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**Premotor cortex contributions
to abstract and action-related relational processing**

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1 INTRODUCTION

The brain region termed the “premotor cortex” constitutes a significant part of the frontal lobes in humans and in non-human primates. Traditionally, accounts of this region’s function did rarely extend beyond ascribing to it a role in the preparation and control of movement and motoric action. For example, Wise (1985) established the concept of the premotor cortex as a distinct cortical field specialized for the cerebral control of movement. He proposed this role to encompass limb stabilization and motor programming as well as preparation of specific voluntary movements, the sensory guidance of movement and the synthesis of skilled motor sequences. A similar view associates premotor cortex with the planning, programming, initiation, guidance, and execution of simple and skilled motor tasks (Passingham, 1993). In the past, premotor functions have thus been restricted to behaviors requiring motor or sensorimotor computations.

In more recent years, the attention of researchers in neurophysiology, behavioral and cognitive neuroscience has increasingly been drawn to potential non-motor functions of this brain region. While premotor computations may precede any overt motor performance, it became clear that premotor neural activity does not necessarily result in overt movement. With the advent of imaging techniques such as PET and fMRI especially, reports of “activation” in premotor cortex for tasks and processes that were highly unlikely to be motor-related suggested that PMC might support some non-motor, purely “cognitive” functions. In this respect, an interesting observation is the greatly increased size of the premotor cortex – in comparison with the primary motor cortex – in the human brain as compared to the monkey: in the latter, roughly 45 % of the precentral motor cortex is taken up by premotor cortex, whereas in humans, this fraction increases to more than 85 % (Blinkov & Gleser, 1968; von Bonin, 1944).

It has been proposed that premotor cortex carries out neural computations sufficiently general and abstract in order to contribute to a wide range of motor, attentional, and cognitive processes (Fiebach & Schubotz, 2006). As an early example of this view might serve the “premotor theory of attention”, which postulates that the control of goal-directed action, i.e. programming explicit ocular movements, and the control of attention are closely linked because they are governed by shared sensorimotor mechanisms which are in turn subserved by the premotor cortex (Rizzolatti, Riggio, Dascola, & Umiltà, 1987; Sheliga, Riggio, & Rizzolatti, 1994). However, only a limited amount of research has since been guided by the explicit goal of exploring the cognitive functions of brain areas belonging to the premotor cortex, and theories explicitly focusing on this point are still rare. An exception is the account of the perception and prediction of external events as a function of the motor system, summarized in Schubotz (2007), which will be addressed in more detail in subsequent sections of this work.

Introduction

Currently, concepts such as “embodied cognition” (Niedenthal, Barsalou, Winkielman, Krauth-Gruber, & Ric, 2005; L. Smith & Gasser, 2005), “grounded cognition” (Barsalou, 2008), or “motor cognition” (e.g. Jackson & Decety, 2004) are becoming increasingly popular, which take the perspective that “higher” cognitive abilities may have evolved from “lower” sensory and motor functions. In this view, cognitive functions, such as for example executive control or attention, are no longer seen as central and unitary systems which regulate perception and action but remain anatomically and functionally distinct from specialised peripheral mechanisms involved in sensory-perceptual and motor processing. Instead, neural structures subserving these specialised mechanisms are considered an integral part of cognitive performance.

Thus, abstract cognition may have its roots in evolutionarily older functions such as motor control. This concept inspired and motivated the work presented in this thesis. Based on a review of the literature on premotor cortex function, it will be proposed that this brain region may be centrally involved when relational information has to be processed, both in the context of motoric action and in the context of abstract cognitive tasks. The theoretical discussion will be complemented by an empirical investigation including two functional magnetic resonance imaging (fMRI) studies.

In the next chapter, the theoretical background to the research project is detailed. The first issue to be addressed will be the question of what is meant by “premotor cortex” in terms of anatomical structure and connectivity patterns. The knowledge gained to date about motor and non-motor functions of the premotor cortex is then described, before proceeding to delineate the rationale for the empirical work and, in subsequent chapters, describing and discussing the goals, methods and results of the experiments.

2 THEORETICAL BACKGROUND

2.1 Anatomy of the premotor cortex

2.1.1 Structure

The premotor cortex (PMC) forms part of the frontal lobes of the brain. Together with the primary motor cortex, it constitutes the agranular frontal isocortex, bordered anteriorly by the granular prefrontal cortex.

The structure of the premotor cortex has been most extensively studied in nonhuman primates – the most prominent example being the macaque monkey – using techniques such as cytoarchitectural and histochemical staining or transmitter receptor autoradiography. Unlike in humans, a single most widely used description of the structural parcelling within the motor cortices has emerged for the macaque brain (Matelli, Luppino, & Rizzolatti, 1985, 1991). According to this F-nomenclature, the agranular frontal cortex of the monkey can be divided into seven F-fields (Figure 2.1).

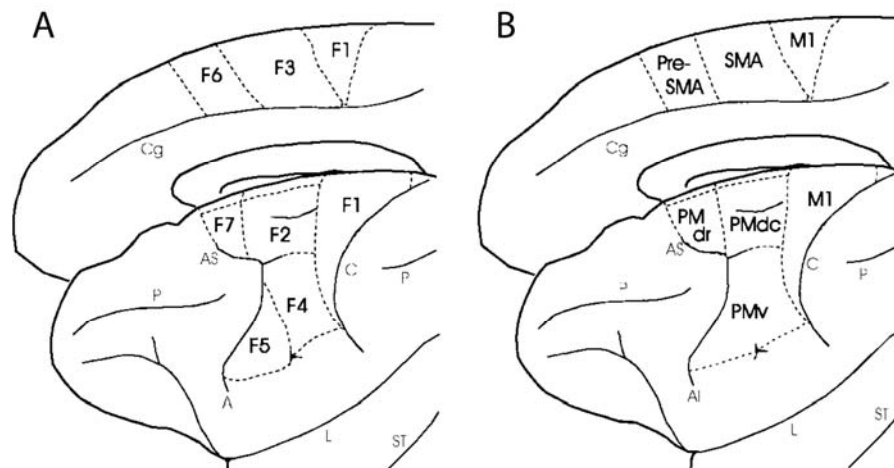


Figure 2.1 Proposed subdivisions of the agranular frontal cortex of the monkey (modified from Luppino & Rizzolatti, 2000): (A) Histochemical and cytoarchitectonic map of Matelli et al. (1985; 1991), (B) Modern functional subdivision.

The first of these, F1, lies immediately anterior to the central sulcus and is identical with primary motor cortex (M1). Anteriorly adjacent to F1 and extending to the fundus of the arcuate sulcus, fields F2-F7 together make up the premotor cortex. The main feature distinguishing the premotor fields from F1 is the absence of the giant pyramidal cells in cortical layer V. The absence of the inner granular layer IV distinguishes them from the prefrontal cortex. Premotor areas on the mesial surface are F3, also called

the supplementary motor area or SMA proper, and F6 or preSMA. The dorsal part of the lateral surface is taken up by fields F2 and F7, while F4 and F5 constitute the ventrolateral premotor cortex. In the monkey, the arcuate sulcus forms a macroanatomical landmark indicating the border between agranular premotor and granular prefrontal cortex.

In humans, such clear macroanatomical boundaries are largely lacking. In general, there is much less agreement on the structural properties and subdivisions of the premotor cortex in the human brain. A first effort, and one that to this day remains the most influential account, is Korbinian Brodmann's (1909) description of the cytoarchitecture of the human cortex. In Brodmann's maps, the cortex is divided into 52 regions later called Brodmann's areas (BA) which are differentiated by their histological characteristics. In this map, the premotor cortex is formed by area 6 and encompasses the anterior portion of the precentral gyrus and the posterior part of the superior frontal gyrus laterally as well as the adjacent posterior part of the mesial frontal gyrus and anterior portion of the paracentral lobule (Figure 2.2).

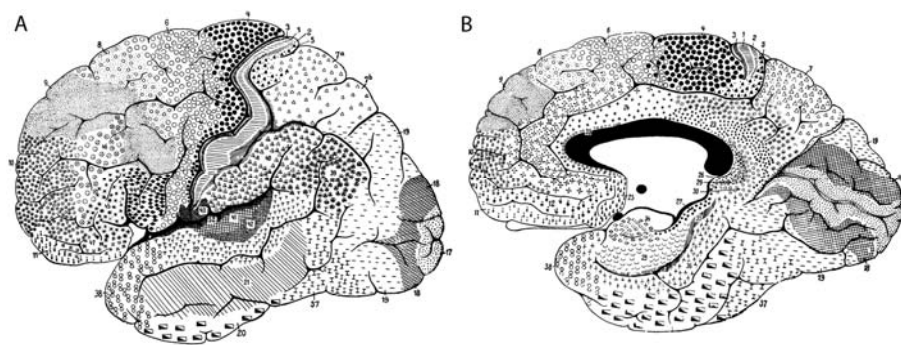


Figure 2.2 Histological maps of Brodmann (1909): (A) lateral areas, (B) mesial areas.

Likewise, in the maps of Campbell (1905) and von Economo and Koskinas (1925), the premotor cortex is described as a single area termed “intermediate precentral area” or “area FB”, respectively. Vogt and Vogt (1926) propose a first subdivision of the agranular cortex anterior to the primary motor cortex. They differentiate between an area 6α , occupying most of the precentral gyrus, and area 6β on the superior and middle frontal gyri (Figure 2.3A). An alternative, much more detailed structural parcelling of the human frontal cortex has also been proposed by Sanides (1962; Figure 2.3B), which has however been met with very little acceptance in the neurosciences.

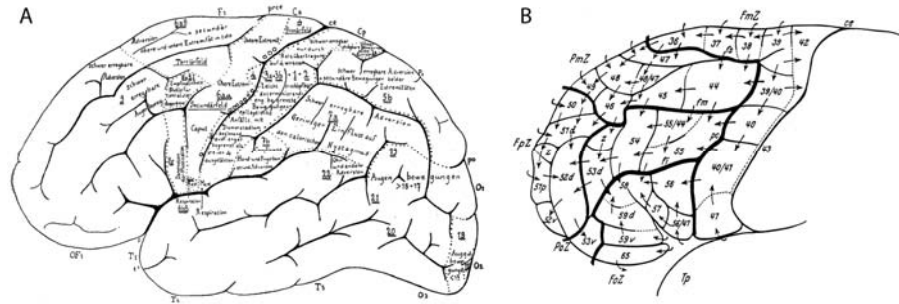


Figure 2.3 Structural subdivisions of the human cortex according to (A) Vogt and Vogt (1926) and (B) Sanides (1962).

A successful modern approach to cytoarchitectonic mapping relies on quantitative analysis of architectural similarities and dissimilarities between cortical areas and multivariate statistical analysis to define borders between these areas in contrast to the much more observer-dependent methods of the earlier efforts. In addition, the use of larger samples allows it to take the inter-individual structural variability into account, constructing probabilistic cytoarchitectonic maps in standard stereotaxic space (Amunts & Zilles, 2001). Both the posterior (Geyer et al., 1996) and anterior (Geyer, 2004) borders of the premotor cortex or area 6 have been mapped employing this methodology. The results show that the inter-individual variability of the position of the border between area 6 and the prefrontal areas is much higher than the variability in the position of the border between area 6 and the primary motor cortex (area 4). On the mesial surface, the latter coincides approximately with the VPC line (vertical posterior commissure line; the line that traverses the posterior commissure vertical to the line passing through both the anterior and posterior commissures). Overlap is maximal between the VPC and VAC (vertical anterior commissure) lines and decreases in more anterior direction. In most brains, the area 6/prefrontal border lies rostral to the VAC line. On the lateral convexity, this border lies considerably more posterior, with the area of maximum overlap on the crown of the precentral gyrus (Geyer, 2004).

This approach has provided no evidence for structural subdivisions within area 6. Also, a structural parcelling of the human premotor cortex analogous to Matelli's F-fields has so far not been confirmed. However, an immunochemical study suggests the existence of a rostral area 6r and a caudal area 6c in the dorsolateral premotor cortex (Baleydier, Achache, & Froment, 1997). These areas are differentiated by their neurofilament architecture and roughly parallel the Vogts' (1926) classification. Also, converging evidence from different studies using a variety of methods confirms the existence of a subdivision of the mesial premotor cortex in the human brain into a posterior part, usually called the SMA, and an anterior part, usually termed pre-SMA, approximately at the VAC line (Baleydier et al., 1997; Zilles et al., 1996; Zilles et al., 1995).

Theoretical Background

Some effort has been directed at establishing homologies between the structural subdivisions of the premotor cortex in the monkey and the human brain (e.g. Petrides & Pandya, 1994). Most of these approaches have also used functional in addition to structural information. Several authors agree that two mesial premotor areas corresponding to F3 and F6 or SMA and pre-SMA exist in both species; and also, that the two areas which occupy the dorsal part of the precentral gyrus and the caudal part of the superior frontal gyrus in humans correspond to monkey areas F2 and F7, respectively (Preuss, Stepniewska, & Kaas, 1996; Rizzolatti, Fogassi, & Gallese, 2002; Zilles et al., 1995). There is more dissent regarding the border between the ventral and the dorsal part of the lateral premotor cortex in the human, with some authors placing it roughly at the level of the inferior frontal sulcus (Preuss et al., 1996), others (Rizzolatti et al., 2002; Rizzolatti, Luppino, & Matelli, 1998) slightly inferior to the level of the superior frontal sulcus, approximately at $z = 50$ as expressed in the coordinate system of Talairach and Tournoux (1988) (Figure 2.4). Controversy also exists regarding the possible human homologues of areas F4 and F5. Preuss proposes that macaque ventral premotor cortex corresponds to the inferior part of BA 6 and the posterior part of BA 44 in the human, with no subdivisions (Preuss et al., 1996). In contrast, Rizzolatti and his colleagues take the homologue of area F4 to be human inferior BA 6, and the homologue of area F5 to consist in the entire opercular part of the inferior frontal gyrus (BA 44) (Rizzolatti et al., 2002; Figure 2.4) or even to additionally encompass anteriorly adjacent BA 45 (Rizzolatti et al., 1998).

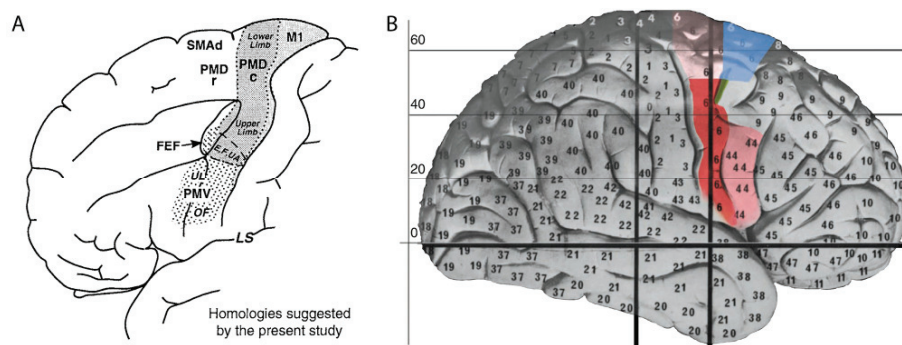


Figure 2.4 Ventral and dorsal subdivisions of premotor cortex according to (A) Preuss et al. (1996), (B) Rizzolatti et al. (2002).

Presently, it seems to be general consent that human BA 44 could be regarded as a “premotor” area or as a transitional area between premotor and prefrontal cortices, since its cytoarchitectural properties show it to be dysgranular rather than granular (Bucy, 1944).

A final consideration concerns the location of the frontal eye field (FEF), a region in which eye movements can be triggered by electrical cortical stimulation. In the monkey, the FEF lies in the rostral bank

of the arcuate sulcus, mostly rostral to the precentral motor areas within the granular prefrontal cortex. In contrast, in the human brain, it is presumably located entirely within the agranular premotor cortex, close to the intersection of the superior frontal and superior precentral gyri, as evidenced by both cytoarchitectonic (Rosano, Sweeney, Melchitzky, & Lewis, 2003) and functional studies (Paus, 1996).

2.1.2 Connectivity

The existing knowledge about connectivity patterns of premotor cortex areas is very elaborate in the monkey, and a lot less so in humans. Indeed, this knowledge stems almost entirely from studies in non-human primates, due to the impossibility of using methods such as *in vivo* tract-tracing techniques in humans. However, there is some functional evidence that networks comparable to the parietofrontal circuits (detailed below) are active in humans. And even when investigating the function of one specific brain area, as attempted in the present studies, it is necessary to keep in mind this area's connections with other parts of the nervous system in order to arrive at a correct interpretation of results and an appropriate model of function.

In general, the areas constituting the premotor cortex are extensively connected with each other and with the prefrontal and parietal cortices (Matelli & Luppino, 2001). Intrinsic connections are not ubiquitous, however: whereas there are rich interconnections within the ventral and the dorsal premotor cortices, there are few connections between these two areas, indicating a functional divergence (Ghosh & Gattera, 1995; Kurata, 1991).

Likewise, mesial premotor areas F3 and F6 have different input and output properties. Thalamic input into F3 comes from the nucleus ventralis lateralis pars oralis (VLo). F3 receives cortical afferents mainly from F6 and the lateral premotor fields, the somatosensory cortex, posterior parietal areas PE and PEci, the cingulate cortex and from primary motor area F1. F3 has corticospinal and corticobulbar descending projections. In contrast to F3, F6 receives thalamic projections from the nucleus ventralis anterior pars parvocellularis (VApc), area X and the nucleus medialis dorsalis. Cortical afferents into F6 originate mainly from F5 and F7, the prefrontal cortex and the cingulate cortex. F6 is not connected with F1, and only sends corticobulbar descending projections (He, Dum, & Strick, 1995; Keizer & Kuypers, 1989; Luppino, Matelli, Camarda, & Rizzolatti, 1993; Matelli & Luppino, 1996; Rizzolatti, Luppino, & Matelli, 1996).

Posterior dorsal premotor area F2 receives thalamic input from the nucleus ventralis posterolateralis pars oralis (VPLo), nucleus ventralis lateralis pars caudalis (VLc), and nucleus ventralis lateralis pars oralis (VLo) (Matelli & Luppino, 1996). Its cortical afferents originate in cingulate areas 24a, 24b and 24d and in temporal area MST; it receives, if any, only little input from the prefrontal cortex (area 46d),

but, like F3, has connections with F1. Anterior dorsal area F7, by comparison, receives input from several thalamic nuclei, not including VLo, and area X. Cortical input comes from cingulate areas 24a, 24b and 24c and temporal area STP. F7 is not connected to F1, but has strong connections with several prefrontal cortex areas including 8A, 8B, 45, 46d and 12 (Barbas & Pandya, 1987; Matelli & Luppino, 1996; Rizzolatti & Luppino, 2001). In addition, both F2 and F7 have multiple but segregated connections with parietal lobe areas. These constitute the anatomical basis for several parietofrontal circuits that are central for the description of premotor cortex functions and will therefore be described in more detail below.

Posterior ventral area F4 receives its main thalamic input also from VLo, and additional input from the same thalamic nuclei that send projections to its superior neighbor, area F2. Thalamic input into F5, in contrast, comes mainly from area X (Matelli, Luppino, Fogassi, & Rizzolatti, 1989), making it apparent that thalamic projections to the premotor fields are largely segregated into two families, one targeting predominantly the anterior, the other the posterior premotor areas.

Area F4 has strong connections with area F3 of the mesial premotor fields, while area F5 has strong connections with area F6. Both receive input from the cingulate, but only F5 receives input from the prefrontal cortex, albeit less than areas F6 or F7. Projections to primary motor area F1 originate from both F4 and, to a lesser extent, from F5, making F5 the only area in the anterior premotor cortex that has significant connections with F1 (Luppino et al., 1993; Matelli, Camarda, Glickstein, & Rizzolatti, 1986; Rizzolatti & Luppino, 2001). Areas F4 and F5 again are strongly connected with the parietal cortex as part of the parietofrontal circuits described in the next paragraph.

Connectivity defines the central structural entities determining premotor cortex functionality: multiple fronto-parietal loops, working in parallel and performing sensorimotor transformations essential in the guidance of behavior. According to Rizzolatti and his colleagues (Matelli & Luppino, 2001; Rizzolatti et al., 1998), each parietal area sends projections to several frontal areas while each frontal area receives input from several parietal areas. However, connections are typically strongest between one specific frontal and one specific parietal area with similar functional properties. Six principal circuits exist in the monkey – half of them involving dorsal, half of them ventral premotor areas - which are delineated in the following (summarized from Rizzolatti et al., 1998) and illustrated in Figure 2.5.

PEc/PEip-F2 dimple circuit: Area PEip occupies the rostral part of the mesial bank of the intraparietal sulcus, area PEc lies dorsal to it on the convexity. Neurons in both areas are involved in the analysis of somatosensory stimuli for movement organization. In addition, PEip neurons discharge in association with arm movements, with broad directional tuning (Iwamura & Tanaka, 1996; Kalaska, Cohen, Prud'homme, & Hyde, 1990).

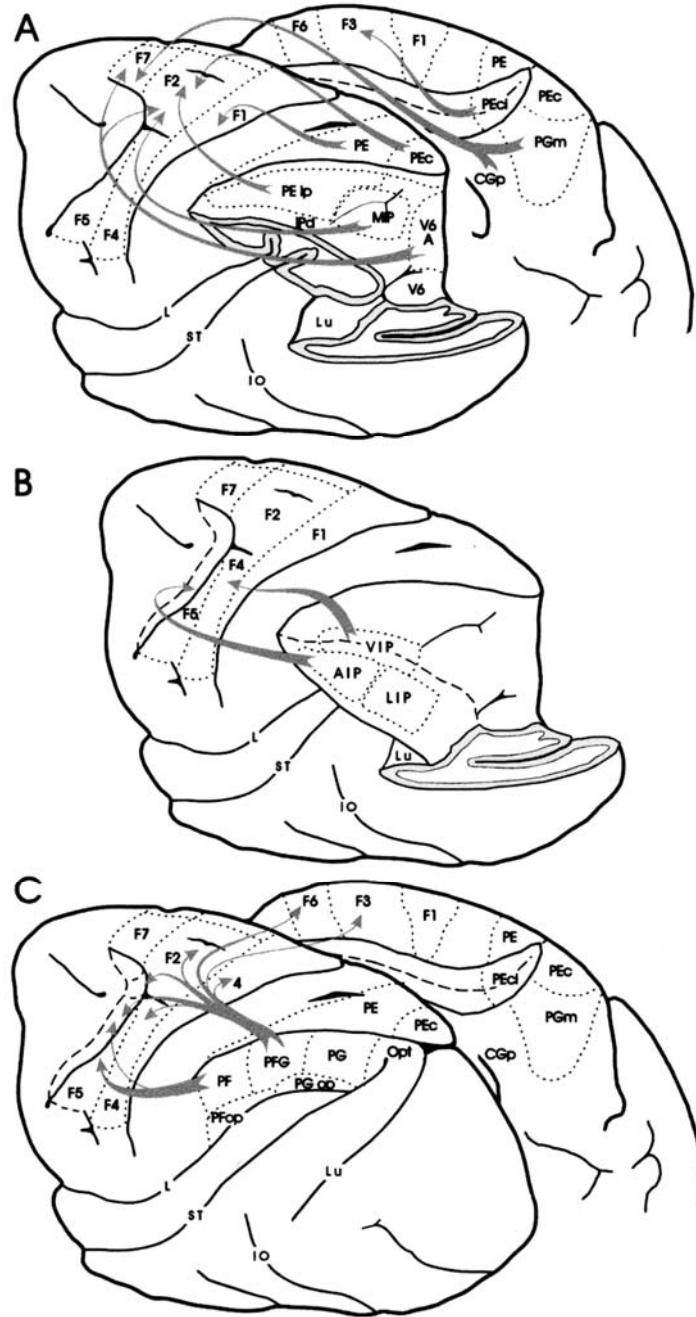


Figure 2.5 Main posterior parietal projections to the motor cortex in the macaque: (A) from areas located in the superior parietal lobule, (B) from areas located in the lateral bank and in the fundus of the intraparietal sulcus, and (C) from areas located on the convexity of the inferior parietal lobule (Rizzolatti et al., 1998).

Theoretical Background

In the F2 dimple region, movements of arms and legs are represented in a somatotopic fashion. F2 dimple neurons discharge during the delay before a movement and at movement onset, indicating a role in motor preparation (Kurata, 1994; Wise, Boussaoud, Johnson, & Caminiti, 1997); they show responses to sensory, predominantly to proprioceptive, stimuli (Rizzolatti et al., 1998). Consequently, it is suggested that the function of the PEip/PEc-F2 dimple circuit is planning and controlling arm (and probably leg) movements on the basis of somatosensory information.

MIP-F2 ventrorostral circuit: Areas MIP and V6a, which also sends projections to the ventral part of F2, lie on the mesial bank of the intraparietal sulcus, immediately posterior to area PEip. MIP and V6a neurons respond to visual in addition to somatosensory stimulation (Colby & Duhamel, 1991; Galletti, Fattori, Battaglini, Shipp, & Zeki, 1996). V6A neurons also discharge in association with eye and arm movements (Galletti, Fattori, Kutz, & Battaglini, 1997). Corresponding to their parietal counterparts, neurons in the ventrorostral region of F2 show responses not only to proprioceptive, but also to tactile and visual stimuli. This region contains some signal-related neurons, i.e. neurons responding to visual stimuli instructing a movement (Caminiti, Ferraina, & Johnson, 1996; Tanne, Boussaoud, Boyer-Zeller, & Rouiller, 1995). The MIP/V6A-F2 ventrorostral circuit thus uses somatosensory and visual information for the planning and control of arm movements. Monitoring and controlling arm position during the transport phase of the hand toward the target possibly also is one of the major functions of this circuit.

PGm-F7 circuit: Area PGm is located on the mesial aspect of the superior parietal lobule and is architectonically similar to lateral area PG (Pandya & Seltzer, 1982). There is not much known about the functions of this complex area other than that its neurons discharge during eye and/or arm movements (Ferraina, Garasto et al., 1997; Ferraina, Johnson et al., 1997), so clues as to the function of this circuit must come from frontolateral area F7, the main destination of PGm projections. In F7, neurons exist that discharge before or during arm movements, and others that discharge in response to visual stimuli (di Pellegrino & Wise, 1991), suggesting a role in the spatial localization of external stimuli for reaching movements.

VIP-F4 circuit: Area VIP occupies the fundus of the intraparietal sulcus. VIP neurons respond to visual stimuli, part of them also to tactile stimuli. The visual responses are often selective for the type, direction or speed of stimulus motion (Bremmer, Duhamel, Ben Hamed, & Graf, 1997; Colby, Duhamel, & Goldberg, 1993). Bimodal neurons' tactile receptive fields are usually located on the face, co-registered with their visual receptive fields, and neurons respond to visual stimuli preferentially when these appear close to the body in peripersonal space. Premotor area F4 contains representations of hand, arm, neck and mouth movements. F4 neurons are active during proximal reaching movements or oro-facial movements, but not during distal movements (Gentilucci et al., 1988; Godschalk, Lemon, Nijs, &

Kuypers, 1981). Regarding their sensory responses, about half of the neurons show responses associated with tactile stimuli only, the other half show responses associated with both visual and tactile stimuli, whereas there are virtually no purely visual neurons (Fogassi et al., 1996). Tactile receptive fields are located on the arm, face and upper body, and again, co-registered with the same neuron's visual receptive field. Taken together, these properties suggest that the VIP-F4 circuit has its role in encoding the peripersonal space and in transforming object locations into appropriate movements toward them.

AIP-F5ab circuit: Area AIP is located in the rostral part of the lateral bank of the intraparietal sulcus. AIP neurons show activity related to hand and finger movements during grasping actions. This area also contains visually responsive neurons which discharge during fixation of an object. In most neurons exhibiting both motor and visual responses, the characteristics of the objects that elicit the visual response also correspond to the grip type able to trigger the motor response (Sakata, Taira, Murata, & Mine, 1995; Taira, Mine, Georgopoulos, Murata, & Sakata, 1990). Parietal area AIP sends its main projections to a subarea of premotor F5, area F5ab on the posterior bank of the inferior arcuate sulcus. Neurons in this area are active during goal-directed hand and/or mouth movements. Their activity is selective for specific actions, e.g. grasping, holding, or even for a specific grip type during grasping (Rizzolatti et al., 1988). As in area AIP, many F5ab neurons also discharge in response to visual presentation of objects without any concurrent movement (Murata et al., 1997). Thus, the function of the AIP-F5ab circuit seems to be to transform the intrinsic properties of an object into the appropriate hand movements.

PF-F5c circuit: The second subarea of F5, located on the cortical convexity just posterior to the arcuate sulcus, contains neurons whose motor properties are comparable to those in area F5ab, although their visual responses differ (Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996). F5c contains neurons that discharge during the observation of manual actions, not merely the presentation of objects. Thereby, the selectivity for one particular action applies to both the motor and the visual response. These “mirror” neurons are also present in area PF in the inferior parietal lobule (cf. Fogassi et al., 2005), from which area F5c receives its predominant input, suggesting that the PF-F5c circuit functions as an action-observation matching system involved for example in the imitation and recognition of the actions of others (see also section 2.2.4).

2.2 Premotor cortex functions in action

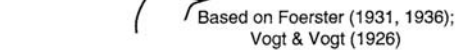
The present investigation sought to advance the understanding of the functions of a brain area defined primarily by its structural properties. In humans, it is more difficult to establish direct structure-function relationships than it is in non-human primates or other animals, as for ethical reasons, func-

tional in vivo and anatomical post-mortem studies of course cannot be performed in the same brain. However, with the development of new techniques such as fMRI or transcranial magnetic stimulation (TMS) in recent years, there have been numerous attempts to replicate findings and concepts established in the monkey also in humans, using more indirect methods. Conversely, some findings in humans have inspired subsequent investigations in the monkey. To deliver a more complete account of what is known to date about premotor functionality, the following review of the literature will therefore be based on studies in both the monkey and the human, with a focus on existing neuroimaging literature.

2.2.1 Motor control and execution of movements

The first functions attributed to the premotor brain areas were related to the initiation and control of movements. In the 1930s, Wilder Penfield and his colleagues started to electrically stimulate the lateral motor cortex of epileptic patients during surgery. They found that movements on the contralateral side of the body could be elicited by this stimulation, and that the cortical representation of the body parts was organized in a somatotopic fashion, termed the “motor homunculus” (Penfield & Boldrey, 1937; Penfield & Rasmussen, 1950). A similar organization (“motor simiusculus”) could later be confirmed in nonhuman primates (Woolsey et al., 1952). At about the same time, the work of Foerster (1931; 1936) revealed that the electrophysiological stimulation of area 6 also induced discrete movements on the contralateral side of the body (Figure 2.6A), but that more current was needed in area 6 as compared to area 4. Anterior premotor areas are less excitable than posterior premotor areas (Godschalk, Mitz, van Duin, & van der Burg, 1995; Preuss et al., 1996; Uematsu et al., 1992), in accordance with the fact that, in general, posterior premotor areas send descending projections to the spinal cord, while projections from the anterior premotor fields terminate in the brain stem (He, Dum, & Strick, 1993; He et al., 1995; Keizer & Kuypers, 1989). Penfield and Welch (1951) observed that stimulation of the SMA also triggered motor responses, but they did not find a somatotopic map of the body, in contrast to earlier findings in the lateral motor areas. In monkeys however, evidence for a somatotopic representation of the body in the SMA could be found (Luppino, Matelli, Camarda, Gallese, & Rizzolatti, 1991; Woolsey et al., 1952).

In more recent years, a multitude of studies have been conducted in this field, many using the techniques of intracortical microstimulation and single-cell recording in the monkey. They have strengthened the view that not one, but multiple distributed and overlapping somatotopies exist in the lateral and mesial motor areas (see also Graziano & Aflalo, 2007). An illustrative example is presented in Figure 2.6B.



motor areas in the Aotus monkey. Figures cited from Preuss et al. (1996).

lucci et al., 1988; Hatanaka, Nambu, Yamashita, Takada, & Tokuno, 2001; Rizzolatti et al., 1988).

& Schlag-Rey, 1987).

Neuroimaging studies in humans have confirmed the existence of multiple representations of body movements in the premotor brain areas. Simple flexion and extension movements of the fingers, arm and knee induced several independent activations in primary motor cortex, SMA proper and dorsal premotor cortex (Fink, Frackowiak, Pietrzyk, & Passingham, 1997). In this study, evidence for a rough somatotopic organization was found for the SMA, but not for the lateral premotor areas. An early PET study (Colebatch, Deiber, Passingham, Friston, & Frackowiak, 1991) found activation for simple movements of the fingers, hand and shoulder in the contralateral premotor cortex and in the SMA, among other brain areas. In dorsal PMC, the increase in regional cerebral blood flow (rCBF) was stronger for the shoulder movement than for the distal movements; this was taken as evidence for an extensive representation of proximal movements in PMd, comparable to findings in the monkey. A recent meta-analysis of neuroimaging studies in humans (Schubotz & von Cramon, 2003) made it clear that across motor tasks involving different effectors, from the foot to the mouth, a dorsal-to-ventral somatotopy is evident in lateral premotor cortex (see also Figure 2.12).

A putative difference between dorso- and ventrolateral PMC, which has received some support from later research, is that PMd is involved predominantly in the control of spatially guided movements, for example pointing or reaching, whereas PMv primarily controls motor tasks involving the hand and fingers, such as grasping and grip selection. Activation in PMd was reported during preparation and performance of reach-to-point movements to visual targets (Kawashima, Roland, & O'Sullivan, 1994, 1995), during tracking a moving target with the index finger (Grafton, Mazziotta, Woods, & Phelps, 1992) and for reach-to-grasp and reach-to-point movements directed at objects (Filimon, Nelson, Hagler, & Sereno, 2007; Grafton, Fagg, Woods, & Arbib, 1996). The activation was contralateral to the moving arm in each case. In contrast, activation in PMv (and in the anterior part of the intraparietal sulcus) was found when subjects manipulated complex three-dimensional objects for an extended amount of time, which required a constant change of finger configuration, as opposed to the manipulation of a simple sphere (Binkofski, Buccino, Posse et al., 1999; Binkofski, Buccino, Stephan et al., 1999). Activation reported in premotor areas was bilateral, but more accentuated on the contralateral side.

Neuroimaging studies have further shown that premotor cortex participates not only in the execution, but also in the preparation of single movements (Boussaoud, 2001; e.g. Deiber, Ibanez, Sadato, & Hallett, 1996). Lastly, involvement of PMC in the selection of movements according to arbitrary rules has repeatedly been demonstrated: when subjects learned to make an association between a cue and the direction of a movement (Deiber et al., 1991; Deiber et al., 1997), and when they had to select more complex movements based on arbitrary cues (Grafton, Fagg, & Arbib, 1998).

2.2.2 Motor sequence organization and sequence complexity

Both the mesial and lateral premotor areas are suggested to be involved in the temporal sequencing of movements in various ways, and evidence for this again comes from studies in nonhuman primates as well as from studies in human subjects.

Using single-cell recordings in macaques, neuronal functioning associated with the organization of multiple movements into sequences has been most intensively investigated by Jun Tanji, Keisetsu Shima and their collaborators (Shima & Tanji, 1998, 2000; Tanji, 2001; Tanji & Shima, 1994; Tanji, Shima, & Mushiake, 1996). The monkeys learned to perform sequences of turn-, push- and pull-movements on a manipulandum. Authors identified several different classes of sequence-tuned neurons in the SMA and pre-SMA, whose interplay provides a model how this sequential organization can be achieved on the neuronal level.

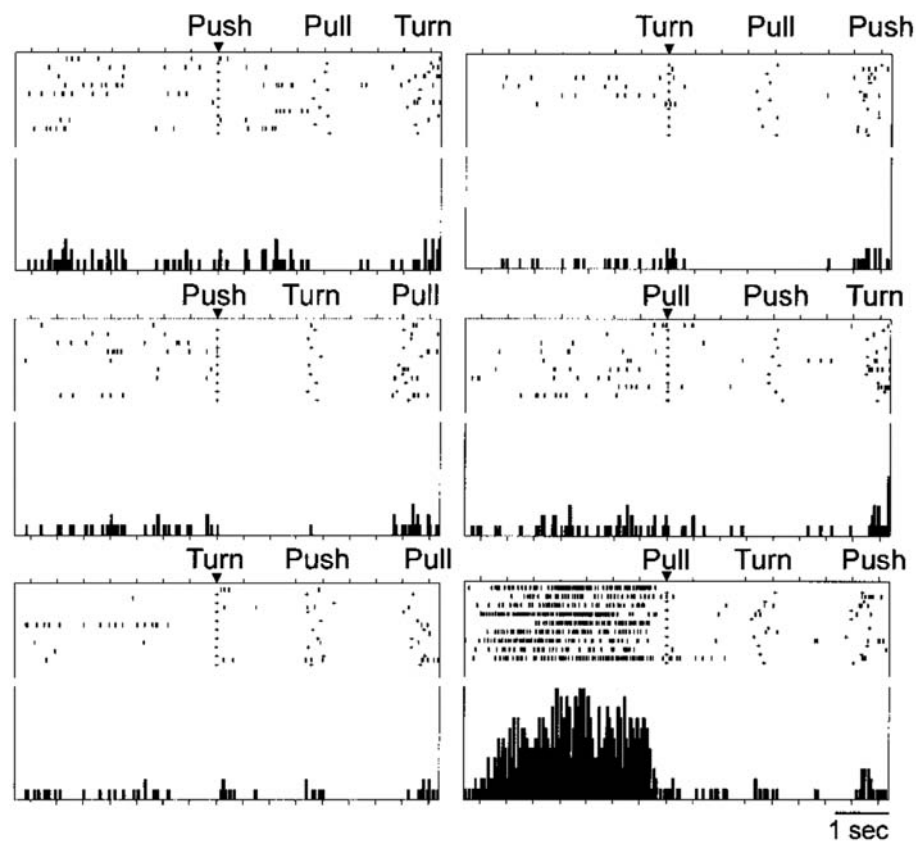


Figure 2.7 Activity of a sequence-selective preparatory neuron in the pre-SMA exhibiting preferential activity to a specific order of 3 movements performed without sensory guidance. This neuron is active during the waiting period before initiating the 1st movement but only if the sequence of upcoming movements is in the order pull, turn, and push (Shima & Tanji, 2000).

At the start, retrieval of the specific sequence to perform is reflected by the activity of sequence-selective preparatory neurons – neurons that fire during preparation of one sequence, e.g. pull-turn-push, but not during preparation of other sequences (Figure 2.7).

The second class of neurons are those showing rank-order selective preparatory activity: they fire during preparation of, for example, the third movement in the sequence, regardless of which sequence and which movement are performed (Figure 2.8). Other neurons of this type might be selective for other ranks or a combination of two ranks. In contrast, neurons showing movement-selective preparatory activity fire during the preparatory period of one specific movement, for example the pull movement, irrespective of the sequence to be performed and the position of this movement in the sequence. Together, the activity of these two types of neurons determines which movement is performed when in the sequence.

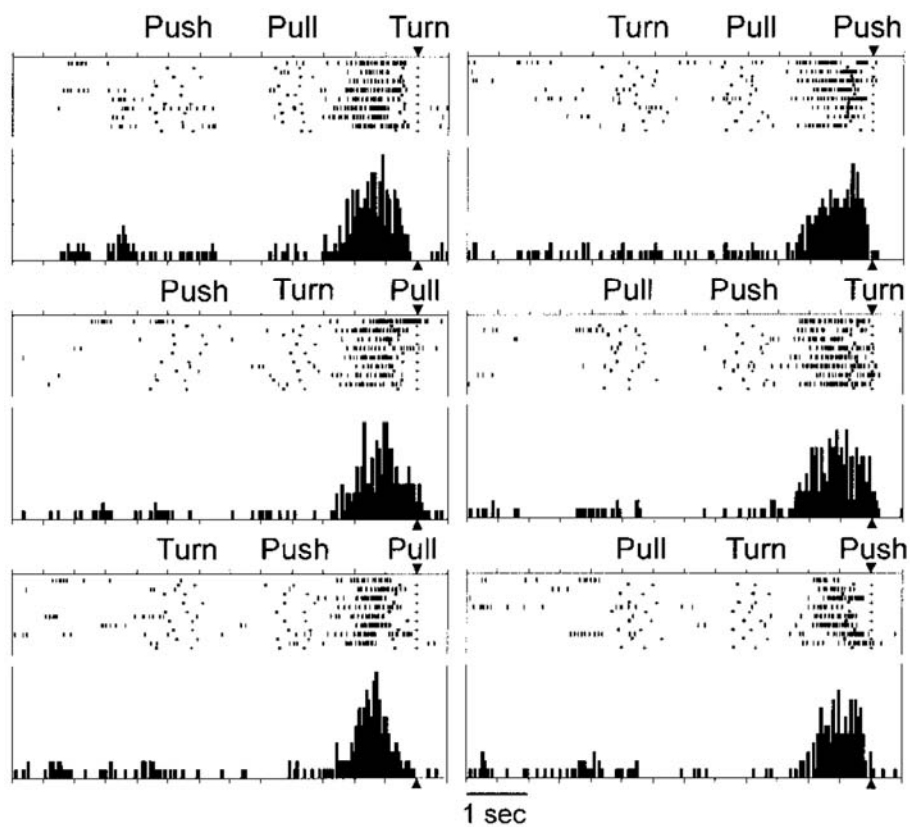


Figure 2.8 Activity of a rank-order selective preparatory neuron in the pre-SMA. It discharges while the monkey is preparing to initiate the 3rd movement, irrespective of the type of movement or the sequence (Shima & Tanji, 2000).

A fourth class of neurons provide the link from one element in the sequence to the next: interval-selective neurons fire while the monkey is preparing one movement, e.g. “pull”, but only if the next movement is another specified movement, e.g. “push”, but not if it is “turn” – again regardless of sequence or rank order of the movements.

In addition to the classes of neurons just described, which are active during the preparatory period before movements, there is another class of neurons showing activity immediately before and during movements. These movement-related neurons can also be selective for a specific sequence, rank order or movement. Finally, neurons exist that are only active after the third and final movement; these neurons might signal the end of the sequence.

It has further been shown that in monkeys, lesions to the SMA (Brinkman, 1984; Chen, Thaler, Nixon, Stern, & Passingham, 1995; Halsband, 1987) as well as reversible inactivation of either the SMA or pre-SMA by muscimol injection (Shima & Tanji, 1998) disrupt the performance of movement sequences guided by memory. In an attempt to replicate the latter result in humans, Gerloff and co-workers (1997) found that the application of TMS over the mesial motor areas disrupted the performance of complex, but not simple finger movement sequences.

Functional data in humans suggest a differential involvement of SMA and pre-SMA in the execution of sequential motor tasks. While SMA proper seems to play a dominant role in well-learned, “automatic” sequences, pre-SMA appears to be crucial for learning new sequences, as shown in a study with professional pianists playing either scales (automated sequences) or unfamiliar pieces of music (Sergent, Zuck, Terriah, & MacDonald, 1992). Furthermore, activation shifts from pre-SMA to SMA proper as a sequential task becomes more and more automatic (Grafton, Mazziotta, Presty et al., 1992; Hikosaka et al., 1999; Jenkins, Brooks, Nixon, Frackowiak, & Passingham, 1994; Seitz & Roland, 1992).

Regarding the role of the lateral premotor areas in motor sequence performance, functional investigations in humans have centered on the acquisition and on the complexity of sequences. With few exceptions, the task employed is to press keys on a keyboard with the fingers of one hand, usually the right. A number of studies have shown that activity in lateral PMC positively co-varies with complexity determined by both sequence length (Boecker et al., 1998; Catalan, Honda, Weeks, Cohen, & Hallett, 1998; Sadato, Campbell, Ibanez, Deiber, & Hallett, 1996) and sequence type (Dassonville et al., 1998; Rao et al., 1993; Van Oostende, Van Hecke, Sunaert, Nuttin, & Marchal, 1997; Wexler et al., 1997); this could also be confirmed in an fMRI study using a parametric approach (Haslinger et al., 2002). Activity in left dorsal and ventral PMC correlated with two measures of complexity employed, both the number of fingers and number of transitions in the sequences, when sequence length was kept constant (Harrington et al., 2000). This complexity-related premotor activation was left-lateralized, no matter whether

the sequence was executed with the right or left hand (Haaland, Elsinger, Mayer, Durgerian, & Rao, 2004). Furthermore, Elsinger and colleagues (2006) found evidence that higher sequence complexity has a greater effect on lateral PMC and SMA activation, not only during execution, but also during preparation of a motor sequence; and this was true especially if the sequence was performed based on information in memory.

Neuroimaging findings also suggest that the premotor cortex is involved in the acquisition of movement sequences; however, studies have yielded somewhat conflicting results regarding laterality of PMC activation and involvement during different learning stages. Activity in ipsilateral (Grafton, Hazeltine, & Ivry, 1995, 2002; Hazeltine, Grafton, & Ivry, 1997) and contralateral (Seitz & Roland, 1992) premotor cortex has been reported to increase during advanced stages of learning; in SMA this was true especially for implicit learning (Grafton et al., 1995, 2002). In contrast, several studies found higher premotor activation during learning of novel sequences as compared to performance of pre-learned sequences: in right PMv (Toni, Ramnani, Josephs, Ashburner, & Passingham, 2001) and bilaterally in PMd (Jenkins et al., 1994; Müller, Kleinhans, Pierce, Kemmotsu, & Courchesne, 2002). Whereas Jenkins and co-workers (1994) found that the SMA, contrary to lateral premotor cortex, was more involved in sequence retrieval than in sequence learning, concurrent activation in lateral and mesial PMC for sequence learning was reported in the latter study (Müller et al., 2002). Moreover, this activity was present in both early and late stages of learning. Finally, Sakai and colleagues (2002) contrasted the performance of sequences in which both the order and the timing of key presses were fixed – in other words, in which learning could occur – with sequences in which both aspects were random, and detected bilateral PMd and left PMv activation in this contrast.

2.3 Premotor cortex functions in perception

2.3.1 Perceptual responses

While premotor cortex plays a central role in preparation and control of movements, neuronal activity in this brain region is by no means exclusively related to motor functions.

Extensive research efforts have been directed at identifying responses to sensory stimuli in PMC neurons using single cell recording in nonhuman primates. Mapping the entire premotor cortex in anesthetized monkeys, responses to tactile and visual stimuli could be recorded throughout (Graziano & Gandhi, 2000). The representations of tactile stimuli were organized somatotopically, analogous to the somatotopy of motor responses, with neurons responding to touch of the leg, arm, hand, face and mouth found in progressively more ventral regions of the precentral gyrus. In the mesial premotor cor-

tex, neurons responding to visual stimuli are mainly found in the pre-SMA, while neurons responding to somatosensory stimuli are found more often in the SMA (Hummelsheim, Bianchetti, Wiesendanger, & Wiesendanger, 1988; Matsuzaka, Aizawa, & Tanji, 1992).

In ventral area F4, 87% of neurons were found to respond to sensory stimuli; there were unimodal tactile (30%), unimodal visual (14%) and bimodal visuotactile neurons (Fogassi et al., 1996). The receptive fields of the tactile and bimodal neurons were on the face, neck, trunk, and arms. Receptive fields of the visual neurons were located in the space near the body. For bimodal neurons, visual and tactile receptive fields were co-registered – a specific neuron’s visual receptive field was in the space adjacent to the tactile receptive field. In addition, the body parts these receptive fields are typically registered to are also the body parts whose motion is represented by the same neuron. In F4, approaching objects were the most effective visual stimuli. And importantly, for the large majority of visual neurons, the receptive fields maintained their location with respect to the body parts they were anchored to, regardless of eye-position and even when the body part was moved, suggesting that these neurons code space in somatocentered coordinates.

Neurons in premotor area F5 show distinct responses to highly complex visual stimuli. It was found that many neurons in subarea F5ab, the so-called canonical neurons, in addition to their motor activity also discharge during the presentation of 3D objects (Murata et al., 1997; Rizzolatti & Fadiga, 1998). These responses are mostly specific for objects of a certain size, shape, and orientation; and the specificity in the visual response matches the specificity the same neuron shows for the motor response (Figure 2.9). Moreover, it could be shown that this object-related neuronal activity is not due to motor preparation, since it occurred also in conditions in which there was explicitly no action directed toward the object.

In subarea F5c, a different class of visually responsive neurons exist. These “mirror neurons” show motor-related activity during specific goal-directed actions. They also discharge when the monkey observes another individual performing an action similar to that encoded by the neuron (Figure 2.10; Ferrari, Gallese, Rizzolatti, & Fogassi, 2003; Gallese et al., 1996; Rizzolatti, Fadiga, Gallese et al., 1996). The observed hand actions that most commonly activate mirror neurons are grasping, holding, manipulating and placing objects, but there are also mirror neurons for mouth actions. Neurons can be selective for one or more actions. Importantly, mirror neurons respond to the action goal, not the motor specifics of the action observed, and presentation of the object alone is not sufficient to activate them. In general, they also do not respond to the sight of a mimed action.

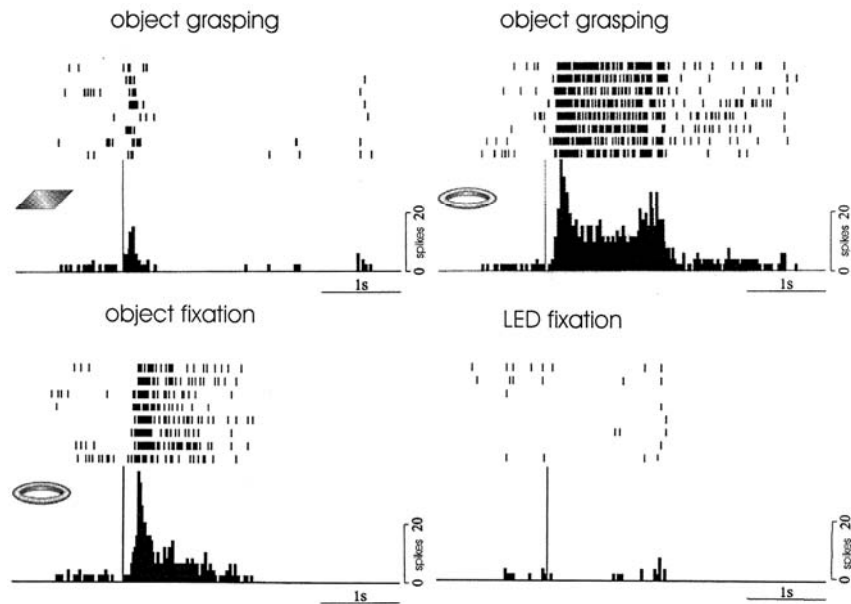


Figure 2.9 Discharge of a canonical neuron in area F5ab that shows selective responses to a ring-shaped object (modified from Rizzolatti & Luppino, 2001).

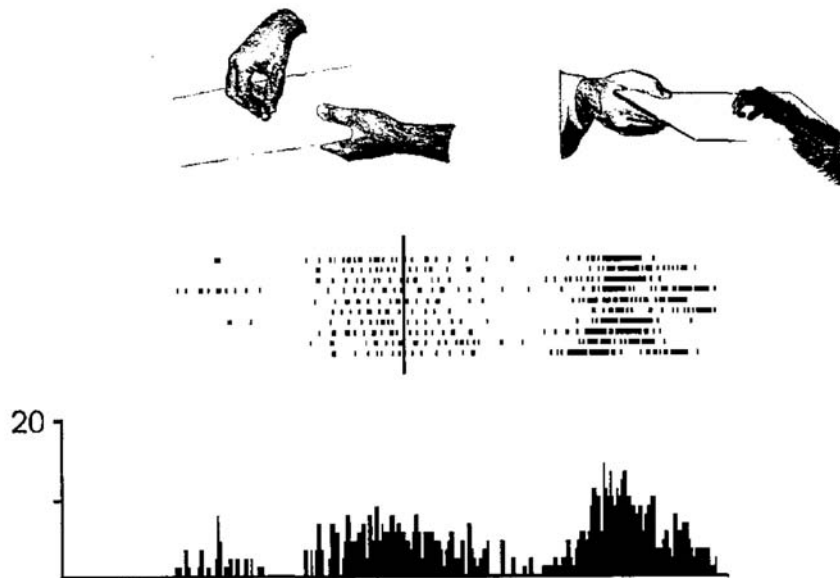


Figure 2.10 Activity of a "mirror" neuron in area F5 discharging in response to the experimenter grasping an object and during the monkey's grasping action (Rizzolatti, Fadiga, Gallese et al., 1996).

Taken together, these findings on the nature of motor and sensory responses in ventral premotor areas F4 and F5 were suggested to reflect the existence of a “vocabulary” of potential motor acts in these brain areas (Fadiga, Fogassi, Gallese, & Rizzolatti, 2000; Rizzolatti et al., 1988). In this view, premotor cortex is not only involved in the execution of actions, but also internally represents these actions in terms of “motor ideas”. This vocabulary of potential actions can be accessed either by external – observation of objects and actions – or by internal stimuli – e.g. motor preparation –, and it might even provide the neurobiological basis for space representation, imitation and understanding of actions made by others as well as semantic categorization of objects.

Evidence for the existence of neuronal responses to sensory stimuli in human premotor cortex is limited in comparison to the monkey literature. In one fMRI study, the equivalence of polymodal information processing in monkeys and humans was tested. For moving visual, tactile and auditory stimuli, overlap of activation was found in right PMv, along with the intraparietal sulcus and postcentral gyrus (Bremmer et al., 2001). Activation in dorsal and ventral PMC, including an area corresponding to primate areas for multimodal analysis and motor planning, was apparent for the analysis of auditory movement (Griffiths, Green, Rees, & Rees, 2000). Using a newly developed stimulation device for mapping somatosensory-evoked brain activations during fMRI, Dresel and co-workers (2008) found a premotor cortex response to tactile stimulation of both the hand and the face.

In human subjects, left premotor cortex seems to be selectively modulated by action-related sounds, as indicated by ERP (Pizzamiglio et al., 2005) and fMRI (Galati et al., 2008) studies. Areas in PMC are active during listening to and execution of both hand and mouth actions (Gazzola, Aziz-Zadeh, & Keysers, 2006; Lahav, Saltzman, & Schlaug, 2007). This activity was proposed to be somatotopic in that the hand action activation foci were located dorsal to the foci for mouth actions, and it could be shown that the same areas were also active during visual presentation of the actions (Gazzola et al., 2006).

Furthermore, there is evidence for activity in human premotor cortex that is suggested to be equivalent to the activity of the canonical neurons in monkeys. Activation in both dorsal and ventral lateral PMC has been found in neuroimaging studies when subjects viewed real tools, i.e. objects with a common use, or pictures of tools. This activation could be observed in comparisons of the object viewing condition to scrambled image control conditions (Creem-Regehr & Lee, 2005; Grafton, Fadiga, Arbib, & Rizzolatti, 1997) or in comparison to objects of other categories such as animals, faces or houses (Chao & Martin, 2000). The latter authors suggested that the premotor activation may be due to the automatic retrieval of information about hand movements associated with the manipulable objects. This notion could be substantiated in a study by Creem-Regehr and colleagues (2007) who trained subjects to perform specific actions on novel objects (“tools”). When these objects were later viewed or used during fMRI, activation was apparent in left PMv, contrasted against viewing or using novel objects with

which no actions were associated (“shapes”). Moreover, the perception of tools, in contrast to non-object visual control stimuli or non-manipulable objects, is associated with left hemisphere PMC activation also in tasks other than pure viewing, such as judgement of orientation, motor imagery, silent naming or generation of the corresponding action verb (Chao & Martin, 2000; Grafton et al., 1997; Grezes & Decety, 2002). Grèzes et al. (2003) directly tested the correspondence to canonical neurons and found that both passive observation of objects and grasping the objects elicited activation in the same area of left PMv.

Finally, there is also activity in human PMC that has been suggested to be the equivalent of mirror neuron activity in monkeys. More specifically, the PMC is suggested to play a role in the observation and imagery of actions. Evidence for this assumption is reviewed briefly in the next section.

2.3.2 Observation and imagery of actions

The discovery of “mirror” neurons in the premotor cortex of the monkey has inspired a wealth of research directed at uncovering a similar mechanism in humans. However, findings are diverse with respect to comparison of conditions and localization of activations. A number of neuroimaging studies have found activation in the inferior frontal gyrus (BA 44 and/or BA 45) or in the precentral gyrus related to the observation of finger movements (Iacoboni et al., 1999; Molnar-Szakacs, Iacoboni, Koski, & Mazziotta, 2005), hand movements (Decety et al., 1997) or the observation of grasping actions (Grafton, Arbib, Fadiga, & Rizzolatti, 1996; Grezes et al., 2003; Rizzolatti, Fadiga, Matelli et al., 1996). Observation of human movement and object-directed actions performed by human and robotic actors were all shown to activate large parts of the precentral gyrus (Gazzola, Rizzolatti, Wicker, & Keysers, 2007; although see Perani et al., 2001), as did the observation of complex object manipulation sequences (Molnar-Szakacs, Kaplan, Greenfield, & Iacoboni, 2006). The finding that action execution and observation share voxels, on a single-subject level, in dorsal, ventral, and mesial PMC (Gazzola & Keysers, 2008) substantiates the suggested role of PMC in both execution and observation of actions.

Buccino and co-workers (2001) investigated the observation of actions performed with different effectors. The observation of actions made by mouth, hand and foot was contrasted with respective controls: observation of a static face, a static hand and a static foot. fMRI revealed that the observation of both transitive and intransitive actions led to a somatotopic activation of the premotor cortex, where the foot actions were represented most dorsally and the mouth actions most ventrally. These results were recently replicated for observation of distal, proximal and axial intransitive movements (Sakreida, Schubotz, Wolfensteller, & von Cramon, 2005). A somatotopy of premotor activations in observation

of action and biological motion could further be substantiated in a meta-analysis of fMRI and PET studies (Schubotz & von Cramon, 2003; see Figure 2.12).

To summarize, in light of the not quite consistent results especially from the neuroimaging studies, the notion of a unitary “mirror system” in the human brain can be disputed, but nevertheless, there is evidence that premotor brain regions are involved in the observation of actions performed by others.

Regarding the imagery of actions, a single-cell recording study targeting premotor F5 in monkeys yielded some intriguing results. It showed that a large part of neurons with “mirror” properties become active also when the final part of the action, the hand-object-interaction, is hidden and can therefore only be inferred (Umiltà et al., 2001; Figure 2.11). This implies that the motor representation of an action performed by others can be internally generated in the observer's premotor cortex, even when a visual description of the action is lacking.

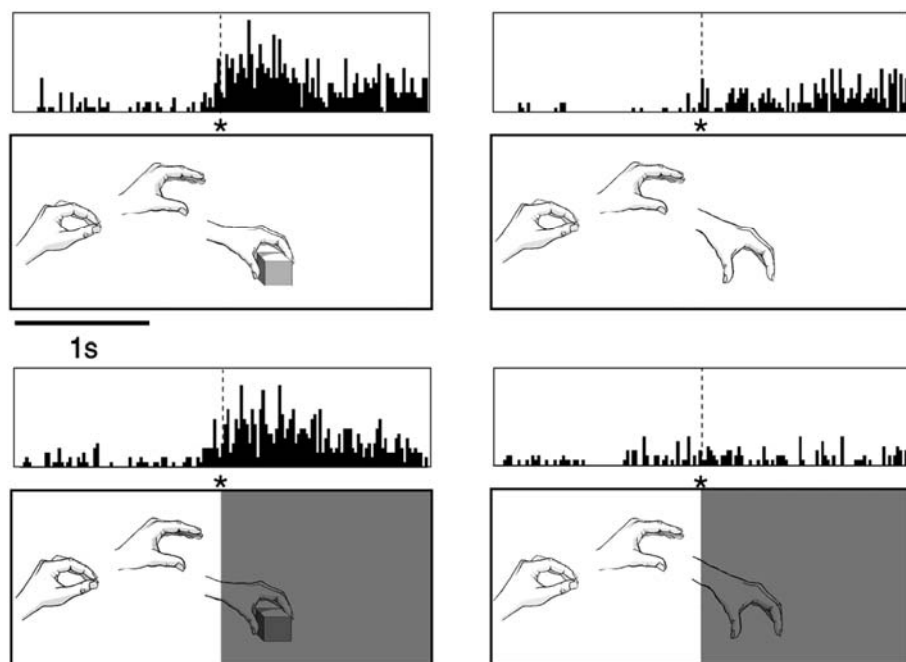


Figure 2.11 Activity of a neuron responding to action observation in full vision and in hidden condition, but not in mimed conditions (modified from Umiltà et al., 2001).

This neuronal mechanism might be part of the explanation for neuroimaging findings that implicate PMC in motor simulation or the imagery of actions. Again, studies differ quite considerably regarding the contrasts employed and the location of premotor activation reported.

Compared against rest or against executed movements, tasks involving the imagination of finger or hand movements activated large portions of the mesial and lateral premotor areas (Deiber et al., 1998; Gerardin et al., 2000; Stephan et al., 1995), as did imagined object grasping compared to object viewing (Grafton, Arbib et al., 1996). Mental simulation of object manipulation was shown to elicit activation in both ventrolateral (Decety et al., 1994) and dorsolateral PMC (Grezes & Decety, 2002). Imagination of grasping tools and grasping 3D geometrical objects, compared against viewing scrambled images, likewise activated dorsal PMC, in this case bilaterally (Creem-Regehr & Lee, 2005).

Johnson and co-workers (2002) could show that simulating a reaching movement with either hand also activates dorsal PMC bilaterally. Furthermore, Filimon et al. (2007) found that executed, observed and imagined reaching movements, contrasted against passive viewing of objects, all activated dorsolateral PMC at the level of the superior frontal sulcus. In light of these findings, it has been suggested that imagery of reaching or arm movement, i.e. spatially guided action, primarily recruits dorsal premotor areas, whereas imagery of finger movement or grasping, i.e. hand configuration, primarily recruits ventral premotor areas. Evidence for this notion is again provided by the meta-analysis of Schubotz and von Cramon (2003), who reviewed neuroimaging studies in humans investigating motor imagery performed with different effectors as well as imagery of non-biological motion and objects (see Figure 2.12). This functional gradient within lateral PMC might also account for some of the divergent findings in the literature on action observation.

Regarding the involvement of the mesial premotor cortex in action imagery, a meta-analysis by Grèzes and Decety (2001) suggests that activations found during imagery and observation of actions are mostly located rostral to the activations found during execution.

2.4 Premotor cortex functions in abstract cognitive tasks

2.4.1 Serial prediction

In the previous sections, evidence has been presented that premotor cortex is instrumental in a variety of brain functions ranging from motor control and preparation of movements to action observation and imagery. The idea that PMC is involved in non-motor perceptual-attentional tasks has been taken further in a recent research program testing the hypothesis that the premotor cortex might serve as an

internal forward model of environmental dynamics in different domains (for a detailed review, see Schubotz, 2004).

A series of fMRI studies was conducted employing the serial prediction task (SPT; Schubotz, 1999), a perceptual sequencing paradigm. In this task, subjects have to extract and predict repetitive sensory patterns within sequentially presented stimuli. Sequential prediction performance is tested after stimulation by a forced choice judgment on the occurrence of a sequential violation. Importantly, the stimuli are usually abstract and do not have any motor significance. Control tasks, e.g. target detection or serial-match-to-sample, provide the same amount of sensory information without requiring the identification or prediction of a sequence.

A first study (Schubotz, Friederici, & von Cramon, 2000) found that rhythm monitoring, i.e. attention to the temporal structure, in both auditory and visual sequences elicited extensive activation in premotor areas, namely the SMA, pre-SMA, precentral gyrus and opercular part of the inferior frontal gyrus bilaterally. A follow-up study (Schubotz & von Cramon, 2001b) confirmed premotor activation for attention to interval properties of visual stimulus sequences, but also reported it for ordinal, in this case spatial, properties of sequences. Thereby, dorsal premotor areas were engaged preferably in spatial-ordinal processing, ventral premotor areas in rhythmic-interval processing. In addition, motor significance was instructed for part of the sequences, i.e. these sequences had to be monitored with the intention to reproduce them later. Results indicated that activity in premotor areas was modulated by attended stimulus properties rather than by motor significance of stimuli. It could further be shown that premotor activation in the SPT is not due to mere attention to motion (Schubotz, 2004).

Another experiment investigated whether different perceptual properties draw on different sub-sections of lateral premotor cortex (Schubotz & von Cramon, 2001a). A visual SPT was employed that varied three types of sequential information simultaneously: spatial, object and rhythm information. It was found that prediction of all types of sequences activated a common network comprising left ventral premotor cortex, pre-SMA and anterior intraparietal sulcus. Moreover, in a direct comparison of perceptual properties, it was shown that attention to spatial information specifically activated bilateral dorsal premotor cortex, attention to object information specifically activated left ventral precentral gyrus, and attention to rhythm information specifically activated the inferiormost portion of ventral premotor cortex (BA 6/44) bilaterally. Results confirmed the hypothesis that predicting sequences attending to different perceptual properties engages those premotor sub-sections that would also be engaged in transforming the respective sensory pattern into a corresponding motor pattern, reflecting again the somatotopical representation of effectors in PMC (sensorimotor mapping, cf. sections 2.1.2, 2.2.4). Hence, findings were taken as evidence for a body-referenced representation of attended environmental dynamics, later termed the habitual pragmatic event map (HAPEM; Schubotz, 2007). Support for the

existence of such a map could also be drawn from a study replicating the somatotopy of premotor activations when attending to spatial, object and rhythm properties, but this time employing an auditory SPT with stimuli being artificial sounds (Schubotz, von Cramon, & Lohmann, 2003).

Additional experiments established that abstract 2D visual figures which do not have any pragmatic properties can indeed trigger activation within premotor areas involved in hand-object interaction, but only if their dynamic properties are attended. In contrast, variation of stimulus features potentially related to motor significance, i.e. “graspability” of stimuli, did not influence premotor activation (Schubotz & von Cramon, 2002b). The notion that premotor cortex activity can be modulated in the absence of changing motor requirements was confirmed by Schubotz and von Cramon (2002c). This study showed activation in PMC to co-vary positively with the complexity of the to-be-predicted sequences, a finding reminiscent of PMC involvement in the complexity of sequential motor tasks. Moreover, this co-variation proved to be property-specific: it was present in the premotor hand field for complexity of object size sequences, but not pitch sequences, while the opposite was true in the premotor vocal field (BA 6/44). A follow-up study using a parametric approach (Schubotz & von Cramon, 2002a) additionally indicated that PMC activation was sensitive to two measures of sequential complexity: both an increase in the length of sequences and a variation of sequential trend led to a corresponding increase of activation in dorsal and ventral premotor areas.

In a review (Schubotz & von Cramon, 2003), the conclusions about premotor functionality that could be drawn from studies with the SPT up to this point were summarized as follows: PMC was shown to be engaged in prospective attention to sensory events; PMC was suggested to be flexible with respect to sensory representations; PMC fields showed modality preference, but no specialization; and finally, PMC correlates of prospective attention were suggested to follow a pragmatic body map. A meta-analysis of serial prediction studies substantiated the latter assertion, the results of which are presented in Figure 2.12. This meta-analysis also encompassed, as mentioned previously in this chapter, studies on motor execution, observation, imagery, and imagery and observation of nonbiological motion and objects. It is obvious from Figure 2.12 that the maps of lateral premotor cortex emerging for motor and cognitive tasks are quite similar.

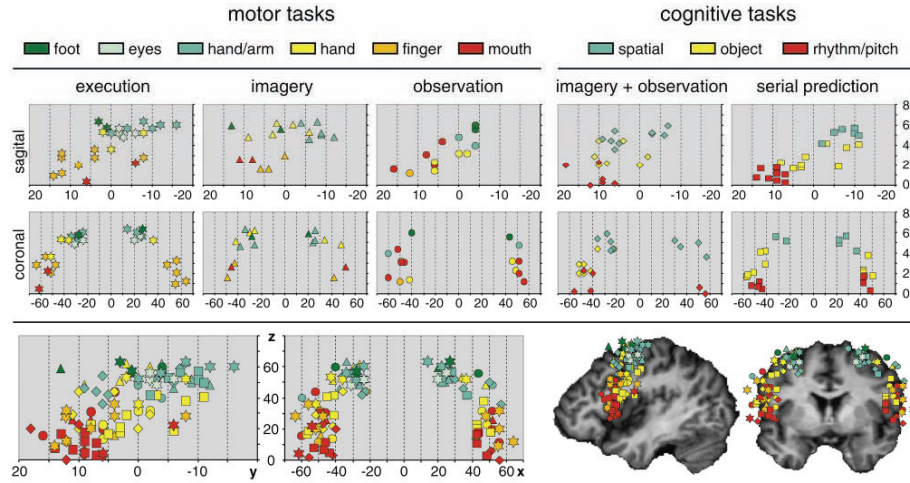


Figure 2.12 Somatotopy of premotor activations in motor and in cognitive tasks as evidenced by a meta-analysis of fMRI and PET studies (Schubotz & von Cramon, 2003). Talairach coordinates of premotor activation maxima reported in studies of execution, imagery, and observation of action or biological motion, imagery and observation of nonbiological motion and objects, and during non-motor serial prediction tasks are plotted. For studies included in the meta-analysis, see Schubotz and von Cramon (2003).

More recently, an fMRI study directly compared PMC engagement in serial prediction, action observation and motor imagery (Schubotz & von Cramon, 2004). Activation elicited by all three conditions, each compared against a target detection control task, overlapped in ventrolateral premotor cortex (BA 6) in the left hemisphere. Results confirmed the hypotheses that the prediction of sequential sensory patterns suffices as a model for understanding actions, and that PMv may be exploited for both biological and abstract sequential representations. Building on evidence from this and other studies on serial prediction, Schubotz (2007) introduced a framework for the involvement of the motor system in the prediction of external events. It was proposed that a predictive account of premotor functionality can be generalized from action to event perception, and that simulation of events is achieved using sensorimotor forward models that are housed in PMC and that are neuroanatomically ordered according to the styles of transformations they describe.

In summary, the presented work on PMC involvement in serial prediction suggests that the common denominator of premotor function might be the representation or processing of sequential information, independent from overt or covert motor functions.

2.4.2 Relational reasoning

The research program by Schubotz and collaborators is to date the only one directly targeting non-motor and non-action-related functions of premotor cortex. However, numerous imaging studies investigating a variety of “higher” cognitive functions in humans have reported activation in premotor regions for various contrasts, although they largely did not comment or elaborate on these findings. For the present investigation, the observation is important that this premotor activation seems to be apparent especially when relational computations are required in reasoning tasks.

A typical instance of deductive reasoning is transitive inference, where conclusions have to be reached by integrating relations that share one dimension. Acuna and co-workers (2002) had subjects pre-learn an ordered list of arbitrarily assigned visual shapes. During fMRI, subjects performed transitive inference on pairs of shapes that were not previously presented together. Contrasting this transitive inference task to a height comparison control task revealed activations related to reasoning. This network included, among other brain areas, the pre-SMA and lateral premotor cortex in both hemispheres. Goel and Dolan (2001), also using fMRI, investigated deductive reasoning with three-term syllogisms that consisted of propositions with either concrete or abstract content. Their findings indicate that both the concrete and abstract relational arguments, compared against baseline conditions that did not require reasoning, recruit the pre-SMA and bilateral PMd. The same authors later extended this involvement of premotor areas from deductive reasoning, i.e. evaluating the validity of syllogisms, to inductive reasoning, i.e. evaluating the plausibility of inductive arguments (Goel & Dolan, 2004). Another fMRI study provided evidence that mesial premotor cortex especially is involved in three-term relational reasoning as well as evaluating inferences on the basis of conditional propositions (Knauff, Mulack, Kassubek, Salih, & Greenlee, 2002). Furthermore, in the same study it could be shown that activation was higher in the SMA for the relational as compared to the conditional arguments.

In addition, left dorsal precentral gyrus and SMA are engaged when subjects have to make semantic decisions about abstract properties of verbally presented items, in contrast to making decisions about the perceptual properties of the same items (R. F. Goldberg, Perfetti, Fiez, & Schneider, 2007). Involvement of PMC in relational reasoning is further substantiated by the results of Green et al. (2006) who found activation in large parts of the left ventral precentral gyrus for the evaluation of both analogical relations and categorical relations between visually presented words.

2.5 Evidence from patient studies

In the previous sections, the basis for the description of human premotor cortex functions has been limited to electrophysiological and neuroimaging studies. Results obtained with these methods are necessarily correlative – it is impossible to decide whether involvement of a certain brain region is tantamount to a critical, causative role this region plays for a certain function, or whether the activation observed is only caused by a task-irrelevant outflow of activation into this region. Therefore, it is worthwhile to also consider findings from neurological patients with damage to the premotor cortex. If the function under study is impaired in patients with a PMC lesion, but unimpaired in healthy controls or patients in which the PMC is spared, it should follow that PMC is critical for the performance of that function. However, only a limited number of such studies exist, since isolated lesions of premotor cortex areas are very seldom. Nevertheless, for several of the functions discussed so far there is corroborating evidence from patient studies.

Motor output in patients is reduced when a lesion caused by stroke involves the PMC as compared to when it does not (Miyai, Suzuki, Kang, Kubota, & Volpe, 1999). Damage to PMC is most often caused by stroke, less often by traumatic brain injuries or tumors. Thereby, upper limb movement is typically more impaired than lower limb movement. Damage to dorsolateral PMC is associated with a weakness of contralateral shoulder and hip muscles (Freund, 1985; Freund & Hummelsheim, 1984). A single-case study on a patient with an isolated lesion of left SMA proper found decreased performance of an action involving reaching-grasping an object and placing it (Gentilucci et al., 2000).

The majority of patient studies investigating effects of PMC lesions have focused on sequential motor tasks, though. It has long been known that damage to premotor cortex leads to deficits in motor sequencing, i.e. the integration and coordination of several movements in time (G. Goldberg, 1985; Luria, 1966). Lesions of the SMA especially disturb the programming of simultaneous and sequential movements with both arms or hands (Dick, Benecke, Rothwell, Day, & Marsden, 1986; Laplane, Talairach, Meininger, Bancaud, & Orgogozo, 1977). Impairments in interlimb coordination have also repeatedly been observed in patients with lesions to dorsolateral PMC (Freund, 1985, 1990), whereby proximal limb movements were more affected than distal movements (Freund & Hummelsheim, 1985). Unimanual imitating performance and gesture comprehension of patients with unilateral PMC lesions did not differ significantly from control subjects, whereas bimanual tasks were severely disturbed, in particular when executing different movements simultaneously with the right and left hands was required (Halsband et al., 2001).

Findings from Halsband et al. (1993) substantiate a critical role for both SMA and lateral PMC in the generation from memory of sequences that fit into a precise timing plan. Reproduction of a finger

Theoretical Background

movement sequence was impaired in patients with damage to either mesial or lateral premotor cortex; and this impairment was most pronounced when both hands had to be used in an alternating manner. Patients with left mesial lesions involving the SMA especially had severe difficulties to produce rhythms from memory, though they were able to produce the rhythms under auditory pacing.

Furthermore, patients with PMC lesions fail to associate pre-learned hand movements with arbitrary visual, tactile and auditory cues (Halsband & Freund, 1990), confirming a critical role for PMC in sensorimotor integration.

In comparison, PMC involvement in perceptual and higher cognitive functions has been investigated in only a small number of clinical studies. Category-specific semantic disturbances after damage to certain brain areas can provide some indirect information. It was found that lesions are preferentially located in the left frontal lobe when the category "verbs" is selectively affected, and in left fronto-parietal areas when disturbances concern man-made artefacts and body parts. More specifically, patients with difficulties in naming and retrieving information about tools often have left frontal lobe lesions including the left premotor cortex (review in Gainotti, Silveri, Daniele, & Giustolisi, 1995). A study in unilateral stroke patients revealed that these patients have significant deficits in the perception of biological motion, and that the deficits were greatest when the lesion sites were in either the superior temporal or the frontal premotor areas (Saygin, 2007).

Last but not least, a critical role for PMC in the perceptual processing of sequential information could be substantiated by a patient study employing the serial prediction task (Schubotz, Sakreida, Tittgemeyer, & von Cramon, 2004). Patients with lesions to either the ventral premotor or the inferior parietal cortex showed impairments in predicting spatial sequences, object sequences and rhythm sequences; in contrast, patients with prefrontal lesions showed no performance deficits compared to healthy control subjects.

3 RATIONALE FOR THE EXPERIMENTAL WORK

In the previous chapter, evidence from studies in non-human primates, in healthy human subjects and in patients has been cited to give an overview about the various functions that have been ascribed to the premotor cortex. Premotor brain areas participate in the execution and control of actions. In contrast to primary motor cortex however, activity in premotor areas is not modulated primarily by the kinematic requirements of movement. Rather, PMC function centers on the preparation of movements, their selection according to sensorimotor associations and the coordination of movements in sequences of varying complexity. PMC is hence involved in the acquisition and planning of action sequences. In particular, lateral PMC is suggested to hold precompiled subroutines or “action ideas” (Fadiga et al., 2000) which can be thought of as relational representations that guide action; whereas mesial PMC selects and links these representations to make up higher-order actions (Shima & Tanji, 1998, 2000). Thus, it can be stated that PMC plays a role in relational processing in action-related contexts.

However, premotor cortex involvement is also apparent apart from motor requirements. PMC is active in response to sensory stimuli of different modalities, during observation and during imagery. PMC figures prominently in the processing of abstract stimulus sequences and is engaged in a range of highly abstract relational reasoning tasks. It has hence been suggested that PMC serves as an interface which can be exploited for the representation of sequentially structured events – relational representations – in a broad range of behaviors including abstract cognitive tasks, and that relational processing in PMC amounts to the acquisition and application of transformations in both action and cognition (Schubotz, 2007).

In summary, the available evidence points to an involvement of premotor cortex in both action-related and abstract tasks when relational knowledge has to be manipulated. Hereby, relational knowledge is comprised of cognitive representations that include elements and relations between elements, and that represent situations or activities in the world (Halford, Wilson, & Phillips, 1998). Relational knowledge is conceived of as content-independent, flexible and modifiable. The acquisition and use of relational knowledge is seen as central to a number of cognitive functions such as problem solving, hypothesis testing, categorization or reasoning. The function of planning, in particular, relies heavily on the processing of relations.

The empirical work presented in the next chapters aimed at further characterizing the ways in which premotor cortex contributes to relational processing in the action and abstract domains. Involvement of PMC in action-related and abstract tasks has been directly compared before (Schubotz & von Cramon, 2004). Crucially however, this comparison was between different tasks, and not within the

same task. The goal of the experimental work was therefore to directly compare, within one and the same paradigm, the processing of relational information in the motor and the cognitive domain. Furthermore, the special role of PMC in the processing of sequential information was to be investigated experimentally in more detail.

Consequently, the first experiment examined whether PMC engagement is rather determined by the domain, i.e. the abstractness of the relational information processed, or by the type of relational computations required, i.e. the processing of sequential relations in contrast to the integration of relations. The second experiment sought to concretize PMC involvement in relational processing in the action domain, differentiating between the objects and the goals of actions, as well as PMC involvement in processing sequential relations in the two domains, differentiating between sequences of abstract transformations and sequences of subgoals in actions; it also provided the opportunity to partially replicate the results of the first experiment.

We chose to use functional magnetic resonance imaging and to employ a paradigm adapted from Raven's Progressive Matrices (Raven, 1938), a widely utilized test centrally requiring the processing of relations between elements of the stimulus display. Importantly, this instrument could be adapted for our purposes to include an action condition in addition to the abstract condition. In the next chapter, the original Progressive Matrices test is introduced and our modifications are explained, followed by a brief description of fMRI basic principles.

4 METHODS

4.1 Progressive Matrices paradigm

The progressive matrices were developed by John C. Raven and first introduced in 1938 as a test of intelligence, or more specifically, to assess the “eductive” ability – a person’s ability to think clearly and make sense of complexity (Raven, 1938). Raven’s progressive matrices became and remain widely used and are today regarded as one of the best instruments to measure Spearman’s *g*, the general intelligence factor (Snow, Kyllonen, & Marshalek, 1984; Spearman, 1904), and also to measure fluid intelligence in contrast to crystallized intelligence (Cattell, 1963). Due to their non-verbal task and answer formats, the matrices are used especially with clinical populations, in children and in the elderly, and when the abilities of people from very different ethnic, cultural or social backgrounds are to be compared. In addition to the Standard Progressive Matrices (SPM), a comparably easier version has been developed, the Coloured Progressive Matrices (CPM), as well as a more demanding version, the Advanced Progressive Matrices (APM), for use within different contexts.

Although computerized versions exist now, traditionally the subject is presented with a booklet depicting one problem per page. Each problem consists of a pattern of abstract stimuli, presented in a 2x2 or 3x3 matrix, in which one element is missing. The subject’s task is to identify the element that would be required to complete the matrix correctly, and to select this element from a number of answer alternatives. Importantly, the subject is given no information on what it is that determines the correct element, or on the principles that guided the construction of the matrices. Hence, in essence, solving the matrices requires analogical reasoning, the ability to identify similarities and dissimilarities between elements of the stimulus display. As such, processing the relations between matrix stimuli is central to the performance in this test.

Long after the matrices tests had first been published and put into use, several studies have investigated their internal structure, and attempted to specify in more detail the cognitive processes involved (e.g. Babcock, 1994; Rock & Nolen, 1982; Schmidtke & Schaller, 1980). The most extensive analysis of cognitive processing in the Raven Progressive Matrices has been presented by Carpenter, Just and Shell (1990). Using performance characteristics such as verbal protocols, eye-fixation patterns and errors, it was found that all subjects employed an incremental, reiterative strategy for encoding and inducing the regularities in each problem. The authors identified five different types of rules – or relations – that govern the variation among the matrix entries in all but very few problems: elements can be constant in a row, but changing down a column; quantitative pairwise progression, i.e. a decrement or increment between adjacent entries in an attribute such as size, position or number; distribution of three values of

a categorical attribute, e.g. figure type, across a row or column; distribution of two values while the third is null; and finally, figure addition or subtraction. Important for the research presented here, if a matrix is constructed applying the “quantitative pairwise progression” rule, entries in this matrix will follow a *sequence*; the application of any of the other rules will not yield a sequential matrix structure. In the methods descriptions of Experiments 1 and 2, it will be explained in detail how matrices governed by the different rules were constructed, and how this served our purpose of examining different types of sequential and non-sequential relational processing in the brain.

To be able to compare relational processing in abstract and action-related contexts, we designed an action version of the matrices task using photographs of simple object-directed hand actions as stimulus material. In the action conditions, the rules that governed the variation between matrix entries concerned the objects the actions were performed with as well as the types and goals of the actions. Again, details and examples will be provided in the methods sections of the experiments.

Our adapted paradigm was based on the SPM version published by the German Beltz Test GmbH (Heller, Kratzmeier, & Lengfelder, 1998). Limitations regarding the size and resolution of the stimulus display on the monitor during fMRI scanning prompted us to construct matrices with two rows rather than three; for the same reason, we presented four answer alternatives for each problem instead of eight as in most of Raven’s original items.

4.2 Functional magnetic resonance imaging

Since there are a number of elaborate overviews and textbooks on fMRI fundamentals and methodology (e.g. Buxton, 2007; Huettel, Song, & McCarthy, 2004; Jaencke, 2005; Jezzard, Matthews, & Smith, 2001), in the following section the basic principles of this method will only briefly be summarized.

Functional magnetic resonance imaging has become a widely used technique to investigate brain correlates of cognitive functions. With its specific advantages and disadvantages, it complements other methods for the study of brain function. We chose fMRI because in comparison to EEG or MEG, fMRI has superior spatial resolution; this comes at the expense of poor temporal resolution, however. In contrast to PET, fMRI is non-invasive, meaning that there is no need for external contrast agents and subjects are not exposed to ionizing radiation.

Not every research question lends itself to the study with fMRI, though; for example, studying the execution of body movements or complex action sequences with this method is practically impossible, since for the most part, subjects lie supine in the rather narrow tube of an MRI scanner during data

acquisition, there is very little room for manipulating objects, and any head movement corrupts the measured signal and is therefore to be avoided.

4.2.1 Physical and physiological mechanisms

The central element of such a magnetic resonance imaging system is a 5-10 ton superconductive magnet. The object to be imaged, e.g. a human brain, is positioned inside the bore of this magnet in a strong, highly homogeneous magnetic field. The protons contained in the tissue, for example the hydrogen nuclei in water and lipids, spin and therefore have a magnetic moment. In the MRI magnetic field, the magnetic moments of a fraction of these protons align with the magnetic field vector, producing a bulk magnetization that precesses around this vector. This precessing motion occurs with a specific frequency, the Larmor frequency, which is directly influenced by the strength of the magnetic field. If one now applies a radiofrequency (RF) pulse exactly matching the Larmor frequency, the orientation of the spins can be flipped so that the bulk magnetization is perpendicular to the main magnetic field, resulting in a transverse magnetization. In this state, the precessing spins will induce a current in a surrounding electrical circuit that can be picked up by an antenna (or coil) around the object to be imaged.

After the RF pulse is turned off, the spins slowly return to their original orientation, a process called relaxation. Consequently, the transverse magnetization slowly decreases, as does the signal measured by the coil, until the RF pulse is applied again. By combination of different types of pulses and different intervals between pulses, MRI sequences suited for specific purposes can be created, for example EPI or MDEFT sequences. In addition, magnetic field gradients are employed to vary the magnitude of the magnetic field, and thus the resonance frequency, from point to point, making it possible to localize the source of the signal. The tissue, i.e. the spins' micro-environment, determines the interaction of the spins with their surroundings and therewith the decay of the MR signal. This process is described by the relaxation times, called for example T1 or T2. By emphasizing one relaxation process over the other, images with different characteristics can be created, optimal for imaging e.g. either anatomical structures, or a certain type of tissue, or functional characteristics.

To probe brain function with MRI, most often BOLD (blood oxygenation level dependent) contrast imaging is employed. This method uses the different magnetic properties of the hemoglobin in dependence of its oxygen concentration: the higher the proportion of fully saturated hemoglobin (oxyhemoglobin) relative to deoxyhemoglobin, the brighter the MR image will be. Furthermore, there is a link between neuronal activity, blood supply and blood oxygen concentration. The mechanism of neurovascular coupling describes that when neurons in a certain area of the brain are active, the blood flow to this area increases, along with the concentration of the oxyhemoglobin. Conversely, the rationale be-

hind BOLD contrast imaging posits that an increase in oxyhemoglobin concentration reflects neuronal activity in that area.

The BOLD effect is a dynamic response. In the first moments of stimulus processing in a brain region, a transient decrease in oxygen concentration can be observed, termed the initial dip. This is followed by an increase in oxygen concentration that eventually reaches a plateau as the stimulus is maintained. The increase in the BOLD signal is assumed to be proportional to the underlying neural activity. After the end of the stimulation, the BOLD signal first decreases to below its initial level (the undershoot effect) before finally returning to baseline. The mathematical model of the BOLD response is called the hemodynamic response function (HRF) and forms the basis for the analysis of fMRI data. During the course of an fMRI experiment, BOLD images are continuously acquired while a subject is performing in the paradigm. Typically, a brain volume consisting of several slices, i.e. a series of images covering the whole brain, is measured every 1-3 seconds. In very general terms, differences in neuronal activity are then inferred from brightness differences in the BOLD images at specified points in time.

Concluding this section, it is important to stress that using BOLD contrast, one obtains only an indirect measure of neuronal activity in the brain, and many of the neurophysiological processes underlying this method are not fully understood.

4.2.2 Study design and fMRI data analysis

In designing the experimental paradigm for an fMRI study, there is one principal decision to be made regarding the schema for stimulus presentation: either a block design or an event-related design can be employed. In the former, stimuli of one condition are presented in a block, followed by a block of stimuli of another condition. Historically, the block design is the precursor of event-related designs, and much less used now. Its advantages are a large BOLD signal change relative to baseline and higher statistical power; hence, block designs deliver very robust results. The main drawback of this method is, apart from criticisms regarding the assumptions, that stimulus randomization strategies cannot be employed. In the research presented here, event-related designs were used. With these, it is not only possible to randomize the presentation of stimuli from different conditions. This method also allows the detection of transient variations in hemodynamic responses, thus permitting the analysis of individual responses to trials, e.g. errors made or subjective judgments of stimuli, as well as the analysis of practice effects. Block designs and event-related designs can also be combined; this is then called a mixed design.

Because the BOLD signal change related to stimulation is relatively small in comparison to the background noise that has a similar magnitude, repeated stimulation, signal averaging and statistical process-

ing of the data are necessary. The general process of fMRI data analysis, implemented in some way or the other in the majority of fMRI software packages available, is outlined in the next paragraphs.

Once the BOLD images have been acquired, the data are pre-processed before the actual statistical analysis. The first step is usually to correct for the subject's head motion, provided that not too much of this motion occurred. Otherwise, the respective subject might have to be excluded from further analyses. Realignment of data is then performed to account for the fact that not all the slices in one brain volume are acquired at exactly the same time point during one scan. This is followed by registration, i.e. the data of all subjects are brought into the same coordinate system. Optional pre-processing steps can then follow, for example application of spatial filters to spatially smooth the data or application of temporal high- or lowpass filters, used for example to remove variance resulting from low-frequency signal drift.

After pre-processing, a first-level statistical analysis is conducted, most often based on the general linear model. Hereby, the HRF is modelled using a mathematical function representing the shape of the BOLD response, e.g. a gamma or Poisson function. A model equation is set up containing the observation data, the design matrix, and an error term. Subsequently, parameter estimates are calculated to describe each condition's impact on the BOLD response, given the observed data and the HRF model. For each subject, statistical inference can then be performed, for example using t- and z-statistics or Bayesian approaches. This results in "activation" maps describing whether the difference between parameter estimates of the given conditions is significantly different from zero. Again, it has to be kept in mind that this "activation" merely represents statistically significant differences in the BOLD response, not neural activity per se.

In most studies, the first-level single subject analyses are then followed by second-level analyses, assessing the differences in activation between conditions on the level of the whole group of subjects. Importantly, so far all the statistics have been calculated separately in each voxel. At this point, it is often necessary to employ some type of cluster size threshold or multiple comparison correction to account for the multitude of statistical tests performed, to be sure not to report false positive activations.

This standard approach to analysis of fMRI data can be supplemented by other methods for specific purposes and to answer more detailed questions. This could include for example region of interest (ROI) analyses in addition to the whole-brain analyses, conjunction analyses, connectivity analyses or principal component analysis.

In the data analysis of the two fMRI experiments that we have conducted, we followed the general procedure as delineated above, employing the general linear model. Details on the specific methods and

Methods

parameters we adopted for the individual steps of data processing can again be found in the methods sections of the experiments.

5 EXPERIMENT 1

5.1 Introduction

Employing functional magnetic resonance imaging and a reasoning task adapted from Raven’s progressive matrices, Experiment 1 examined to what extent involvement of the premotor cortex in the processing of relations would be determined by the domain and by the level of relational information processing.

Regarding the domain, i.e. the abstractness of the relational information processed, classical views would predict that PMC processes relations in the motor domain, while more anterior prefrontal areas process relations in the cognitive domain. Considering more recent findings however (Schubotz, 2007; Schubotz & von Cramon, 2001a, 2004), it could also turn out that both action and abstract relational processing rely on PMC.

Regarding the level of processing, we considered two types of relational computations that could be required in the matrices task. Since PMC has been shown to be especially involved in the processing of action or abstract *sequences* (Kettner, Marcario, & Port, 1996; Müller et al., 2002; Sakai et al., 2002; Tanji, 2001; Toni et al., 2001), we hypothesized that PMC would be recruited whenever sequential relations have to be generated or detected, as compared to non-sequential relations. Furthermore, we investigated whether PMC would be involved when relational integration is required, i.e. when several of such relations have to be integrated to make up higher-order relations. Neuroimaging studies using abstract matrices tasks have implicated prefrontal cortex, especially anterior prefrontal areas, in this function (Christoff et al., 2001; Kroger et al., 2002; Prabhakaran, Smith, Desmond, Glover, & Gabrieli, 1997). However, PMC activation has been shown to be modulated by the complexity of motor tasks (Elsinger et al., 2006; Harrington et al., 2000; Haslinger et al., 2002; Wexler et al., 1997) as well as the complexity of perceptual sequences (Schubotz & von Cramon, 2002a, 2002c). As an explorative hypothesis, PMC might therefore be involved in relational integration in our paradigm, either in both or differentially in the action and abstract domains.

Experimental factors and anatomical hypotheses

The design of Experiment 1 corresponded to a balanced 2x2x2 factorial design with factors DOMAIN, INTEGRATION and TYPE.

Firstly, the factor DOMAIN was implemented by employing both an abstract version of the matrices task, in which stimuli were closely modelled on the original Raven’s matrices, and a newly designed

Experiment 1

action version using photographs of simple object-directed hand actions as stimulus material. In the abstract version, rules to be inferred and applied to solve the matrices concerned visuospatial relations between elements of abstract graphical images, whereas in the action version, rules concerned real objects and the way they were manually manipulated. According to the first hypothesis tested, PMC should be activated by action matrices rather than by abstract ones.

The factor TYPE was implemented by employing two different types of rules, one requiring sequential processing of stimuli (Raven’s matrices rule “Quantitative pairwise progression”; “sequential” hereafter), the other non-sequential processing (Raven’s matrices rule “Distribution of three values”; “distributive” hereafter) (Carpenter et al., 1990). The sequential rule consists in the repeated application of one single transformation command within matrix rows (e.g. “add one more item”) and entails a strict sequential progression from the right to the left entry of the matrix (or vice versa). In contrast, the distributive rule amounts to the application of three transformation commands that differed within matrix rows (horizontally) but amounted to the same set between matrix rows (vertically). Thus, these matrices did not prescribe any specific progression or order of rule applications. According to the second hypothesis, PMC was expected to be active in matrices generated by sequential rules rather than by non-sequential ones.

Regarding the third and orthogonal factor INTEGRATION, each matrix was governed either by one rule or by a combination of two rules. We expected activation in PMC to be elevated by the requirement to process two-rule as compared to one-rule matrices, either to an equal extent in both domains or in the action, but not in the abstract domain.

5.2 Methods

5.2.1 Subjects

Eight male and eight female university students (mean age 26.4 years; range 21-34 years) participated in the fMRI study. All participants provided written informed consent, and the study was conducted according to the guidelines of the ethics committee of the University of Leipzig. All subjects were right-handed as assessed using a German translation of the Edinburgh Handedness Inventory (Oldfield, 1971). None had any history of neurological or psychiatric illness, and all had normal or corrected-to-normal vision.

5.2.2 Stimuli and task

Stimuli were modelled on the Raven's Progressive Matrices (Heller et al., 1998; Raven, 1938). In the upper part of each stimulus display, five individual stimuli (graphical images or photographs) and a wildcard – always in the lower right position – formed a 3x2 matrix. Below the matrix, four slightly smaller stimuli were presented as answer alternatives. The subjects' task was to find the graphical image or photograph that would complete the matrix correctly. Subjects were made aware that for each matrix problem there was one and only one correct solution.

Matrices were constructed by the combination of three factors, as delineated above.

Factor DOMAIN: In abstract problems, stimuli were abstract, black-and-white graphical images that resembled the stimuli used in the original Raven's matrices. In action problems, stimuli were black-and-white photographs of simple hand actions performed on small everyday objects.

Factor INTEGRATION: One-rule and two-rule matrices were presented. One-rule matrices were governed by a single rule. In contrast, two-rule matrices were governed by two rules that had to be considered simultaneously to determine the correct solution, thus requiring integration of relations.

Factor TYPE: Rules of the types described in the analysis of Carpenter et al. (1990) were used in the construction of the matrices. The rule governing a one-rule matrix, regardless of domain, could be either "constant in a row but changing down a column", "quantitative pairwise progression" (sequential) or "distribution of three values" (distributive). Rule combinations governing the two-rule matrices were the sequential rule combined with itself or with the "constant in a row" rule, or else the distributive rule combined with itself or with the "constant in a row" rule. The "constant in a row" rule was included to ensure variation in the systematics of the matrices, and the rule combinations were chosen to guarantee an equal proportion of matrices governed by the different rule types. The same rule combinations were used in the abstract and in the action conditions.

To verify the classification of items according to the different rule types, a rating study was conducted. Fifteen subjects that did not take part in the fMRI experiment classified the matrices as sequential or distributive. Across all conditions, items were classified correctly with a high significance ($t(14) = 15.70$, $p < .001$). Significantly more often, the abstract/sequential ($t(14) = 32.92$, $p < .001$) and the action/sequential ($t(14) = 49.95$, $p < .001$) matrices were classified as sequential than as distributive; conversely, both the abstract/distributive ($t(14) = 6.20$, $p < .001$) as well as the action/distributive ($t(14) = 2.11$, $p < .05$) items were rated significantly more often as distributive than as sequential.

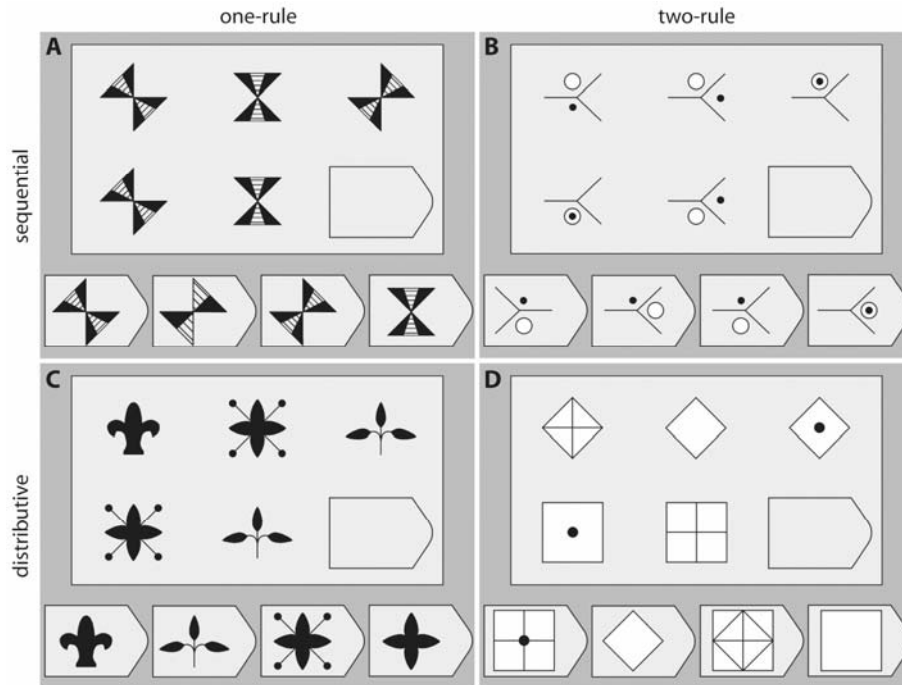


Figure 5.1 Example matrices in the abstract domain: (A) one-rule/sequential, (B) two-rule/sequential, (C) one-rule/distributive and (D) two-rule/distributive conditions. The correct answers are (alternative from left): third (A), third (B), first (C) and fourth (D).

Examples for abstract and action matrix problems constructed following the different rules are given in Figures 5.1 and 5.2. In Figure 5.1, abstract matrices are presented, each corresponding to a combination of levels of the two other factors INTEGRATION and TYPE. In Figure 5.2, analogous action matrices are presented.

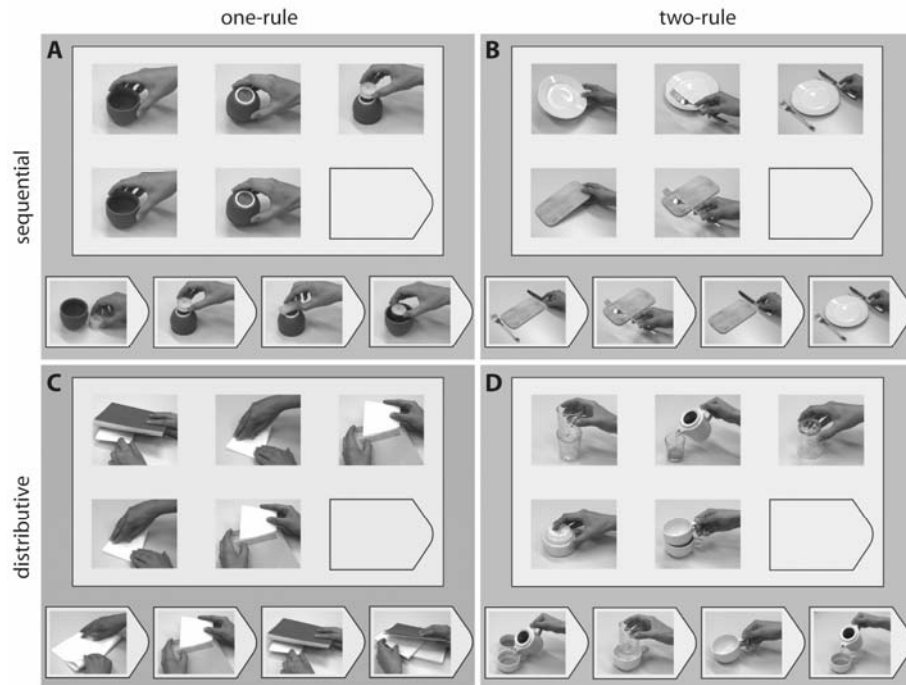


Figure 5.2 Example matrices in the action domain: (A) one-rule/sequential, (B) two-rule/sequential, (C) one-rule/distributive and (D) two-rule/distributive conditions. The correct answers are (from left): second (A), first (B), third (C) and fourth (D).

5.2.3 Behavioral procedure

A total of 96 matrices were presented, corresponding to 96 experimental trials. Matrices were presented in a pseudo-randomized fashion with a different order for every subject, interspersed randomly with an additional 20 baseline trials in which a blank screen was shown for 15 sec. An experimental trial started with a fixation cross presented in the middle of the screen for 1000 ms, followed by the presentation of the stimulus display which remained on the screen until the subject's response, but for a maximum of 25 sec. The response was to be indicated by pressing the keyboard button spatially corresponding to the selected alternative, with one of the four fingers of the right hand. Response time (RT) was measured as the time from problem onset to button press. Following their response, subjects received a correctness feedback, and the next trial started after a variable delay of 4000-5000 ms.

The instructions stressed accuracy over speed. Immediately before scanning, subjects completed a brief training session outside the scanner, solving one problem of each domain and rule or rule combination.

5.2.4 Imaging procedure

MRI scanning was performed on a 3T Siemens Trio scanner (Siemens, Erlangen, Germany). Functional images were obtained using a gradient-echo EPI sequence (TE 30 ms, flip angle 90°, TR 2000 ms). 24 axial slices with a thickness of 4 mm and an interslice gap of 1 mm (FOV 19.2 cm, 64x64 matrix, in-plane resolution 3 x 3 mm) were acquired parallel to the AC-PC line. During scanning, subjects viewed the screen via a head-mounted visual stimulation device, and had the four fingers of their right hand positioned on the response buttons.

Immediately before the functional experiment, a set of two-dimensional anatomical images was acquired using an MDEFT sequence (Norris, 2000; Ugurbil et al., 1993). In addition, high-resolution whole-brain images (160 slices, 1 mm thickness) were acquired for each subject in a separate session and subsequently standardized to Talairach stereotactic space (Talairach & Tournoux, 1988) to provide an individual 3D reference data set.

5.2.5 Imaging data analysis

Analysis of MRI data was carried out using the software package LIPSIA (Lohmann et al., 2001). Functional data were motion-corrected offline with the Siemens motion correction protocol. To correct for the temporal offset between the slices acquired in one scan, a cubic-spline-interpolation was applied. Slice gaps were then interpolated to generate output data with a spatial resolution of 3x3x3 mm.

To align the functional data slices with a 3D stereotactic coordinate reference system, a rigid linear registration with six degrees of freedom (3 rotational, 3 translational) was performed. The rotational and translational parameters were acquired on the basis of the MDEFT slices and subsequently transformed by linear scaling to a standard size to achieve an optimal match between these slices and the individual 3D reference data set. The resulting parameters were then used to transform the functional slices using trilinear interpolation, so that the resulting functional slices were aligned with the stereotactic coordinate system. A temporal highpass filter with a cutoff frequency of 1/130 Hz was used for baseline correction of the signal, and the data were spatially smoothed using a 3D Gaussian kernel of 5 mm FWHM.

The statistical evaluation was based on a least-squares estimation using the general linear model for serially autocorrelated observations (Friston, 1994; Friston, Holmes, Poline et al., 1995; Friston, Holmes, Worsley et al., 1995; Worsley & Friston, 1995). Only correctly answered trials entered the analysis. Error trials were modelled as a single separate condition but not analyzed. Given the potential for very long events, and to account for RT differences between trials, the duration of the individual

events in the model was adjusted to match the response time on each trial. The event-related design matrix was generated with a synthetic hemodynamic response function (Friston et al., 1998; Josephs, Turner, & Friston, 1997). The model equation, including the observation data, the design matrix and the error term, was convolved with a Gaussian kernel of dispersion of 4 sec FWHM to deal with the temporal autocorrelation (Worsley & Friston, 1995).

In the following, contrast-images, i.e. parameter estimates of the raw-score differences between specified conditions, were generated for each subject. The single-subject contrast-images were then entered into a second-level random effects analysis for each of the contrasts, consisting of a one-sample t-test across the contrast images of all subjects that indicated whether observed differences between conditions were significantly distinct from zero (Holmes & Friston, 1998). Subsequently, t-values were transformed into Z-scores. To ensure that only activations, but not deactivations relative to baseline are reported, contrasts were masked with a contrast of all experimental conditions versus baseline. Multiple comparison correction was performed by employing a combination of individual voxel probability thresholding and minimum cluster-size thresholding, whereby the uncorrected probability threshold was set to $p = .001$ and the cluster size threshold was computed using Monte-Carlo simulations (Forman et al., 1995; Xiong, Goa, Lancaster, & Fox, 1995). This procedure resulted in a minimum size of 486 mm^3 for clusters of activation to be reported at a significance level of $p < .05$ (corrected).

The whole-brain analyses were complemented by a region of interest (ROI) analysis. The ROI was defined as described in the Results section. For each condition and subject, parameter estimates were averaged across all voxels of the ROI and subsequently entered into repeated measures ANOVAs.

5.3 Results

5.3.1 Behavioral performance

Participants' mean response time (RT) across all conditions was 7.60 sec (SE 0.43). The effects of the factors domain (abstract, action) and integration (one-rule, two-rule) on RT data were analyzed using a two-way repeated measures ANOVA. As expected, two-rule matrices took longer to solve than one-rule matrices ($F(1,15) = 164.75, p < .001$). Action matrices were solved slower than abstract matrices ($F(1,15) = 19.42, p < .01$), and there was a significant interaction ($F(1,15) = 46.60, p < .001$) indicating that the RT difference between two-rule and one-rule matrices was higher in the action than in the abstract domain (Fig. 5.3A).

A second two-way ANOVA was conducted to determine the effect of rule type (sequential, distributive) on RT, again including the factor domain. As shown in the previous analysis, RT was longer for

Experiment 1

action than for abstract matrices ($F(1,15) = 18.91, p < .01$). RT was also longer for matrices containing the distributive rule than for matrices containing the sequential rule ($F(1,15) = 46.15, p < .001$), however, the interaction effect was not significant (Fig. 5.3B).

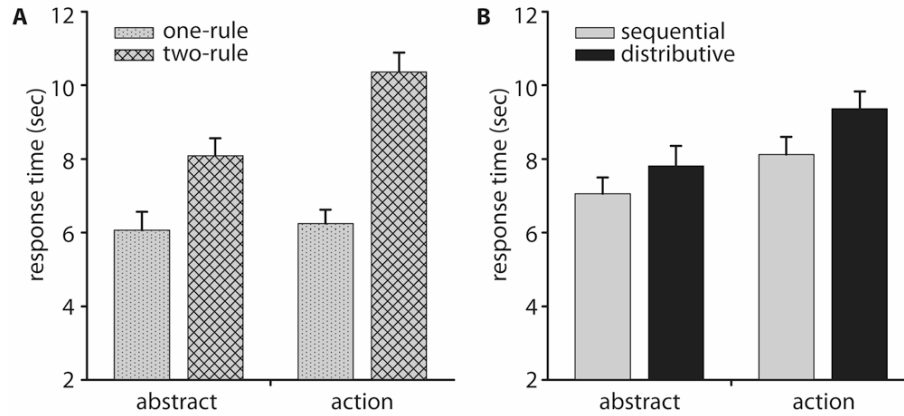


Figure 5.3 Effects of (A) domain and requirement for relational integration and (B) domain and rule type on response time (RT).

The overall error rate was low ($M = 5.53\%$, $SE = 0.99$). Analogous to the RT analysis, a two-way repeated measures ANOVA showed that two-rule matrices, in addition to taking longer to solve, also elicited more errors than one-rule matrices ($F(1,15) = 24.41, p < .001$). Error rates did not differ between domains, and there was no interaction (Fig. 5.4A). The ANOVA testing the effects of domain and rule type on error rates found no difference between problems governed by the sequential or the distributive rule, but a significant interaction ($F(1,15) = 6.32, p < .05$) as illustrated by Figure 5.4B.

Although this was a $2 \times 2 \times 2$ design, a three-way ANOVA was not employed for two reasons. Firstly, the experimental hypotheses did not extend to the three-way interactions. In addition, in case of the error rate as the dependent variable, the data did not fulfil the requirement for performing the three-way ANOVA (normal or near-normal distribution within the cells of the design) due to the fact that most subjects made very few errors. However, the data fulfilled the requirement for the two separate two-way ANOVAs. For clarity, analogous analyses were performed on the error rate and response time data.

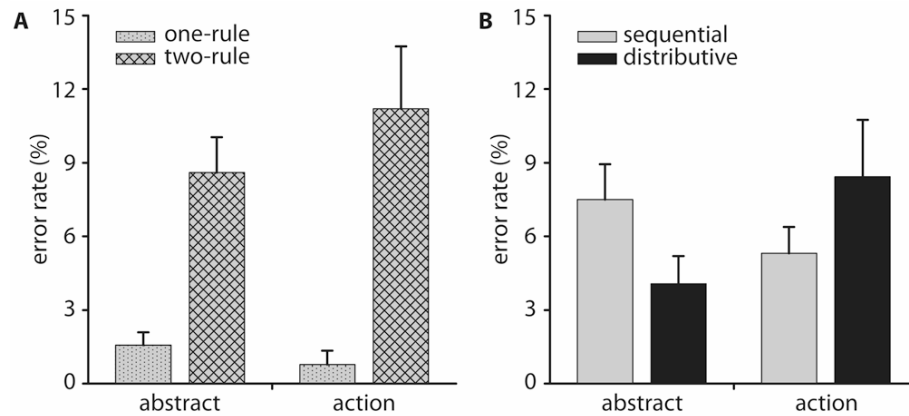


Figure 5.4 Effects of (A) domain and requirement for relational integration and (B) domain and rule type on error rates.

5.3.2 Imaging results

In order to analyze which brain regions are involved in relational processing in each of the two domains, the main effect of domain was examined. Figure 5.5A shows the contrast of action matrices versus abstract matrices (displayed in red) and the reverse contrast, abstract versus action matrices (blue), collapsed across factors integration and rule type. Areas activated in these contrasts are detailed in Table 5.1. The analyses revealed that action matrices compared to abstract matrices elicited bilateral activations in a number of brain regions. Most prominently, activation in the lateral occipitotemporal cortex extended from the middle occipital gyrus into the posterior parts of the middle and superior temporal gyri and the superior temporal sulcus. Clusters of activation were also present in the fusiform gyri and in the middle part of the inferior frontal sulci in both hemispheres. The reverse contrast, abstract compared to action matrices, yielded clusters of activation in the cuneus and inferior parietal lobules bilaterally, as well as in the right posterior intraparietal sulcus and right cerebellar hemisphere. No activation was apparent in premotor cortex. Since in solving the two-rule matrices, substantially more reasoning was required than in the one-rule matrices, and there was a significant domain by integration interaction regarding RT, we also computed the contrasts between action and abstract matrices specifically for the two-rule conditions. However, the resulting activations were largely comparable to the collapsed condition (Figure 5). Importantly, no additional cluster of activation emerged in PMC for this analysis compared to when collapsing across one-rule and two-rule trials.

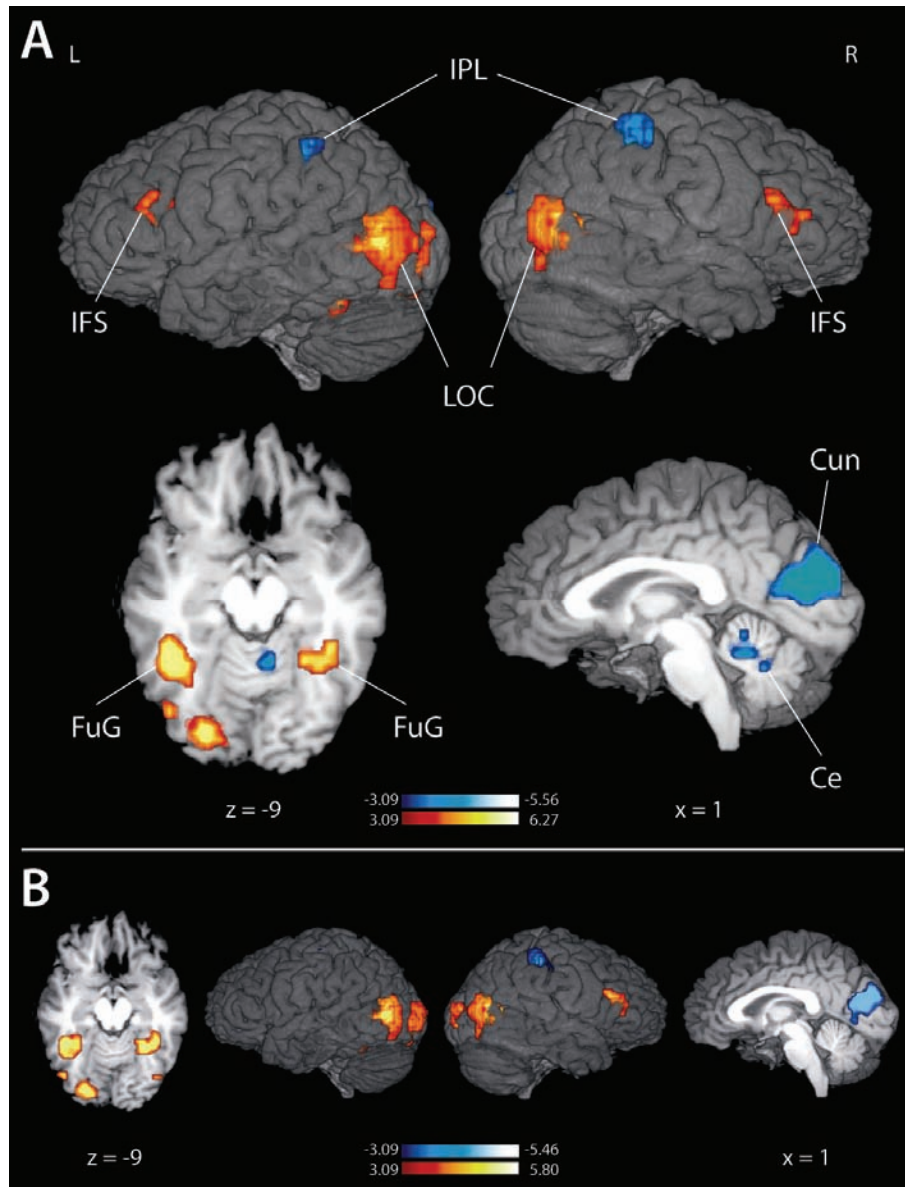


Figure 5.5 Brain correlates of domain of relational processing. Brain areas significantly activated in the action > abstract contrast are displayed in red, activations in the reverse contrast abstract > action are displayed in blue. (A) For both contrasts, trials were collapsed across factors integration and rule type. (B) The same contrasts for the two-rule trials only, collapsed across rule type. Group-averaged Z-maps ($n=16$) are overlaid onto an individual subject anatomical image ($p<.05$, corrected).

Table 5.1 Anatomical specification, hemisphere, mean Talairach coordinates (x,y,z), volume (in mm³) and maximal Z-scores of significantly activated clusters for the contrast of action vs. abstract matrices and the contrast of abstract vs. action matrices.

Area		x	y	z	mm ³	Zmax
Action vs. Abstract						
Posterolateral temporal cortex/lateral occipital cortex (LOC)	L	-53	-70	9	10341	6.28
Posterolateral temporal cortex/lateral occipital cortex	R	46	-67	12	7776	5.42
Fusiform gyrus (FuG)	L	-41	-43	-9	2538	4.47
Fusiform gyrus	R	25	-52	-12	1296	3.85
Inferior frontal sulcus (IFS)	L	-47	23	21	891	3.96
Inferior frontal sulcus	R	46	29	12	945	4.24
Abstract vs. Action						
Cuneus (Cun)	R/L	4	-79	21	12501	5.57
Inferior parietal lobule (IPL)	L	-41	-40	39	567	4.36
Inferior parietal lobule	R	46	-37	45	2241	4.78
Posterior intraparietal sulcus	R	19	-67	51	810	4.10
Cerebellar hemisphere (Ce)	R	10	-52	-18	1674	4.51

Brain regions recruited for integration of relations were determined by computing the two-rule matrices versus one-rule matrices contrast, collapsing across domain and rule type. The resulting map is displayed in Figure 5.6; details on clusters of activation are given in Table 5.2. A network of primarily frontal and parietal areas was evident. Frontal activations were pronounced in the left hemisphere. They encompassed the posterior part of the mesial and lateral superior frontal gyrus, the precentral sulcus, extending anteriorly along the inferior frontal sulcus with extensive activation in the adjacent middle and inferior frontal gyri into the lateral part of the frontopolar cortex. Activation was also apparent in the left anterior insula, right posterior superior frontal sulcus and middle frontal gyrus. In addition, relational integration elicited extensive activation in the precuneus, the superior and inferior parietal lobules in both hemispheres as well as some activation bilaterally in posterior inferior temporal sulcus and in the cerebellar hemispheres. Again, this contrast did not reveal activation in premotor brain areas.

To investigate whether brain regions were differentially involved in relational integration in any of the two domains, the domain by integration interaction contrast was computed. After performing the multiple comparison correction, this contrast did not yield any brain areas that showed a significant interaction of these two factors.

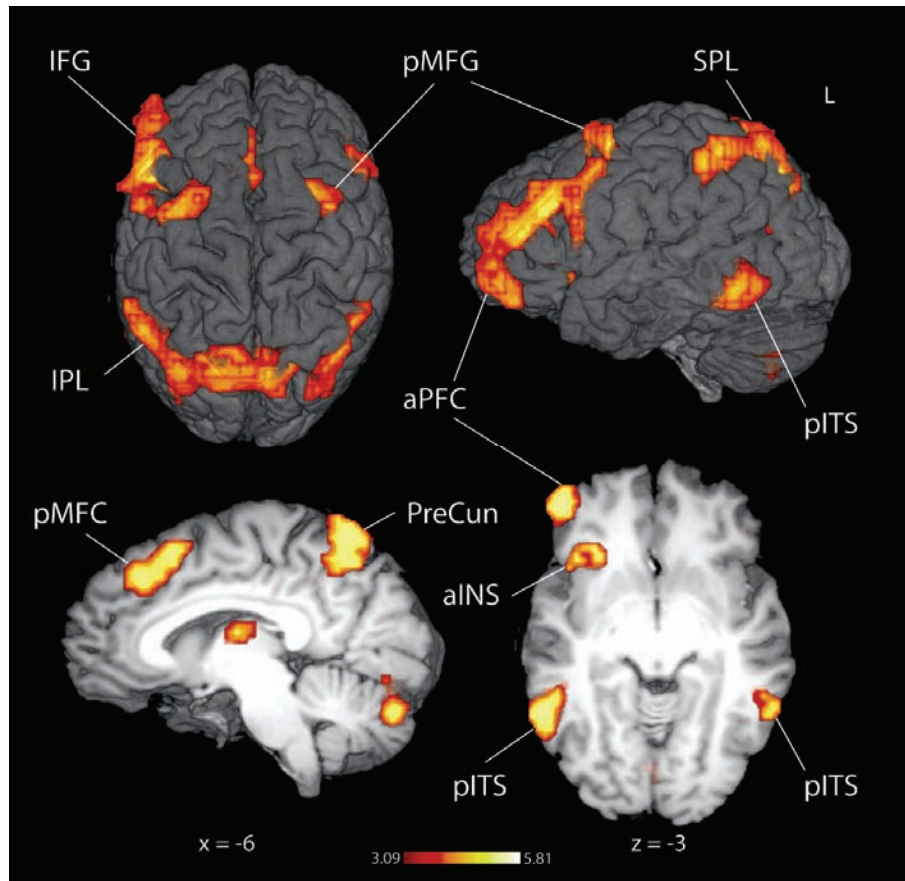


Figure 5.6 Brain correlates of requirement for integration. Two-rule > one-rule contrast, collapsed across factors domain and rule type.

Table 5.2 Anatomical specification, hemisphere, mean Talairach coordinates (x,y,z), volume (in mm³) and maximal Z-scores of significantly activated clusters for the contrast of two-rule vs. one-rule matrices.

Area		x	y	z	mm ³	Zmax
Two-rule vs. One-rule						
Posterior middle frontal gyrus (pMFG), inferior (IFG) and middle frontal gyrus	L	-32	2	51	17793	5.81
Posterior mediofrontal cortex (pMFC)	L	-8	29	36	2619	4.45
Anterior insula (aINS)	L	-41	17	0	1215	4.25
Posterior middle frontal gyrus	R	22	8	42	1674	4.63
Precentral sulcus	R	28	2	27	1593	3.88
Middle frontal gyrus	R	37	32	21	918	3.87
Inferior and superior parietal lobule (IPL/SPL), precuneus (PreCun)	L	-35	-70	39	15795	5.71
Inferior parietal lobule	R	31	-73	39	4941	5.04
Posterior inferior temporal sulcus (pITS)	L	-53	-52	-6	2808	5.00
Posterior inferior temporal sulcus	R	52	-52	-3	810	3.79
Globus pallidus	L	-14	-4	3	1404	4.03
Cerebellar hemisphere	R	28	-70	-30	10989	4.72
Cerebellar hemisphere	L	-35	-67	-33	729	3.96

In order to assess activation patterns related to the rule type manipulation, the BOLD signal was averaged over all trials containing the sequential rule and all trials containing the distributive rule, respectively, collapsing across domain and rule number. Since no matrices were presented that contained both of these rules, the two conditions were mutually exclusive. The contrasts of distributive rule matrices versus sequential rule matrices and vice versa were computed. The resulting activations are listed in Table 5.3 and illustrated in Figure 5.7. In view of our target region premotor cortex, a prominent cluster of activation in the right ventrolateral PMC was found, in which BOLD response was higher for sequential rule matrices than for distributive rule matrices. This pattern was also observed for two regions in the right inferior parietal lobule and the posterior part of the right middle temporal gyrus, respectively. Only one cluster of activation emerged in the contrast of distributive rule matrices versus sequential rule matrices, this cluster encompassing the superior part of the precuneus and cuneus in the left hemisphere.

The whole-brain analyses showed no evidence for a main effect of domain or a main effect of integration in premotor cortex. As predicted, PMC showed a main effect of rule type. Therefore, an ROI analysis was conducted in order to confirm the whole-brain findings and to examine the effects of the other factors in this specific premotor ROI in more detail.

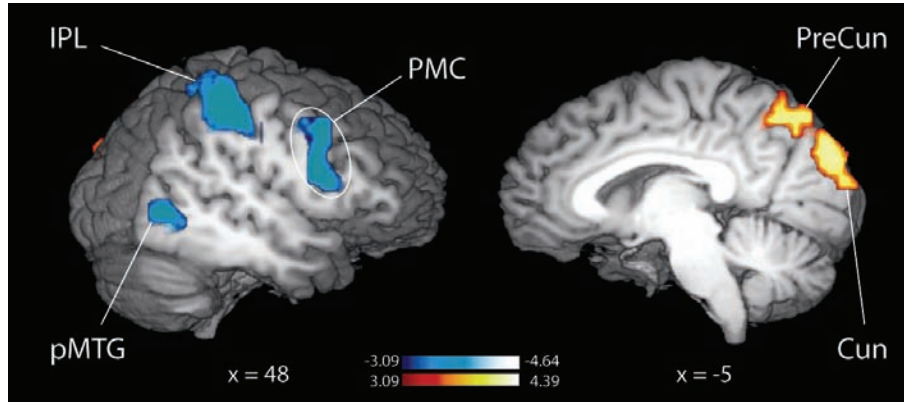


Figure 5.7 Brain correlates of rule type manipulation. The contrast of distributive > sequential rule matrices is displayed in red, the reverse contrast sequential > distributive in blue. For both contrasts, trials were collapsed across factors domain and integration. The circle illustrates the approximate position of the PMC ROI. For the exact definition of the ROI, see text.

Table 5.3 Anatomical specification, hemisphere, mean Talairach coordinates (x,y,z), volume (in mm³) and maximal Z-scores of significantly activated clusters for the contrast of distributive vs. sequential rule matrices and the contrast of sequential vs. distributive rule matrices.

Area		x	y	z	mm ³	Zmax
Distributive vs. Sequential						
Cuneus, precuneus	L	-8	-91	33	3591	4.40
Sequential vs. Distributive						
Premotor cortex (PMC)	R	40	5	24	2160	3.86
Inferior parietal lobule	R	49	-31	42	5967	4.65
Posterior middle temporal gyrus (pMTG)	R	40	-58	3	999	4.36

The PMC ROI was defined as all voxels constituting the cluster of activation within right ventrolateral PMC in the sequential vs. distributive rule contrast (see Table 5.3 and Figure 5.7). A three-way repeated measures ANOVA with factors domain, integration and rule type was performed on the parameter estimates. A significant main effect of rule type confirmed that BOLD response in this region was higher for sequential than for distributive rule matrices ($F(1,15) = 36.30$, $p < .001$). The main effects of domain and integration did not yield significant results. The only significant interaction was domain by rule type ($F(1,15) = 20.48$, $p < .001$). However, a closer examination of this interaction by use of paired t-tests showed that in PMC, BOLD response was elevated for sequential as compared to distributive rule matrices both in the abstract ($t(15) = 6.32$, $p < .001$) and the action conditions ($t(15) = 3.052$, $p < .01$) (Fig. 5.8). In summary, the ROI analysis well corroborated and substantiated the results from the whole-brain contrasts.

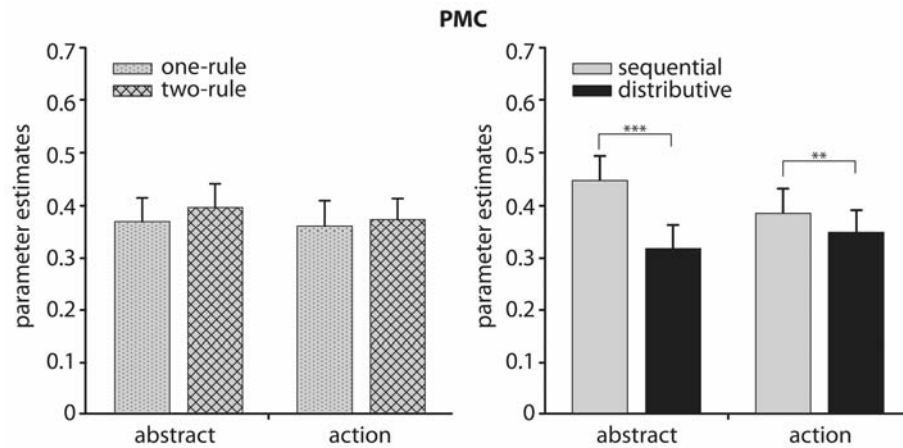


Figure 5.8 Results of ROI analysis. Effects of requirement for relational integration and rule type in PMC. *** $p < .001$ ** $p < .01$

5.4 Discussion

Experiment 1 investigated the role of the premotor cortex in relational processing. Specifically, we focused on two potential factors as determinants of PMC involvement, namely on the processing domain, considering action-related versus abstract relational processing, and on the type of relational processing, considering processing of sequential relations and relational integration.

Processing domain

The contrasts between action and abstract matrices did not reveal any significant activation differences in PMC, a result that could be confirmed by the ROI analysis. Our first hypothesis, derived from traditional accounts of PMC function, can thus be rejected: PMC is not more involved in relational processing in the action than in the abstract domain. While this absence of a significant difference in activation does not constitute proof that PMC is engaged in relational reasoning in the two domains to the same extent, nevertheless, it is consistent with the notion of PMC involvement not only in motor-related behavior, but also in purely cognitive tasks. PMC involvement therefore seems not to be determined by the domain of processing, but rather by the type of processing required in the task.

However, a number of other brain regions, predominantly non-frontal, showed activation in dependence of the domain of relational processing. These results could be in part replicated, in part explicated in more detail in the second experiment. To avoid repetitions, they will therefore be discussed together with the results of Experiment 2 (see chapter 6.3).

Relational Integration

Data replicated prior imaging studies' findings on relational integration in abstract matrices tasks (Kroger et al., 2002; Prabhakaran et al., 1997). In line with these previous accounts, we conceived relational integration as the simultaneous consideration of several relations between matrix entries. In this conceptualization, integration does not just entail the actual step of inserting the results of the current subtask into a stored representation, but also includes the maintenance of these representations during periods of subtask processing (De Pisapia, Slomski, & Braver, 2007). The present results confirm that a widespread bilateral fronto-parietal network is recruited for relational integration. Mesial frontal activation extended into the pre-SMA, although without reaching a local maximum there. Likewise, while a large portion of lateral prefrontal cortex was activated, this activity extended into a small part of the precentral sulcus, but without reaching a local maximum or the surface of the precentral gyrus. Accordingly, the prefrontal cortex (PFC) but not lateral PMC can be considered significantly enhanced by relational integration. In addition, neither PMC nor any of the areas constituting the relational integration network were differentially activated by relational integration in the abstract or the action domain, as shown by both the whole-brain analyses and the ROI analysis.

These results have several implications. Firstly, the respective network was found engaged by relational integration in both abstract and action-related matrices. Data thereby extend previous findings beyond the abstract into the action domain, providing evidence for the domain-generalty of this network. Secondly, we had hypothesized PMC to be involved in relational integration on the basis of findings that PMC processes the complexity of motor and perceptual sequences. However, these types of sequential complexity seem to be distinct from the relational complexity in matrices tasks in terms of the brain areas recruited.

Sequential and non-sequential relations

Considering the engagement of PMC in relational processing guided by sequential and non-sequential rules, it was apparent that the two rule types elicited differential activation in PMC – but again, independent of domain. BOLD response in right ventrolateral PMC was significantly higher for sequential as compared to distributive rule problems, and this was true in both the action and the abstract conditions. For each sequential rule matrix there existed a specific transformation command that could be applied to get from the first to the second stimulus in a row and again to get from the second to the third stimulus. Thus, adjacent entries within matrices could be readily concatenated into a coherent sequence by applying one transformation command. Stronger involvement of PMC under these conditions strengthens the argument for a role of this region in providing generic transformation styles for applications in different behavioral and cognitive domains (Schubotz, 2007). For instance, it has been

shown that ventral PMC can be exploited for both action-related and abstract sequential representations (Schubotz & von Cramon, 2004). The results of Experiment 1 inform this view in that they show that activation in PMC is not only elicited when sequential prediction is asked for, but also in a task in which stimuli are presented all at once but nevertheless related to one another by sequential relations.

Co-activations of PMC in this contrast were found in the anterior intraparietal sulcus (aIPS) and the motion sensitive area (MT), both of which are known to project to ventrolateral PMC (Ghosh & Gattera, 1995). The aIPS is known to provide ventrolateral PMC with pragmatically relevant object descriptions (Borra et al., 2008; Fagg & Arbib, 1998); area MT is engaged in the processing of motion (Grossman et al., 2000). These co-activations lend further support to the view that transformations in the cognitive-perceptual domain are to a certain extent comparable to those in the motor domain (Schubotz, 2007). Considering the present findings from this perspective, the notion of pragmatic relevance or pragmatic meaning can be more generally framed as pertaining to those properties of an object that are subjected to transformational computations in PMC. On the other side, activity in area MT suggests that by concatenation of matrix entries the imagination of dynamic transformation was elicited. This finding extends prior findings on area MT which has been suggested not only for the perception of motion, but also for the imagination of motion (Goebel, Khorram-Sefat, Muckli, Hacker, & Singer, 1998) and for the perception of merely implied motion (Kourtzi & Kanwisher, 2000; Senior et al., 2000).

Hierarchical theories on frontal organization

The results of Experiment 1 relate to a growing literature on prefrontal cortex and frontal organization in general. Specifically, PFC has not only been implicated in relational integration in abstract matrices tasks, but also in the integration of propositions for evaluating semantic analogies (Bunge, Wendelken, Badre, & Wagner, 2005; Green et al., 2006). We can now extend PFC involvement in relational integration from the visuospatial and semantic domain to action-related cognition. Furthermore, this area has been shown to be central to functions such as branching and multitasking (Braver & Bongiolatti, 2002; Dreher, Koechlin, Tierney, & Grafman, 2008; Koechlin, Basso, Pietrini, Panzer, & Grafman, 1999), leading to the development of several recent theories of anterior-to-posterior functional hierarchies within the PFC, some including the PMC (Badre, 2008; Badre & D'Esposito, 2007; Koechlin & Summerfield, 2007). One of these models proposes that action selection is guided by hierarchically ordered control signals, processed in a network of brain regions organized along the rostrocaudal axis of lateral PFC and PMC (Koechlin, Ody, & Kouneiher, 2003). Thereby, rostral PFC is held to be central to behaviors and mental activities requiring simultaneous engagement in multiple tasks that are not serially organized into a pre-established superordinate plan, enabling it to overcome the serial constraints that

Experiment 1

are in effect in more posterior brain areas (Koechlin & Hyafil, 2007). Our finding that PFC is activated for relational integration, whereas PMC is not, is supportive of these hierarchical models which postulate the most anterior regions of PFC to become involved at the highest stages of executive processing. PMC's pronounced involvement in sequential rule matrices might, in addition, be indicative for this region's preference for serial cognitive processing, in accordance with the model of Koechlin and Hyafil (2007). Related to this, the results of Experiment 1 are also in agreement with a model postulating that prefrontal areas such as Broca's area contribute to the generation of higher-level organization in actions and language while operating upon lower-level, serially organized representations provided by the premotor cortex (Fiebach & Schubotz, 2006).

Process-specificity and domain-specificity

A further theoretical issue our data are relevant to is the ongoing question of process- versus domain-specificity in PFC organisation. In domain-specific models, functional dissociations between brain regions reflect the same fundamental process operating on different categories of information, while in process-specific models, they reflect the operation of different processes, regardless of the type of information being processed (Gilbert et al., 2006). Our findings are particularly relevant to the notion that anterior PFC regions are domain-independent, whereas more posterior regions of the frontal lobes are domain-specific (Bunge et al., 2005; Sakai & Passingham, 2003; E. E. Smith & Jonides, 1999). Our study is a direct test of both a process-specific and a domain-specific hypothesis regarding PMC. Indeed, our data provide no evidence for selective involvement of PMC in relational processing in one of the two domains studied. Instead, PMC was preferentially activated for sequential processing, but in both domains. Consequently, our results are consistent with a process-specific account, but inconsistent with a domain-specific account of PMC function. Our study therefore suggests that cognitive functioning within PMC is process-specific, but domain-independent.

Conclusion

Experiment 1 aimed to make a contribution to clarifying the functional significance of premotor cortex in relational information processing. Findings suggest that the role of PMC in relational processing is not primarily determined by the abstractness of the relational information processed, i.e., by the informational domain. Rather, involvement of this brain area is modulated by the type of relational processing, with lateral PMC being engaged for the concatenation of sequentially related entities into coherent sequences, but not for the integration of multiple relations in parallel.

6 EXPERIMENT 2

6.1 Introduction

In Experiment 1, we had investigated the influence of the domain – abstract versus action-related – and the influence of two types of relational information processing – sequential relations and integration of relations – on premotor cortex activation using a matrices task.

In a direct comparison of abstract and action-related matrices, we had found PMC not to be differentially activated; we had concluded that the role of PMC was not primarily determined by the abstractness of the relational information processed. Meanwhile, a closer look at the action problems employed in Experiment 1 reveals that the relations between the matrix entries concerned two aspects important for characterizing an action, namely the action itself or the *goal* of the action as well as the *object* the action is performed with. In most of the action problems in Experiment 1, these two aspects were not separated, but varied concurrently. However, it might make an important difference to PMC involvement whether the relations governing a matrix problem concern the objects or the goals of the actions. The premotor cortex has repeatedly been suggested to code actions preferentially in terms of the action goal in tasks such as observation or imitation of actions (Chaminade, Meltzoff, & Decety, 2002; Gazzola et al., 2007; Iacoboni et al., 2005; Koski et al., 2002), even in single-cell studies in monkeys (Rizzolatti et al., 1988; Rizzolatti, Gentilucci et al., 1987; Umiltà et al., 2008). PMC activation is differentially modulated by information about the identity of an object or about the way the object is manipulated during goal inference of real actions and pretend actions (Schubotz & von Cramon, 2009). On the other hand, PMC activation has been reported for mere presentation of action-related objects in a variety of tasks (Chao & Martin, 2000; Creem-Regehr et al., 2007; Creem-Regehr & Lee, 2005; Grafton et al., 1997; Grezes et al., 2003; Grezes & Decety, 2002). A first aim of Experiment 2 was therefore to put the hypothesis of domain-independent processing within PMC to a more stringent test by focusing more strongly on the action conditions. Specifically, we investigated whether it would be sufficient for PMC to become more engaged in relational processing in our matrices task when the relations between matrix stimuli concerned the action objects, or whether PMC was more engaged when the rules governing the matrices referred to the action goals.

There was one further consideration to make, concerning the representation of action goals, and which relates to the second aspect of relational processing investigated in Experiment 1, the processing of sequential relations. Action goals are organised hierarchically and sequentially, meaning that a number of lower-order goals or sub-goals is processed in a sequential fashion to reach a higher-order goal (Byrne & Russon, 1998; Grafman, 1989; Newell & Simon, 1972; Ward, 2005). Both lateral and mesial

Experiment 2

premotor cortex have been ascribed a role in the organization of movements into sequences (Boecker et al., 1998; Gerloff et al., 1997; Gordon, Lee, Flament, Ugurbil, & Ebner, 1998; Grafton et al., 2002; Roland, Larsen, Lassen, & Skinhoj, 1980; Shima & Tanji, 1998, 2000), although no neuroimaging study so far has investigated sequences of complex actions involving objects. PMC also serves the representation of sequentially structured events in abstract perceptual tasks (review in Schubotz & von Cramon, 2003). In Experiment 1, we had found that lateral PMC was engaged more for reasoning with sequentially structured matrices than with non-sequential matrices, and this was true for both the abstract and action-related matrices. In Experiment 2, we now aimed to replicate this finding for the abstract condition; furthermore, we wanted to investigate whether this differential involvement of PMC would persist when the sequential structure of a matrix refers to a sequence of sub-goals constituting a higher-order action, i.e. when these sub-goals are presented in a sequential or non-sequential manner.

As in Experiment 1, we employed a relational reasoning task adapted from Raven's Progressive Matrices (Raven, 1938), following the construction principles as explicated by Carpenter and colleagues (1990). Three conditions were created. Also as in Experiment 1, in the abstract condition the stimuli making up the matrices were abstract graphical images resembling the original stimuli, and the rules underlying the composition of the matrices concerned the number and identity of stimulus elements. In the two action conditions, matrix stimuli were again photographs of simple hand actions performed on everyday objects. In the action/object condition, reasoning principles concerned the number and identity of objects, similar to the abstract condition, with the difference being the presentation of action stimuli. In contrast, in the action/goal condition, reasoning principles centred on the goal of the actions depicted, while the visual appearance of the stimuli was equivalent to the action/object condition. Hereby, the sequence of goals as depicted by the single photographs could either follow a "natural" sequence of sub-goals, leading to attainment of a higher-order goal (sequence-correct), or the sequence was violated (sequence-incorrect). Again, brain activity was assessed using fMRI.

Since in Experiment 1 the requirement to process two rules governing the matrices was not found to modulate PMC activation in comparison to the one-rule matrices, the latter condition was dropped in Experiment 2 so that all matrices contained two rules.

6.2 Methods

6.2.1 Subjects

Fifteen university students (8 female) participated in the fMRI experiment. Mean age was 24.7 years, age range 21-29 years. All participants provided written informed consent. The study was conducted

according to the guidelines of the ethics committee of the University of Leipzig. All subjects were right-handed with a laterality quotient higher than 89 as assessed using a German translation of the Edinburgh Handedness Inventory (Oldfield, 1971). No participant had any history of neurological or psychiatric illness, and all had normal or corrected-to-normal vision.

6.2.2 Stimuli and task

The general layout of the stimuli was the same as in Experiment 1, with the 3x2 matrix and wildcard in the upper and four answer alternatives in the lower part of the stimulus display. The task was again to find the graphical image or photograph that would complete the matrix correctly. Subjects were made aware that for each matrix problem there was one and only one correct solution, and the instructions stressed accuracy over speed.

Matrices were constructed to fall into three conditions (Figure 6.1), each encompassing 30 matrices in two sub-conditions.

The first of these was the abstract condition, in which the individual stimuli were again abstract black-and-white graphical images that resembled Raven's original stimuli (Heller et al., 1998; Raven, 1938). For 15 of the abstract matrices, the construction principle to be inferred by the subjects in order to solve the matrices concerned the number of individual stimuli – or parts thereof – in the matrix entries. This number could be either increasing or decreasing ("quantitative pairwise progression" rule; Carpenter et al., 1990), giving the matrices a sequential structure (Figure 6.1A) analogous to the abstract/sequential condition in Experiment 1. For the other 15 abstract matrices, the construction principle concerned the identity of the individual stimuli ("distribution of three values" rule; Carpenter et al., 1990), so these matrices followed the distributive rule as in Experiment 1 (Figure 6.1B).

In addition to the abstract condition, there were two "action" experimental conditions in which matrices were composed of black-and-white photographs of simple hand actions performed on everyday objects.

The first of these was the action/object condition. In this condition, within the single photographs constituting a matrix, the number and/or identity of the objects was varied while the type of action depicted – the action goal – stayed the same in all photographs. Again, in 15 of the action/object matrices the number of objects was varied in a sequential fashion (Figure 6.1C), while in the other 15 matrices the identity of the objects was varied following the distributive rule (Figure 6.1D). Thus, the reasoning principles were the same as in the abstract condition, while the presentation of stimulus material was action-related.

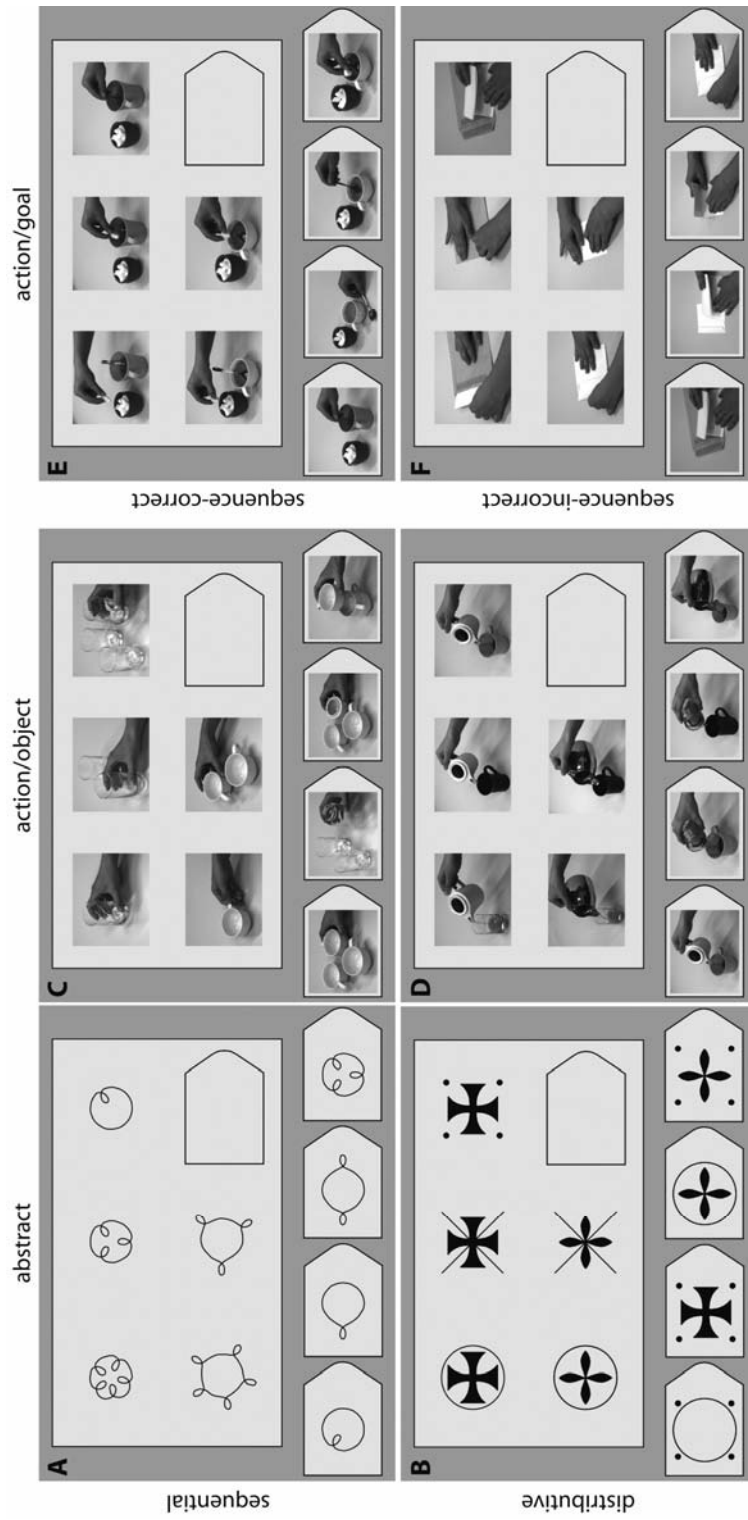


Figure 6.1 Example matrices for Experiment 2: (A) abstract-sequential, (B) abstract-distributive, (C) action/object-sequential, (D) action/object-distributive, (E) action/goal-sequential correct, and (F) action/goal-sequential incorrect conditions. The correct answers are (alternative from left): second (A), fourth (B), first (C), fourth (D), third (E) and second (F).

In contrast, in the third experimental condition – the action/goal condition – the objects were the same in all individual photographs of one matrix. What was varied was the type of action depicted, i.e. the goal to be achieved by the object manipulation. Thus, in this condition, the action goal had to be inferred from each photograph to arrive at a correct solution for the whole matrix problem, while in the action/object condition, this was not necessary.

6.2.3 Rating study

A final experimental manipulation concerned the sequential structure within the matrices in the action/goal condition. In a preceding behavioral study with 30 participants, all six possible arrangements of the three action photographs potentially constituting one row in each matrix of the action/goal condition were presented to the subjects. Thereby, the three photographs depicted three single actions that together constituted a higher-order action when performed in the right order. In the rating study, the subjects' task was to indicate, on a 5-point Likert scale, how sensible the subject felt the sequence of actions to be. Then, for 15 of the matrices of the action/goal condition the sequences with the highest sensibility rating were chosen (referred to as “sequence-correct” condition in the following). Thus, in the sequence-correct condition, the sequence of the three action goals depicted within one matrix row followed a sensible sequence of sub-goals, as would be required for the attainment of a higher-order goal in the case of real actions (Figure 6.1E). For the other 15 of the action/goal matrices, the sequences with the lowest sensibility rating were chosen (“sequence-incorrect”), so that in this condition, the natural sequence of sub-goals was violated (Figure 6.1F). The chosen sequences in the “sequence-correct” condition had received a mean sensibility rating of 4.97 points (SE 0.02) and the chosen sequences in the “sequence-incorrect” condition a mean sensibility rating of 1.53 points (SE 0.10), a difference that proved to be highly statistically significant ($t(29) = 33.88, p < .001$).

6.2.4 Behavioral procedure

In the scanning session, a total of 90 matrices were presented, in a pseudo-randomized fashion with a different order for every subject. Each matrix corresponded to one experimental trial. The course of events within one trial was identical to Experiment 1. Interspersed randomly with the experimental trials were 20 baseline trials in which a blank screen was shown for 15 sec. Immediately before scanning and outside the scanner, subjects completed a short training session consisting of 13 problems, at least one from each condition and none of which were presented during the scanning session.

6.2.5 Imaging procedure and data analysis

The MRI procedure in Experiment 2 was identical to Experiment 1, with none of the parameters changed.

MRI data were analyzed using the software package LIPSIA (Lohmann et al., 2001) and following the same procedure as described for Experiment 1, with a few exceptions driven by parameters of the design and data in Experiment 2: The temporal highpass filter employed for baseline correction of the signal had a cutoff frequency of 1/120 Hz, and the data were spatially smoothed using a 3D Gaussian kernel of 6 mm FWHM.

As in Experiment 1, only correctly answered trials were included in the analysis, error trials were modelled separately, but not analyzed, and the duration of the individual events in the model was adjusted to match the response time on each trial to account for RT differences between trials. The procedure employed for multiple comparison correction also corresponded to the procedure used in Experiment 1; for Experiment 2, the cluster size threshold computed for clusters of activation to be reported at a significance level of $p < 0.05$ (corrected) was equal to a minimum size of 810 mm³.

6.3 Results

6.3.1 Behavioral performance

Across conditions, matrix problems were solved with a mean response time (RT) of 9.50 sec (SE 0.11). RT was longer in the action/object than in the abstract condition ($t(14) = 3.71$, $p < .01$), and longer in the action/goal than in the action/object condition ($t(14) = 6.17$, $p < .001$) (Figure 6.2A). Within the abstract condition, there was no difference between sequential and distributive rule matrices; likewise, within the action/goal condition, there was no RT difference between sequence-correct and sequence-incorrect matrices (Figure 6.2B). Overall, problems were solved with good accuracy (mean error rate 7.18 %, SE = 0.95). There were no error rate differences between the action/object and the abstract condition or between the action/goal and the action/object condition (Figure 6.3A). As was the case for RT, error rates did not differ between sequence-correct and sequence-incorrect matrices; however, in the abstract condition, subjects made more errors on distributive than on sequential rule trials ($t(14) = 2.20$, $p < .05$) (Figure 6.3B).

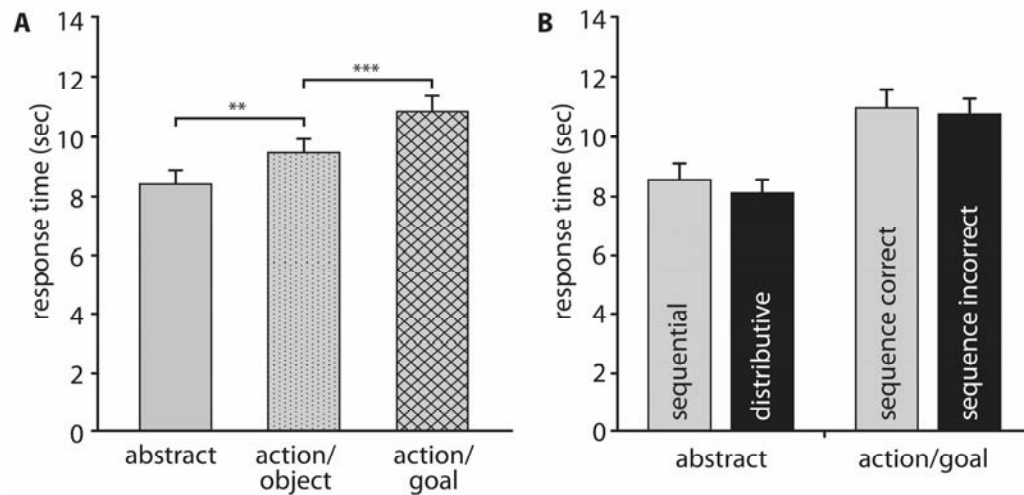


Figure 6.2 Effects of experimental manipulations on response time (RT). *** $p < .001$ ** $p < .01$

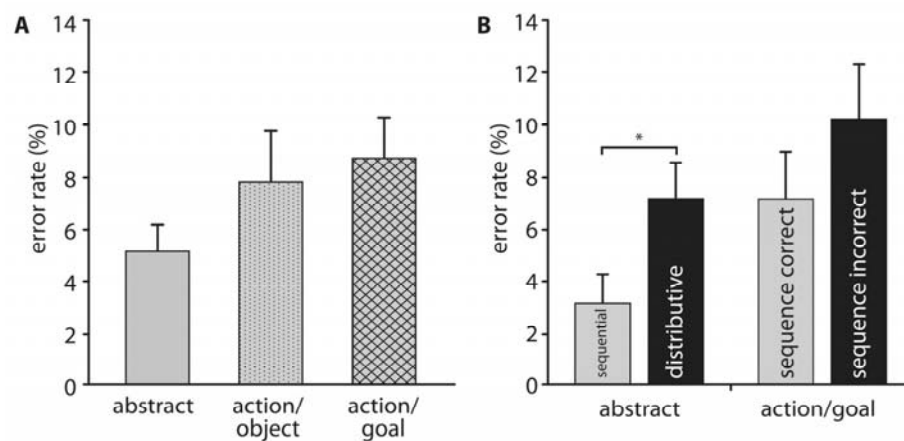


Figure 6.3 Effects of experimental manipulations on error rate. * $p < .05$

6.3.2 Imaging results

Brain activation related to the presentation of abstract and action-related stimuli – whereby in both cases, the reasoning principles concerned the objects – was determined by computing the contrasts between the action/object versus the abstract condition and vice versa. Activated areas are shown in Figure 6.4 and detailed in Table 6.1. For the action/object condition (shown in red), most prominently, large clusters of activation were evident in the lateral occipitotemporal cortex in both hemispheres, extending into the posterior part of the superior temporal sulcus. Further activation showed bilaterally

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in the fusiform gyrus, in the left superior parietal lobule, left orbitofrontal cortex and mesially in posterior cingulate cortex.

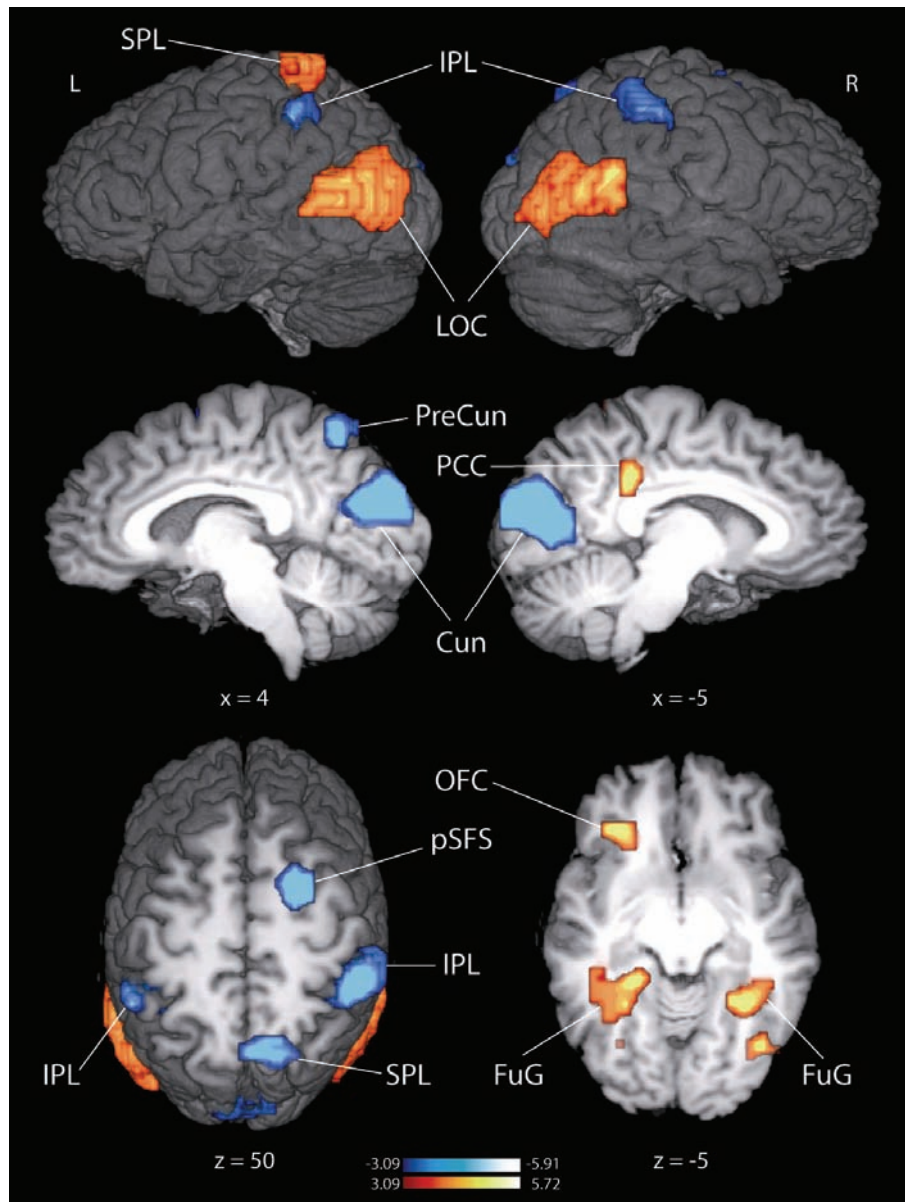


Figure 6.4 Brain correlates of domain of relational processing in Experiment 2. Brain areas significantly activated in the action/object > abstract contrast are displayed in red, activations in the reverse contrast abstract > action/object are displayed in blue. Group-averaged Z-maps (n=15) are overlaid onto an individual subject anatomical image ($p < .05$, corrected).

Table 6.1 Anatomical specification, hemisphere, mean Talairach coordinates (x,y,z), volume (in mm³) and maximal Z-scores of significantly activated clusters for the contrast of action/object vs. abstract matrices and the contrast of abstract vs. action/object matrices.

Area		x	y	z	mm ³	Zmax
Action/Object vs. Abstract						
Posterolateral temporal cortex/lateral occipital cortex (LOC)	L	-50	-67	18	14148	5.73
Posterolateral temporal cortex/lateral occipital cortex	R	43	-73	9	14067	5.22
Fusiform gyrus (FuG)	L	-32	-46	-9	4644	4.39
Fusiform gyrus	R	31	-46	-12	3483	4.52
Superior parietal lobule (SPL)	L	-38	-43	66	2268	4.47
Posterior cingulate cortex (PCC)	L	-11	-40	36	1431	4.72
Orbitofrontal cortex (OFC)	L	-29	29	-3	1161	4.22
Abstract vs. Action/Object						
Cuneus (Cun)	R/L	-8	-79	15	15741	5.91
Posterior superior frontal sulcus (pSFS)	R	22	-1	51	1890	4.93
Superior parietal lobule	R	10	-67	51	1755	4.21
Inferior parietal lobule (IPL)	L	-44	-40	42	2295	5.07
Inferior parietal lobule	R	46	-31	45	3618	5.17

The reverse contrast, abstract versus action/object (displayed in blue in Figure 6.4), revealed activation in the posterior superior frontal sulcus and posterior superior parietal lobule in the right hemisphere and bilaterally, although more accentuated in the right hemisphere, in the anterior part of the inferior parietal lobule. Finally, the superior part of the cuneus, above the calcarine sulcus, showed stronger activation for abstract than action/object matrices in both hemispheres.

Brain activation related to processing relations concerning action goals was determined by computing the contrast between the action/goal and the action/object condition. The resulting network of areas is shown in red in Figure 6.5, and details on activated areas can be found in Table 6.2. The network includes the left dorsal premotor cortex, as well as a large cluster of activation bilaterally in the parietal cortex extending from the precuneus, middle intraparietal sulcus and posterior inferior parietal cortex into occipitotemporal cortex, again encompassing a large part of the posterolateral superior temporal cortex. The reverse comparison - action/object versus action/goal condition - only revealed one cluster of activation in the anterior cingulate cortex (displayed in blue in Fig. 6.5).

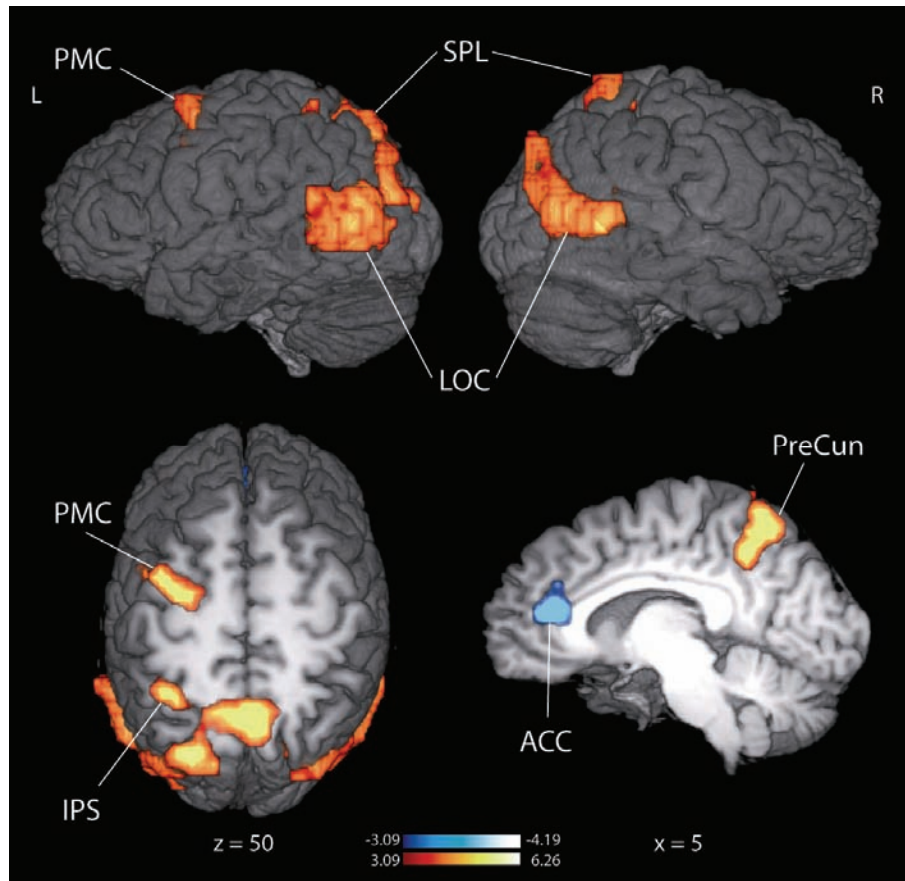


Figure 6.5 Brain correlates of processing action goals. Brain areas significantly activated in the action/goal > action/object contrast are displayed in red, activations in the reverse contrast action/object > action/goal are displayed in blue.

Table 6.2 Anatomical specification, hemisphere, mean Talairach coordinates (x,y,z), volume (in mm³) and maximal Z-scores of significantly activated clusters for the contrast of action/goal vs. action/object matrices and the contrast of action/object vs. action/goal matrices.

Area		x	y	z	mm ³	Zmax
Action/Goal vs. Action/Object						
Premotor cortex (PMC)	L	-26	-4	57	3078	3.93
Intraparietal sulcus (IPS)	L	-32	-46	48	864	3.96
Posterolateral temporal cortex/lateral occipital cortex (LOC), posterior inferior and superior parietal lobule (SPL), precuneus (PreCun)	L/R	-50	-67	18	26433	5.66
Posterolateral temporal cortex/lateral occipital cortex, posterior inferior parietal lobule	R	46	-64	12	13473	6.26
Action/Object vs. Action/Goal						
Anterior cingulate cortex (ACC)	R/L	1	35	15	3078	4.19

Within the abstract condition, sequential rule matrices as compared to distributive rule matrices elicited activation in the right posterior superior frontal sulcus and in the right ventral premotor cortex (Figure 6.6, blue; Table 6.3). Right-hemispheric activation was further apparent in a large part of the anterior inferior parietal lobule and in the posterior middle temporal gyrus; a region in left anterior intraparietal sulcus was activated as well. The reverse contrast, abstract distributive versus sequential rule matrices, revealed activation bilaterally in the cuneus only (Figure 6.6, red).

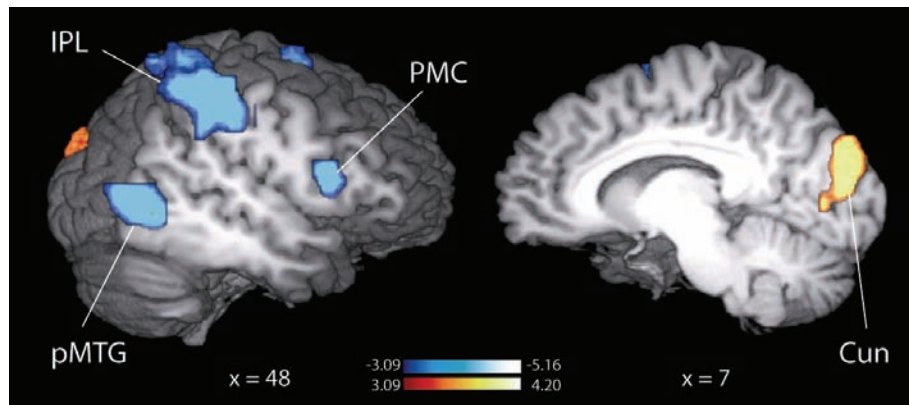


Figure 6.6 Brain correlates of rule type manipulation, separately for the abstract condition. The contrast of distributive > sequential rule matrices is displayed in red, the reverse contrast sequential > distributive is displayed in blue.

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Table 6.3 Anatomical specification, hemisphere, mean Talairach coordinates (x,y,z), volume (in mm³) and maximal Z-scores of significantly activated clusters for the contrast of abstract distributive vs. sequential rule matrices and the contrast of abstract sequential vs. distributive rule matrices.

Area		x	y	z	mm ³	Zmax
Abstract Distributive vs. Sequential						
Cuneus (Cun)	R/L	4	-88	12	4185	4.20
Abstract Sequential vs. Distributive						
Premotor cortex (PMC)	R	46	11	12	999	4.76
Posterior superior frontal sulcus	R	22	-1	60	1944	4.73
Inferior parietal lobule (IPL)	R	40	-49	48	12231	4.92
Anterior intraparietal sulcus	L	-35	-34	45	1431	4.06
Posterior middle temporal gyrus (pMTG)	R	46	-58	0	2808	5.17

Finally, the effect of sequential order manipulation on brain activation in the action/goal condition was assessed by computing the contrast between the sequence-incorrect and the sequence-correct matrices (Figure 6.7, Table 6.4). This comparison revealed activation in the SMA, with the center of mass in the right hemisphere, and activation in the posterior part of the precuneus. No activated areas were apparent in the reverse comparison.

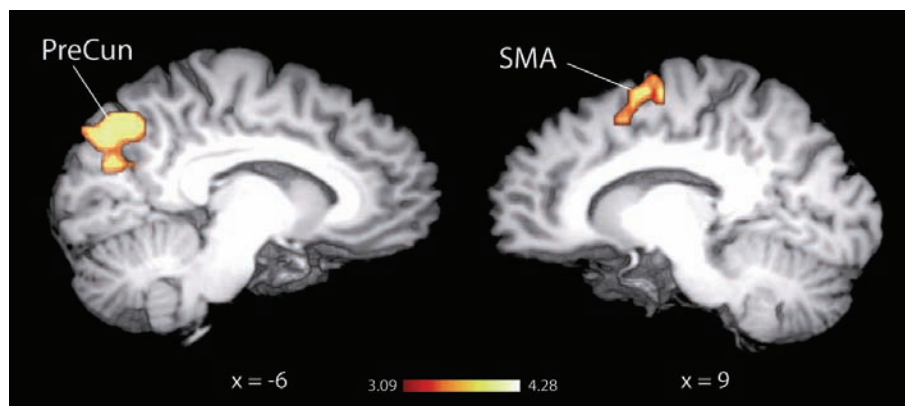


Figure 6.7 Brain correlates of sequential order manipulation in the action/goal condition. The contrast of sequence-incorrect > sequence-correct matrices is displayed. The reverse contrast did not yield activation.

Table 6.4 Anatomical specification, hemisphere, mean Talairach coordinates (x,y,z), volume (in mm³) and maximal Z-scores of significantly activated clusters for the contrast of sequence-incorrect vs. sequence-correct matrices.

Area		x	y	z	mm ³	Zmax
Sequence-incorrect vs. Sequence-correct						
Supplementary motor area (SMA)	R	7	-4	60	1161	4.01
Precuneus (PreCun)	R/L	-5	-79	39	2484	4.29

6.4 Discussion

Experiment 2 was conducted to more closely investigate premotor cortex involvement in both aspects of relational processing – the domain and type of relations – explored in Experiment 1.

Specifically, in Experiment 2 we asked whether PMC would still be equally engaged in reasoning with abstract and action matrices when the reasoning principles governing the action matrices differentiated between action objects and action goals. A second aim was to replicate preferential PMC involvement in reasoning with sequentially structured matrices, and to test whether this preference would extend to action matrices in which the sequential structure specifically refers to a sequence of sub-goals of a more complex action.

Comparison of action/object and abstract matrices

Firstly, the comparison of the action/object versus the abstract condition was designed to reveal brain activation related to the presentation of action photographs in contrast to abstract graphical figures as stimulus material, whereby the reasoning principles in both conditions concerned the number or identity of the “objects”.

The most prominent clusters of activation evident in that contrast were located in lateral occipitotemporal cortex in both hemispheres. These large clusters of activation encompassed a number of functionally defined high-level visual processing areas, most notably the extrastriate body area (EBA) and human motion area (MT/V5), as well as the posterior superior temporal sulcus (pSTS). EBA responds selectively to visual presentation of the whole or part of a human body (Downing, Jiang, Shuman, & Kanwisher, 2001; Spiridon, Fischl, & Kanwisher, 2006) and EBA activation in our paradigm likely reflects the presence of photographed hands in the action, but not in the abstract condition. Area MT/V5 is activated by the presence of motion in a visual display, both non-biological (Tootell et al., 1995; Watson et al., 1993) and biological motion (Grossman et al., 2000). However, activation in MT/V5 can also be elicited by implied motion contained in still pictures, both of humans and of ob-

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jects (Kourtzi & Kanwisher, 2000; Senior et al., 2000). There was no motion present in our stimulus displays, but the stimuli in the action conditions were designed to imply a specific action and thus, movement of hands and objects. A related argument applies to the involvement of pSTS in this contrast. The pSTS is also activated by biological motion (Grossman et al., 2000) – this holds especially for hand actions (Bonda, Petrides, Ostry, & Evans, 1996) – and it can also be elicited by imagination of biological motion (Grossman & Blake, 2001). It seems that the motion implied in the action photographs was processed by the visual system, even though in solving the action/object matrices, considering the way the objects were manipulated was less relevant.

The activation in the fusiform gyrus for action/object versus abstract stimuli is consistent with this area's role in the processing of the pragmatic meaning of objects, especially of tools as manipulable objects with an associated function (Chao, Haxby, & Martin, 1999). Specifically, right and left fusiform gyrus activation has been found for viewing and imagined grasping of tools vs. abstract shapes (Creem-Regehr & Lee, 2005), and also for processing the visual attributes of familiar objects (Gauthier, Tarr, Anderson, Skudlarski, & Gore, 1999; Vandenberghe, Peeters, Fannes, & Vandenberghe, 2006). In addition, the activation in OFC in this contrast likely has to be seen in connection with the clusters of activation just discussed. The central OFC as a multisensory integration area receives projections from both inferior and superior temporal brain areas (Carmichael & Price, 1995). Thus, OFC activation in this contrast might reflect the transmission of highly processed visual information from these more posterior areas to OFC (Wallis, 2007).

Finally, activation in the contrast of action/object versus abstract matrices showed in a region of posterior cingulate cortex (PCC). PCC is most often discussed as having a central role in episodic memory retrieval. It consistently shows activation when subjects correctly recognize previously encountered memory items (Bunge et al., 2005). Moreover, Sugiura and colleagues (2005) found a PCC region similar to ours activated when subjects judged places and objects as familiar to them. This leads us to suggest that PCC activation in our experiment is due to the subjects' recognition of the objects depicted in the action photographs, which were familiar everyday objects (e.g. plate, cup, pen and so on) in contrast to the figures of the abstract condition, which were unfamiliar to all subjects.

In summary, visual presentation of action/object in contrast to abstract stimuli in our relational reasoning task elicited activation primarily in posterior and inferior temporal brain areas implicated in higher visual perception. Activation in these areas was evident although the task was not explicitly to monitor the stimuli. Rather, the percept had to serve as the basis for subsequent rule extraction and application. A very similar pattern of results was evident in Experiment 1, where large clusters of activation with comparable extent and location showed bilaterally in posterior occipitotemporal cortex and fusiform gyrus when action matrices were compared against abstract matrices (cf. Figure 5.5). The results of Ex-

periment 2 suggest that the factors discussed in the previous paragraphs - presentation of body parts and familiar objects, motion implied in the action photographs – also play a role in interpreting the respective activations in Experiment 1.

Reasoning with matrices of the abstract as compared to the action/object condition elicited activation in the caudalmost part of the superior frontal sulcus – an area which corresponds to the postulated location of the human frontal eye field (FEF) (Paus, 1996) – in conjunction with activation in the inferior parietal lobule and the posterior part of the superior parietal lobule. The FEF and posterior parietal cortex are key elements of a network for visuospatial attention (Corbetta & Shulman, 2002; Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999; Mesulam, 2000). We take the activation of this network to reflect enhanced processing of the visuospatial aspects of the stimuli in the abstract condition, in the absence of information about familiar objects as in the action/object condition. In addition, substantial activation in the superior part of the cuneus was apparent in the same contrast. A cue to understanding this activation comes from a study by Beauchamp and colleagues (2002), who compared human and tool motion against moving abstract gratings. The opposite comparison – gratings vs. humans/tools – yielded only one cluster of activation, bilaterally in the cuneus. This finding is paralleled in our study by the cuneus activation found for abstract compared to action/object stimuli. However, this analogy rests tentative since there was no motion present in our stimuli. The upper part of the cuneus distinctly above the calcarine sulcus is taken up by extrastriate visual areas V3 and V3a (Zilles & Rehkaemper, 1998), both implicated primarily in the perception of the form of visual stimuli (Dumoulin & Hess, 2007; Ress, Backus, & Heeger, 2000; e.g. Zilles & Rehkaemper, 1998). Thus, the higher level of activity in the cuneus might reflect that in the abstract condition, the visual system relies more on a detailed analysis of the form of the matrix stimuli to establish the relations between them.

Again, these interpretations likely also apply to the clusters of activation apparent in the cuneus and lateral parietal lobe in the contrast of abstract versus action matrices in Experiment 1 (cf. Figure 5.5), which were again comparable in extent and location.

Notably, no area in premotor cortex showed activation in the contrast of action/object versus abstract matrices or in the reverse contrast, also corroborating the findings in Experiment 1. It can thus now be stated more precisely that PMC is not differentially involved in relational processing in the action as compared to the abstract domain if relations in the action domain concern the objects of the actions. PMC does not automatically become more engaged in relational processing when the stimulus material is action-related or when manipulable objects are presented.

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Action/goal and action/object matrices

When the relations between the goals of the actions had to be processed, as in the action/goal condition, as compared to when the relations concerned the objects of the actions, as in the action/object condition, BOLD response was higher in premotor, posterior parietal and posterior temporal areas.

Specifically, frontal activations were located in the dorsal premotor cortex (PMd), particularly in the anterior part of the precentral gyrus bordering the precentral sulcus. It has been the ventral part of the premotor cortex (PMv) that has been implicated in action imagery (Decety et al., 1994; Schubotz & von Cramon, 2004) or action goal representation (Iacoboni et al., 2005; Johnson-Frey et al., 2003; Koski et al., 2002). However, there are also several studies reporting more dorsal premotor activations (Creem-Regehr & Lee, 2005; Gerardin et al., 2000; Grafton, Arbib et al., 1996; Grezes & Decety, 2001, 2002). Grafton and colleagues (1996) found PMd to be activated both when subjects reached to and grasped an object as well as when they reached and pointed to that object. Activations in PMd rather than PMv have been reported for preparation and execution of reaching movements (Kawashima et al., 1994; Kertzman, Schwarz, Zeffiro, & Hallett, 1997). Moreover, Koski and colleagues (Koski et al., 2002) reported PMd activation when the goal of a hand movement to be imitated was a position in space. Taken together, these findings suggest that as soon as the action to be executed, imitated or imagined involves a spatial goal or some spatial displacement of the arm and/or hand, more dorsal premotor regions become involved, in comparison to pure grasping where only the hand and fingers are involved (e.g. Binkofski, Buccino, Stephan et al., 1999; Grafton, Arbib et al., 1996).

Compared to simple grasps, most of the actions depicted in our action stimuli actually implied a transport phase of the arm and hand and the moving of objects through space to a different position several centimetres away and relative to other objects. The focus was more on the spatial configuration of hands and objects than on the local interactions of the hand with the object. Thus, it is plausible that in the action/goal condition, brain areas involved in reaching situations, i.e. when an object's position in space drives the spatial parameters of the arm and hand movement, rather than brain areas involved in the control of grasping actions became engaged. A study by Majdandzic et al. (2009) supports this assumption, showing that during action observation, object properties relevant for grasp selection are related to activation in PMv, while the end state of an action in terms of a spatial goal is related to activation in PMd.

The activations in parietal cortex in the same contrast further corroborate this interpretation. Bilateral activation was apparent in the mesial bank of the intraparietal sulcus, in conjunction with the superior parietal lobule and the precuneus, i.e. the mesial aspect of the parietal cortex. In humans, the parietal regions involved in the representation of reaching movements lie posterior and mesial to the region

involved in the representation of grasping movements (Culham, Cavina-Pratesi, & Singhal, 2006; Greffes & Fink, 2005). This reflects the dissociation of parietofrontal circuits for the control of reaching versus grasping in the macaque (Matelli & Luppino, 2001; Rizzolatti et al., 1998). In fact, neuroimaging studies confirm the involvement of dorsal premotor, mesial intraparietal and superior parietal brain areas – a network very similar to our findings – in execution, observation and imagery of reaching (Filimon et al., 2007) and motor simulation of hand and arm rotation (Johnson et al., 2002).

In addition, the contrast between the action/goal and the action/object condition revealed clusters of activation bilaterally in LOC. The location and extent of these clusters were highly similar to the occipitotemporal activations observed in the contrast of the action/object as compared to the abstract condition. This finding is consistent with evidence that posterolateral temporal brain regions are not only engaged in the perception of higher-order features of visual action-related stimuli, as discussed above, but that these regions also process actions at a more conceptual level. In a study by Kable and colleagues (2002), BOLD response was increased bilaterally in area MT and adjacent regions of lateral temporal cortex when subjects had to match drawings according to the action that was illustrated by them. Furthermore, Kable and Chatterjee (2006) could show adaptation of activation in lateral occipitotemporal cortex, specifically including EBA, MT and pSTS, to occur when a certain action was repeatedly presented as opposed to when the actor was repeated. They took this area to be involved in action-selective processing and activity in this area to distinguish between particular actions. Distinguishing between different actions – performed on the same objects – was exactly what was necessary in the action/goal in contrast to the action/object condition. Thus, in our studies, posterolateral temporal cortex was recruited when subjects reasoned with action as compared to abstract stimuli, and the same area became especially involved with the requirement to consider the goal of the depicted actions.

Sequential order manipulation in the abstract condition

The comparison of sequential rule matrices versus distributive rule matrices specifically for the abstract condition revealed activation in a predominantly right-hemispheric network encompassing the ventral premotor cortex, anterior inferior parietal lobule and posterior middle temporal gyrus. This pattern of activation is largely comparable to the activations elicited by sequential as compared to distributive rule matrices in Experiment 1 (cf. Figure 5.7, Table 5.3). In particular, the activation found in PMv is consistent with the results of the ROI analysis (cf. Figure 5.8). We thus successfully replicated preferential PMC involvement in reasoning with sequentially structured matrices for the abstract condition.

The reverse comparison, distributive vs. sequential rule matrices, revealed activation solely in the cuneus, as in Experiment 1 (cf. Figures 5.7, Table 5.3).

Sequential order of sub-goal sequences

Finally, activation related to the sequential order of action/goal matrix stimuli was evident in the SMA and in the precuneus. This activation was stronger for sequence-incorrect than for sequence-correct matrices. The mesial premotor cortex encompassing the SMA and pre-SMA has been shown to be centrally involved in sequencing movements (Gerloff et al., 1997; Gordon et al., 1998; Grafton et al., 2002; Shima & Tanji, 1998, 2000; Tanji, 2001). Most investigations in this area so far have been conducted using sequences of simple movements such as key presses. However, our results suggest that SMA may also play a role in controlling the sequential structure of more complex action sequences composed of distinct subgoals. The problems in the sequence-incorrect condition, in which a sequential structure was present, but violated, may have placed a greater demand on this sequence-control function of SMA.

As to the precuneus' involvement, Cavanna and Trimble (2006) posit a general role of the precuneus in spatially guided behavior and in visuospatial imagery. The precuneus is suggested to especially process the spatial aspects of imagined movement. In line with this, it was shown that the precuneus codes the spatial components of motor sequence processing, and that activity in precuneus correlates with higher sequential complexity (Sadato et al., 1996). The spatial representation of sequential movements performed from memory also activates posterior rather than anterior parts of the precuneus, consistent with the location of activation in our experiment. In light of these views, it is plausible that the precuneus is activated for sequence-incorrect rather than for sequence-correct matrices, as the former stimuli could have a higher level of complexity, and could require a higher amount of visuospatial imagery. This interpretation would also be consistent with evidence that the activation level in precuneus increases as a function of effort during a spatial working memory task (Wallentin, Roepstorff, Glover, & Burgess, 2006).

Differential involvement of action-related brain areas in a cognitive task

In Experiment 2, we found several brain areas engaged in action-related processing to be also recruited in a cognitive task requiring relational reasoning. Fadiga and Craighero (2004) put forward the idea that the motor system is involved “whenever the idea of an action is evoked”. However, our results argue for a differential involvement of the parts of the system. We can now specify this in more detail by finding that posterior and inferior temporal brain areas are preferentially involved when reasoning with action as compared to abstract stimuli. For these brain regions, visual presentation of action-related stimuli is sufficient to elicit activation. In contrast, a premotor-parietal-temporal network implicated in the execution, observation and imagery of actions is only active in our task when the goals of actions have to be inferred. This suggests that this network supports the representation of the goal of an action

not only in action execution and observation, but also in more cognitive tasks such as action planning and reasoning. Moreover, the SMA as a premotor area implicated in the control of motor sequences is also involved in processing the structure of sub-goal sequences in a relational reasoning paradigm, providing further evidence for a comparable role of the brain regions underlying action execution also in higher cognitive processing.

Our results mirror findings in the domain of semantic knowledge, where it has been shown that retrieval of conceptual action knowledge, in contrast to retrieval of knowledge about objects, likewise activates a network encompassing occipitotemporal cortex, inferior and superior parietal as well as premotor cortex (Assmus, Giessing, Weiss, & Fink, 2007). On a more general level, our findings also relate to the dual-route hypothesis of a ventral pathway for object recognition and a dorsal pathway for visually guided actions (Goodale & Milner, 1992; Milner & Goodale, 2006; Mishkin & Ungerleider, 1982), as in our study, inferotemporal areas, namely the fusiform gyrus, were specifically activated when reasoning principles centered on concrete objects, while posterior parietal and premotor areas showed specific activation when reasoning principles concerned the action performed (Shmuelof & Zohary, 2005).

7 GENERAL DISCUSSION

In recent years, there has been a surge in research efforts directed at establishing the functions of specific brain regions. For the premotor cortex, as for many other brain areas, this has resulted in a multitude of studies employing very different methods and paradigms, all implicating PMC in a variety of both motor and abstract processes and functions. To advance the understanding of PMC functionality however, it would be desirable to establish more general principles and mechanisms that might underlie these specific functions. Along these lines, in this thesis the starting point for the experimental work was the assertion that a central function of the premotor cortex might be the processing of relational information, be it in the context of motor behavior or in the context of abstract cognitive tasks. This was investigated with two fMRI experiments, comparing relational information processing in an abstract and an action version of the same matrices reasoning paradigm, and considering different types of relations.

Premotor cortex contributions

The results of Experiment 1 did not provide any evidence that premotor cortex was involved in relational reasoning differentially in an action-related or an abstract matrices task, as evidenced by a direct comparison. Experiment 2 confirmed that activation in PMC was not differentially modulated by the abstractness of the stimulus material, in accordance with the notion that PMC figures in relational processing in different cognitive domains.

In addition, Experiment 2 revealed that premotor cortex – as part of an action-related network of brain areas also including the posterior parietal and posterior temporal cortex – was especially engaged in this reasoning task when the goals of the actions depicted had to be considered. This finding suggests that PMC subserves action goal representation in a wide variety of cognitive tasks ranging from action execution or observation to highly complex reasoning tasks.

Together, these results can be taken to reflect the fact that action representations and their cerebral correlates play a role in a much wider range of cognitive operations than suggested by traditional motor accounts of PMC function, in accordance with the proposition underlying this investigation (Jackson & Decety, 2004; Schubotz, 2004, 2007).

Regarding the type of relations, the experiments provided evidence for the assertion that premotor cortex plays a special role in processing sequential relations in abstract and action-related contexts. In both experiments, it could be established that activation in PMC was modulated by the sequential structure of the matrices. A most striking finding was the robust involvement of ventrolateral PMC in the ab-

stract conditions when the matrices had a strictly sequential structure, compared to matrices in which the stimuli did not follow a sequence. These results confirm and, in being obtained with an entirely novel paradigm, extend the notion that PMC subserves the representation of sequentially structured events in a broad range of behaviors including abstract cognitive tasks (Schubotz & von Cramon, 2003, 2004).

However, the experiments also indicated a dissociation of ventrolateral and mesial PMC with respect to the processing of sequential information. While lateral PMC showed activation when successful sequential concatenation of stimuli, especially with respect to abstract relations, was possible, mesial PMC (SMA) showed effort-related activation when this concatenation was not as easily achieved in the case of sub-goal sequences of more complex actions.

Methodological considerations

Functional magnetic resonance imaging has been the method of choice for the present investigation because this technique makes it possible to study the functions of the brain non-invasively in healthy humans. If the premises and assumptions underlying fMRI are correct (see for example Goense & Logothetis, 2008; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001), this method allows the identification of the neural correlates of cognitive functions with previously unparalleled spatial accuracy. However, fMRI as a method still has the limitation that it is an indirect rather than a direct measure of neuronal function. Importantly, in contrast to e.g. single cell recordings, only the activity of large populations of neurons at the same time can be registered with fMRI. Thus, if no “activation” was found in a specific brain region in a particular contrast in the experiments, this does not exclude that some neurons in this brain area are nevertheless active in connection with the cognitive process in question. The method may not have been sensitive enough to pick up this activity.

Conversely, if “activation” is found in the same voxels in two different contrasts, as it was the case in several instances in the experiments presented here, it cannot be excluded that completely different, but spatially overlapping populations of neurons are in fact active with each cognitive process. However, to date there is no method that overcomes these interpretational limitations. The development of higher-resolution fMRI technology may help to alleviate these problems in the future. Repeating the experiments presented in this work using fMRI at higher field strengths would certainly yield valuable results and possibly help to more precisely specify the premotor cortex regions associated with different functions. As it has been suggested that it is microstructure rather than macrostructure that parallels function in the brain, it would be especially desirable to be able to obtain microstructural information about individual subjects’ brains to optimize localization of function.

In both experiments, there were considerable response time differences between conditions, although during the creation and selection of the individual items, care was taken to minimize these. In the analysis of the fMRI data, the differences were accounted for by incorporating the RT information into the general linear model. It has still been argued that the differences in BOLD activation between contrasts might result from the differences in the time spent on task. If a brain area shows activation in response to the RT difference between conditions, it should show activation in all contrasts with a similar difference. In Experiment 1 for example, the RT difference between the abstract and action conditions was comparable to the RT difference between the sequential and distributive rule type conditions. However, the networks of activated brain areas apparent in the action > abstract and in the distributive > sequential contrasts were vastly different, as were the networks apparent in the respective reverse contrasts. Conversely, very similar patterns of activation were obtained when comparing sequential against distributive matrices in Experiments 1 and 2, although in Experiment 1, the difference in RT for these two conditions was negative, whereas in Experiment 2 it was positive (although not significant). These arguments speak against the assumption that the reported activation is simply due to response time differences, and for the validity of the interpretations regarding the cognitive processes involved.

Outlook

In this thesis, it has been argued that the premotor cortex figures in representing relations in different cognitive domains. Relational processing was studied experimentally employing a matrices relational reasoning task. However, representing relations is also at the heart of cognitive functions such as problem solving, hypothesis testing or categorization. In particular, the function of planning relies heavily on processing relational representations, as planning entails representing relations between different components of a task (Halford et al., 1998). Furthermore, in the literature, the notion of planning is ambiguously used. On the one hand, planning refers to something leading to overt goal-directed behavior. On the other hand, planning means something resulting in the formation of inner strategies. Following the argumentation underlying this work, the premotor cortex can be expected to play a central role in both motor and abstract planning, due to its involvement in representing relations in both domains, and especially in view of the suggestion that forward models are at the basis of PMC functionality (Schubotz, 2007). This notion could be a worthwhile direction for future research, investigating the role of PMC in planning more directly, for example using both motor and abstract planning tasks that have a more proactive (sequencing) component than the reasoning or serial prediction tasks employed previously. However, devising a suitable motor planning task, especially one that preferably targets complex actions involving objects, has proven a special challenge for neuroimaging studies given the limitations of the scanner environment.

The abstractness of the relational information processed has been investigated as a potential factor modulating PMC involvement. This has been operationalized through presenting abstract and action-related stimulus material in the context of a relational reasoning task. However, especially in the context of planning, “abstractness” might also refer to other dimensions such as the time scale an action or plan encompasses. Thereby, motor plans might rather span shorter periods of time, whereas abstract plans might encompass longer periods, considering e.g. “making coffee” in contrast to “getting a university education”. Ruby, Sirigu and Decety (2002) investigated the neural correlates of long-term and short-term planning employing a script-ordering task. Their PET data indicate different networks within the brain to be activated for short-term and long-term planning. Specifically, their results suggest that short-term planning may involve motor representations, but long-term planning may not. The focus of the study by Ruby and colleagues (2002) was on brain areas within the parietal cortex. To specifically investigate the role of the premotor cortex in concrete and abstract planning would certainly add valuable aspects to the knowledge about PMC function in processing relations of different abstractness.

Concluding remarks

In this thesis, the notion was elaborated and investigated that a specific frontal region, the premotor cortex, might have its central function in the processing of relational representations. Evidence could be accumulated for the assumption that relational information processing in PMC is domain-general rather than domain-specific, and that the PMC has a special role in processing sequential information in different contexts. This transcends more traditional descriptions of PMC as an area performing exclusively motor-related computations, underlining a role for PMC in both thought and action. These findings add to a growing body of research aimed at uncovering basic principles of function that might underlie PMC involvement as it appears in various studies and paradigms. In the future, the goal must increasingly be to formulate more general models and theories that explicitly integrate findings from different lines of research, from studies in humans and animals, and that are also better able to explain PMC function in the context of networks of associated brain regions, to arrive at a thorough understanding of premotor cortex functionality.

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ABBREVIATIONS

ANOVA	Analysis of variance
BA	Brodmann's area
BOLD	Blood oxygen level dependent
EBA	Extrastriate body area
EEG	Electroencephalography
EPI	Echo-planar imaging
ERP	Event-related potential
FEF	Frontal eye field
fMRI	Functional magnetic resonance imaging
FOV	Field-of-view
FWHM	Full width half maximum
HRF	Hemodynamic response function
MDEFT	Modified driven equilibrium Fourier transform
MEG	Magnetoencephalography
MR	Magnetic resonance
MRI	Magnetic resonance imaging
OFC	Orbitofrontal cortex
PCC	Posterior cingulate cortex
PET	Positron emission tomography
PFC	Prefrontal cortex
PMC	Premotor cortex
PMd	Dorsal premotor cortex
PMv	Ventral premotor cortex
pSTS	Posterior superior temporal sulcus
RF	Radio frequency

Abbreviations

ROI	Region of interest
RT	Response time
SMA	Supplementary motor area
SPM	Standard progressive matrices
SPT	Serial prediction task
TE	Time to echo
TMS	Transcranial magnetic stimulation
TR	Repetition time
VAC	Vertical anterior commissure
VPC	Vertical posterior commissure

BIBLIOGRAPHISCHE DARSTELLUNG

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Premotor cortex contributions to abstract and action-related relational processing

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Traditionally, preparation and control of movements have been the primary functions ascribed to the premotor cortex (PMC). In recent years however, attention has increasingly been focused on potential non-motor functions of this brain region. The notion that abstract cognition may have its roots in evolutionarily older functions such as motor control especially motivated the present work, at the heart of which is the proposition that the premotor cortex may be centrally involved when relational information has to be processed, both in the context of motoric action and in the context of abstract cognitive tasks. Two fMRI-Experiments were conducted employing a paradigm adapted from Raven's Progressive Matrices. Experiment 1 examined whether PMC engagement is rather determined by the domain, i.e. the abstractness of the relational information processed, or by the type of relational computations required. The results suggest that cognitive functioning within PMC is process-specific but domain-independent. Thereby, involvement of PMC is not modulated by the informational domain, but by the type of relational processing, with lateral PMC being engaged for the concatenation of sequentially related entities into coherent sequences, but not for the integration of multiple relations in parallel. Experiment 2 put the hypothesis of domain-independent processing within PMC to a more stringent test by focusing on the action conditions, separating out action objects and action goals, and in addition sought to concretize PMC involvement in processing sequential relations in the two domains. It was found that PMC is not differentially involved in relational processing in the action as compared to the abstract domain if relations in the action domain concern the objects of the actions. However, PMC activation was found for processing goal relations in contrast to object relations, which suggests that PMC subserves action goal representation in a wide variety of cognitive tasks including highly complex reasoning tasks. Furthermore, activation in PMC was modulated by the distinction whether or not the sub-goals of a higher-order action were presented in a sensible sequence. In summary, evidence could be accumulated for the assumption that relational information processing in PMC is domain-general rather than domain-specific, and that the PMC has a special role in processing sequential information in different contexts. This transcends more traditional descriptions of PMC as an area performing exclusively motor-related computations, underlining a role for PMC in both thought and action.

ZUSAMMENFASSUNG

Der prämotorische Cortex (PMC) umfasst einen beträchtlichen Teil des Frontallappens bei Menschen und anderen Primaten. Seine Funktion wurde lange ausschließlich in der Vorbereitung und Kontrolle von Motorik und Bewegungsverhalten gesehen (z.B. Wise, 1985; Passingham, 1993). Erst in den letzten Jahren konzentrierte sich das Forschungsinteresse von Neurophysiologen und kognitiven Neurowissenschaftlern stärker auf potentielle nicht-motorische Funktionen dieser Gehirnregion. Nach diesen neueren Erkenntnissen sind die neuronalen Verarbeitungsprozesse im prämotorischen Cortex viel genereller und abstrakter, so dass er zur Ausführung einer ganzen Reihe von motorischen, attentionalen und kognitiven Prozessen beiträgt (Fiebach und Schubotz, 2006; Schubotz, 2007). Die Vertreter von Konzepten wie "grounded cognition" (Barsalou, 2008) oder "motor cognition" (z.B. Jackson und Decety, 2004) stellen weiterhin heraus, dass „höhere“ kognitive Funktionen sich aus „niedrigen“ sensorischen und motorischen Funktionen entwickelt haben. Abstraktes Denken könnte daher seine Wurzeln in evolutionär gesehen älteren Funktionen, wie z.B. der motorischen Kontrolle, haben. Diese Sichtweise war der Ausgangspunkt für die vorliegende Arbeit, der die zentrale These zugrunde liegt, dass der PMC eine wichtige Rolle bei der Verarbeitung relationaler Information spielt, sowohl im Kontext von Motorik und Handlung, als auch im Kontext abstrakter Denkprozesse.

Der prämotorische Cortex ist zentral in die Ausführung und Steuerung von Handlungen involviert. Im Gegensatz zu primär motorischen Arealen wird die neuronale Aktivität in der Prämotorik jedoch nicht von kinematischen Faktoren bestimmt. Die Funktion des PMC besteht vielmehr in der Vorbereitung von Bewegungen, deren Auswahl nach Maßgabe sensomotorischer Assoziationen sowie der Koordination von Bewegungssequenzen unterschiedlicher Komplexität (Deiber et al., 1996; Grafton et al., 1998; Sakai et al., 2002). Somit ist der PMC am Erwerb und an der Planung von Handlungssequenzen beteiligt. Es wird insbesondere angenommen, dass der laterale Teil des PMC Speicherort für vorgefertigte Subroutinen oder „Handlungsideen“ ist (Fadiga et al., 2000), die als die Handlung steuernde, relationale Repräsentationen betrachtet werden können. Der mesiale Anteil des PMC (das supplementär-motorische Areal, SMA) wiederum trägt bei zur Auswahl und Verknüpfung dieser Repräsentationen zu Handlungseinheiten höherer Ordnung (Shima und Tanji, 1998, 2000). Es kann somit festgehalten werden, dass der PMC eine wichtige Rolle bei der Verarbeitung relationaler Information im Kontext von Handlungen spielt.

Andererseits ist der prämotorische Cortex unter bestimmten Umständen auch unabhängig von motorischen Erfordernissen beteiligt. Als Antwort auf sensorische Reize in verschiedenen Modalitäten wird Aktivität im PMC registriert, ebenso bei der Beobachtung und Vorstellung von Handlungen, Objekten und bei räumlichen Denkprozessen (z.B. Grafton, Arbib et al., 1996; Bremner et al., 2001; Grezes und

Decety, 2002). Der PMC spielt eine herausragende Rolle bei der Verarbeitung von Sequenzen abstrakter Stimuli und bei hoch-abstrakten, relationalen Denkaufgaben (Acuna et al., 2002; Schubotz und von Cramon, 2003). Es wird vermutet, dass der prämotorische Cortex als Schnittstelle fungiert, die zur Repräsentation sequentiell strukturierter Ereignisse – relationaler Repräsentationen – in vielen Verhaltensbereichen, einschließlich abstrakter kognitiver Aufgaben, genutzt wird. Relationale Informationsverarbeitung im PMC besteht daher im Aufbau und in der Anwendung von Transformationen in Handlung und Denken (Schubotz, 2007).

Zusammenfassend weisen die vorliegenden Erkenntnisse darauf hin, dass der prämotorische Cortex sowohl bei handlungsbezogenen als auch bei abstrakten Aufgaben immer dann involviert ist, wenn die Verarbeitung relationalen Wissens erforderlich ist. Die empirische Arbeit, die im Folgenden umrissen wird, zielte auf eine stärkere Charakterisierung des Beitrags ab, den der PMC bei der relationalen Informationsverarbeitung in der abstrakten ebenso wie in der Handlungsdomäne leistet.

Dazu wurden zwei Experimente mit der Methode der funktionellen Magnetresonanztomografie (fMRT) durchgeführt. Das experimentelle Paradigma lehnte sich an Ravens Progressive-Matrizen-Test an (Raven, 1938). Zentrales Element dieses weit verbreiteten Testverfahrens ist die Ableitung und Anwendung von Relationen, d.h. Beziehungen zwischen den Elementen der als Stimuli verwendeten Matrizen.

Experiment 1 untersuchte, inwieweit die Beteiligung des PMC von der Domäne, d.h. der Abstraktheit der relationalen Information, oder eher von der Art der erforderlichen Verarbeitungsprozesse abhängt. Bezüglich der Domäne würden klassische Theorien vorhersagen, dass der PMC Relationen in der motorischen Domäne verarbeitet, während die Verarbeitung relationaler Information in der kognitiven Domäne von anterior-präfrontalen Gehirnregionen realisiert wird. Neueren, oben erwähnten Erkenntnissen zufolge könnte es jedoch durchaus der Fall sein, dass die Verarbeitung sowohl von Handlungs- als auch von abstrakten Relationen im PMC stattfindet. Bezüglich der Art der Prozesse wurde untersucht, ob der PMC an relationaler Integration beteiligt ist, d.h. dann, wenn mehrere einzelne Beziehungen zu Relationen höherer Ordnung integriert werden müssen. Weiterhin wurde die Hypothese aufgestellt, dass der PMC herangezogen würde, wenn sequentielle im Gegensatz zu nicht-sequentiellen Relationen abgeleitet oder entdeckt werden müssen.

Sechzehn Probanden nahmen an dem Experiment teil, für das ein 3T Siemens Trio MRT-Gerät eingesetzt wurde. Jeder Proband erhielt 96 Matrizen-Aufgaben und hatte für die Lösung jeder einzelnen maximal 25 Sekunden Zeit. In der Instruktion wurde die Wichtigkeit von möglichst fehlerfreier im Gegensatz zu möglichst schneller Bearbeitung betont. Jede Aufgabe enthielt im oberen Teil eine Matrix aus 3 Spalten und 2 Reihen grafischer Abbildungen oder Fotografien, in der jeweils das rechte untere Ele-

ment durch einen Platzhalter ersetzt war, und darunter vier Lösungsmöglichkeiten zur Auswahl. Die Aufgabe des Probanden war es, unter dieser Auswahl diejenige Grafik oder dasjenige Bild zu finden, die bzw. das die Matrix korrekt vervollständigt.

Das Design umfasste die drei Faktoren Domäne, Integration und Regeltyp, mit jeweils zwei Stufen. Die Domäne relationaler Informationsverarbeitung wurde operationalisiert durch den Einsatz einer abstrakten Version der Matrizen einerseits und einer neu entwickelten handlungsbezogenen Version andererseits, in der die Elemente der Matrizen Fotografien von einfachen objektbezogenen Handlungen waren. In der abstrakten Bedingung bezogen sich die abzuleitenden Regeln auf visuell-räumliche Beziehungen zwischen den grafischen Elementen, in der Handlungsbedingung dagegen auf alltägliche Objekte und die Art, wie sie manipuliert wurden. Matrizen wurden weiterhin auf der Grundlage von zwei verschiedenen Regeltypen konstruiert: Regeln, die eine sequentielle Verarbeitung der Stimuli erforderten (sogenannte „quantitative pairwise progression“; „sequentiell“ im Folgenden), sowie Regeln, die eine nicht-sequentielle Verarbeitung erforderten („distribution of three values“; „distributiv“ im Folgenden) (Carpenter et al., 1990). Schließlich konnte eine Matrix entweder eine oder zwei Regeln enthalten; nur beim Lösen von Zwei-Regel-Matrizen war deren relationale Integration erforderlich.

Im Kontrast von Handlungsmatrizen zu abstrakten Matrizen war ausgedehnte Aktivierung vor allem im lateralen occipitotemporalen Cortex und im Gyrus fusiformis in beiden Hemisphären zu beobachten. Der umgekehrte Kontrast zeigte großflächige Aktivierungen im Cuneus sowie in inferior-parietalen Arealen. In keinem der beiden Kontraste war jedoch eine Aktivierung des PMC ersichtlich; auch eine region-of-interest-Analyse (ROI-Analyse) lieferte dort keine Anhaltspunkte für Unterschiede in der Hirnaktivität. Dies legt nahe, dass die erste Hypothese, die aus traditionellen Vorstellungen über die Funktion des PMC abgeleitet worden war, nicht zutrifft: der PMC ist an der Verarbeitung relationaler Information in Bezug auf Handlungen nicht stärker beteiligt als in Bezug auf abstrakte Aufgaben. Dies ist konsistent mit der Auffassung, nach der der PMC nicht nur eine Rolle im motorischen Verhalten, sondern auch bei rein kognitiven Aufgaben spielt.

Das Lösen von Matrizenaufgaben, die zwei Regeln enthielten, verglichen mit Aufgaben, die nur eine Regel enthielten, rief Aktivierung in einem ausgedehnten fronto-parietalen Netzwerk hervor, wobei die frontalen Aktivierungen stärker links lateralisiert waren. Die Beobachtung von Aktivität in diesem Netzwerk in Verbindung mit dem Erfordernis zur relationalen Integration repliziert die Ergebnisse früherer Bildgebungsstudien (Prabhakaran et al., 1997; Kroger et al., 2002). Auch in diesem Kontrast zeigte sich kein Effekt in prämotorischen Arealen. Da der PMC an der Verarbeitung der Komplexität motorischer und perzeptueller Sequenzen beteiligt ist, lag die Vermutung nahe, dass dies auch für relationale Integration zutreffen könnte. Die Ergebnisse zeigen jedoch, dass sich diese Arten sequenzieller

Zusammenfassung

Komplexität hinsichtlich der beteiligten Gehirnregionen von der relationalen Komplexität in Matrizenaufgaben offensichtlich unterscheiden.

Im Kontrast von sequentiellen verglichen mit distributiven Matrizen wurden rechtshemisphärische Aktivierungen im ventrolateralen PMC, im inferioren Parietallappen und im posterioren Anteil des Gyrus temporalis medius registriert. Der entgegengesetzte Kontrast enthielt nur einen Aktivierungscluster im Präcuneus und Cuneus. Das gemessene BOLD-Signal im PMC war für sequentielle Matrizen höher als für distributive, und zwar sowohl in der abstrakten als auch in der Handlungsbedingung, was durch eine ROI-Analyse bestätigt werden konnte. Das stärkere Engagement des PMC unter diesen Bedingungen unterstreicht die Rolle, die diese Gehirnregion bei der Bereitstellung von generischen Transformationen in verschiedenen kognitiven und Verhaltensbereichen spielt (Schubotz, 2007). Die ausgeprägte Beteiligung des PMC bei der Verarbeitung sequentiell strukturierter Matrizen kann weiterhin als Anzeichen für den Vorrang serieller Informationsverarbeitungsprozesse in dieser Region gelten, in Übereinstimmung mit dem Modell von Koechlin und Hyafil (2007).

Zusammenfassend deuten die Ergebnisse von Experiment 1 darauf hin, dass die kognitive Verarbeitung im PMC prozessspezifisch, aber domänenunabhängig ist – dass also die Rolle des PMC bei der relationalen Informationsverarbeitung nicht primär von der Domäne der Information bestimmt wird, sondern eher von der Art des Verarbeitungsprozesses. Dabei ist der PMC an der Verknüpfung von Einzelinformationen zu kohärenten Sequenzen beteiligt, nicht jedoch an der simultanen Integration multipler Relationen.

In Experiment 2 wurde die Hypothese einer domänenunabhängigen Informationsverarbeitung im PMC einer noch stärkeren Prüfung unterzogen, indem der Fokus auf die Handlungsbedingungen gelegt wurde. Es wurde untersucht, ob es für ein stärkeres Engagement des PMC bei der Verarbeitung relationaler Information im Rahmen der verwendeten Matrizenaufgabe ausreichen würde, wenn die Relationen zwischen den Matrix-Elementen sich auf die Objekte der Handlungen bezögen, oder ob vielmehr ein stärkeres Engagement des PMC dann zu verzeichnen wäre, wenn die Relationen die Handlungsziele betrafen. Diese zwei Aspekte waren in Experiment 1 nicht unabhängig voneinander variiert worden. Ein weiteres Ziel von Experiment 2 war es, die Rolle des PMC bei der Verarbeitung sequentieller Information in beiden Informationsdomänen zu konkretisieren. Es wurde untersucht, inwieweit die bevorzugte Beteiligung des PMC beim Bearbeiten sequentiell strukturierter Matrizen bestehen bleiben würde, wenn sich diese sequentielle Struktur explizit auf eine Abfolge von Unterzielen einer Handlung höherer Ordnung beziehen würde, d.h. wenn diese Unterziele eine sinnvolle im Gegensatz zu einer nicht-sinnvollen Handlungsabfolge bildeten.

An Experiment 2 nahmen 15 Probanden teil. Das generelle Layout der Matrizen, die Aufgabenstellung, der experimentelle Ablauf sowie das fMRT-Prozedere waren im Vergleich zu Experiment 1 praktisch unverändert. Jeder Proband erhielt 90 Aufgaben. Es gab drei experimentelle Bedingungen mit jeweils zwei Unterbedingungen. In der abstrakten Bedingung bestanden die Matrizen wieder aus abstrakten grafischen Elementen; die eine Hälfte der Matrizen wurde auf der Basis sequentieller Regeln konstruiert, die andere Hälfte auf der Basis distributiver Regeln. In den zwei Handlungsbedingungen waren die Elemente der Matrizen wieder Fotografien von Handlungen. In der Handlung/Objekt-Bedingung bezogen sich die Regeln auf die Anzahl oder die Identität der verwendeten Objekte, ähnlich wie in der abstrakten Bedingung; auch hier war die Hälfte der Aufgaben sequentiell, die andere Hälfte distributiv strukturiert. Im Gegensatz dazu bezogen sich die Regeln in der Handlung/Ziel-Bedingung auf die Ziele der dargestellten Handlungen. Bei der einen Hälfte der Matrizen war dabei die Abfolge der durch die einzelnen Fotos dargestellten Unterziele korrekt, so dass sich eine sinnvolle Gesamthandlung ergab (Sequenz-korrekt), bei der anderen Hälfte ergab sich keine sinnvolle Reihenfolge (Sequenz-inkorrekt). Die Korrektheit oder Sinnhaftigkeit der einzelnen Abfolgen war in einer vorangegangenen Ratingstudie mit 30 unabhängigen Probanden ermittelt worden. Da in Experiment 1 die Unterscheidung, ob die Matrizen ein oder zwei Regeln enthielten, keinen Einfluss auf das Aktivierungsniveau des prämotorischen Cortex ergeben hatte, wurde diese Unterscheidung in Experiment 2 fallengelassen; alle Matrizen enthielten nun zwei Regeln.

Das Lösen von Handlung/Objekt-Matrizen rief im Kontrast zu abstrakten Matrizen Aktivierungen primär in lateralen occipitotemporalen sowie inferior-temporalen Arealen hervor, denen höhere visuelle Wahrnehmungsfunktionen zugesprochen werden (EBA, pSTS, MT; Grossman et al., 2000; Grossman und Blake, 2001; Spiridon et al., 2006). Im umgekehrten Kontrast war Aktivierung in einem Netzwerk aus superior-frontalen und posterior-parietalen Arealen, das mit visuell-räumlichen Prozessen in Verbindung gebracht wird (Mesulam, 2000; Corbetta und Shulman, 2002), sowie Aktivierung im Cuneus, die eine detailliertere Analyse der Form der visuellen Stimuli reflektieren könnte (Zilles und Rehkaemper, 1998; Beauchamp et al., 2002), zu beobachten. Die Aktivierungen waren zum großen Teil vergleichbar mit denen in den Kontrasten zwischen abstrakter und Handlungs-Bedingung in Experiment 1. Darüber hinaus zeigte sich auch hier kein Effekt im PMC für Handlung/Objekt-Matrizen, was ebenfalls die Ergebnisse von Experiment 1 bestätigt. Es kann daher jetzt genauer festgehalten werden, dass der PMC dann nicht in unterschiedlicher Weise an relationaler Informationsverarbeitung in abstrakter und Handlungs-Domäne beteiligt ist, wenn die Beziehungen in der Handlungs-Domäne die Objekte der Handlungen betreffen.

Im Kontrast zwischen Handlung/Objekt- und Handlung/Ziel-Bedingung war Aktivierung im linken dorsalen PMC sowie bilateral im intraparietalen Sulcus und superioren parietalen Cortex zu beobach-

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ten. Dieses Netzwerk ist an der internen Simulation von Arm- und Handbewegungen mit ausgeprägter räumlicher Komponente beteiligt (Grafton, Fagg et al., 1996; Johnson et al., 2002; Filimon et al., 2007), desgleichen an der Repräsentation des Handlungsziels bei der Imitation von Handlungen (Koski et al., 2002). Diese Befunde lassen vermuten, dass der PMC eine Rolle bei der Repräsentation von Handlungszielen im Kontext verschiedener kognitiver Prozesse spielt, von der motorischen Ausführung oder der Beobachtung einer Handlung bis hin zu hoch komplexem abstrakten Denken und Schlussfolgern.

Der Kontrast zwischen sequentiell und distributiv strukturierten Matrizen innerhalb der abstrakten Bedingung zeigte Aktivierungen im rechten ventrolateralen PMC, im anterioren Teil des inferioren Parietallappens sowie dem posterioren Anteil des Gyrus temporalis medius, was ebenfalls eine Replikation der Ergebnisse von Experiment 1 darstellt.

Schließlich konnte innerhalb der Handlung/Ziel-Bedingung im Kontrast von sequenz-inkorrekten verglichen mit sequenz-korrekten Matrizen Aktivierung im SMA sowie im posterioren Teil des Präcuneus registriert werden. Dies deutet darauf hin, dass der mesiale Anteil der Prämotorik (SMA) auch eine Rolle bei der Strukturierung von komplexeren Handlungssequenzen, die aus mehreren Unterzielen bestehen, spielen könnte. Dabei nahmen vermutlich die Aufgaben der sequenz-inkorrekten Bedingung, in der die übliche Reihenfolge verletzt war, diese Sequenz-Kontrollfunktion stärker in Anspruch als die der sequenz-korrekten Bedingung.

Die angeführten experimentellen Befunde reihen sich ein in eine zunehmende Anzahl von Forschungsarbeiten, die das Ziel verfolgen, fundamentale Prinzipien aufzudecken, die den diversen Funktionen des PMC zugrunde liegen könnten, wie diese sich in verschiedenen Studien und Paradigmen gezeigt haben. Sie unterstützen die Auffassung, wonach die Verarbeitung relationaler Information im PMC eher domänenübergreifend als domänenspezifisch stattfindet, und dass der PMC eine besondere Rolle bei der Verarbeitung von Informationen über Sequenzen in verschiedenen Kontexten spielt. Dies geht weit über die traditionelle Charakterisierung des PMC als ein Areal, in dem die neuronale Verarbeitung ausschließlich auf motorische Prozesse gerichtet ist, hinaus und unterstreicht die Bedeutung des PMC sowohl für Handlung als auch für Kognition.

SUMMARY

The brain region termed the “premotor cortex” (PMC) constitutes a significant part of the frontal lobes in humans and in non-human primates. Traditionally, accounts of this region’s function did rarely extend beyond ascribing to it a role in the preparation and control of movement and motoric action (e.g. Wise, 1985; Passingham, 1993). In recent years however, the attention of researchers in neurophysiology, behavioral and cognitive neuroscience has increasingly been drawn to potential non-motor functions of this brain region. It has been proposed that PMC carries out neural computations sufficiently general and abstract in order to contribute to a wide range of motor, attentional, and cognitive processes (Fiebach and Schubotz, 2006; Schubotz, 2007). In addition, concepts such as “grounded cognition” (Barsalou, 2008) or “motor cognition” (e.g. Jackson and Decety, 2004) take the perspective that “higher” cognitive abilities may have evolved from “lower” sensory and motor functions. Thus, abstract cognition may have its roots in evolutionarily older functions such as motor control. This notion inspired and motivated the present work, at the heart of which is the proposition that the premotor cortex may be centrally involved when relational information has to be processed, both in the context of motoric action and in the context of abstract cognitive tasks.

Premotor brain areas participate in the execution and control of actions. In contrast to primary motor cortex however, activity in premotor areas is not modulated primarily by the kinematic requirements of movement. Rather, PMC function centers on the preparation of movements, their selection according to sensorimotor associations and the coordination of movements in sequences of varying complexity (Deiber et al., 1996; Grafton et al., 1998; Sakai et al., 2002). PMC is hence involved in the acquisition and planning of action sequences. In particular, lateral PMC is suggested to hold precompiled subroutines or “action ideas” (Fadiga et al., 2000) which can be thought of as relational representations that guide action; whereas mesial PMC selects and links these representations to make up higher-order actions (Shima and Tanji, 1998, 2000). Thus, it can be stated that PMC plays a role in relational processing in action-related contexts.

However, premotor cortex involvement is also apparent apart from motor requirements. PMC is active in response to sensory stimuli of different modalities, during observation and during imagery (e.g. Grafton, Arbib, et al., 1996; Bremner et al., 2001; Grezes and Decety, 2002). PMC figures prominently in the processing of abstract stimulus sequences and is engaged in a range of highly abstract relational reasoning tasks (Acuna et al., 2002; Schubotz and von Cramon, 2003). It has hence been suggested that PMC serves as an interface which can be exploited for the representation of sequentially structured events – relational representations – in a broad range of behaviors including abstract cognitive tasks,

Summary

and that relational processing in PMC amounts to the acquisition and application of transformations in both action and cognition (Schubotz, 2007).

In summary, the available evidence points to an involvement of premotor cortex in both action-related and abstract tasks when relational knowledge has to be manipulated. The empirical work summarized in the following aimed at further characterizing the ways in which PMC contributes to relational processing in the action and abstract domains. To this end, two functional magnetic resonance imaging (fMRI) experiments were conducted. They employed a paradigm adapted from Raven's Progressive Matrices (Raven, 1938), a widely utilized test centrally requiring the processing of relations between elements of the stimulus display.

Experiment 1 examined whether PMC engagement is rather determined by the domain, i.e. the abstractness of the relational information processed, or by the type of relational computations required. Regarding the domain, classical views would predict that PMC processes relations in the motor domain, while more anterior prefrontal areas process relations in the cognitive domain. Considering the recent findings however, it could also turn out that both action and abstract relational processing rely on PMC. Regarding the type of relational processing, it was investigated whether PMC becomes involved when relational integration is required, i.e. when several relations have to be integrated to make up higher-order relations. It was furthermore hypothesized that PMC would be recruited whenever sequential relations have to be generated or detected, as compared to non-sequential relations, since PMC has been shown to be especially involved in the processing of action or abstract sequences.

Sixteen subjects participated in the fMRI experiment. Scanning was performed on a 3T Siemens Trio scanner. Subjects were presented with 96 consecutive matrix problems and given up to 25 sec to solve each of them. Instructions stressed accuracy over speed. Each problem's stimulus display consisted of, in the upper part, a 3x2 matrix of graphical images or photographs with a wildcard in the bottom right corner, and four answer alternatives in the lower part. The subjects' task was to find the graphical image or photograph that would complete the matrix correctly.

The design corresponded to a balanced 2x2x2 factorial design with the factors domain, integration and type. The factor domain was implemented by employing an abstract version of the matrices task as well as a newly designed action version using photographs of simple object-directed hand actions as stimulus material. In the abstract conditions, rules to be inferred and applied concerned visuospatial relations between graphical elements, whereas in the action version, rules concerned real objects and the way they were manually manipulated. The factor type was implemented by employing two different types of rules, one requiring sequential processing of stimuli ("Quantitative pairwise progression"; "sequential" hereafter), the other non-sequential processing ("Distribution of three values"; "distributive" hereafter)

(Carpenter et al., 1990). Regarding the third factor integration, each matrix was governed either by one rule only or by a combination of two rules. Relational integration was required in two-rule matrices only.

Action matrices compared to abstract matrices elicited extensive activation, most prominently in the lateral occipitotemporal cortex and fusiform gyrus in both hemispheres. The reverse contrast yielded large clusters of activation in the cuneus and inferior parietal lobules. Importantly, no activation was apparent in premotor cortex in either contrast, a result that could also be confirmed by a region-of-interest (ROI) analysis. The first hypothesis, derived from traditional accounts of PMC function, can thus be rejected: PMC is not more involved in relational processing in the action than in the abstract domain. This is consistent with the notion of PMC involvement not only in motor-related behavior, but also in purely cognitive tasks.

The contrast of two-rule versus one-rule matrices revealed that a widespread bilateral fronto-parietal network was recruited for relational integration, where frontal activations were pronounced in the left hemisphere. This replicated prior imaging findings (Prabhakaran et al., 1997; Kroger et al., 2002). Again, this contrast did not reveal activation in premotor brain areas. PMC had been hypothesized to be involved in relational integration on the basis of findings that PMC processes the complexity of motor and perceptual sequences. However, these types of sequential complexity seem to be distinct from the relational complexity in matrices tasks in terms of the brain areas recruited.

In the contrast of sequential rule matrices compared to distributive rule matrices, clusters of activation were found in the right ventrolateral PMC, inferior parietal lobule and the posterior middle temporal gyrus. Only one cluster of activation in the precuneus and cuneus emerged in the reverse contrast. The ROI analysis confirmed that BOLD response in PMC was higher for sequential than for distributive rule matrices in both the action and the abstract domain. Stronger involvement of PMC under these conditions strengthens the argument for a role of this region in providing generic transformation styles for applications in different behavioral and cognitive domains (Schubotz, 2007). PMC's pronounced involvement in sequential rule matrices might, in addition, be indicative for this region's preference for serial cognitive processing, in accordance with the model of Koechlin and Hyafil (2007).

In summary, the results of Experiment 1 suggest that cognitive functioning within PMC is process-specific but domain-independent, and that the role of PMC in relational processing is not primarily determined by the informational domain. Rather, involvement of this brain area is modulated by the type of relational processing, with lateral PMC being engaged for the concatenation of sequentially related entities into coherent sequences, but not for the integration of multiple relations in parallel.

Summary

Experiment 2 put the hypothesis of domain-independent processing within PMC to a more stringent test by focusing on the action conditions. It was investigated whether it would be sufficient for PMC to become more engaged in relational processing in the matrices task when the relations between matrix stimuli concerned the action objects, or whether PMC would be more engaged when the rules governing the matrices referred to the action goals. These two aspects had not been separated, but varied concurrently in Experiment 1. Furthermore, Experiment 2 sought to concretize PMC involvement in processing sequential relations in the two domains. It was investigated whether preferential PMC involvement in reasoning with sequentially structured matrices would persist when the sequential structure of a matrix refers to a sequence of sub-goals constituting a higher-order action, i.e. when these sub-goals are presented in a sequential rather than non-sequential manner.

Fifteen subjects participated in the fMRI experiment. The task, fMRI procedure, behavioral procedure and general layout of the matrices were kept as in Experiment 1. Every participant was presented with 90 matrix problems. Three conditions with two sub-conditions each were created. In the abstract condition, stimuli again were abstract graphical images; and again, half of the stimuli were constructed following the sequential rule, half of the stimuli following the distributive rule. In the two action conditions, matrix stimuli were action photographs. In the action/object condition, reasoning principles concerned the number and identity of objects, similar to the abstract condition, with the difference being the presentation of action stimuli; in this condition, again half of the stimuli followed the sequential, half followed the distributive rule. In contrast, in the action/goal condition, reasoning principles centred on the goal of the actions depicted. Hereby, the sequence of goals as depicted by the single photographs could either follow a sensible sequence of sub-goals, leading to attainment of a higher-order goal (sequence-correct), or the sequence was violated (sequence-incorrect). The “correctness” or sensibility of the sequences was determined in a preceding rating study with 30 independent participants. Since in Experiment 1 the requirement to process two rules was not found to modulate PMC activation in comparison to the one-rule matrices, the latter condition was dropped in Experiment 2 so that all matrices contained two rules.

Action/object matrices contrasted against abstract matrices elicited activation mostly in lateral occipito-temporal and inferior temporal brain areas that have been implicated in higher visual perception (EBA, pSTS, MT; Grossman et al., 2000; Grossman and Blake, 2001; Spiridon et al., 2006). The reverse contrast revealed activation in a network of superior frontal and posterior parietal areas related to visuospatial processing (Mesulam, 2000; Corbetta and Shulman, 2002), as well as activation in the cuneus that was taken to reflect detailed analysis of the form of visual stimuli (Zilles and Rehkaemper, 1998; Beauchamp et al., 2002). Very similar patterns of activation had been evident in Experiment 1 when contrasting action and abstract matrices. Moreover, no area in PMC showed activation in these con-

trasts, also corroborating the findings in Experiment 1. It can thus be stated more precisely that PMC is not differentially involved in relational processing in the action as compared to the abstract domain if relations in the action domain concern the objects of the actions.

In the contrast of action/goal versus action/object matrices, activation was found primarily in left dorsal PMC, bilateral intraparietal sulcus and superior parietal cortex, a network engaged in motor simulation of spatially determined arm and hand actions (Grafton, Fagg, et al., 1996; Johnson et al., 2002; Filimon et al., 2007) and action goal representation during imitation (Koski et al., 2002). This finding suggests that PMC subserves action goal representation in a wide variety of cognitive tasks ranging from action execution or observation to highly complex reasoning tasks.

The contrast of abstract sequential versus abstract distributive matrices yielded clusters of activation in the right ventral PMC, anterior inferior parietal lobule and posterior middle temporal gyrus, thus replicating the results of Experiment 1. Finally, in the action/goal condition, contrasting the sequence-incorrect matrices against the sequence-correct matrices revealed activation in the supplementary motor area (SMA) and the posterior part of the precuneus. This suggests that mesial PMC (SMA) may also play a role in controlling the sequential structure of more complex action sequences composed of distinct subgoals. The problems in the sequence-incorrect condition, in which a sequential structure was present, but violated, may have placed a greater demand on this sequence-control function of SMA.

These experimental findings add to a growing body of research aimed at uncovering basic principles of function that might underlie PMC involvement as it appears in various studies and paradigms. Evidence could be accumulated for the assumption that relational information processing in PMC is domain-general rather than domain-specific, and that the PMC has a special role in processing sequential information in different contexts. This transcends more traditional descriptions of PMC as an area performing exclusively motor-related computations, underlining a role for PMC in both thought and action.

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VERZEICHNIS DER PUBLIKATIONEN UND VORTRÄGE

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SELBSTÄNDIGKEITSERKLÄRUNG

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Leipzig, den 19.10.2009

Maria Golde

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