsal premotor cortex (PMd) and the parietal reach region (PRR). Using a multi-class support vector machine decoder, we were able to decode the executed reach force in all three areas, but interestingly we were not able to decode the intended reach force in any of the areas. The results from our first study indicate that the reach network does not integrate force when preparing a reach movement for which the required force had to be inferred from the force of the previous reach.

The second study (Chapter 3) investigated if the primate fronto-parietal reach network encodes the reach effort, during the movement selection (intended reach effort). We trained one macaque monkey to perform an effort-guided reach selection task. The monkey learned to associate reaches toward one of two reach goals to be physically more effortful compared to the alternative reach goal, by applying forces

to modulate reach effort. While the monkey performed the task, we recorded the neural population activity from the arm area of M1, PMd, and PRR. We were able to decode the reach effort in PMd and the arm area of M1 before a reach goal was selected. After a reach goal was selected and when the reach was executed, we were able to decode reach effort in all three areas of the reach network. The results from our second study suggest that the reach network integrates effort when preparing and selecting between reach movements, when the effort of a present trial had to be inferred from the effort of the previous reach.

4.1. Force information integration differs if force expectations are generated using visual or haptic information

The results from our first study, showed similarities and dissimilarities to past studies. Similar to observations made in the fronto-parietal grasp network (Intveld et al., 2018), we found that the all three areas of the fronto-parietal reach network encode the executed reach force. Yet, none of the areas encoded the intended reach force. We argue that dissimilarities we observed could be related to the fact that there was no visual information provided to the animal that could have been used to predict forces. Instead, the animal had to infer the force of the present trial from the force of the previous trial, therefore force predictions relied on the sensorimotor memory. The sensorimotor memory is generated when, for instance, an object has been lifted before, and the predictions of the object weight are accurately stored (Johansson & Westling, 1984). When generated by applying an appropriate amount of force to successfully lift an object, the sensorimotor memory could remain stored, even when the duration between lifts were prolonged (Gordon et al., 1993). It has been hypothesized that the sensorimotor memory might be stored in primary motor cortex (Li et al., 2001) and the corticospinal system (Loh et al., 2010).

Expectations of an object's weight are often driven by visual properties of the objects, like object size (Buckingham, 2014; Saccone & Chouinard, 2019) or object material (Buckingham et al., 2009). Previous studies showed that fingertip force scaling (Buckingham et al., 2011) and grip force scaling (Dafotakis et al., 2008) relied on visual information. A study that supports our argument, that visual information influences force predictions, which could explain differences when force information is integrated was conducted by Dafotakis and colleagues (2008). Dafotakis and colleagues showed that when visual information of the object size was used to infer object weight, transcranial magnetic stimulation over PMv, but not the hand area of M1 or AIP, interfered with predictive force scaling of grip force. Newer studies, utilizing transcranial magnetic stimulation over the anterior intraparietal cortex, showed that AIP had a transient role during predictive force scaling, when force scaling was based on visual information (van Polanen et al., 2022). This could explain why Intveld and colleagues (2018) observed grasp force encoding during the movement preparation in PMv and AIP, but not the hand area of M1.

While these studies were conducted in the grasp network, studies with similar results, conducted in the reach network, can be found. Chouinard and colleagues (2005) showed that repetitive transcranial magnetic stimulation of the primary motor cortex disrupted the scaling of forces based on haptic information inferred from a previous trial, while repetitive stimulation of the dorsal premotor cortex disrupted the scaling of forces based on visual information. This would suggest that the arm area of M1 and PMd play different roles in anticipatory force scaling. Since we did not provide the animal with visual information that could have been used to predict forces, PMd and PRR did not encode reach force during the movement preparation. Given the studies discussed in this section, we postulate that PMd and PRR should encode the intended reach force when the animal is provided with visual information that could be used to predict forces. We further argue that force predictions based on visual

information and haptic information are complementary processes used to optimize force predictions. This can be useful when the visual information did not allow to form correct weight expectations of an object, resulting in object weight to vary from the expected object weight. It has been shown that in such situations, when force predictions used to lift the object based on visual information were inaccurate, force predictions were adjusted within a few lifts to match the actual weight of the object (Flanagan et al., 2008; Flanagan & Beltzner, 2000; Grandy & Westwood, 2006). This would explain the behavioral results from our first study, where we observed that movement velocities adapted within two trials to changes of the force condition.

Other studies showed that object properties are estimated better when visual and haptic information is combined (Buckingham & Goodale, 2010; Ernst & Banks, 2002; Helbig & Ernst, 2007), which adds to the argument that visual information and haptic information are both used to optimize force predictions. It has been postulated that the sensorimotor system uses strategies that minimize the prediction error when an object's weight varied and object weight predictions could not be made accurately (Cashaback et al., 2017). It could therefore be assumed that sensorimotor system might be able to weigh visual and haptic information differently, whenever one could minimize the prediction error better than the other.

4.2. Force information integration differs in simple actions compared to action selections

While the arguments presented explained the results from our first study well, the arguments seemed to be less suited to explain the results from our second study. Here we studied force information integration when the sensorimotor system prepared and selected between two motor goals before executing the motor command. The results from our second study suggest that the sensorimotor system integrates the force information when preparing and selecting between reach

movements, even though the force information has to be inferred from the previous trial. If we would use the former argument and applied it to our results from the second study, we would assume that the sensorimotor system does not integrate the force information when preparing and selecting between reach movements. Therefore, this argument seems less suited to explain the results from our second study. Even if argued that second study did not exclusively rely on haptic information since visual information was used to instruct motor goals, this does not explain our results entirely. This leads to the conclusion that force information integration seems to be different during action selection.

If we assume that decision processes are not separate from sensorimotor processes, it would make sense to presume that the sensorimotor system encodes all decision variables relevant for action selection. Previous studies showed that the fronto-parietal reach network encodes benefit-related decisions variables (de Lafuente et al., 2015; Kubanek & Snyder, 2015; Pastor-Bernier & Cisek, 2011; Ramkumar et al., 2016). Such benefit-related decisions variables can contribute to a biased competition when more than one reach goal is available (Pastor-Bernier & Cisek, 2011). During action selection the physical effort associated with an action is a crucial cost-related decision variable. One parameter that increases the reach effort of a reach movement, is force (Morel et al., 2017). Thus, force can be used to increase reach effort. If reach effort, as a decision variable, was encoded in the fronto-parietal reach network it should contribute to a biased competition in these areas. This would explain why we were able to decode, to a degree, the reach effort from areas PMd and M1 before a decision and from all three areas of the fronto-parietal reach network after the decision. We therefore postulate that force information integration might differ, depending on whether it is used in an action selection context or not.

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Affidavit

I hereby declare that I, Julia Wanda Nowak, have written this thesis, titled “Force information integration in the primate fronto-parietal reach network”, independently and with no other aids and sources than quoted.

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