Premotor contributions to the control of action: Selection, preparation, and monitoring

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Contents

1 Introduction

1.1 Voluntary action

Humans display an almost endless repertoire of motor behavior. We breathe, walk in the garden looking at flowers, balance our posture during walking, stop to pick some flowers, decide to throw the yellow one away in favor of the red, retract a leg when stung by a bee, adjust our posture to provide some relief for the painful leg, and comment upon the complexity of life.

These movements differ in the way in which we have voluntary control over them. Reflexes, such as retracting our leg when we feel pain being inflicted, are a well-known example of movements over which we have almost no voluntary control. Habits, defined as movements that are so 'overlearned' that they have become involuntary and will be executed independent of the outcome of the response, are another such example. These reflexes and habits can be contrasted with actions over which we have full voluntary control (Dickinson, 1985).

Our movement skills also differ in the way we acquire the ability to perform them. Shadmehr and Wise (2005) distinguish three types of learning of motor skills, i.e., three types of motor learning. The first type is concerned with acquiring new motor skills during the course of evolution, through random mutations in a species' genetic code and natural selection of adaptive mutations. Reflexes, such as retracting a limb when feeling pain from being stung by a bee, belong to the class of motor skills acquired through evolution. The second type of motor learning is concerned with the acquisition of motor skills during the lifetime of an organism and maintaining a suitable level of performance in response to changes. Within this type of motor learning, we can distinguish between skill acquisition and motor adaptation. Skill acquisition refers to learning how to perform a new motor action such as learning to walk. Motor adaptation refers to the ability to adapt the execution of a motor skill, such as learning to walk with an injured leg or, in a more experimental setting, learning how to make accurate reaching movements following the application of forcefield designed to consistently interfere with movements in a reaching paradigm (Shadmehr and Mussa-Ivaldi, 1994). The third type of motor learning concerns decision-making: learning which action to perform given a certain environmental input and knowing when to execute it. These different types of motor learning may rely on partly dissociable neural systems in the human brain (Brasted and Wise, 2005).

The research presented in this thesis is concerned with the neural control of *voluntary actions*. Passingham (1993) has defined these as actions that are made in the context of choosing among alternative, learned actions based on attention to those actions and their consequences. These are actions over which we have full control, i.e. we can choose to execute or withhold them depending on the circumstances, and which we have learned to perform during our lifetime. Therefore, voluntary actions as defined above fall into the third category of Shadmehr and Wise (2005).

The question addressed in this thesis is: What is the role of a specific part of the human brain, the premotor cortex, in the *selection and preparation* of voluntary actions and the *evaluation* of these actions following their

execution?

The studies described focus on simple motor tasks, mostly employing arbitrary stimulus-response associations (Wise et al., 1996; Wise and Murray, 2000). In these tasks the stimuli and the responses they instruct have no obvious (often spatial) relationship with one another, but are totally arbitrary and have to be learned. This type of stimulus-response mappings are at the core of the flexibility of the behavior of higher level animals and the ability of humans to respond to symbolic cuing of behavior (Wise and Murray, 2000).

The remainder of this introductory chapter provides a framework for the studies discussed in Chapters 2-6. A review of the literature regarding the two specific action control processes that will be investigated in this thesis, namely motor preparation and performance monitoring, is given in the context of this framework. Furthermore, a brief review of the anatomy of the premotor cortex is provided. This chapter concludes with a brief overview of the rest of the thesis.

1.2 Movement preparation

Planning a movement

As described above, reflexive movements and habits will be executed whenever the organism receives the appropriate stimulus. A reflex is thus a stereotypical movement. Parameters such as the goal of the action, e.g., preventing (further) harm to the organism, the part of the body to be moved, and the type of movement are all predetermined. In contrast, for voluntary actions the goals and preconditions for movement execution and the precise parameters of the movement are not predetermined and can vary according to task circumstances. This implies that a simple input-output model of the brain, in which all the brain does is transform the stimulus input to a motor output in a one-to-one mapping, is inadequate to describe the neural processes underlying voluntary actions (Jeannerod, 1997). Neural representations of various aspects of the voluntary action, including but not limited to the goal of the action, the internal state of the organism (e.g., hunger), the position of the limbs, and specific submovements of the action are necessary for the successful planning of voluntary actions.

One of the challenges in the study of the neural control of actions is to investigate how these various aspects of a motor plan are represented in the brain, and how they are integrated in order to successfully select and execute a purposeful movement (Hikosaka et al., 1999; Willingham, 1998). Jeannerod (1997) postulates that these representations—together referred to as the movement representation—depend on sustained neuronal discharges arising in structures relevant to the various stages of the preparation of motor acts. In accordance with this suggestion, a fruitful approach in studying the neural representations of action has been to record the activity of single neurons of the macaque brain while these monkeys perform variations of an instructed delay paradigm. In these experiments monkeys perform visuomotor conditional tasks with instructed delays between an

original instruction cue and a later presented trigger (or 'go') cue. By manipulating various aspects of the instruction and trigger cues (e.g., informational value, reward) this paradigm can be used to study neuronal activity related to various aspects of motor planning.

Probing movement representations in human and non-human primates

The instructed delay task allows the experimenter to distinguish phasic neural responses associated with processing of the stimulus (signal-related activity) from sustained activation associated with the online preparation of the movement plan (set-related activity), and phasic activity purely related to the actual motor execution following the trigger cue (Wise and Mauritz, 1985; Alexander and Crutcher, 1990). Using this simple delayed response task, electrophysiologists can distinguish between signal-, set-, and movement-related activity in various regions of the macaque premotor cortex. The set-related activity recorded in such a paradigm corresponds with the pragmatic definition of a movement representation suggested by Jeannerod, namely that movement representations are reflected in sustained preparatory activity which extends in time until the moment of movement execution (Jeannerod, 1997).

Early neurophysiological studies on preparatory activity in humans relied mostly on measures derived from EEG recorded at the scalp (Coles and Rugg, 1995). Most notably, the Bereitschaftspotential [(Kornhuber and Deecke, 1964), see Jahanshahi and Hallett (2003) for a review] and related measures such as the Contingent Negative Variation (Walter et al., 1964) and the lateralized readiness potential (Coles, 1989) have proved to be robust indices of preparatory activity in the human brain. However, although providing millisecond resolution, they can only provide limited information about the neural origin of the obtained signals.

Positron emission tomography (PET) and functional magnetic resonance imaging [fMRI, see Matthews (2003) for an introduction] have the potential to image activity in the whole brain at a high spatial resolution, but suffer from poor temporal resolution. One common method employed to circumvent this problem is to subtract activity elicited in two conditions, one that is hypothesized to engage the process of interest, and one that is hypothesized to not engage the process of interest but all the other processes engaged in the other condition, the so-called control condition. Consequently, a number of studies have been performed comparing conditions where participants could or could not prepare a movement (Kawashima et al., 1994; Deiber et al., 1996). These studies rely on the assumption of pure insertion of cognitive processes, that is they assume that each cognitive component evokes an additional physiological activation that is the same irrespective of the cognitive or physiological context. However, the assumption of pure insertion underlying this approach, that it is possible to create conditions which differ in only one aspect which does not interact with other processes, does not always hold (Friston et al., 1996b; Zarahn et al., 1999).

Only recently have advances in event-related fMRI (Josephs et al., 1997) allowed the imaging of set-related activity in the human brain using paradigms related to those described above in primate studies. Making full use of these newly developed methods, Toni and colleagues [for reviews see Toni et al. (2001b) and Toni and Passingham (2003)] conducted a series of studies aimed at investigating movement representations. Assuming that bridging a temporal gap between an instruction and trigger stimulus requires sustained preparation of motor response driven by internal presentations (Jeannerod, 1997), Toni and colleagues developed a method to separate sustained activity during the delay-period from transient stimulus- and response-related activity in the standard delayed-response paradigm (Toni et al., 1999). It is important to note that, although in this approach activations in different conditions can be compared, it does not necessitate the assumption that the two conditions are the same in all but the process of interest.

This approach was subsequently employed to image movement representations over the whole brain (Toni et al., 2002a). Consistent with the hypothesized distributed nature of the neural substrates of movement representations, Toni reported delay-period activity not only in parietal and frontal regions which form part of the dorsal cortical stream traditionally associated with visuomotor processing (Milner and Goodale, 1995), but also in extrastriate and posterior temporal regions. To further characterize the unique contribution of these areas, a follow-up study investigated which of these regions showed delay-related activity modulated by the likelihood of the response (motor preparation) and which were not (motor intention). The results showed that delay-related activity in precentral regions was modulated by the probability of responding, while parietal regions showed equal activity regardless of the probability of responding (Thoenissen et al., 2002). This finding is consistent with earlier suggestions from studies in nonhuman primates of intention-related activity in the posterior parietal cortex (Kalaska and Crammond, 1995; Snyder et al., 1997). Subsequent research in a number of laboratories has employed this approach and similar approaches to study the influence of reward expectancy on preparatory activity (Ramnani and Miall, 2003), the coding of behavioral rules (Bunge et al., 2003), and the biasing of information processing for upcoming action selection through task context (Sakai and Passingham, 2003; Sakai and Passingham, 2006) in the human brain.

The results of these studies demonstrate the feasibility of studying the neural substrates of various aspects of movement representations, applying paradigms derived from studies employing non-human primates to image neural contributions to preparatory motor control in the functioning human brain. In Chapters 2 and 3 a similar approach will be employed to further study these preparatory processes.

1.3 Action monitoring

Action monitoring and the error-related negativity

To optimize behavioral performance it is not only essential for an organism to be able to integrate information in an appropriate manner so as to select and execute the appropriate action; it is also vital to be able to evaluate the executed behavior. The ability to determine whether a selected action has produced the appropriate result is not only useful for adapting future behavior but also essential for learning new behavior. Starting in the 1960s, a body of work has described the effects of error detection on subsequent behavior (Rabbitt, 1966; Laming, 1979). Research into error processing received an enormous impulse in the early 1990s with the discovery of the error-related negativity (ERN, or error negativity N_e), which led to the establishment of the subfield of action or performance monitoring[1].

The ERN is a negative deflection in the human event-related brain potentials following incorrect responses, and has been commonly reported in speeded-response tasks where the participant knows what the correct response should have been. The ERN peaks about 80 ms following the erroneous response, and has a fronto-central scalp distribution. This component was first described by researchers in Dortmund (Falkenstein et al., 1990) and Illinois (Gehring et al., 1993). Subsequent research has revealed the effects of various factors on ERN amplitude such as the importance of correct responding (Gehring et al., 1993), fatigue (Scheffers et al., 1999), error awareness (Nieuwenhuis et al., 2001), error certainty (Scheffers and Coles, 2000), degree of error (Bernstein et al., 1995), and the probability of remedial actions (Coles et al., 1995).

Furthermore, a component similar to the ERN has been described following negative feedback in tasks where participants cannot themselves evaluate their behavior but need to rely on external performance feedback, such as time-estimation tasks (Miltner et al., 1997) and guessing or gambling tasks (Gehring and Willoughby, 2002; Holroyd et al., 2004a; Nieuwenhuis et al., 2004b; Ruchsow et al., 2002). This component was subsequently termed the 'feedback-ERN'[2] to distinguish it from its response-locked counterpart, the 'response-ERN' [see Nieuwenhuis et al. (2004a) for a review].

Early reports suggested that the ERN might be generated in the anterior cingulate cortex (ACC), consistent with observations of error-related activity in the ACC of monkeys (Gemba et al., 1986). Subsequent studies using source modeling indeed showed an ACC source for both the response-ERN (Dehaene et al., 1994) and the feedback-ERN (Miltner et al., 1997). More-

[1] In this thesis we employ the term 'action monitoring' to distinguish the evaluation of the *selection* of the appropriate action (action monitoring) which is the topic of this thesis, from the correct *performance* of the selected action (performance monitoring) (De Bruijn et al., 2003; Krigolson and Holroyd, 2006) .

[2] Recently, the feedback-ERN and related components have also been referred to as the 'feedback negativity' (Nieuwenhuis et al., 2005a) or the 'medial frontal negativity' (Gehring and Willoughby, 2002). It is still a topic of debate whether these components are a manifestation of the same neural process (Holroyd et al., 2002; Gehring and Willoughby, 2004).

over, this source was independent of the effector with which the error is committed (Holroyd et al., 1998) or the modality of error feedback (Miltner et al., 1997). These results were subsequently corroborated by work using functional MRI showing error-related activity in the ACC and, in most studies, the pre-supplementary motor area (pre-SMA) (Carter et al., 1998; Kiehl et al., 2000; Ullsperger and Von Cramon, 2001; Ullsperger and Von Cramon, 2003; Menon et al., 2001). Importantly, a study investigating activation related to response- and feedback-related error detection confirmed that the two activate a common source in the dorsal ACC (Holroyd et al., 2004c). Conversely, pre-SMA was only activated by response errors. We will return to this point in Chapter 5 of this thesis.

Models of action monitoring

As described by Coles (Coles et al., 2001), early theories of the ERN built on theories of internal representations of action (Wolpert et al., 1995; Jeannerod, 1997). According to the original 'mismatch hypothesis', the neural system involved in action monitoring is composed of two modules: a monitoring system that detects errors and a remedial action system that deals with behavioral adjustments. The monitoring system functions as a comparator, comparing representations of the correct response with representations of the actual response. Since the original ERN studies focused mostly on speeded response tasks, in which most errors are due to premature responding before all necessary information is extracted from the stimulus (Gratton et al., 1988), a representation of the correct response can be derived from further, continued processing of the stimulus, after the system has committed to executing a particular action. The representation of the correct response is then compared to an efference copy of the response that is actually being executed. When a mismatch between the two representations is detected, a signal indicating that an error has occurred is sent to the remedial action system. The remedial action system can then inhibit or correct the erroneous response and adjust behavior on the next trial, for instance by slowing of responses (Rabbitt and Rodgers, 1977; Coles et al., 1995).

The 'reinforcement learning theory' of the ERN (Holroyd and Coles, 2002) (see Fig. 1.1 for a schematic representation) extends the original mismatch hypothesis. This model is based on findings in non-human primates, suggesting that the basal ganglia monitor ongoing events and predict the outcome of these events (Barto, 1995; Houk et al., 1995). When an event is better (positive prediction error) or worse (negative prediction error) than predicted, this will result in a phasic increase or decrease of dopamine neuron firing, respectively (Schultz et al., 1997). These dopaminergic 'prediction error signals' are relayed to various parts of the striatum and frontal cortex. According to the reinforcement learning model, when a negative prediction error disinhibits pyramidal neurons in the ACC this leads to the generation of the ERN. The error detection is thus done in subcortical areas, not in the ACC. Moreover, the model suggests that an error can be detected based on an efference copy of the executed movement or on the basis of negative per-

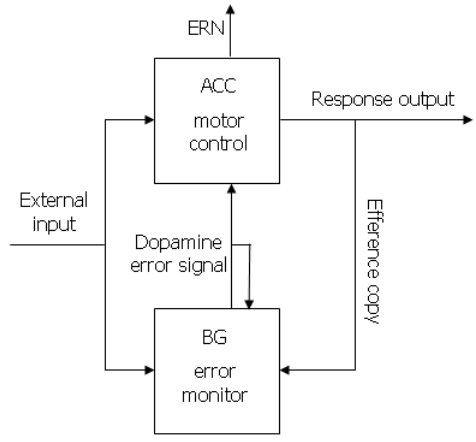

Figure 1.1: Schematic representation of the reinforcement learning model of the ERN. Adapted from Holroyd and Yeung (2003).

formance feedback, depending on which source of information is available first. In this manner, the reinforcement learning theory can explain both the response- and the feedback-ERN. Furthermore, consistent with the notion that the goal of a voluntary action can change according to task circumstances, the ERN has been shown to be highly context-dependent (Holroyd et al., 2004a), as is activity in most areas associated with the evaluation of behavioral outcome (Nieuwenhuis et al., 2005a).

Importantly, in this framework, the function of the ACC is not error detection, but the *selection of actions* for the task at hand (Holroyd and Coles, 2002; Holroyd et al., 2004b). The ACC functions as a 'control filter', selecting which motor plan will receive access to the motor execution system. In this framework the ACC is sensitive to behaviorally relevant events and one of its functions is to bring erroneous behaviors in line with desired goals (Holroyd et al., 2004b).

It should be noted that a number of alternative models on the function of the ACC in action monitoring have been proposed, the most prominent of which is the conflict detection theory (Carter et al., 1998). However, we will save a comparison of these models for the discussion in Chapter 7.

Anterior cingulate cortex, action selection, and error processing

The error processing work in this thesis was inspired by the Holroyd and Coles (2002) reinforcement learning model, viewed from a motor-learning perspective. In this context, one of the main theoretical advantages of the Holroyd and Coles model is that it suggests a possible link between the error processing literature and the extensive literatures on reinforcement learning, reward processing, and motor learning.

Although recent literature on error processing has tended to focus on

the ACC[3] as solely involved in registering when a desired outcome was not produced by an action, involvement of the ACC in other cognitive and motor functions is well established (Duncan and Owen, 2000; Fonteijn and Buur, 2005; Posner and DiGirolamo, 1998). Early studies suggested that the ACC is particularly important during situations that require—using the terminology of cognitive psychology—supervisory attentional control (Norman and Shallice, 1986). Indeed, the ACC is activated in response to errors, during the free selection of actions (Frith et al., 1991), and in situations of low response certainty (Barch et al., 2000). However, ACC is not activated under circumstances which require merely stimulus selection (Rushworth et al., 2002; Van Veen et al., 2001). Moreover, the ACC does not seem to be active during working memory for stimuli, but sustained activation has been reported during maintenance of motor codes (Petit et al., 1998). Thus, the role of the ACC in behavioral control seems limited to the control of actions.

The challenge is to find a role of the ACC in the control of action that can explain its activity in a wide variety of tasks, including its responsiveness to errors. One possible framework is that the ACC integrates information concerning a particular action with its potential outcome. This would be consistent with the extensive cortical input to the ACC, which places it ideally to integrate information related to reward and the organism's internal state into motor intentions (Paus, 2001). There is widespread support for this framework in the macaque literature. As described above, activity in ACC single neurons has been associated with response errors (Gemba et al., 1986) and cells in the ACC fire especially when a reduction of reward signals a change in behavior (Shima and Tanji, 1998). Moreover, reward-related activity in the ACC can also be shown before the response, when the appropriate action has to be selected (Matsumoto et al., 2003), suggesting that the ACC has a role in determining which action should be executed to obtain the most reward. Further evidence for this comes from lesions studies showing that macaques with ACC lesions lack the ability to determine which response will yield the most rewarding outcome (Hadland et al., 2003). Studies in rats have shown that rats with ACC lesions will not select the more effortful of two possible actions, even if the relative pay-off is higher, something that normal rats can do (Walton et al., 2003).

Similar results are only beginning to be obtained from humans (Bush et al., 2002; Williams et al., 2004), but the combined evidence from humans, macaques, and rats suggests that the ACC has a role beyond the 'simple' monitoring of responses as suggested by some theories on action monitoring, at the very least biasing the selection of appropriate responses based on the expected outcome. Returning to the models of action monitoring discussed above, we see that the reinforcement learning model accommodates some of the properties described in the framework in this section. Indeed, according to the reinforcement learning model the ACC has an active role in the *selection* of actions based on the expected outcome of the action (Holroyd et al., 2004b). Also consistent with the model, the ACC seems to

[3]Unless otherwise specified the term 'ACC' refers to the dorsal ACC (Bush et al., 2002), see also section 1.4 for a more elaborate discussion of the subfields of the ACC relevant for this thesis.

work in conjunction with the ventral striatum (Salamone et al., 1994), although the precise mechanisms of this interaction are currently not fully understood (Walton et al., 2005). Because of its bridge function between the action-monitoring and action-control literatures, the reinforcement learning model provides an appropriate starting point for research into the neural control of actions in the medial premotor areas, including the ACC.

1.4 Premotor cortex

The previous two sections have described approaches to study various aspects of motor control, ranging from the initial selection to the preparation and finally the evaluation of the action. None of these processes is the result of the neural activity in one single brain region. Rather, these processes likely result from the interaction of a number of regions (McIntosh, 2000). This thesis is concerned with the role of a subset of these regions, namely the premotor cortices, to these action control processes. This section provides an overview of the anatomical characteristics of the various premotor areas of the brain relevant for the rest of this thesis.

Views on the premotor cortex

Large portions of the lateral convexity and the medial wall of each hemisphere of the frontal lobes of the primate brain contribute to movement. According to the traditional view of the primate premotor cortex, the frontal lobes contain a region termed the 'premotor cortex' which integrates information from the parietal and frontal cortices and sends its output to the primary motor cortex (M1) (see Figure 1.2). M1 was viewed as the primary origin of cortical commands to the spinal cord and the place where the specific commands for movement were generated; in contrast, the premotor area was defined as that part of the frontal lobes that projected directly to M1. While M1 was involved in the execution of action, the premotor cortex was proposed to be involved in higher-order aspects of motor control.

However, this framework has been challenged by the discovery that the frontal lobes contain multiple, cytoarchitectonically and functionally heterogeneous premotor areas, which each have the capacity to influence motor output not only via M1, but also via direct connections to the spinal cord [see Dum and Strick (2005) for an extensive review]. These regions all have a full representation of the body and are frequently active during the planning and/or execution of a movement. Early studies contributing to this framework used electrical stimulation to differentiate regions within area 6[4]. However, this approach failed to produce consensus on the subdivisions of the lateral surface. More recent approaches for determining the location of premotor cortex are, among others, based on differentiating neuroanatomical connections to various parts of the premotor cortices (Passingham et al., 2002) and mapping of neurotransmitter receptors (Zilles et al., 1995).

[4]Unless otherwise specified, references to brain areas by a number refer to anatomical areas as described by Brodmann (Brodmann, 1909), reporting different subdivisions within the traditional supplementary motor area.

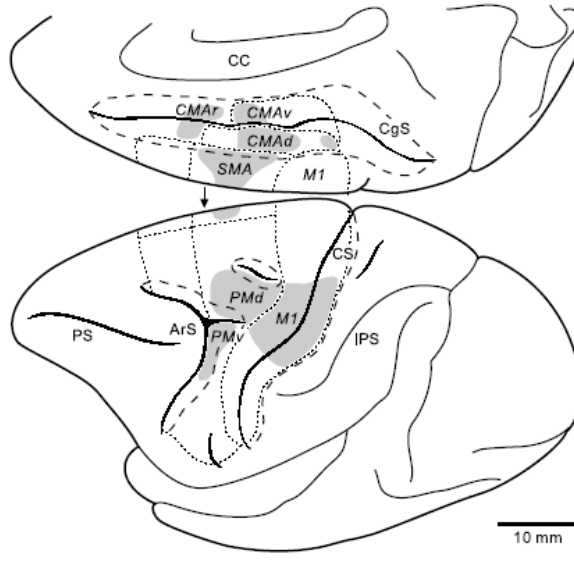

Figure 1.2: Motor areas in the frontal lobe of the macaque brain. Shaded areas indicate regions with direct connections to the spinal cord. Top: medial view. Bottom: lateral view. Abbreviations: ArS=arcuate sulcus; CC=corpus collosum; CgS=cingulate sulcus; CS=central sulcus; IPS=intraparietal sulcus; PS=principal sulcus; SF=superior frontal sulcus; IF=inferior frontal sulcus. See text for other abbreviations. Adapted from Dum and Strick (2002).

This section provides a brief overview of the divisions of the lateral and medial premotor cortices. We will focus mostly on the connectivity of each region with the spinal cord and cortical areas. Since the connectivity of each region places critical constraints on the types of computational processes a certain brain area can perform, it is hoped that describing the connectivity of the relevant regions will help us in defining its functional characteristics in the experimental chapters (Passingham et al., 2002). We will only refer to the functional properties of these regions in passing, leaving an extensive discussion of this for the later chapters. The majority of the findings discussed in this section are based on data obtained in macaque monkeys, since techniques for investigating the connectivity between regions in the human brain, such as diffusion-weighted imaging, have only recently started to become available (Johansen-Berg et al., 2004; Rushworth et al., 2006).[5]

Premotor areas on the medial wall

The medial portion of area 6, in front of the hindlimb representation of the primary motor cortex, was traditionally defined as the supplementary mo-

[5]This section will only discuss connections relevant to arm movement, which might differ from the connections relevant for leg or eye movements (Dum and Strick, 2005). Furthermore, this section does not deal with premotor areas specifically associated with eye movements, such as the frontal and supplementary eye fields.

tor area (SMA) (Penfield and Welch, 1951). However, based on connectivity (Luppino et al., 1993), cytoarchitecture and neurochemistry (Zilles et al., 1995), and functionality (Matsuzaka et al., 1992) the traditional SMA is now recognized to consist of at least two distinct regions, the pre-supplementary motor area (pre-SMA) and the SMA proper (henceforth: SMA). The border between these two regions can roughly be taken to be a line through the anterior commissure perpendicular to the line between the anterior and posterior commisures (Fig. 1.3). Like other premotor areas, the SMA projects directly to the primary motor cortex and the spinal cord, while the pre-SMA does not have substantial projections to either of these regions (Dum and Strick, 1991a; He et al., 1993; Luppino et al., 1993). Conversely, pre-SMA is interconnected with a number of prefrontal and other non-primary motor areas (Luppino et al., 1993), suggesting that this region should be considered more as a 'prefrontal' region than as a premotor area.

The cingulate sulcus of primates contains three separate motor areas: the rostral cingulate motor area (CMAr), the caudal cingulate motor area in the ventral bank of the sulcus (CMAv), and the caudal cingulate motor area in the dorsal bank of the sulcus (CMAd). Picard and Strick (1996; 2001) have proposed that these areas correspond to the human anterior rostral cingulate zone (RCZa), posterior rostral cingulate zone (RCZp), and the caudal cingulate zone (CCZ), respectively (Fig. 1.3). All of these areas are interconnected with M1 and the spinal cord (Dum and Strick, 1991a). The cingulate motor areas are densely interconnected, have relatively weak connections to the lateral premotor areas, and receive connections from subdivisions of parietal area 7. CMAv and CMAd receive additional projections form area 5. Along with the ventral premotor cortex (see below), CMAr and CMAv are the only 'real' premotor areas that receive substantial input from the dorsolateral prefrontal cortex, most notably from area 46 and, additionally for CMAr, area 9. Furthermore, widespread regions of the limbic cortex target CMAr and CMAv, providing these regions with access to information about the state of the entire organism as well as an integrated view of the body in space (Dum and Strick, 2005). As described above, a number of medial premotor areas are involved in action monitoring and higher-order aspects of motor control.

Lateral premotor cortex

The lateral premotor cortex (Fig. 1.2) was first described functionally by Fulton (1935). Recent studies in macaques have distinguished between a dorsal and a ventral lateral premotor cortex (PMd and PMv respectively), each containing a rostral and a caudal subdivision (Barbas and Pandya, 1987) and each strongly interconnected with M1, the spinal cord, and SMA. Both PMd and PMv are involved in the preparation of motor actions and strongly interconnected with the parietal cortex. These connectivity patterns are quite different for PMd and PMv, however. Parietal inputs to PMd originate from the superior parietal lobule and the parieto-occipital area and parietal inputs to PMv from the anterior intraparietal area (AIP), area PEip, the anterior portion of the inferior parietal gyrus, and the somatosensory cortices

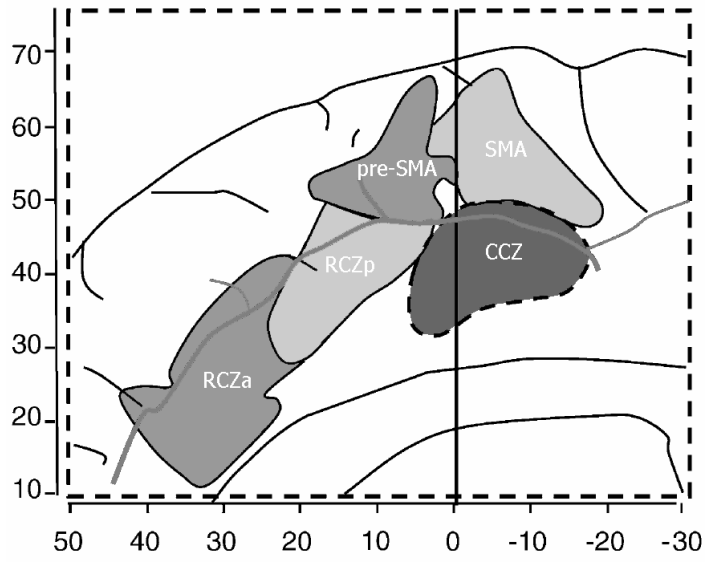

Figure 1.3: Motor areas of the medial wall of the human brain. X and Y-axis depict Y and Z-coordinates according to the atlas of Talairach and Tournoux (1988), respectively. See main text for abbreviations. Adapted from Picard and Strick (1996).

(Tanné-Gariépy et al., 2002). For frontal connectivity, as noted above, only PMv is connected with area 46, and, in addition, to the precentral operculum. Conversely, only PMd is connected with pre-SMA. These differential connectivities reflect different contributions to visuomotor control (Davare et al., 2006). PMd specifically is activated consistently in tasks involving arbitrary visuomotor associations (Wise et al., 1996).

Similar to the pre-SMA/SMA distinction, it has been proposed that the PMd can be divided into a more caudal 'motor' part, with extensive connections to M1 and the spinal cord and a more rostral 'frontal' part, which has extensive connections to the frontal cortex (Barbas and Pandya, 1987). This distinction has also been highlighted in functional studies. For instance, Boussaoud and colleagues reported that while more neurons in caudal PMd fire during the concrete preparation of an action, rostral PMd neurons are more active when attention is being directed to the stimulus itself (Boussaoud and Wise, 1993; Boussaoud, 2001). We will return to this point in Chapter 2.

The homology between human and non-human primate lateral premotor cortices is still an issue of debate. For instance, in macaques the main border between premotor and frontal cortex is the arcuate sulcus, of which there is no obvious homologue in humans. However, some suggestions for homology between macaques and humans have been proposed by Rizzolatti and colleagues (Rizzolatti et al., 1998; Rizzolatti and Luppino, 2001). For instance, the PMv of monkeys can be divided into two distinct cytoarchitectonic fields, termed F4 and F5 by Matelli and colleagues (Matelli et al.,

1985). The border between two homologue regions in human is debated, but it has been argued that F5 corresponds to the human area 44. This proposal has been particularly influential in research on action observation (Rizzolatti and Arbib, 1998).

In summary, this section has outlined the connectivity patterns of various premotor areas. Most premotor areas are connected with M1, the spinal cord, and areas of the parietal lobe that also project directly to the spinal cord. Pre-SMA and the rostral parts of the PMd and PMv differ from this pattern and may be described as 'frontal' regions, each one synapse away from a premotor area. All regions described show a distinct pattern of connectivity, which has been taken to suggest that each of these cortical areas may operate as a functionally distinct system that differentially generates and controls specific aspects of motor behavior (Dum and Strick, 1991b).

Of course, there are a number of brain regions other than M1 and the premotor cortices that contribute to the generation and control of action. The parietal cortex especially has been implicated in various aspects of visuomotor processing (Snyder et al., 2000; Rushworth and Taylor, 2006). This thesis will focus specifically on the premotor cortex, however. Parietal cortex connectivity and functionality will only be addressed in the experimental chapters when relevant to the discussion of the results obtained. This, of course, does not mean the functionality of parietal cortex is not essential to obtaining a complete model of the neural correlates on motor control.

1.5 Outline of this thesis

The following chapters are aimed at providing further insight into the functionality of some of the premotor regions described above. As described above, the research in this thesis will follow two general themes: that of *action selection and preparation* and of *action evaluation*. Studies reviewed in the introduction of the first theme, action preparation, have consistently shown activation in parietal and lateral premotor areas. The medial premotor cortex has traditionally been associated with internally generated actions [but see Petit et al. (1998)], while the lateral premotor cortex is traditionally more associated with the selection and preparation of externally instructed actions. Note, however, that this distinction is far from established, especially in the case of the medial premotor cortex.

This thesis will further investigate the motor control processes described above by taking a closer look at motor processing, adaptation of motor responses, and error processing and specifically the contributions of the premotor cortices to these functions.

Chapter 2 will focus on the preparatory motor activity by assessing whether it is possible to dissociate at the neural level the functional roles of delay-related activity in the premotor cortex related to maintenance of sensory information versus preparation of upcoming motor responses. Earlier studies focusing on processing of spatial and motor information (Simon et al., 2002) suggested that the premotor/pre-premotor dissociation reflects

the processing of spatial and motor information, respectively. The study reported in Chapter 2 is aimed at exploring this dissociation in the domain of arbitrary visuomotor processing, using a design closely related to that employed in research on nonhuman primates.

Studies on preparatory activity conducted in the laboratory usually assume that they influence neural processing starting from a 'clean sheet'. However, most actions are selected, prepared, and executed in the context of ongoing behavior. Chapter 3 will focus on the effects of the presence of a current motor program on the selection and preparation of new motor plans.

Chapters 4 and 5 will take a closer look at the contribution of the medial premotor areas to error processing. In Chapter 4, event-related potentials are used to take a closer look at the functional significance of the feedback-ERN. Although the response-ERN has been the focus of most ongoing research, and indeed the focus of most theories on the ERN (Botvinick et al., 2001; Yeung et al., 2004), research on the functionality of the feedback-ERN has been important in the formulation of the reinforcement learning model of the ERN (Holroyd and Coles, 2002). This model makes a number of predictions about the behavior of the feedback-ERN. Specifically, Chapter 4 will focus on the kind of information reflected in the feedback-ERN.

Chapter 5 will continue along the path of integrating error processing in motor learning, by investigating error processing in an arbitrary visuomotor learning task. The question is whether there is a single neural system involved in processing errors independent of their source (i.e., external performance feedback or internal error detection) and whether activity in the neural system is modulated by the stage of learning, as suggested by the reinforcement learning theory of error processing (Holroyd and Coles, 2002).

Finally, Chapter 6 is devoted to exploring whether it is possible to further extend the applicability of theories on error processing into the domain of action observation. A number of models of motor control have been employed recently to the domain of action observation (Miall, 2003; Wolpert et al., 2003). Chapter 6 will focus on probing the action monitoring system as described in the reinforcement learning model in action observation.

Chapter 7 will summarize the results obtained, discuss these in the context of recent models of motor control, and provide suggestions for further research.

2 Cerebral dynamics and topography of preparatory activity

This chapter is a modified version of:
Mars RB, Coles MGH, Hulstijn W, Toni I. Cerebral dynamics and topography of preparatory activity. Manuscript submitted for publication

Abstract

Flexible goal-oriented behavior requires the ability to carry information across temporal delays. Neurally, this ability is associated with sustained neural firing. In cognitive terms, this ability has often been associated with the maintenance of sensory material on-line, as during short-term memory tasks, or with the retention of a motor code, as during movement preparation tasks. The general issue addressed in this paper is whether short-term storage of sensory information and preparation of motor responses rely on different anatomical substrates.

We used fMRI to measure sustained and time-varying delay-related cerebral activity evoked during performance of a delay non-match to sample task, where task contingencies rather than explicit instructions ensured that either sensory or motor representations were used to cross the delay period on each trial. This approach allowed us to distinguish sensory from motor characteristics of delay-related activity evoked by task contingencies, rather than differences in the control of short-term storage driven by verbal instructions.

Holding sensory material on-line evoked both sustained and time-varying delay-related activity in prefrontal regions, whereas movement preparation evoked delay-related responses in precentral areas. Sustained activity in the intraparietal sulcus was sensitive to the presence of memoranda, but indifferent to the type of information that was retained in memory. Our findings indicate that short-term storage of sensory information and preparation of motor responses rely on partially segregated cerebral circuits. In the frontal lobe, these circuits are organized along a rostro-caudal dimension, corresponding to the sensory or motor nature of the stored material.

2.1 Introduction

Adaptive behavior requires the ability to make decisions, avoiding stereotyped reactions to an environmental impulse (Glimcher, 2003). For instance, it can be beneficial, following a sensory instruction, to delay a response until it is appropriate. Under these circumstances, the brain needs to bridge a temporal gap between perception and action. In neural terms, this ability relies on the maintenance of information through internally-generated sustained activity (Fuster and Alexander, 1971; Goldman-Rakic, 1987; Romo et al., 1999; Vogels et al., 2005). These neural patterns can support different cognitive processes, from the storage of sensory information for prospective behavior (Rainer et al., 1999), to sustained preparation of motor responses (Wise and Mauritz, 1985) and abstract rules (Wallis et al., 2001). Empirical tests of models of working memory have focused on the temporary storage of visuospatial and verbal materials, neglecting movement representations as a relevant informational code (Baddeley, 1992; Smith and Jonides, 1999). Here we test whether the neural implementation of short-term storage of sensory information and the preparation of motor responses involve different anatomical substrates.

Some authors have argued against such a dissociation, since the neural system involved in carrying sensory information over temporal gaps could

also be involved in generating motor plans (Constantinidis et al., 2001). According to this perspective, sensory features of an instruction are maintained on-line and there is no commitment to a specific response until its execution. However, motor preparatory mechanisms do not need to maintain a sensory instruction on-line once the response is selected. Accordingly, other authors have suggested a different interpretation of sustained activity, in which mnemonic and preparatory activities are conceptually and neuronally distinct phenomena (Fuster, 2000).

We have tested whether short-term storage of sensory and motor information rely on spatially segregated cerebral structures. We have exploited a novel task in which participants could cross temporal delays interposed between instructions and responses by using either sensory or motor codes (Toni et al., 2002b). In contrast to previous studies in which participants were instructed to use a particular spatial code to solve a given task (Curtis et al., 2004; D'Esposito et al., 2000; Leung et al., 2002; Simon et al., 2002), our approach assesses differences in delay-related activity evoked by task contingencies, rather than differences driven by verbal instructions. Furthermore, our study is concerned with *arbitrary* stimulus-response mappings, i.e. flexible learned mappings that transcend the stereotypical performance of spatially congruent sensorimotor associations (Wise and Murray, 2000; Toni et al., 2001a).

Participants solved a delayed-non-match-to-sample task between two "sample" visual patterns and a "test" pattern, separated by a variable time delay. The task involved a comparison of their shape (Fig. 2.1). We influenced the type of information carried over the delay period by manipulating the relevance of the shape of the test cue for correct performance. Using fMRI, we measured sustained and time-varying delay-related cerebral activity evoked during task performance. The experimental design allowed us to distinguish delay-related activity from transient stimulus- and motor-related effects; and sensory from motor characteristics of delay-related activity, independently from spatial attention.

2.2 Materials and methods

Participants

We studied 9 right-handed volunteers (2 females, age range 19-27 years), with normal or corrected-to-normal vision. Participants gave informed consent according to institutional guidelines of the local ethics committee (CMO region Arnhem-Nijmegen, Netherlands) and were paid eur. 30 for their participation. Data from 2 additional participants were discarded because their behavioral data indicated that they failed to engage in motor preparation.

Experimental setup

During the scanning session, participants lay supine in the scanner. Head movements were minimized by an adjustable padded head-holder. Visual stimuli covered a visual angle of approximately 6° and were projected onto

a mirror above the participants' heads. Motor responses were recorded via an MR-compatible keypad (MRI Devices, Waukesha, WI), positioned on the right side of the participant's abdomen. Stimulus presentation and response collection were controlled by a PC running Presentation 0.81 (Neurobehavioral Systems, San Francisco, CA).

Behavioral procedures

To ensure optimal task performance during the scanning sessions, participants were trained extensively beforehand. In total, there were four training sessions and one scanning session occurring over three consecutive days. In the first training session (day 1), participants learned, by trial and error, to perform a visuomotor associative task (160 trials) relating four shapes to two movements of their right hand (Fig. 2.1A). Two shapes instructed the flexion of the index finger; the other two shapes instructed the flexion of the middle finger. During each trial, one of the four shapes [instruction cue (IC), 300 ms] was visually presented. A variable delay (0.5–2.5 s in steps of 0.5 s) was followed by a tone [trigger cue (TC), 300 ms]. The TC informed the participants to deliver the motor response specified by the IC. On each trial, immediately after the movement, a visual feedback stimulus (a green 'V' or a red 'X') was presented (200 ms), informing the participants whether the movement was correct or not.

In the second training session (day 1), participants learned, by trial and error, to perform a delayed non-match to sample (DNMS) task (Toni et al., 2002b) (800 trials). Two "sample" shapes (instruction cue, IC) out of a set of six (Fig. 2.1B-C) were visually presented for 500 ms. The set of IC shapes was constituted by the four shapes used in the first training session (i.e. shapes associated with a particular finger movements) and by two novel shapes not associated with any movement. A variable delay (1-5 s in steps of 1 s during the first 400 trials; 1-21 s in steps of 5 s during the subsequent 400 trials) was followed by the presentation (300 ms) of a "test" shape (trigger cue, TC) out of the same set of four shapes used in the first training session. To solve the DNMS task, the participants were required to press the finger specified by the non-matching shape among the set of three presented shapes (two sample stimuli and one test stimulus). In most trials, the test shape matched one of the two sample stimuli. When this was not the case (see below), the participants were required to press the finger specified by the test shape. The response was to be provided as quickly as possible after the presentation of the trigger cue. The presence of an RT cut-off (range: 2000-700 ms, decreasing every 50 trials) forced participants to emphasize response speed. On each trial, immediately after the movement, a visual feedback stimulus (a green 'V' or a red 'X') was presented (200 ms), informing the participants whether the movement was correct or not. When participants responded after the RT cut-off, a message ('too late') appeared on the screen.

The critical experimental manipulation embedded in the DNMS task was the following. An instruction cue was composed by a pair of shapes that could have instructed *i)* the same movement; *ii)* different movements; *iii)* no

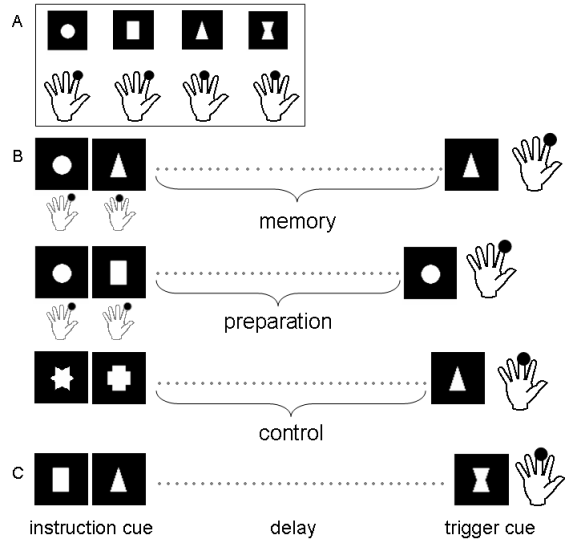

Figure 2.1: Experimental task. Four shapes were matched to two movements (A). Trials in the delayed non-match to sample task (B)were constructed to invoke maintenance of sensory items (MEMORY), movement preparatory activity (PREPARATION), or no memory load (CONTROL). During training, CATCH trials were also presented, to prevent the use of alternative strategies during MEMORY trials (C).

movement (Fig. 2.1B-C). When the two sample shapes instructed the same movement, then the test shape invariably matched one of the two instruction stimuli. It follows that the correct response was completely specified by the instruction shapes. In these trials (PREPARATION trials), the participants could have selected the response after the presentation of the IC, and therefore could hold the movement ready during the delay. Thus, delay-related responses evoked during these trials can be taken to include the effects of carrying motor material over a temporal gap.

When the two sample shapes instructed different movements, then the test shape could have matched (70%) or not one of the two sample stimuli. It follows that the correct response was specified by the comparison between sample and test shapes. In these trials (MEMORY trials), the participants needed to wait until the presentation of the test shape to be able to compare the sensory characteristics of test and sample stimuli and select the appropriate response. In those trials in which the test shape did not match any of the two sample stimuli (30%), the participant applied the rule that required them to press the finger specified by the test shape (see above). These were CATCH trials (Fig. 2.1C). Their presence allowed us to probe whether the participants were solving the MEMORY trials by applying an alternative strategy to the one detailed above. Namely, during MEMORY trials, the participants could have simply opted for performing the movement that was not instructed by the TC. This alternative strategy did not require the participants to hold the IC shapes on-line, but it relied on the TC being invariably matched to one of the two sample stimuli. Therefore, if the participants used

this alternative strategy, they would have been unable to perform the CATCH trials correctly. Therefore, delay-related responses evoked during MEMORY trials can be taken to include the effects of carrying sensory material over a temporal gap.

When the two sample shapes instructed no movement, then the test shape did not match any of the two sample stimuli, since the TC was drawn from a set of four shapes previously associated with a specific movement. It follows that the correct response was completely specified by the test shape alone. In these trials (CONTROL trials), the participants needed to wait until the presentation of the TC to select the appropriate response, and the sample shapes did not need to be compared with the TC in order to solve the task. Therefore, delay-related responses evoked during these trials can be taken to reflect effects not specifically associated with carrying sensory or motor material over a temporal gap.

On the third training session (day 2), participants were further trained on the DNMS task for 250 trials, with delays varying between 1 and 21 sec (in steps of 5 sec). For the last 200 trials, participants performed the task without visual feedback.

The fourth training session (day 3) took place just before the start of the scanning session. Participants practiced the DNMS task for 50 trials before entering the MR scanner and for 50 trials inside the scanner just before scanning. Afterwards, the scanning session started, and participants performed the task for 120 trials. During the scanning session, the delay between IC and TC varied between 1-21 sec (uniform distribution), and the inter-trial interval varied between 1-13 sec (uniform distribution). Feedback was not provided. Furthermore, unknown to the participants, there were no CATCH trials during the scanning session. Catch trials were removed in order to keep the length of the scanning session to a minimum. An equal number of MEMORY, PREPARATION, and CONTROL trials were presented.

These settings optimized the ability of our DNMS task to induce participants to bridge temporal delays interposed between instructions and responses by using either sensory or motor codes. By the same token, it should be emphasized that our task cannot be compared to the trial-unique DNMS tasks used to assess item recognition (Kowalska et al., 1991; Suzuki et al., 1993).

Experimental timing

The experimental timing and the wide range of delays enabled us to characterize the evoked hemodynamic responses at a finer temporal resolution than the actual TR (Josephs et al., 1997) and allowed us characterize the BOLD responses to independent components (Toni et al., 1999; Mars et al., 2005) aligned with the instruction cue, with the trigger stimulus, and extending over the delay period. The extensive range of delays ensured that the participants were ready to respond at any time after the presentation of the instruction cue (Toni et al., 2002b). The pseudorandom presentation of different trial types ensured that the participants could not anticipate the order of the conditions.

Behavioral analysis

Mean response times (RTs) and error rates (ERs) measured during the scanning session were analyzed separately and considered as dependent variables in a 3 $\times$ 5 repeated measures ANOVA with main effects of TRIAL TYPE (3 levels: MEMORY, PREPARATION, and CONTROL) and DELAY LENGTH (5 levels, arising from the subdivision of the instructed delays into bins of equal duration). Participants were considered as a random factor. The alpha-level was set at 0.05, univariate approach, Huynh-Feldt corrected.

Image acquisition

Images were acquired using a 3T Trio scanner (Siemens, Erlangen, Germany). BOLD sensitive functional images were acquired using a single shot gradient EPI sequence (TR/TE 2.430s/40 ms, 33 transversal slices, ascending acquisition, voxel size 3.5 $\times$ 3.5 $\times$ 3.5 mm). Following the experimental session, structural images were acquired using a MP-RAGE sequence (TR/TE/TI 2.3 s/3.93 ms/1100 ms, voxel size 1 $\times$ 1 $\times$ 1 mm).

Image analysis

Functional data were pre-processed and analyzed using SPM2 (Statistical Parametric Mapping, www.fil.ion.ucl.ac.uk/spm). The first five volumes of each participant's data set were discarded to allow for T1 equilibration. The image timeseries were spatially realigned using a sinc interpolation algorithm that estimates rigid body transformations (translations, rotations) by minimizing head-movements between each image and the reference image. The timeseries for each voxel were realigned temporally to the time of acquisition of the middle slice. Subsequently, images were normalized onto a custom MNI-aligned EPI template (based on 28 male brains acquired on the Siemens Trio scanner at the F.C. Donders Centre) using both linear and 16 nonlinear transformations and resampled at an isotropic voxel size of 2 mm. Finally, the normalized images were spatially smoothed using an isotropic 8 mm full-width-at-half-maximum Gaussian kernel. Each participant's structural image was spatially coregistered to the mean of the functional images (Ashburner and Friston, 1997) and spatially normalized by using the same transformation matrix applied to the functional images.

The fMRI timeseries were analyzed using an event-related approach in the context of the General Linear Model. Analysis of the imaging data considered main effects of trial Type and trial Epoch [10 levels: IC, MEMORY-DELAY$_{sust}$, PREPARATION-DELAY$_{sust}$, CONTROL-DELAY$_{sust}$, MEMORY-DELAY$_{ramp}$, PREPARATION-DELAY$_{ramp}$, CONTROL-DELAY$_{ramp}$, MEMORY-TC, PREPARATION-TC, CONTROL-TC]. IC- and TC-related effects were modelled as delta functions. DELAY-related activities were modelled as i)square-waves time locked to the onset/offset of the corresponding IC/TC and extending over the delay period (DELAY$_{sustained}$ component); and as *ii)* triangular-waves time locked to the onset/offset of the corresponding IC/TC and ramping-up over the delay period (DELAY$_{ramp}$ component). Delay-related activity was thus defined by

a time interval rather than by a specific time point, and we accounted for both sustained and (linearly) time-varying activity occurring over the delay period. Each of these ten functions was then convolved with a canonical hemodynamic response function (Friston et al., 1998), and down-sampled at each scan in order to generate 10 regressors modeling the main effects described above. Separate covariates including trials with incorrect or missing responses, corrective responses, trial-by-trial variations in RT, head-related movements (as estimated by the spatial realignment procedure) and a constant term over scans were also considered in the model. Furthermore, we included terms describing the average white-matter intensity and cerebral-spinal fluid intensity as extracted from the EPI timeseries following a standard segmentation procedure (Verhagen et al., 2006). These regressors were meant to capture scan-by-scan variations in global signals un-confounded by task-related BOLD changes. Data was high-pass filtered (cut-off 500 s) to remove low frequency confounds, such as scanner drifts. Temporal autocorrelation was modelled as an AR(1) process.

Statistical inference

The statistical significance of the estimated evoked hemodynamic responses was assessed using t-statistics in the context of a multiple regression analysis. The null hypothesis was that the variance explained by a given regressor was consistent with the residual error, once the variance explained by the other components of the model was accounted for. Linear compounds (contrasts) were used to determine the effects associated with each task component, generating t-values for each voxel in the image, i.e. statistical parametric maps (SPM) of t-values. In particular, for each of the three experimental conditions described above (PREPARATION, MEMORY, CONTROL), we isolated both differential delay-related responses (indicated by ">") and common delay-related responses (indicated by "∩") (Nichols et al., 2005). Furthermore, we assessed both sustained delay-period activity and activity showing increasing activity during memory and preparation intervals. This time-varying activity was also taken into account following reports of increasing memory-related activity with increasing load (Narayanan et al., 2005) and increasing preparatory activity with increasing response probability (Schoffelen et al., 2005).

We assessed the spatial distribution of the following effects:

1. We isolated sustained delay-related responses showing stronger activity during the MEMORY trials than during the PREPARATION and CONTROL trials, ensuring that this differential activity was driven by relative increases during the MEMORY trials rather than decreases during the PREPARATION and CONTROL trials. These constraints were implemented in the following contrast: (MEMORY-DELAY$_{sust}$ > PREPARATION-DELAY$_{sust}$) ∩ (MEMORY-DELAY$_{sust}$ > CONTROL-DELAY$_{sust}$), *masked by* (PREPARATION-DELAY$_{sust}$ > 0 ∩ CONTROL-DELAY$_{sust}$ > 0).

2. We isolated sustained delay-related responses showing stronger activity during the PREPARATION trials than during the MEMORY and CON-

TROL trials, ensuring that this differential activity was driven by relative increases during the PREPARATION trials rather than decreases during the MEMORY and CONTROL trials. These constraints were implemented in the following contrast: (PREPARATION-DELAY$_{sust}$ > MEMORY-DELAY$_{sust}$) ∩ (PREPARATION-DELAY$_{sust}$ > CONTROL-DELAY$_{sust}$), *masked by* (PREPARATION-DELAY$_{sust}$ > 0 ∩ CONTROL-DELAY$_{sust}$ > 0).

3. We isolated sustained delay-related responses showing common differential activity during MEMORY and PREPARATION trials as compared to the CONTROL trials. These constraints were implemented in the following contrast: (MEMORY-DELAY$_{sust}$ > CONTROL-DELAY$_{sust}$)∩ (PREPARATION-DELAY$_{sust}$ > CONTROL-DELAY$_{sust}$).

4. We isolated time-increasing delay-related responses evoked during the MEMORY trials as compared to the PREPARATION trials, ensuring that this differential activity was driven by relative increases during the MEMORY trials rather than decreases during the PREPARATION trials. These constraints were implemented in the following contrast: (MEMORY-DELAY$_{ramp}$ > PREPARATION-DELAY$_{ramp}$), masked by (MEMORY-DELAY$_{ramp}$ > 0).

5. We isolated time-increasing delay-related responses evoked during the PREPARATION trials as compared to the MEMORY trials, ensuring that this differential activity was driven by relative increases during the PREPARATION trials rather than decreases during the MEMORY trials. These constraints were implemented in the following contrast: (PREPARATION-DELAY$_{ramp}$ > MEMORY-DELAY$_{ramp}$), masked by (PREPARATION-DELAY$_{ramp}$ > 0).

Gaussian field theory allowed us to make inferences corrected for the number of non-independent comparisons (Friston et al., 1995b). The effective degrees of freedom of the error term took into account the temporal autocorrelation of the data (Friston et al., 1995a).

The statistical inferences adopted a cluster-level threshold of $p < 0.05$, corrected for multiple comparisons over the whole brain using the family-wise error correction (Friston et al., 1996a). Cluster-level statistics considers the spatial extent of activity lying above a given intensity threshold. In this study the intensity threshold was set at a conservative t=4 [conservative in the context of cluster-level statistics, Friston et al. (1994)]. This allowed us to maximize the anatomical specificity of the inferences (high intensity threshold) while preserving the increased power of cluster-level statistics. Tables 2.1 and 2.2 report the corresponding intensity level t-values.

For areas displaying time-varying delay-related activity, we plotted the BOLD signal time-course during the scanning session for each condition separately. In particular, we calculated the inter-subject average and standard error of the peak BOLD response for each of 10 consecutive and equally spaced time bins along the delay period.

Anatomical inference

Anatomical details of significant signal changes were obtained by superimposing the SPMs on the structural images of each subject in MNI coordinates. The atlas of Duvernoy (Duvernoy et al., 1991) was used to identify relevant anatomical landmarks. When applicable, Brodmann Areas were assigned on the basis of the SPM Anatomy Toolbox (Eickhoff et al., 2005), i.e. the anatomical position of our significant clusters and local maxima was formally tested against published three-dimensional probabilistic cytoarchitectonic maps.

2.3 Results

Behavioral performance

Fig. 2.2 illustrates the mean error rate (ER) and response time (RT) as a function of delay during the three trial types, obtained during the scanning session. The data indicate that our design was successful in inducing participants to bridge the gap between IC and TC by using different mental representations. Participants were faster and made fewer errors during the PREPARATION trials than during the CONTROL and MEMORY trials (main effect of TRIAL TYPE - ER: $F(2,16)= 22.929$, $p < 0.001$; RT: $F(2,16)= 48.76$, $p < 0.001$). Also, there was a significant main effect of delay on error rate ($F(4,32) = 4.371$, $p = 0.006$). Crucially, delay length differentially affected the PREPARATION and the MEMORY trials (TRIAL TYPE $\times$ DELAY LENGTH interaction – ER: $F(8,64)= 3.26$, $p = 0.004$). Post-hoc comparisons revealed that during MEMORY, but not during PREPARATION or CONTROL, the error rate increased as a function of the delay interposed between the IC and the TC ($p < 0.003$). This indicates that the mental representations used to bridge the temporal gap between IC and TC during the MEMORY trials were more labile than those used during the PREPARATION trials. Because Figure 2.2 shows a strong trend on RT, we assessed the modulation of RT by delay in each condition, using a linear regression for each participant. Participant's beta weights were tested at the second level using a one-tailed t-test. This post-hoc analysis revealed shortening in RT with increasing delay length in both PREPARATION ($p = .044$) and CONTROL ($p = .007$) conditions, but not in the MEMORY condition.

A paired-samples t-test was performed on the RTs on correct MEMORY and CATCH trials measured during the third training session (last 200 trials) in order to ensure that participants were retaining sensory information during the MEMORY trials (see Methods - Behavioral Procedures). Note that, apart from the presence of CATCH trials, the task procedures used during this training session were identical to those used during the scanning session. RTs evoked during the MEMORY and CATCH trials did not differ ($t(8) = 1.057$, n.s.), indicating that in both conditions participants used a similar strategy to solve the task (Toni et al., 2002b).

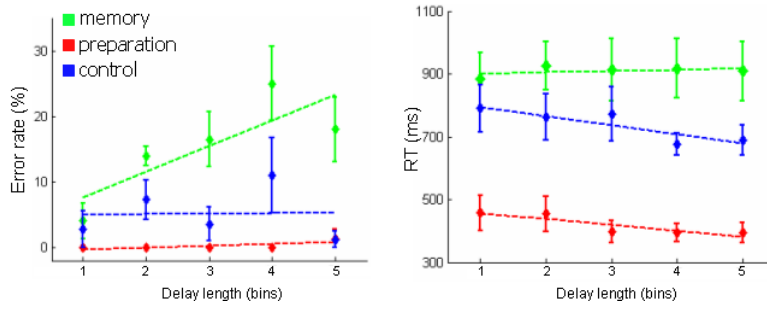

Figure 2.2: Behavioral data. Error percentages (left panel) and reaction times on correct trials (right panel) in the CONTROL, PREPARATION, and MEMORY conditions as a function of delay length, obtained during the scanning session. Curves are fitted first order polynomials; error bars indicate ±SEM. For a color version of this illustration, see p. 130.

Imaging data: Sustained delay-related activity

The following section describes the SPMs associated with sustained delay-period activity. Significant differential delay-related responses are listed in Table 2.1.

First, we isolated sustained delay-related responses showing stronger activity during the MEMORY trials than during the PREPARATION and CONTROL trials, ensuring that this differential activity was driven by relative increases during the MEMORY trials rather than decreases during the PREPARATION and CONTROL trials [i.e., (MEMORY-DELAY$_{sust}$ > PREPARATION-DELAY$_{sust}$) ∩ (MEMORY-DELAY$_{sust}$ > CONTROL-DELAY$_{sust}$), masked by (PREPARATION-DELAY$_{sust}$ > 0 ∩ CONTROL-DELAY$_{sust}$ > 0)]. This contrast revealed two significant clusters of activity (Fig. 2.3, in green). One cluster (local maximum at -6, 8, 52) was located along the mesial aspect of the superior frontal gyrus, within the 50% probabilistic boundary of cytoarchitectonically defined BA6, and encroaching into the pre-SMA (Picard and Strick, 1996). A second cluster (local maximum at -28, -6, 70) was located along the caudal superior frontal sulcus, at the border between BA6 and BA8 (Eickhoff et al., 2005).

Second, we isolated sustained delay-related responses showing stronger activity during the PREPARATION trials than during the MEMORY and CONTROL trials, ensuring that this differential activity was driven by relative increases during the PREPARATION trials rather than decreases during the MEMORY and CONTROL trials [i.e., (PREPARATION-DELAY$_{sust}$ > MEMORY-DELAY$_{sust}$) ∩ (PREPARATION-DELAY$_{sust}$ > CONTROL-DELAY$_{sust}$), masked by (PREPARATION-DELAY$_{sust}$ > 0 ∩ CONTROL-DELAY$_{sust}$ > 0)]. This contrast revealed two significant clusters of activity (Fig. 2.3, in red), contiguous but distinct and caudal to the MEMORY clusters described above. One cluster (local maximum at -6, -12, 54) was located along the mesial aspects of the superior frontal gyrus, within the 100% probabilistic boundary of cytoarchitectonically defined BA6 (Eickhoff et al., 2005), and encroaching into the SMA (Picard and Strick, 1996). A second cluster (local maximum at -36,

(MEMORY$_{sust}$ > PREPARATION$_{sust}$) ∩ (MEMORY$_{sust}$ > CONTROL$_{sust}$) (masked incl. by PREPARATION$_{sust}$ > 0 ∩ CONTROL$_{sust}$ > 0)				
Anatomical region	*MNI coordinates*			*t value*
	x	y	z	
Mesial sup frontal g	-6	8	52	6.82
Sup frontal s	-28	-6	70	6.49

(PREPARATION$_{sust}$ > MEMORY$_{sust}$) ∩ (PREPARATION$_{sust}$ > CONTROL$_{sust}$) (masked incl. by PREPARATION$_{sust}$ > 0) ∩ (CONTROL$_{sust}$ > 0)				
Anatomical region	*MNI coordinates*			*t value*
	x	y	z	
Mesial sup frontal g	-6	-12	54	11.59
Central s/Precentral g	-36	-26	48	6.11

MEMORY$_{sust}$ > CONTROL$_{sust}$ ∩ PREPARATION$_{sust}$ > CONTROL$_{sust}$				
Anatomical region	*MNI coordinates*			*t value*
	x	y	z	
Intraparietal s	-44	-52	54	6.42
Putamen	-26	6	-12	4.52

Table 2.1: Imaging results: Differential delay-related sustained activity.

-26, 48) was located along the central sulcus extending onto the precentral gyrus. Probabilistic cytoarchtectonic maps (Eickhoff et al., 2005) place this cluster at the border between BA3, 4 and 6.

Third, we isolated sustained delay-related responses showing common differential activity during MEMORY and PREPARATION trials as compared to the CONTROL trials [i.e., (MEMORY-DELAY$_{sust}$ > CONTROL-DELAY$_{sust}$)∩ (PREPARATION-DELAY$_{sust}$ > CONTROL-DELAY$_{sust}$)]. This contrast revealed two significant clusters of activity. One cluster (local maximum at -44, -52, 54, Fig. 2.4) was located along the intraparietal sulcus, posterior to the 20% probabilistic boundary of cytoarchitectonically defined BA2 (Eickhoff et al., 2005). A second cluster (local maximum at -26, 6, -12) was located in the middle third of the left putamen.

Imaging data: time-varying delay-related activity

The following section describes the SPMs associated with linearly time-varying delay-related activity, i.e. BOLD signals increasing during the delay length. Significant effects are listed in Table 2.2.

First, we isolated time-increasing delay-related responses evoked during the MEMORY trials as compared to the PREPARATION trials, ensuring that

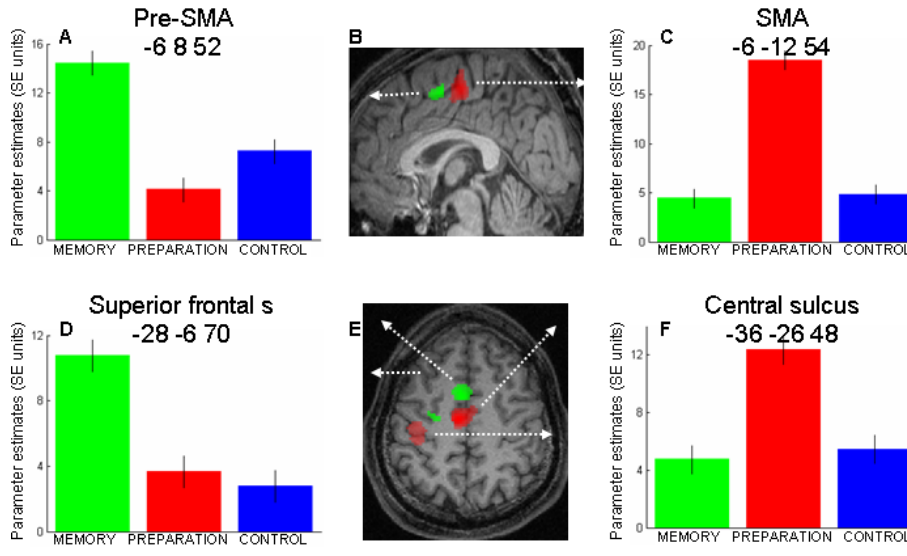

Figure 2.3: Differential delay-related sustained activity. Anatomical location (panels (B) and (E); SPM(t)s of the contrasts detailed in Table 2.1, overlaid on spatially normalized anatomical sections of one participant) and effect sizes (panels (A), (C), (D), and (F); parameter estimates of multiple regression in SEM units) of regions modulated by the task contingencies during the delay period. Regions with stronger sustained activity during delay periods of either MEMORY trials (in green) or PREPARATION trials (in red) are shown on sagittal (B) and transverse (E) anatomical sections. Clusters of delay-related activity supporting task performance during PREPARATION trials were distributed along the caudal precentral cortex (central sulcus, SMA-proper), whereas MEMORY trials evoked activity along the caudal prefrontal cortex (Brodmann area 6/8 and pre-SMA). For a color version of this illustration, see p. 130.

this differential activity was driven by relative increases during the MEMORY trials rather than decreases during the PREPARATION trials [i.e., (MEMORY-DELAY$_{ramp}$ > PREPARATION-DELAY$_{ramp}$), masked by (MEMORY-DELAY$_{ramp}$ > 0)]. This contrast revealed a significant cluster of activity (Fig. 2.5A, in green, local maximum at -40, 62, -2), located on the middle frontal gyrus, anterior to cytoarchitectonically defined BA9/46 (Rajkowska and Goldman-Rakic, 1995), and thus in BA10.

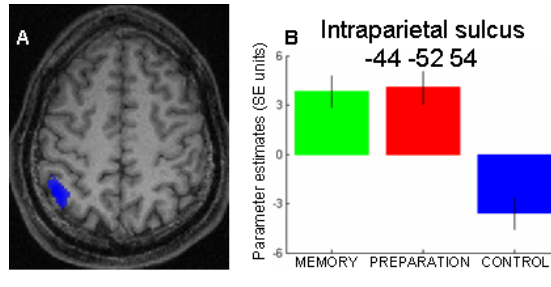

Figure 2.4: Common delay-related sustained activity. Anatomical location (A) and effect sizes (B) of a region with stronger delay-related sustained activity during PREPARATION and MEMORY trials than during CONTROL trials. Other conventions as in Fig. 2.4. For a color version of this illustration, see p. 131.

MEMORY$_{ramp}$ > PREPARATION$_{ramp}$ masked incl. by MEMORY$_{ramp}$ > 0)				
Anatomical region	*MNI coordinates*			*t value*
	x	y	z	
Middle frontal g	-40	62	-2	4.57

PREPARATION$_{ramp}$ > MEMORY$_{ramp}$ (masked incl. by PREPARATION$_{ramp}$ > 0)				
Anatomical region	*MNI coordinates*			*t value*
	x	y	z	
Precentral g	-52	2	46	5.50

Table 2.2: Imaging results: Differential delay-related time-varying activity.

Second, we isolated time-increasing delay-related responses evoked during the PREPARATION trials as compared to the MEMORY trials, ensuring that this differential activity was driven by relative increases during the PREPARATION trials rather than decreases during the MEMORY trials [i.e., (PREPARATION-DELAY$_{ramp}$ > MEMORY-DELAY$_{ramp}$), masked by (PREPARATION-DELAY$_{ramp}$ > 0)]. This contrast revealed a significant cluster of activity (Fig. 2.5C, in red, local maximum at -52, 2, 46), located on the precentral gyrus, within the 70% probabilistic boundary of cytoarchitectonically defined BA6

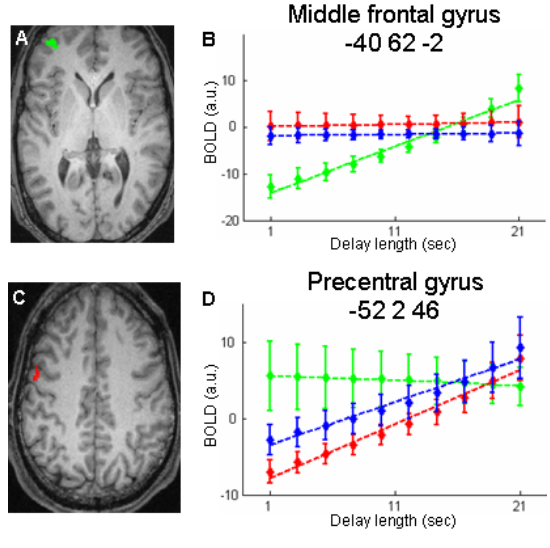

Figure 2.5: Differential delay-related time-varying activity. Anatomical location (panels (A) and (C); SPM(t)s of the contrasts detailed in Table 2.1) and effect sizes (panels (B) and (D)) of regions modulated by the task contingencies during the delay period. Regions with stronger time-varying activity during delay periods of either MEMORY trials (in green) or PREPARATION trials (in red) are shown on transverse anatomical sections. Delay-related activity increasing as a function of delay time during PREPARATION trials was found along the precentral gyrus (BA6), whereas MEMORY trials evoked activity along the middle frontal gyrus (BA10). For a color version of this illustration, see p. 131.

(Eickhoff et al., 2005). Activity in this cluster increased with delay length during both PREPARATION and CONTROL trials, but was not modulated by delay length in the MEMORY condition.

2.4 Discussion

We measured the spatial distribution of delay-related cerebral activity evoked by holding on-line either sensory material or motor responses, while having accounted for and removed the effects of presenting the sensory material and providing the motor response. In medial and lateral frontal cortex, different clusters of delay-related activity supported task performance, according to the nature of the information retained during the instructed delay. Some regions showed sustained activity throughout the delay period, whereas in other regions activity increased as a function of delay length. In posterior parietal cortex, clusters with delay-related activity were indifferent to the type of information that was retained in memory. We infer that short-term storage of sensory information and preparation of motor responses rely on partially segregated cerebral circuits. In the following paragraphs, we discuss our findings and their implications for current models of working memory.

Behavioral performance

During scanning, participants solved the DNMS task at three different levels of proficiency (Fig. 2.2). Participants responded faster during the PREPARATION than during the CONTROL trials, indicating that in the former condition the participants were preparing to execute the movement specified by the sample cue. During both CONTROL and PREPARATION trials, performance became faster as a function of delay length, indicating that the participants took into account the increasing likelihood of providing a response as delay length increased. Crucially, during MEMORY trials, accuracy decreased as a function of delay length, whereas during PREPARATION trials, performance was homogeneously error-free across delay lengths (Fig. 2.2). This indicates that the type of information retained during the MEMORY trials was more labile and of a different kind than that used during the PREPARATION trials.

Sustained activity in precentral cortex

We found sustained delay-related activity over the lateral and mesial aspects of the left precentral cortex. The pre-supplementary motor area (pre-SMA) and a caudal portion of the superior frontal gyrus (BA6/8; Fig. 2.3E, in green) showed strong sustained activity during the delay-period of the MEMORY trials, but less so during PREPARATION and CONTROL trials. Since MEMORY and CONTROL trials had comparable movement selection requirements, the pre-SMA activity cannot reflect a generalized readiness to select a response (Petit et al., 1998). Rather, our results confirm that this region deals with rules that convert sensory material or intentions into the associated movements (Bunge, 2004; Hoshi and Tanji, 2004; Lau et al., 2004).

The cluster on the superior frontal sulcus falls in the same region (BA6/8) previously shown to be involved in holding visuo-spatial information on-line during a working memory task, both in humans (Rowe et al., 2000) and in macaques (Sawaguchi and Yamane, 1999). This finding is important since it is not immediately compatible with domain-specific accounts of working memory (Levy and Goldman-Rakic, 2000; Smith and Jonides, 1997) that would predict a medio-lateral spatial segregation between regions supporting the on-line maintenance of identity and visuo-spatial features of a sensory item.

In contrast to the MEMORY-related sustained activity found in pre-SMA and BA6/8, both SMA and lateral precentral gyrus (BA6; Fig. 2.3) were particularly active during the delay-period of the PREPARATION trials. This finding illustrates how a substantial portion of the delay-related sustained activity that can be found in the caudal precentral gyrus is specifically related to the preparation of a motor response, over and above the effects of elapsing time (as indexed by the CONTROL trials) or holding sensory items on-line (as indexed by the MEMORY trials; Fig. 2.3F).

Overall, these results fit with the general partition of the precentral cortex into 'premotor' and 'pre-premotor' territories (Picard and Strick, 2001). Here we show that this anatomical distinction has a cognitive counterpart with respect to the nature of the material held on-line during a delay period. There was a clear rostro-caudal distribution of MEMORY- and PREPARATION-related effects (Fig. 2.3), indicating that the contributions of the frontal lobe to working memory could also be organized along a rostro-caudal dimension, corresponding to the sensory or motor nature of the stored material. This interpretation unifies previous distinctions made between motor preparation, visuospatial attention, and rule processing on the lateral surface (Boussaoud, 2001; Bunge et al., 2003) and between motor preparation and processing of visuomotor rules on the mesial surface (Bunge, 2004; Crone et al., 2006; Hoshi and Tanji, 2004; Lau et al., 2004; Maier et al., 2002). This interpretation is also consistent with the results of a related TMS study (Van den Hurk, Mars, Van Elswijk, Hegeman, Pasman, Bloem, and Toni, submitted for publication) showing that cortico-spinal excitability is altered when holding a movement on-line, but not during the maintenance of sensory material. This result fits with the fact that premotor regions, but not pre-premotor regions, have direct output to the primary motor cortex and the spinal cord (Picard and Strick, 2001).

Sustained activity in the intraparietal sulcus

Independent studies have shown that the posterior parietal cortex is involved in the maintenance of both sensory items (Rowe et al., 2000; Todd and Marois, 2004) and motor intentions (Andersen and Buneo, 2002; Kalaska and Crammond, 1995; Platt and Glimcher, 1999; Snyder et al., 1997; Thoenissen et al., 2002) over time intervals of seconds. Here we illustrate how the delay-related sustained activity evoked in this region is specifically related to the presence of memoranda, as evidenced by the relative decrease in activity in the CONTROL condition, whether these memoranda

specify a motor response or not, as evidenced by the comparable responses during MEMORY and PREPARATION trials (Fig. 2.4B). These results appear consistent with the suggestion that this region contributes to the temporary storage of information (Jonides et al., 1998; Thoenissen et al., 2002), and more specifically storage in a format accessible to decision-making processes (Toth and Assad, 2002). However, our results do not exclude the possibility that MEMORY- and PREPARATION-related effects remain spatially segregated at a spatial scale below our resolution, i.e. that different neurons within the intraparietal sulcus exhibit sensory memory and motor preparatory activity, respectively (Quintana and Fuster, 1999).

Time-varying delay-related activity

We found two regions which showed increasing activity with increasing delay length in one or more specific conditions. A cluster along the the middle third of the rostral precentral gyrus showed increasing activity during PREPARATION and CONTROL trials, but not during MEMORY trials (Fig. 2.5D). This time-varying precentral response appears to be related to the time-varying characteristics of the RT observed in the PREPARATION and CONTROL trials. Given that the cerebral effect (delay-related activity) precedes the behavioral effect (RT), it is plausible that this region might contribute to biasing a generic motor plan with contextual information generalized over trials, namely the conditional probability of providing a response at a given time, given that no response has yet been required (Schoffelen et al., 2005). Our results confirm that this temporal inference is not necessarily linked to the implementation of a specific motor plan (Coull et al. 2004), since behavioral and cerebral effects occur during both PREPARATION and CONTROL trials. On the other hand, the contributions of this precentral region appear to be embedded in a motor circuit, since there was no response (and no anticipatory behavior) when the incoming test stimulus was more than a simple motor instruction (MEMORY trials).

The anterior portion of the middle frontal gyrus (BA10) showed time-varying delay-related activity in the MEMORY trials only (Fig. 2.5A). This time-varying prefrontal response appears related to the time-varying characteristics of the error rate observed in the MEMORY trials (Fig 2.2). However, since the our analysis was confined to correct trials only, our effect is not a trivial by-product of increasing error rate. It has been shown that maintaining sensory information on-line requires additional resources as delay length increases (Ploner et al., 1998; White et al., 1994). Therefore, it is plausible that this prefrontal region might contribute to support activity in other cerebral structures more specifically involved in maintenance of the sensory items (Fig. 2.3D) only for the longer delays. This role appears to fit with previous reports suggesting that this region is not involved in allocating attentional resources per se (Koechlin et al., 1999), but rather it is involved in biasing cognitive operations performed by other cortical regions (Sakai and Passingham, 2003; Sakai and Passingham, 2006). Furthermore, our findings are in line with the suggestion that BA10 involvement requires more than the implementation of a single sensorimotor rule (Ramnani and

Owen, 2004). Specifically, this region contributed to those trials where a sensory item needed to be compared with similar items in memory, but not to PREPARATION and CONTROL trials.

Conclusions

Our findings point to crucial differences in how prefrontal, precentral, and parietal regions contribute to the basic faculty of holding information online during a temporal gap between perception and action. The intraparietal cortex appears to be involved in online maintenance of sensory material with motor implications. Caudal precentral cortex appears to be involved in holding a movement online, provided that the movement can be fully specified in advance. Dorsal prefrontal cortex (border BA6/8) appears to be involved in the maintenance of sensory material and of the sensorimotor rules that allow for the selection of an appropriate response in the near future. Furthermore, both precentral (BA6) and prefrontal (BA10) regions reveal time-varying delay-related activity that is presumably involved in biasing sustained preparatory and mnemonic responses as a function of contextual information generalized over trials (i.e. the conditional probability of providing a response or selecting a rule, given that no response has been yet required).

In summary, these findings illustrate that the contributions of the frontal lobe to working memory are organized along a rostro-caudal dimension, corresponding to the sensory or motor nature of the stored material.

3 On the programming and reprogramming of actions

This chapter is a modified version of:
Mars RB, Piekema C, Coles MGH, Hulstijn W, Toni I. On the programming and reprogramming of actions. Manuscript submitted for publication

Abstract

Actions are often selected in the context of ongoing movement plans. Most studies of action selection have overlooked this fact, implicitly assuming that the motor system is passive prior to presentation of instructions triggering movement selection. Earlier studies addressed action planning in the context of an already present motor plan, but focused mostly on inhibition of a prepotent response under fierce time pressure. Under these circumstances, inhibition of previous motor plans and selection of a new response become temporally intermingled. Here we explore how the presence of earlier motor plans influences cerebral effects associated with action selection, separating in time movement programming, reprogramming, and execution.

We show that portions of parieto-frontal circuits, including intraparietal sulcus and left dorsal premotor cortex, are systematically involved in programming motor responses, their activity indifferent to the presence of earlier motor plans. We identify additional regions recruited when a motor response is programmed in the context of an existing motor program. Several right-hemisphere regions, previously associated with response inhibition, might be better characterized as involved in response selection. Finally, we detail the specific role of a right precentral region in movement reprogramming that is involved in inhibiting not only actual responses, but also motor representations.

3.1 Introduction

Several studies have addressed the issue of how the goal of an action, the relevant effector, and timing information are integrated into an appropriate motor plan (Andersen and Buneo, 2002; Hesse et al., 2006; Rushworth and Taylor, 2006; Thoenissen et al., 2002; Toni et al., 2001a). This issue has been mainly addressed by assuming that the brain is an input-output device that processes sensory material to generate motor responses; this reflex-like process being set in motion by the presentation of a sensory trigger (Glimcher, 2003). However, it is known that primary motor areas are affected by preparatory processes (Crammond and Kalaska, 2000), and primary visual areas are affected by expectations (Engel et al., 2001), as well as ongoing intrinsically generated activity (Kenet and others 2001). Accordingly, it has been suggested that it might be more appropriate to consider the brain as mainly driven by its own self-sustained internal dynamics (Friston 2005), and by occasional samples of the environment (Bullier 2001; VanRullen and Koch 2003).

These considerations imply that actions are often selected in the context of ongoing preparatory activity for potential responses (Thoenissen et al., 2002). There have been several studies on the planning of actions in the context of an already present motor plan, using countermanding, go/no-go, and stop tasks (Curtis et al., 2005; Garavan et al., 1999; Li et al., 2006). The focus of these studies has been on the mechanisms supporting movement inhibition, and they have consistently implicated a predominantly right-lateralized cerebral circuit, involving the right inferior frontal

gyrus, the right inferior parietal cortex, the pre-supplementary motor area (pre-SMA), and the striatum (Aron et al., 2004; Garavan et al., 1999; Garavan et al., 2002; Liddle et al., 2001; Nachev et al., 2005; Vink et al., 2005).

However, inhibition of a prepotent response, under fierce time pressure, is likely to be accompanied by other concurrent phenomena, such as the selection of a new motor plan, and the implementation of the new response. Previous studies have accounted for these effects by relying on subtraction methods (Donders, 1969), i.e. by assuming that they add linearly, but this assumption is unlikely to hold (Friston et al., 1996b; Sternberg, 1969). Furthermore, putting time pressure on movement selection at the time of reprogramming motor actions is likely to emphasize response conflict due to the presence of multiple motor programs competing for access to the execution system (Botvinick et al., 2001; Nieuwenhuis et al., 2003), rather than capturing the interplay between an external instruction and the intrinsic dynamic of the brain.

Here we explore how the presence of earlier motor plans influences cerebral effects associated with action selection and preparation, separating in time the original movement programming, the movement reprogramming, and the actual movement execution. We address this issue in the context of arbitrary combinations of instructions and movements, i.e. flexible mappings that do not need to rely on spatially or temporally congruent sensorimotor associations (Passingham, 1993; Wise and Murray, 2000).

3.2 Materials and methods

Participants

Eleven right-handed volunteers (3 males, age range 19-29 years), with normal or corrected-to-normal vision participated in this study. Participants gave written informed consent according to institutional guidelines of the local ethics committee (CMO region Arnhem-Nijmegen, Netherlands) and were paid eur. 20 for their participation.

Experimental setup

During the scanning session, participants lay supine in the scanner. Head movements were minimized by an adjustable padded head-holder. Visual stimuli covered a visual angle of approximately 6° and were projected onto a mirror above the participants' heads. Motor responses were recorded via an MR-compatible keypad (MRI Devices, Waukesha, WI), positioned on the right side of the participant's abdomen. Stimulus presentation and response collection were controlled by a PC running Presentation 0.81 (Neurobehavioral Systems, San Francisco, CA).

Behavioral procedure

The experiment consisted of a training session (45 minutes) and a scanning session (1 hour, including acquisition of structural scan). During the train-

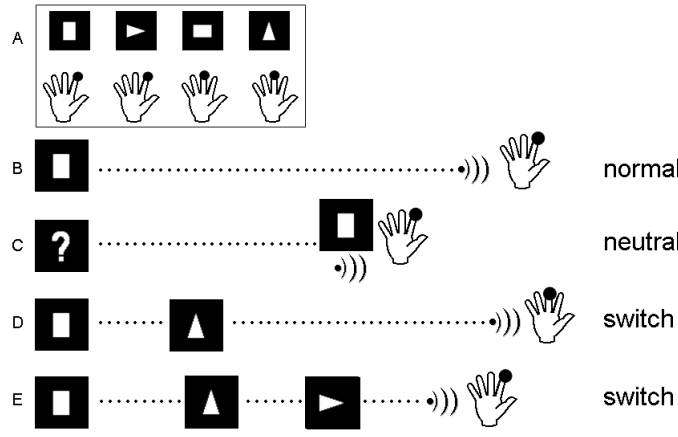

Figure 3.1: Experimental task. (A) Stimulus-response mappings learned during the training session prior to the scanning session. During the scanning session, trials from the NORMAL (B), NEUTRAL (C), and SWITCH (D,E) conditions were presented randomly intermixed. Visual stimuli were presented for 300 ms each. During the variable delay intervals, a fixation cross was presented. An auditory trigger cue signaled participants to execute the instructed response.

ing session, participants were first trained on a delayed response task on trials with the following structure (Fig. 3.1B – NORMAL trials). Participants were presented with one of four visual shapes [instruction cue (IC_{normal})], centrally presented. Two shapes instructed one response (flexion-extension of the index finger of the right hand), the other two shapes instructed another response (flexion-extension of the middle finger of the right hand - Fig. 3.1A). After the IC_{NORMAL} was displayed for 300 ms, it was replaced with a central fixation cross, which remained on screen for the duration of the trial. Following a variable delay (1000-5000 ms) a tone [trigger cue (TC_{NORMAL}), 300 ms] instructed the participants to provide the response specified by the IC_{NORMAL}. Visual feedback, consisting of a green 'V' or a red 'X', was presented for 200 ms immediately after the response. The visual feedback allowed the participants to learn the appropriate stimulus-response mappings by trial and error. Participants were required to execute the instructed response as fast as possible following the TC_{NORMAL}. If participants did not respond within an 800 ms deadline, a 'too late' feedback was presented. This procedure ensured that on these trials the participants prepared the response during the variable delay.

After 40 trials of this type, we introduced NEUTRAL trials, in which the $IC_{NEUTRAL}$ (a question mark) did not specify the movement to be executed in that trial. In this condition, the shape instructing the correct response was presented simultaneously with the tone trigger ($TC_{NEUTRAL}$ - Fig. 3.1C). This procedure ensured that the participants were discouraged from preparing a response during the variable delay. After 40 trials of this type, we introduced SWITCH trials. These trials were identical to NORMAL trials, except that during the variable delay a new IC (IC_{SWITCH}) could have been presented (300 ms). Presentation of the IC_{SWITCH} instructed the participants

do discard the instruction provided by the IC_{NORMAL} (at the beginning of that trial) and prepare the response specified by the IC_{SWITCH}. The trial distribution was such that NEUTRAL and SWITCH trials occurred on approximately 15% of the trials each. Furthermore, on approximately 15% of the SWITCH trials, multiple switches occurred (Fig. 3.1E).

Following an additional 192 practice trials, participants entered the scanner. During the scanning session, they performed 225 trials of the same task as performed during the last phase of the practice, except that performance feedback was no longer provided. Furthermore, delays between ICs and TCs, both within and between trials, varied between 1.5 and 16 seconds (right skewed distribution), such that the occurrence of trial events and onsets of fMRI volumes were not synchronized. This procedure enabled us to homogeneously characterize the hemodynamic responses at a finer temporal resolution than the actual TR (Josephs et al., 1997; Price et al., 1999), and to characterize the BOLD responses evoked by different events within the same trial (Toni et al., 1999; Mars et al., 2005).

In summary, the extensive range of variable delays between ICs and TCs ensured that the participants were ready to respond at any time after the presentation of the instruction cue (Toni et al., 2002b). Furthermore, by presenting the IC_{SWITCH} at unpredictable moments during a small (15%) percentage of the trials, we ensured that it was advantageous for the participants to prepare a response whenever possible. Crucially, by comparing the RTs evoked by NORMAL and NEUTRAL trials during the scanning session, we could determine whether participants complied with our expectations and prepared their response when possible.

Behavioral data analysis

Mean response times for correct trials (RT) and percentage of correct trials (PC) measured during the scanning session were analyzed separately and considered as dependent variables in a repeated measures ANOVA. Participants were considered as a random factor. The alpha-level was set at 0.05, univariate approach, Greenhouse-Geisser corrected.

Image acquisition

Images were acquired using a 3T Trio scanner (Siemens, Erlangen, Germany). BOLD sensitive functional images were acquired using a single shot gradient EPI sequence (TR/TE 2.430s/40 ms, 33 transversal slices, ascending acquisition, voxel size $3.5 \times 3.5 \times 3.5$ mm). Following the experimental session, structural images were acquired using a MP-RAGE sequence (TR/TE/TI 2.3 s/3.93 ms/1100 ms, voxel size $1 \times 1 \times 1$ mm).

Image analysis and statistical inference

Functional data were pre-processed and analyzed using SPM2 (Statistical Parametric Mapping, www.fil.ion.ucl.ac.uk/spm). The first five volumes of each participant's data set were discarded to allow for T1 equilibration. The

image timeseries were spatially realigned using a sinc interpolation algorithm that estimates rigid body transformations (translations, rotations) by minimizing head-movements between each image and the reference image (Friston et al., 1995b). The timeseries for each voxel were realigned temporally to acquisition of the middle slice. Subsequently, images were normalized onto a custom MNI-aligned EPI template (based on 28 male brains acquired on the Siemens Trio scanner at the F.C. Donders Centre) using both linear and 16 nonlinear transformations and resampled at an isotropic voxel size of 2 mm. Finally, the normalized images were spatially smoothed using an isotropic 8 mm full-width-at-half-maximum Gaussian kernel. Each participant's structural image was spatially coregistered to the mean of the functional images and spatially normalized using the same transformation matrix as applied to the functional images.

The fMRI timeseries were analyzed using an event-related approach in the context of the General Linear Model. Statistical models for each participant's data included separate regressors for the different instruction cues (IC_{NORMAL}, $IC_{NEUTRAL}$, IC_{SWITCH}), trigger cues (TC_{NORMAL}, $TC_{NEUTRAL}$), and switch cues. Thus, we created separate regressors for individual trial events, rather than creating regressors modeling activity during whole trials simultaneously. Incorrect responses and trials in which no response occurred were taken into account in separate regressors. Each of these functions was then convolved with a canonical hemodynamic response function and its temporal derivative (Friston et al., 1998), and down-sampled at each scan in order to generate regressors modeling the main effects described above. Separate covariates including trials with incorrect or missing responses, head-related movements (as estimated by the spatial realignment procedure) and their first derivatives, and a constant term over scans were also considered in the model. Furthermore, we also included terms describing the average white-matter intensity and cerebral-spinal fluid intensity as extracted from the EPI timeseries following a standard segmentation procedure. These regressors were meant to capture scan-by-scan variations in global signals unconfounded by task-related BOLD changes (Verhagen et al., 2006). Data was high-pass filtered (cut-off 500s) to remove low frequency confounds, such as scanner drifts. Temporal autocorrelation was modelled as an AR(1) process.

The statistical significance of the estimated evoked hemodynamic responses was assessed using t-statistics in the context of a multiple regression analysis. Contrasts of the parameter estimates for the main effects of all correct trial events were calculated and entered into a one-way, repeated measures ANOVA treating subjects as a random variable (Friston et al., 1999a), and correcting for nonsphericity at each voxel. We report the results of a random-effects analysis, with inferences drawn at the voxel level, corrected for multiple comparisons using the family-wise error correction ($p < 0.05$) (Friston et al., 1996a).

We isolated both differential hemodynamic responses (indicated by "$>$") and common hemodynamic responses (indicated by "$\cap$"). The differential effects were identified by testing the null hypothesis that there was no effect in the Statistical Parametric Map (SPM) of the t statistics describing the differ-

ence between the variance explained by two given regressors (t-contrasts). The common responses were identified by testing the null hypothesis that there was no effect in any of the two constituent SPMs (Nichols et al., 2005). Specifically, we assessed the spatial distribution of the following effects:

1. We isolated responses evoked by selecting a motor response on the basis of a visual instruction cue. These constraints were implemented in the following contrast: $[(IC_{NORMAL} > 0) \cap (IC_{SWITCH} > 0) \cap (TC_{NEUTRAL} > 0)]$.

2. We isolated responses evoked by selecting a motor response in the context of ongoing preparatory activity, over and above the responses evoked by selecting a response per se. These constraints were implemented in the following contrast: $IC_{SWITCH} > IC_{NORMAL}$. We then controlled for a series of potential confounds by limiting the search of effect within the effects revealed by other contrasts. To control for potential effects of differential frequency of IC_{SWITCH} and IC_{NORMAL}, the effects isolated by our contrast were masked by the contrast $IC_{SWITCH} > IC_{NEUTRAL}$. To further ensure that the effects isolated by the contrast were confined to regions specifically interested in movement selection, we also masked by the contrast $[(TC_{NEUTRAL} > IC_{NEUTRAL}) > (TC_{NORMAL} > IC_{NORMAL})]$. This mask identifies cerebral voxels involved in selecting a movement following presentation of a visual instruction ($TC_{NEUTRAL}$, IC_{NORMAL}), over and above the presentation of a visual (non-informative) stimulus ($IC_{NEUTRAL}$), as well as the presentation of auditory cues and the execution of the response (TC_{NORMAL}).

3. Finally, to distinguish reprogramming effects from increased attention to action, effect b) was masked by $IC_{SWITCH} > TC_{NEUTRAL}$. This mask identifies cerebral voxels involved in reprogramming a movement (IC_{SWITCH}), over and above the increased attention to action that can arise when selecting a response under time pressure ($TC_{NEUTRAL}$).

Anatomical inference

Anatomical details of significant signal changes were obtained by superimposing the SPMs on the structural images of each participant in MNI space. The atlas of Duvernoy (Duvernoy et al., 1991) was used to identify relevant anatomical landmarks. When applicable, Brodmann Areas were assigned on the basis of the SPM Anatomy Toolbox (Eickhoff et al., 2005), i.e. the anatomical position of our significant clusters and local maxima was formally tested against published three-dimensional probabilistic cytoarchitectonic maps.

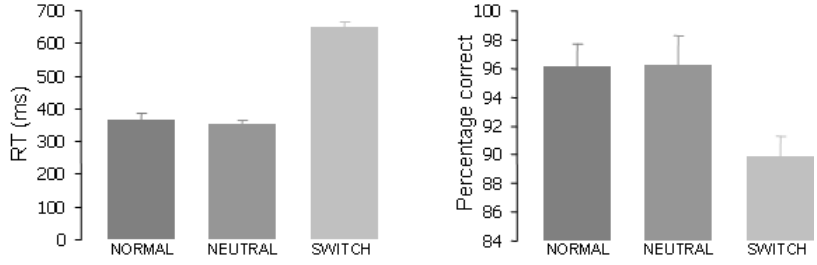

Figure 3.2: Behavioral data. Reaction times for correct trials (A) and percentage correct responses (B) in the three experimental conditions, obtained during the scanning session. Error bars reflect ±SEM.

3.3 Results

Behavioral results

Behavioral data obtained during the scanning session are summarized in Fig. 3.2. Separate ANOVAs on the reaction times on correct trials (RT) and the percentage correct responses (PC) revealed an effect of task condition on both the RT ($F_{(2,20)}$ = 338.7, $p < 0.001$) and PC ($F_{(2,20)}$ = 12.2, p = 0.004). Planned paired t-tests revealed that reaction times were longer and percentage correct was lower in the NEUTRAL conditions, while behavior on the NORMAL and SWITCH trials was identical, both with respect to RT (t_{10} = 1.7, n.s.) and PC (t_{10} = -0.2, n.s.). These data indicate that participants were similarly prepared to respond in the NORMAL and SWITCH conditions, while, as predicted, no preparation was possible in the NEUTRAL condition.

Imaging results – programming actions

All imaging results are listed in Table 3.1 (see Fig. 3.3, 3.4). We first identified regions showing consistent responses evoked by selecting a motor response on the basis of a visual instruction cue [contrast a), ($IC_{NORMAL} > 0$) $\cap$ ($IC_{SWITCH} > 0$) $\cap$ ($TC_{NEUTRAL} > 0$)]. This effect was confined to the ventral visual pathway (bilaterally), the posterior parietal cortex, the left precentral gyrus, and the mesial superior frontal gyrus. Formal tests against published probability maps (Eickhoff et al., 2005) indicated that 94% of the left precentral cluster falls within the probabilistic boundary of BA6, and we could label it as dorsal premotor cortex. The cluster in the mesial superior frontal gyrus also falls within BA6 (probability 70%), and we could label it as pre-SMA (Picard and Strick, 1996).

Given the structure of our task, it could be argued that the effects observed in the pre-SMA are related to task switching (Rushworth et al., 2002; Lau et al., 2006). Namely, on approximately half of the trials, the instruction cue specified a response that was different from the response executed on the previous trial. It has been shown that in speeded response tasks participants might sometimes adopt a strategy to commit to a certain response even before any explicit instruction has been provided (Gratton et al., 1988).

$(IC_{NORMAL} > 0) \cap (IC_{SWITCH} > 0) \cap (TC_{NEUTRAL} > 0)$				
Anatomical region	*MNI coordinates*			*t value*
	x	y	z	
Frontal lobes				
L sup frontal s	-30	-8	64	7.43
Mesial sup frontal g	0	8	52	7.09
Parietal cortex				
L anterior intraparietal s	-44	-38	44	9.46
L posterior intraparietal s	-26	-62	40	7.06
R posterior intraparietal s	32	-54	44	6.27
Occipital/temporal				
R ventral visual pathway	34	-48	-30	9.46
L ventral visual pathway	-40	-62	-30	6.08
$IC_{SWITCH} > IC_{NORMAL}$ masked by $(IC_{SWITCH} > IC_{NEUTRAL}) \cap [(TC_{NEUTRAL} > IC_{NEUTRAL}) > (TC_{NORMAL} > IC_{NORMAL})]$				
Anatomical region	*MNI coordinates*			*t value*
	x	y	z	
Frontal lobes				
L frontal operculum/insula	-42	20	-10	7.16
R inf frontal g	60	18	2	7.76
R precentral g*	42	0	42	6.69
R insula	32	20	-16	6.69
Parietal cortex				
L supramarginal g	-52	-48	40	7.15
R supramarginal g inferior parietal lobule	54	-44	48	8.98
Subcortical				
Caudate nucleus	16	-4	6	5.99

Table 3.1: Imaging results. Anatomical specification, MNI coordinates, and t-values of clusters identified by the programming and reprogramming contrasts. The cluster labeled with * survives further masking as described in the main text.

In principle, it is possible that participants might have opted to select the same response provided in the previous trial, even before the presentation of the IC_{NORMAL}. In this scenario, the IC_{NORMAL} might have included a reprogramming component. To exclude this possibility, we performed a further analysis and compared activity evoked by the presentation of IC_{NORMAL} specifying either the same or a different response than the movement executed in the previous trial. There were no differences in activity between

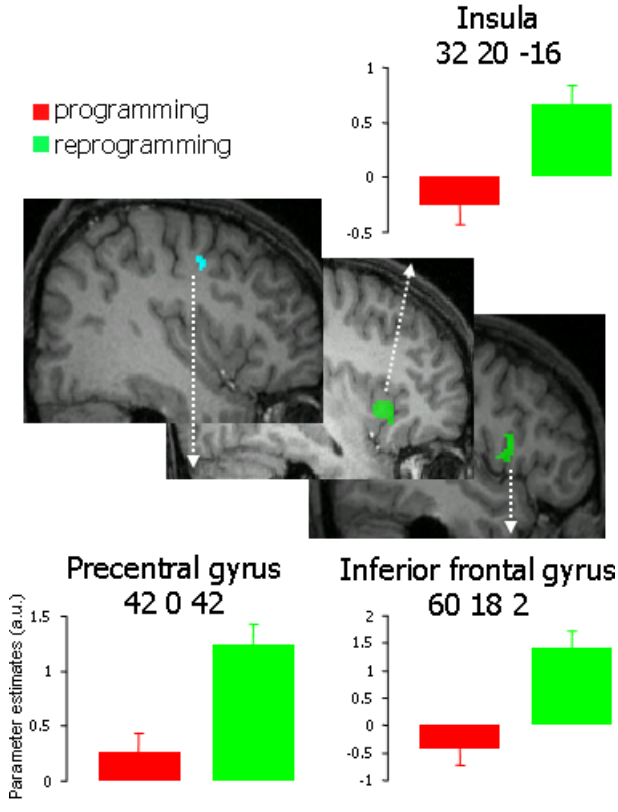

Figure 3.3: Imaging data—right frontal cortex. Anatomical location (SPM(t) of the contrasts detailed in Table 3.1, overlaid on spatially normalized anatomical sections of one participant) and parameter estimates (±90% Confidence Interval boundary) of right frontal clusters activated during action reprogramming. The cluster in cyan is the only cluster surviving a more constrained contrast (incl. masking by $IC_{SWITCH} \cap TC_{NEUTRAL}$), see main text for details. For a color version of this illustration, see p. 132.

these two event types, indicating that our results are not confounded by a switch of task context on certain ICs.

Figure 3.4 illustrates how the three parietal clusters were located in both the superior and inferior portion of this region (namely in the left anterior and posterior intraparietal sulcus, and in the right posterior intra-parietal sulcus). These regions responded whenever a movement needed to be selected, i.e. IC_{NORMAL}, IC_{SWITCH}, and $TC_{NEUTRAL}$.

We did not find any regions that showed more activation in response to the informative instructional cues (IC_{NORMAL}) than in response to the switch cues (IC_{SWITCH})

Imaging results – reprogramming actions

Regions specifically activated in response to the switch cues, over and above the effects associated with the instruction cues, are listed in Table 3.1 (contrast b), $IC_{SWITCH} > IC_{NORMAL}$). In the right hemisphere, there were

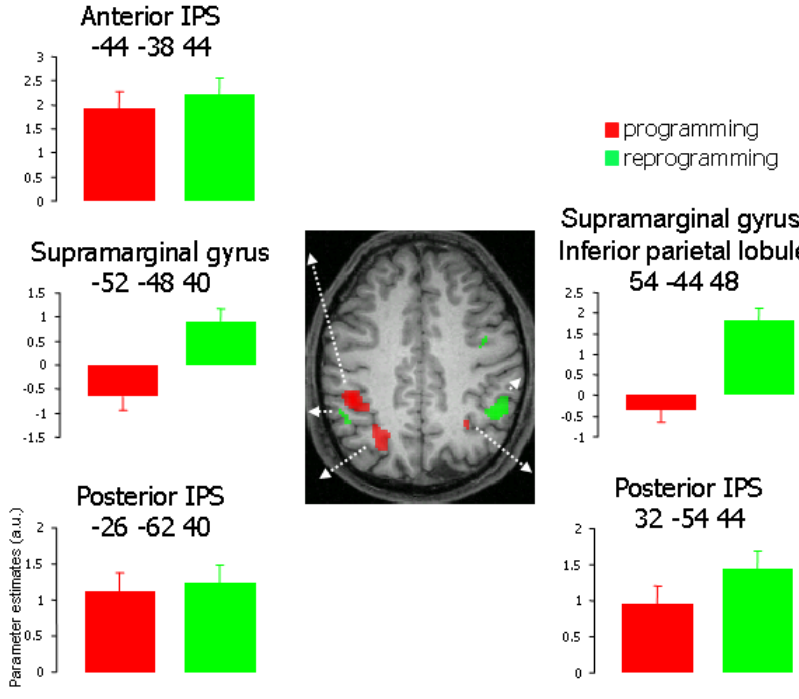

Figure 3.4: Imaging data—parietal cortex. Anatomical location (SPM(t) of the contrasts detailed in Table 3.1, overlaid on spatially normalized anatomical sections of one participants) and parameter estimates (±90 Confidence Interval boundary) of right frontal clusters activated during action programming (red) and reprogramming (green). For a color version of this illustration, see p. 133.

clusters around the right insula (extending into the right inferior frontal gyrus), in the right inferior frontal gyrus [assigned to BA44/45; Amunts et al. (1999)], and in the right precentral gyrus (BA6 border - Fig. 3.3). On the left side, a cluster was found along the left inferior frontal gyrus, extending into the left insula. Additionally, the left supramarginal gyrus and the right supramarginal gyrus and inferior parietal lobule were also activated preferentially in response to the switch cues.

Given that, following the presentation of IC_{SWITCH}, the participants needed to select and potentially execute a response within a short period of time, it could be argued that the activity of the regions identified by contrast b) was a mixture of switch-related effects and increased attention to action associated with selecting a response under time pressure. To disambiguate this mixture of effects, we masked contrast b) with ($IC_{SWITCH} > TC_{NEUTRAL}$). Following this additional constraint, only a right precentral cluster (42 0 42) revealed a specific switch-related effect (Fig. 3.3).

3.4 Discussion

We isolated cerebral activity evoked by selecting a movement in the context of an already present motor plan, while controlling for the effects of pro-

cessing sensory instructions, executing motor responses, and the non-linear interactions (e.g., response conflict) that could arise when these processes occur in close temporal proximity.

We confirm the involvement of a distributed parieto-frontal system in preparing motor responses (Toni et al., 2001a; Rushworth et al., 2003), showing that portions of intraparietal and dorsal precentral cortex are fundamental for selecting responses on the basis of a sensory trigger according to arbitrary visuomotor associations. Crucially, we also illustrate how the contribution of these parieto-frontal circuits is embedded in a larger cerebral network when a new motor program needs to be selected in the context of ongoing preparatory activity for potential responses.

Behavioral performance

Behavioral data indicate that our design was successful in inducing the participants to prepare a motor response after receiving an instruction. Participants responded faster and more accurately on NORMAL and SWITCH trials than on trials where they could not prepare the response in advance of the trigger cue (NEUTRAL trials). Since the participants could not predict the temporal occurrence of the trigger cue that followed the presentation of a switch cue, and given that participants' responses during NORMAL and SWITCH trials were indistinguishable, we infer that the switch cue induced the participants to abort the ongoing preparatory process and to select a new motor program.

Frontal cortex

We found that specific portions of the left dorsal precentral cortex and pre-SMA were similarly activated following the presentation of visual cues specifying the selection of a particular response. These regions revealed the same activity when a movement program was established at the time of movement execution ($TC_{NEUTRAL}$), long before movement execution (IC_{NORMAL}), or in the context of an ongoing preparatory process (IC_{SWITCH}). These findings confirm and extend previous findings on the role of these precentral regions in humans (Amiez et al., 2006; Mars et al., 2006; Toni et al., 2002a), namely transforming a visual instruction cue into the associated movement, according to a learned, arbitrary rule. Here, we further illustrate the crucial contribution of these regions to the visuomotor transformation, their activation being indifferent to the presence of an ongoing motor plan (IC_{SWITCH}) or to the need to respond under time pressure ($TC_{NEUTRAL}$). Furthermore, the presence of robust pre-SMA activity during each instance in which a motor response had to be programmed indicates that this region is not exclusively engaged during the inhibition of an ongoing response following a 'stop' cue (Kelly et al., 2004; Nachev et al., 2005). Rather, pre-SMA is engaged at a higher level of motor programming, dealing with the rules that convert sensory material or intentions into the associated movements (Bunge, 2004; Mars et al., 2006; Rushworth et al., 2004).

Other frontal regions, mainly localized in the right hemisphere, were particularly responsive at the time the IC_{SWITCH} was presented (Fig. 3.3), i.e. during the abortion of the ongoing motor plan and the selection of a new response. To distinguish between these two effects, we formally compared the responses evoked during IC_{SWITCH} and during $TC_{NEUTRAL}$ (where selection but not inhibition was likely to occur). We found that a majority of these right frontal clusters were also activated following the presentation of $TC_{NEUTRAL}$(Table 3.1, Fig. 3.3). This finding indicates that these right frontal regions are not specifically involved in inhibition of the current motor plan (Garavan et al., 1999). Rather, these regions might intervene to support an altered response selection process (Norman and Shallice, 1986). This might be the case when a response must be selected in the context of a current motor plan (following IC_{SWITCH}) or when a response has to be selected under fierce time pressure (following $TC_{NEUTRAL}$).

However, in line with previous work, we also found specific inhibitory responses in the right frontal lobe. There was stronger activity during IC_{SWITCH} than during $TC_{NEUTRAL}$ near (< 10 mm) a middle frontal region previously associated with movement inhibition (Garavan et al., 1999). This finding is consistent with the suggestion that this general region is involved in response inhibition (Garavan et al., 1999). However, here we show that this specific inhibitory effect is localized along the precentral gyrus (i.e., premotor cortex), and not in the middle frontal gyrus (i.e. prefrontal cortex). This result fits with previous reports detailing a macroscopic spatial segregation between neuronal clusters involved in mediating suppression and facilitation of neuromuscular responses (Strafella and Paus, 2001; Thoenissen et al., 2002). Furthermore, here we show that the inhibitory role of this precentral region is not confined to the execution of a response, but extends to its mental representation, i.e. to a motor program held on-line.

On the left side, we observed a large cluster of activation between the insula and the inferior frontal gyrus. This region was activated in response to both IC_{SWITCH} and $TC_{NEUTRAL}$. Since the stimulus-response mappings used in the task were well-learned, and given the corresponding lack of activity following the presentation of IC_{NORMAL}, the effects observed at IC_{SWITCH} and $TC_{NEUTRAL}$ are unlikely to be related to the *learning* of arbitrary stimulus-response associations (Passingham et al., 2000). Rather, our findings appear consistent with the role of this region in selecting the relevant stimulus-response association among a set of ongoing possibilities (Rushworth et al., 2005).

Parietal cortex

Whenever a movement had to be selected, there was activity in the posterior intra-parietal sulcus, irrespective of whether a motor program was already in place or not. This finding is reminiscent of earlier studies showing activation of posterior parietal cortex during the selection and maintenance of movement representations, independently from the likelihood of their execution (Andersen and Buneo, 2002; Thoenissen et al., 2002). Our results also fit with previous fMRI studies showing increased activation of the left pari-

etal cortex when motor sets are changed (Rushworth et al., 2001c) and TMS studies of the left supramarginal gyrus showing interference with the redirection of motor attention (Rushworth et al., 2001b). However, these earlier studies did not directly address the question of whether the reprogramming of a motor plan is associated with re-activation of the same posterior parietal regions involved in the initial action selection, or if reprogramming of a motor plan is also associated with activation of additional clusters. Our results point to the latter scenario: In addition to the parietal regions involved in motor programming, we have isolated an additional region along the left supramarginal gyrus that is specifically recruited during motor reprogramming. More generally, our results confirm a left hemisphere dominance for the selection and preparation of arbitrary visuo-motor associations (Rushworth et al., 2001a; Schluter et al., 2001), and a right hemisphere dominance in reprogramming instructed responses (Garavan et al., 1999). However, it should be emphasized that, although previous reports have interpreted this parietal reprogramming activity in terms of motor inhibition (Aron et al., 2004; Garavan et al., 1999), our results indicate that these regions are more involved in response selection processes than in the inhibition of ongoing movements.

Conclusion

In this study, we examined how the presence of existing motor plans effects cerebral activity related to the programming (i.e., selection and preparation) of voluntary actions. We have argued that this experimental setting is more likely to capture the interplay between sensory instructions and the intrinsic dynamic of the brain than a typical stimulus-response paradigm (Fitts and Peterson, 1964). We show that portions of parieto-frontal circuits involved in selecting and preparing a motor response on the basis of a visual instruction cue are indifferent to the ongoing activity related to the presence of earlier motor plans. This finding points to the obligatory nature of their involvement in the visuomotor process, at least in the context of the arbitrary stimulus-response mappings used in this study. Furthermore, we identified a number of regions that are additionally recruited when a motor response has to be programmed in the context of an existing motor program. Among these regions, we found that several right-hemisphere areas, previously associated with inhibition of an ongoing motor plan, might be better characterized as being involved in response selection. Finally, we detail the specific role of a right precentral region in movement reprogramming that may involve inhibition not only of actual responses, but also of motor representations.

4 Brain potentials and behavioral adjustments elicited by feedback in a time-estimation task

This chapter is a modified version of:
Mars RB, De Bruijn ERA, Hulstijn W, Miltner WHR, Coles MGH (2004) What if I told you: "You were wrong"? Brain potentials and behavioral adjustments elicited by feedback in a time-estimation task. In: *Errors, conflicts, and the brain. Current opinions on performance monitoring*, Ullsperger M, Falkenstein M, ed., pages 129–134. MPI of Cognitive Neuroscience.

Abstract

Recent theories have associated the error-related negativity (ERN) with the arrival of an error signal in the anterior cingulate cortex (Holroyd and Coles, 2002). This error signal is generated when negative events occur, particularly when they are unexpected, and the anterior cingulate uses the error signal to select among appropriate courses of action. We evaluated these ideas by replicating and extending previous studies of the ERN following performance feedback in which participants receive feedback after making a time-production judgment. In three different conditions, participants received (1) correct or incorrect feedback, (2) correct, incorrect-slow, or incorrect-fast feedback, and (3) the same as condition (2), but with the graded incorrect feedback as a function of the degree of error. Behavioral data indicated that participants adjusted their time-estimation as a function of feedback: following incorrect feedback in condition (2), they shortened or lengthened their judgments, and in condition (3) the amount of adjustment was related to the suggested degree of error. An ERN following negative feedback was present in all three conditions, being largest in the first condition. However, no relationship was found between ERN amplitude and behavioral adjustments. These results are discussed in terms of current theories on error processing.

4.1 Introduction

In order to lead a safe and productive life, human beings have to adjust their behavior to suit any particular situation. A principal requirement for this is that an organism is able to evaluate the effects of its actions on the environment and to use this information appropriately. In particular, following an error, or following error feedback, adjustments have to be made to assure that the likelihood of future errors is minimized. In the laboratory, this phenomenon is evident in a slowing of reaction time after incorrect responses in choice-response tasks (Rabbitt, 1966).

As described in Chapter 1, the study of errors has recently been facilitated by the discovery of a component of the event-related brain potential, the error negativity (N_e) or error-related negativity (ERN), that accompanies the detection of errors in choice reaction time tasks (Falkenstein et al., 1990; Gehring et al., 1993). This component has a peak latency of approximately 80 ms following the erroneous response and appears to be generated in the anterior cingulate cortex (ACC) (Dehaene et al., 1994; Holroyd et al., 1998). A similar component, also originating in the ACC, can be observed when participants receive feedback indicating that they have made an error (Miltner et al., 1997). Consequently, this component is termed the feedback-ERN.

In several early studies (Coles et al., 1995; Gehring et al., 1993), a relationship was found between the amplitude of the ERN and various examples of behavioral adjustments. These 'remedial actions' were reflected in the tendency to correct an error, to slow down following an error, and in the force of the error itself. However, to date, no one has investigated the relationship between behavioral adjustments and the feedback-ERN. One aim of the present study was to evaluate this relationship.

The theoretical framework for this study was provided by the reinforcement learning theory of the ERN (Holroyd, 2001; Holroyd and Coles, 2002), which proposes that the ERN is associated with learning-relevant signals that are carried by the mesencephalic dopamine system (MDS). This model is based on the finding that the MDS carries reward signals indicating that ongoing events are 'better' or 'worse' than expected (Schultz, 2002). A monitoring system in the basal ganglia evaluates internal information about self-generated behaviors and external information from the environment, and predicts the expected value, or 'reward', of ongoing events. When the system revises its predictions for the worse, either because of an internally detected inappropriate motor action or upon receiving negative feedback, a phasic decrease of mesencephalic dopamine activity disinhibits apical dendrites of neurons in the ACC, resulting in an ERN [see Holroyd and Coles, (2002) for a more detailed description]. Recent experimental evidence has supported the notion of dopaminergic influence in processes underlying the ERN (De Bruijn et al., 2004; Holroyd et al., 2004a). According to the reinforcement learning theory, the prediction error signals are carried by the MDS to various brain areas, including the ACC, where they are used to adjust behavior to the task at hand: "The anterior cingulate cortex is trained to recognize the appropriate [motor] controller, with reinforcement learning signals conveyed to it via the mesencephalic dopamine system. We [. . .] assume that some of the motor controllers may themselves use those same reinforcement learning signals to identify the appropriate response strategy required of them" (Holroyd and Coles, 2002, p. 685).

In the present study, we further investigated the properties of the feedback-ERN. First, we manipulated the information value of negative feedback in order to investigate how the system underlying generation of the feedback-ERN reacts. Second, we were interested in the relationship between the feedback-ERN and remedial actions. Although the reinforcement learning theory states that the system learns from errors to adjust future behavior to suit the task at hand, it does not make any direct predictions as to how this is reflected at the behavioral level. We addressed these questions in the context of a time-estimation task that has been used previously by Miltner and colleagues (Miltner et al., 1997; Lemke, 2003).

4.2 Materials and methods

Participants

Eight participants (6 female), ranging in age from 20 to 23 (M = 22.0) participated in the experiment. All participants had normal or corrected-to-normal vision. All participants were paid 6 euros per hour plus a bonus depending on their performance. All participants provided written consent according to the institutional guidelines of the local ethics committee (CMO region Arnhem-Nijmegen, Netherlands).

Task

Participants sat comfortably about 50 cm in front of a computer screen in an electrically shielded room. On each trial of the task, participants saw a white star (angle .8°) appear in the center of the screen. Participants were instructed to press a button with the index finger of their right hand when they estimated the star had been on screen for one second. Immediately following the button press, the star disappeared, and a blank screen was presented for 500 ms. Following this, feedback was provided for 500 ms. In the first condition (one block of 150 trials), participants received feedback indicating '+6 cents' on correct trials and '-6 cents' on incorrect trials. In the second condition (one block of 150 trials), participants received feedback indicating '+6 cents' and a white square underneath the text on correct trials, and '-6 cents' with an arrow underneath the text on incorrect trials. The arrow was pointing to the right when participants were too fast in their estimation (indicating that they should 'respond later in time' in the future) and to the left when participants were too slow in their estimation (indicating that they should 'respond earlier in time'). In the third condition (three blocks of 150 trials each), feedback was the same as in the second condition, except that the 'punishment' on incorrect trials was minus 2, minus 6, or minus 10 cents. Participants were instructed that the larger the punishment, the farther off their estimation was. In reality, each punishment level was presented one third of the negative feedback trials. Participants were told they started with fifty cents bonus money and the money won or lost each trial would be added to or subtracted from their bonus money. The blocks of different conditions were presented in the order 3-1-3-2-3 or 3-2-3-1-3 (counterbalanced across participants). To keep the amount of errors equal in all conditions, we used a sliding criterion to determine if a response was correct or incorrect (Miltner et al., 1997; Lemke, 2003). All participants started with a criterion +/- 200 ms. Following correct trials the criterion was decreased 10 ms, following incorrect trials the criterion was increased 10 ms.

Data acquisition and analysis

Brain electrical activity was recorded from 61 Ag/AgCl electrodes, arranged equally over the scalp, referenced to linked earlobe references. Vertical and horizontal electro-oculograms were recorded from sites above and below the left eye and 1 cm external to the outer cantus of each eye. The electrode common was placed on the sternum. All electrode impedances were kept below 5 kΩ. EEG data were amplified using BrainAmp amplifiers and digitized at 250 Hz. Data were filtered off-line with a .03-15 Hz bandpass filter. For each feedback type in each condition, a 700 ms epoch of data (100 ms baseline) was extracted for analysis. Ocular artifact was corrected using the procedure by Gratton et al. (1983) and waveforms of each electrode were checked for amplifier artifacts. Trials containing amplifier artifacts were discarded. Feedback-locked average waveforms were computed for correct and incorrect trials for each condition and for each punishment level in the

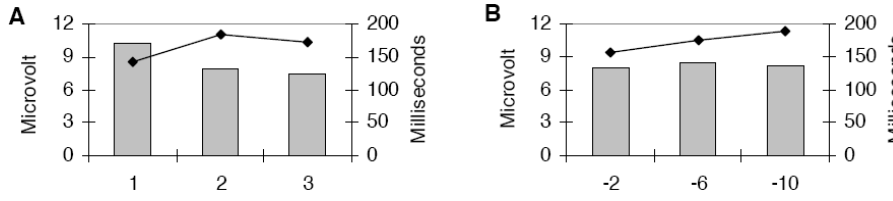

Figure 4.1: Behavioral adjustments (lines) and absolute feedback-ERN amplitudes (bars) across (A) different conditions and (B) different punishment levels.

third condition. The feedback-ERN was defined as the most negative peak, between 200 and 400 ms after feedback onset, in the difference wave of incorrect minus correct trials.

4.3 Results

In this section we will first present evidence from behavioral measures, indicating that the experimental manipulations were effective. We then consider the effects of these manipulations on the ERN and the relationship between the ERN and behavioral adjustment.

Behavioral findings

A comparison of the error rates in the three different conditions showed that the sliding time window was effective. Participants did not differ significantly in error rate in the different conditions ($F(2,14) = 1.576$, n.s.)[1]. However, participants were more accurate in their estimation in the second and third conditions ($F(2,14) = 6.068$, $p = .034$), indicating that they made use of the feedback. To study the use participants made of the feedback, we looked at the absolute adjustment in time estimation participants made after incorrect feedback. As can be seen in Figure 4.1, participants made larger adjustments in the informative conditions ($F(2,14) = 11.563$, $p = .001$). Planned comparisons revealed that conditions two and three differed from the first conditions ($F(1,7) = 13.923$, $p = .007$ and $F(1,7) = 12.503$, $p = .010$), but not from each other ($F(1,7) = 2.376$, n.s.). Analysis of the data from condition three (see Figure 4.1B) indicated that participants made larger adjustments when they received more punishment indicating they had made a larger error ($F(2,14) = 6.216$, $p = .012$). Follow-up analysis showed that a linear trend of increasing behavioral adjustment with increasing levels of punishment was significant ($F(1,7) = 8.217$, $p = .024$). These results indicate that the participants made use of the information provided by the feedback in adjusting their behavior from one trial to the next.

[1]The Greenhouse-Geisser correction was applied when appropriate to correct for possible violations of the analysis of variance assumption of sphericity. The text lists corrected p values.

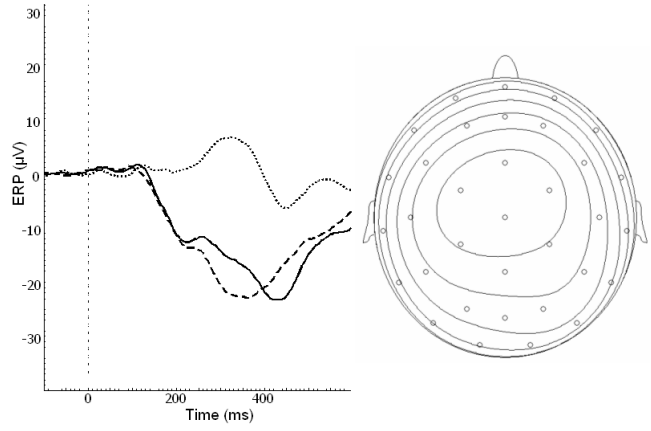

Figure 4.2: ERP results obtained in the first condition. Left panel: Feedback-locked averages for incorrect (solid line) and correct (dashed line) trials and the incorrect minus correct difference wave (dotted line). Right panel: Scalp topography at peak of the ERPs on incorrect trials.

ERP findings

Figure 4.2 shows feedback-locked average waveforms for correct and incorrect trials in the first condition and the scalp distribution of the peak of the negative ERP on incorrect trials. In all three conditions, a negative deviation is present for incorrect as compared to correct trials. This deviation reaches its maximum at electrode Cz, approximately 325 ms after feedback onset. As shown in Figure 4.1A, the amplitude of the waveforms, as measured by the peak of the difference wave, differed among the conditions (F(2,14) = 6.758, p = .009), being larger in the first condition as compared to the other two, more informative, conditions (F(1,7) = 8.958, p = .020 and F(1,7) = 7.501, p = .029)[2]. Analysis of the ERN amplitude in condition three (Figure 4.1B) revealed no significant difference among the three punishment levels (F(2,14) = .197, n.s.).

Relationship between ERN and behavioral adjustments

The relationship between ERN and behavioral adjustments was assessed directly in the following way. First, for each participant, all negative feedback trials in condition one were ordered as a function of the absolute adjustment in time-estimation on the following trial. Then four 'bins' were created representing four levels of adjustment. Third, the average ERP waveforms for each of the four bins were computed and the ERN amplitude for each

[2]It could be argued that the effects obtained are an artifact of the measure used, which is to measure feedback-ERN amplitude using difference waves [cf. (Lemke, 2003; Miltner et al., 1997)]. To show that this is not the case, we also analyzed our data using a "base-to-peak" measure on the negative feedback waveform. The effects were in the same direction (largest ERN in the first condition, smallest ERN in the third condition), although the effect did not reach significance (F(2,14) = 1.691, n.s.).

bin was derived. Analysis of the relationship between bin and ERN amplitude failed to show any effect. There was no difference among the four bins in ERN amplitude ($F(3,21) = 1.498$, n.s.). Another analysis examined the relationship between ERN amplitude and the quality of the participant's estimate on the trial following error feedback. Quality of estimate was defined as the absolute difference between the actual estimate and 1000 ms. As in the prior analysis, four bins were created representing different levels of estimate quality. Again, no significant differences in ERN amplitude among the bins were found ($F(3,21) = 1.040$, n.s.).

4.4 Discussion

The analyses of the behavioral data reveal that participants used the information provided by the error feedback to adjust their behavior. Comparisons across the three experimental conditions indicate that more precise adjustments were evident following more versus less informative feedback. In addition, larger behavioral adjustments were seen when participants received feedback that implied a large error than when they received feedback suggesting a small error. These results all support the inference that our manipulations were successful in influencing the processing of the error-feedback information: Participants utilized the information to the extent that it could be used to guide their future behavior.

Analyses of the electrophysiological data confirmed that the component we identified as a feedback-ERN was in fact a feedback-ERN. The latency, shape of the waveforms, and scalp distribution are similar to those found in previous studies of the feedback-ERN using this paradigm (Lemke, 2003; Miltner et al., 1997). Our results indicate that feedback-ERN amplitude was smaller in the informative conditions (conditions two and three), and was not influenced by the degree of error, as indicated by the feedback in condition three. This suggests a dissociation between the processes underlying generation of the feedback-ERN and the processes responsible for behavioral adjustments. In contrast to the amplitude of the feedback-ERN, the magnitude of behavioral adjustment was larger in the informative conditions and was influenced by the degree of error indicated by the feedback. Further evidence for a dissociation is provided by the analysis of the data in the first condition. Here the ERNs associated with different degrees of adjustment did not differ from each other. However, these results should not be taken to indicate that the feedback-ERN has no role in behavioral adjustments, since feedback-ERN amplitude has repeatedly been shown to correlate with learning (Holroyd and Coles, 2002; Nieuwenhuis et al., 2002). Rather, these results indicate that feedback-ERN does not correlate with direct behavioral adjustments as indexed by changes in RT.

These results are now considered in the context of the reinforcement learning theory of the ERN (Holroyd and Coles, 2002). As discussed earlier, the reinforcement learning theory of the ERN proposes that the mesencephalic dopamine system (MDS) carries reward prediction errors to the ACC and other brain areas involved in selecting appropriate motor responses.

This prediction error could be of (at least) two types. First, it could convey information about both an error in reward prediction and the kind of error that has been made, and could be used to guide a specific remedial action. In this case, one would expect a relationship between the ERN and remedial actions such as the behavioral adjustments measured in the present study. Second, the error signal carried by the MDS could act more as a scalar signal, indicating purely that the goal of an action has not been satisfied. In this case, the additional information provided in the second and third conditions of the current experiment, would be used by systems other than the system that produced the ERN itself.

In his review of reward and the dopamine system, Schultz (2002) suggests that the reward prediction error signals carried by the dopamine reward system indicate the appetitive value of events relative to prediction, but do not discriminate between different types of reward. This may explain why we did not find any effects of the different levels of negative feedback on the ERN. In terms of reward prediction, participants presumably always make their best estimate and thus expect a positive reward of +6 cents. In all cases where negative feedback is given, the expected reward is not obtained. It is this observation that is reflected in the presence of the feedback-ERN in the current data set. The magnitude of the difference between the expected and actual rewards, and the appropriate behavioral adjustments it indicates, might be of relevance to different brain systems, which are concerned with the remedial actions. According to this perspective, the reward prediction error signals are said to convey a scalar signal, signaling either 'good' or 'bad', rather than a 'vector' signal signaling how behavior must be adjusted. A similar conclusion was reached by Hajcak et al. (2006). See also Nieuwenhuis et al. (2004a) for a further discussion of this point in the context of reinforcement learning.

In contrast to these results on the feedback-ERN, a strong modulation by error significance on the amplitude of the response-ERN has been reported repeatedly. In an early study of the response-ERN, participants were instructed to give priority either to response speed or to accuracy (Gehring et al., 1993). Response-ERN amplitude was larger when correct responding was emphasized. A similar result was obtained by Hajcak et al. (2005), who instructed participants what amount of monetary reward could be obtained by correct responding on each particular trial. Furthermore, it has been shown that response-ERN amplitude correlates with the size of behavioral adjustments on the next trial (Gehring et al., 1993), which is not the case for the feedback-ERN as reported in this study. These results demonstrate some potential differences in the behavior of the two ERPs, suggesting that they might not both be generated by a completely overlapping system (see also Chapter 7 for a further discussion of the relationship between error-related activity elicited by response and feedback).

The observation that the ERN is smaller when more information is provided by the feedback replicates the observation made by Lemke (2003). In the more informative conditions, it is reasonable to assume that an alerting signal following error feedback is less important because decisions about remedial actions can be based on the information provided by the feedback.

The computational process required to select an appropriate remedial action is also less complex than that required when the feedback merely indicates that an error has been made [cf. Lemke (2003)]. Similar results have recently been obtained using fMRI (Zanoli et al., 2006).

Conclusion

In summary, we conclude that the systems underlying generation of the feedback-ERN are influenced by the amount of information presented by feedback stimuli [cf. Lemke (2003)], but not by the suggested degree of error. We did not find a direct relationship between feedback-ERN amplitude and the degree of remedial action as indicated by behavioral adjustments, indicating that these measures may result from different, although related, neural processes. We have suggested that the ERN constitutes a scalar signal, related to the occurrence of an error, but does not give any more information concerning the type of error or any behavioral adjustments that should be made. This suggestion is compatible with current theories of reinforcement learning. However, the results pose some important discrepancies between the behaviors of the response- and feedback-ERN, which will need to be addressed in further studies.

5 Neural dynamics of error processing in medial frontal cortex

This chapter is a modified version of:
Mars RB, Coles MGH, Grol MJ, Holroyd CB, Nieuwenhuis S, Hulstijn W, Toni I (2005). Neural dynamics of error processing in medial frontal cortex. *NeuroImage* 28:1007–1013.

Abstract

Adaptive behavior requires an organism to evaluate the outcome of its actions, such that future behavior can be adjusted accordingly and the appropriate response selected. During associative learning, the time at which such evaluative information is available changes as learning progresses, from the delivery of performance feedback early in learning to the execution of the response itself during learned performance. Here, we report a learning-dependent shift in the timing of activation in the rostral cingulate zone of the anterior cingulate cortex from external error feedback to internal error detection. This pattern of activity is seen only in the anterior cingulate, not in the pre-supplementary motor area. The dynamics of these reciprocal changes are consistent with the claim that the rostral cingulate zone is involved in response selection on the basis of the expected outcome of an action. Specifically, these data illustrate how the anterior cingulate receives evaluative information, indicating that an action has not produced the desired result.

5.1 Introduction

Existing data on the neural substrates of action selection indicate that the medial frontal cortex plays a crucial role in selecting actions on the basis of their outcomes (Matsumoto and Tanaka, 2004) and subsequent monitoring of response outcomes (Holroyd et al., 2004b; Ridderinkhof et al., 2004). Rather than attributing a single role to this vast cortical expanse, recent studies have started to associate different functions to the different anatomical structures that lay within the medial frontal cortex (Picard and Strick, 2001; Rushworth et al., 2004). In this context, an anterior portion of the cingulate cortex, the rostral cingulate zone anterior (RCZa), has been specifically associated with processing of error information and selecting appropriate behavioral adjustments (Fiehler et al., 2004; Holroyd and Coles, 2002; Rushworth et al., 2004).

These inferences on the neural bases of error processing have been obtained in the context of a "static" experimental environment, in which the organism knows the behavior that is appropriate for the current situation. Thus, a given response can be evaluated immediately against an internal representation of the correct stimulus-response relationship. Should the response be incorrect, error information is available from an internal error-detection process at the time of the response (Gehring et al., 1993; Holroyd et al., 2005). However, in a novel environment, with as yet unknown stimulus-response associations, error information is not available until the delivery of external performance feedback. This implies that, during the learning of stimulus-response associations by trial and error, the time at which error information is available will change. Prior to learning, error information will not be available until external performance feedback is delivered, but after learning, error information will be available earlier from internal sources at the time of the response itself. Thus, a neural structure that adjusts behavior as a function of the evaluation of response outcomes should dynamically shift its responsivity as a function of learning, from

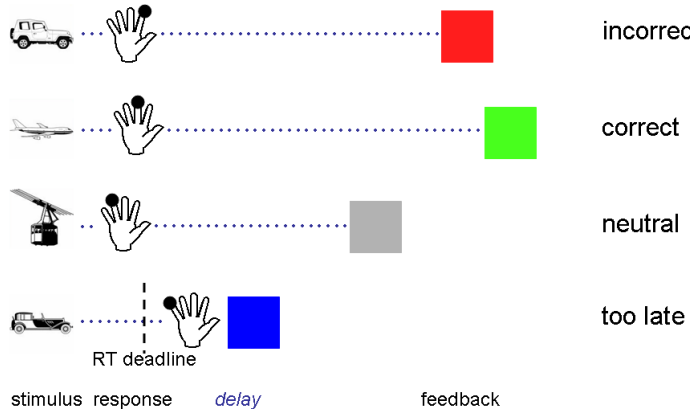

Figure 5.1: Experimental setup. Participants had to learn, by trial and error, arbitrary associations between visual stimuli and motor responses. After a variable delay, visual feedback (red/green square) was provided, indicating correct and incorrect responses. On 50% of the trials, feedback consisted of a noninformative gray square. When responses occurred after the reaction time deadline (750 ms), immediate feedback (blue square) was provided. For a color version of this illustration, see p. 133.

external sources provided by error feedback to *internal* sources associated with the error response itself. We predicted that, following error feedback, activity in the anterior cingulate cortex would decrease as learning proceeds; conversely, following an erroneous response, activity in the anterior cingulate would increase as learning proceeds. These predictions can be derived from a neuro-computational model (Holroyd and Coles, 2002) that formally describes the relationship between neural systems involved in outcome evaluation with those involved in action selection.

To test these predictions, we asked human participants to learn arbitrary visuomotor mappings (Wise et al., 1996; Toni et al., 2001a), using performance feedback, while measuring their cerebral activity using functional magnetic resonance imaging (fMRI). Participants were presented with line drawings, each of which was associated with pressing one of four response buttons (Fig. 5.1).We manipulated the degree of learning achieved during the scanning session by varying the number of times a given visuomotor mapping was presented. For one condition (High Learning, HL), four distinct visuomotor mappings were presented 36 times each over the course of the scanning session, enabling the subject to fully learn the visuomotor associations. For a control condition (Low Learning, LL), 24 different mappings were presented 6 times each. A reaction time (RT) deadline ensured that participants made errors, even during learned performance. Crucially, by varying the delay between response and feedback, and by introducing neutral feedback on some of the trials, we were able to dissociate the hemodynamic responses elicited by response and feedback (see Experimental timing).

5.2 Materials and methods

Participants

We studied eight right-handed male volunteers (mean age = 30.4 years, SD = 13.4) with normal or corrected-to-normal vision after obtaining informed consent according to institutional guidelines of the local ethics committee (CMO region Arnhem-Nijmegen, Netherlands). They were paid 10 per hour for their participation. Imaging data from 5 additional participants were discarded, since these participants either failed to learn the appropriate stimulus-response mappings adequately (2 participants, less than 50% correct on post-scanning forced-choice recall task) or performed without any errors during the last part of the scanning session, indicating that the RT deadline was not tight enough for these participants (3 participants).

Experimental setup

Participants lay supine in the scanner. Head movements were minimized by an adjustable padded head holder. Visual stimuli (visual angle of approximately 6°) were projected onto a mirror above the participants' heads. Motor responses were recorded via an MR-compatible keypad (MRI Devices, Waukesha, WI), positioned on the right side of the subject's abdomen. Stimulus presentation and response collection were controlled by a PC running Presentation 0.51 (Neurobehavioral Systems, San Francisco, CA).

Behavioral procedure

Participants were asked to try to learn arbitrary associations between visual stimuli (black and white drawings of cars, airplanes, boats, etc.) and motor responses (pressing of one of four buttons with the fingers of the right hand) by trial-and-error using performance feedback (Fig. 5.1). We manipulated the degree of learning achieved during the experimental session by varying the number of times a visuomotor mapping was presented. For one condition (High Learning, HL), four distinct visuomotor mappings were presented 36 times each over the course of the scanning session, while for a control condition (Low Learning, LL) 24 different mappings were presented 6 times each. Trials enabling learning (HL) were pseudo-randomly intermixed and matched in number with trials in which learning was less likely to occur (LL). Participants received either performance feedback (green or red square) or neutral feedback (gray square, see Experimental Timing below) after each response, with a variable delay between these two events. To encourage error commission even during learned performance, a stringent reaction time deadline of 750 ms was enforced. When participants responded after this deadline, immediate feedback (blue square) was provided and the trial ended. Participants were instructed to try to avoid this at all costs. Participants practiced the task in the scanner for 50 trials using a different stimulus set before the experimental session.

Following the scanning session, participants performed a forced choice recall test, in which all stimuli of the HL condition and a subset (50%) of the stimuli of the LL condition were presented 7 times each, randomly intermixed. Participants were required to press the button corresponding to each stimulus, as during the scanning session. However, during the recall test, there was no reaction time deadline and no feedback was given, to allow for a reliable assessment of the learning of the stimulus-response mappings.

Imaging procedures

Images were acquired using a 1.5T Sonata scanner (Siemens, Erlangen, Germany). BOLD sensitive functional images were acquired using a single shot gradient EPI sequence (TR/TE 2.2s/40 ms, 28 transversal slices, interleaved acquisition, voxel size 3.5 $\times$ 3.5 $\times$ 3.5 mm). Following the experimental session, structural images were acquired using a MP-RAGE sequence (TR/TE/TI 2250 ms/3.93 ms/850 ms, voxel size 1 $\times$ 1 $\times$ 1 mm).

Experimental timing

Our design was aimed at dissociating response- and feedback-related neurovascular activities despite their temporal proximity. We achieved this by using an event-related fMRI design that has proved effective in dissociating between transient responses time-locked to sensory and motor events (Toni et al., 1999; Thoenissen et al., 2002).

We introduced a variable delay between response and feedback (3.9-5.2 seconds, uniform distribution) and between the trials (1.3-13.5 seconds). Also, we introduced neutral feedback on approximately half of the trials, to decorrelate the stimulus/response and feedback regressors. Furthermore, before actual scanning we ran simulations in order to optimize the range and order of delay lengths, inter-trial intervals, and neutral feedback stimuli and to minimize correlations between the regressors describing the expected BOLD signal to response and feedback events (Friston et al., 1999b).

Following the scanning session, we verified the ability of our design to dissociate response and feedback-related activity by examining the evoked hemodynamic responses in V1 and M1. As expected, we found reliable BOLD responses to both the stimulus/response epoch and the feedback epoch in V1, but only response-related activation in M1 (data not shown).

Data analysis

Imaging data were analyzed using SPM2 (www.fil.ion.ucl.ac.uk/spm/). The first five volumes of each participant's data set were discarded to allow for T1 equilibration. Prior to analysis, data were spatially realigned and corrected for differences in slice acquisition time using the middle slice in time as reference. Each participant's structural image was coregistered to the first of the functional images. Images were then normalized onto the ICBM template (http://www.loni.ucla.edu/ICBM/) using linear transformations only.

Finally, data were spatially smoothed using an isotropic 6 mm FWHM Gaussian kernel.

Using standard multiple regression procedures (Friston et al., 1995b), we partitioned the sources of experimental variance in the fMRI timeseries into main effects of Condition (High Learning or Low Learning), Epoch (activity time-locked either to the response or to feedback presentation) and Outcome (correct or incorrect for response-related data; correct, incorrect, or neutral for feedback-related data). Model regressors were convolved with a canonical hemodynamic response function (Friston et al., 1998). Learning-dependent modulations of activity were modelled as first and second order parametric effects of time on the model regressors. Confounding factors such as trials with late responses, corrective responses, head-related movements, and trial-by-trial variations in RT were also accounted for and included in the model.

In this paper we focus our analysis on the rostral cingulate zone anterior (RCZa), a portion of the anterior cingulate cortex which has previously been associated with response errors (Ullsperger and Von Cramon, 2001), negative feedback (Ullsperger and Von Cramon, 2003), and reductions in reward leading to behavioral adjustments (Bush et al., 2002). This area is suggested to correspond to the monkey rostral cingulate motor area (Picard and Strick, 1996) and is situated in what Bush et al. described as the 'cognitive' division of the anterior cingulate cortex (Bush et al., 2000). We also consider a neighboring portion of the superior frontal gyrus, namely the pre-supplementary motor area (pre-SMA), given its reported role in performance monitoring and action selection (Shima et al., 1996; Rushworth et al., 2004; Ullsperger and Von Cramon, 2001; Fiehler et al., 2004). For each hemisphere, we created two objectively defined spherical volumes of interest (VOIs, Fig. 5.2), centered in the 'arm' regions reported by Picard and Strick (1996), and with a radius of 8 mm. The VOIs covering the RCZa were centered at $\pm$8, 30, 32; the VOIs covering the pre-SMA were centered at $\pm$8, 10, 55, according to the stereotactic coordinates of Talairach and Tournoux (1988) used in the maps of Picard and Strick (1996). These coordinates were converted into the MNI coordinates used by SPM2 using tal2mni (Matthew Brett, http://www.mrc-cbu.cam.ac.uk/Imaging/Common/downloads/MNI2tal/mni2tal.m).

The statistical significance of the estimated evoked hemodynamic responses was assessed using t-statistics in the context of a multiple regression analysis (Poline et al., 2004). Contrasts of the parameter estimates for the Condition $\times$ Time interactions during the incorrect trials were calculated, and entered into a paired t-test, treating subjects as a random variable (Holmes and Friston, 1998). The statistical threshold was set at a value of $p < .05$, corrected for multiple comparisons according to the False Discovery Rate (Genovese et al., 2002) over each of the specified VOIs. To correct for false positives due to the use of multiple VOIs, we applied a further Bonferroni correction to the resulting p-values.

In this study we were interested in assessing differential modulation of time-related signal changes time-locked to feedback or response events during performance of incorrect trials in the HL condition. Accordingly, linear time-dependent increases in activity during the response Epoch on incor-

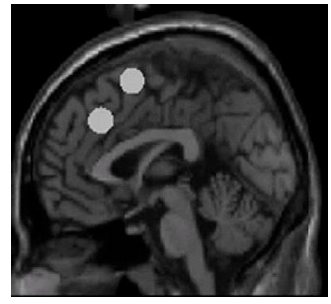

Figure 5.2: Anatomical locations of regions of interest used in the random effects analysis, displayed on the SPM2 canonical single subject T1 image. A spherical region of interest was placed in each hemisphere in each of the anatomically defined structures.

rect trials were compared with the corresponding effect during the feedback Epoch (incorrect trials only). Furthermore, to isolate genuine learning-related changes rather than mere time-related effects, we required the Condition $\times$ Time interaction to be stronger in the HL than in the LL condition. This constrain was imposed by selecting voxels in which the Condition $\times$ Time interaction for the response epoch was stronger in the HL than in the LL condition (inclusive mask thresholded at $p < .05$ uncorrected).

Within the regions identified by our analysis, we calculated the effect sizes for the main and time-related effects, using the ratio of the relevant parameter estimate onto its standard error (Maxwell and Delany, 1990). This allowed us to assess the specificity of the region's activity to errors as compared to correct trials and the presence of main effects of response and feedback.

For analysis of the behavioral data acquired during the scanning session, RT and error rates were each considered as dependent variables in a two-way analysis of variance, with factors Condition (2 levels, HL and LL) and Time (8 levels). After removal of missed trials, the RT time series of each participant was divided into eight equal blocks, providing eight levels for the Time factor.

5.3 Results

Behavioral data

Behavioral data indicated that our design was successful in manipulating the degree of learning achieved by the participants during the scanning session. Participants learned the stimulus-response mappings at a faster rate in the High Learning condition than in the Low Learning condition (Condition $\times$ Time interaction on Error Rate: $F(7,49) = 3.2$, $p = .035$, Fig. 5.3). Although participants never reached error-free performance during the scanning session in either condition (because of the RT deadline), a post-scanning forced choice recall test indicated that more associations

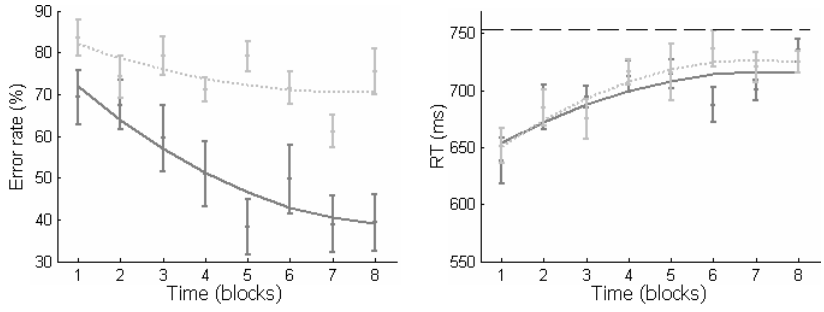

Figure 5.3: Behavioral results. Error rates (left) and RTs (right) on correct trials for the High Learning (dark gray) and Low Learning (light gray) conditions obtained during the scanning session. Curves are fitted first and second order polynomials; error bars indicate ±SEM. It can be seen that subjects learned the stimulus response mappings at a faster rate in the High Learning condition than in the Low Learning condition (left panel). RT did not differ between the two conditions, approaching the RT cut-off (dashed horizontal line) at a similar rate (right panel).

were learned in the High Learning condition (HL: 91%, LL: 43%; t(7) = 12.1, $p < .001$).

RTs on correct trials (Fig. 5.3) did not differ between the two conditions (main effect of Condition: $F(1,7) = .446$, n.s.). Over the course of the scanning session, RT increased to approach the RT cut-off (main effect of Time: $F(7,49) = 5.493$, $p = .008$), but at a similar rate across conditions (Condition $\times$ Time interaction: $F(7,49) = 1.514$, n.s.). The number of missed responses did not differ across conditions (HL: 19.7 % [SD = 15.2]; LL: 18.4 % [SD = 12.3]; t(7) = .908, n.s.).

Imaging data

We isolated BOLD signals satisfying our criteria by testing, in each of the ROIs, for time-dependent response-related increases *and* feedback-related decreases in activity during error trials. In addition, to distinguish genuine learning-related changes from mere time-related effects, we required this interaction to be stronger in the High Learning condition than in the Low Learning condition.

Our VOI analyses identified a region within the rostral cingulate zone anterior (RCZa, Table 5.1) which showed learning-related changes in activation elicited by incorrect responses and negative performance feedback. As illustrated in Fig. 5.4, this region showed greater feedback-related error activation during initial learning. During learning, this feedback-related activation decreased, while the response-related error signal showed a reciprocal increase (Fig. 5.4C).

To further characterize the activity evoked in this region, we calculated effect sizes for each main and time-related effect, normalizing the relevant parameter estimate of the multiple regression onto its standard error (see Materials and Methods). The reciprocity of the dynamic modulation of activity in this cluster is indicated by the presence of significant learning-related effects, but no overall effects of response or feedback. The RCZa showed

Anatomical region	MNI coordinates			Z value
	x	y	z	
Pre-SMA	-8	-12	64	2.80[1]
	2	4	60	2.64[1]
	14	10	60	3.37[1]
RCZa	14	28	32	3.72

Table 5.1: Anatomical specification, MNI coordinates ($p < 0.5$ corrected for multiple comparisons), and Z-values of clusters yielded by the contrast testing for decreasing time-related changes in BOLD signal at the moment of negative performance feedback, and increasing time-related changes in BOLD signal at the moment of the erroneous response. Z-values marked with [1] did not survive Bonferroni correction for testing of multiple VOIs.

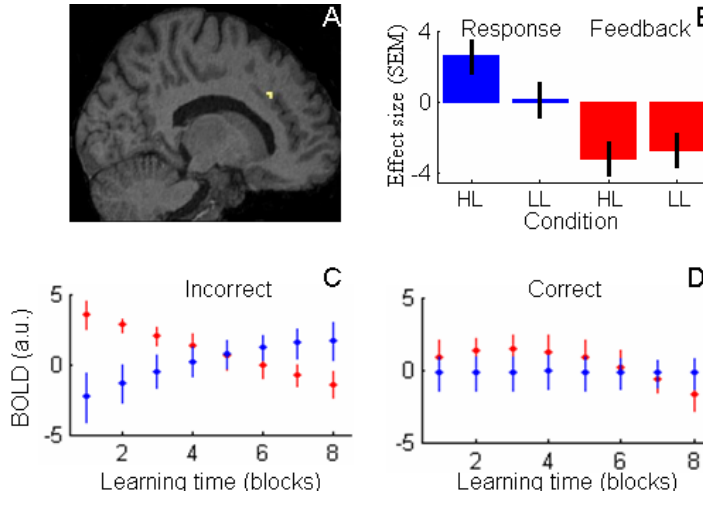

Figure 5.4: Imaging results. Anatomical localization, peak BOLD signal development during learning for both incorrect and correct trials (High Learning condition), and effect sizes for time-related modulation in BOLD response for the RCZa (top row, peak coordinates: 14, 28, 32). (A) SPM(Z) (threshold $p < 0.05$ corrected) superimposed on normalized anatomical sagittal sections of one participant. (B) Effect sizes (in SEM units) for the time-related changes in BOLD response in both the High Learning (HL) and Low Learning (LL) conditions, indicating stronger modulations of activity in the High Learning condition. (C,D) Peak BOLD signal (in arbitrary units, SEM) over the course of learning, following response (blue) and feedback (red) for incorrect (C) and correct trials (D). For display purposes, the fMRI time series of each subject were subdivided into eight blocks of equal length. The actual statistical model of the fMRI data considered time as a continuous parametric effect (see Materials and methods). It can be seen that error feedback-related activation decreases as learning proceeds, while error response-related activation increases, and these effects are reciprocal. For a color version of this illustration, see p. 134.

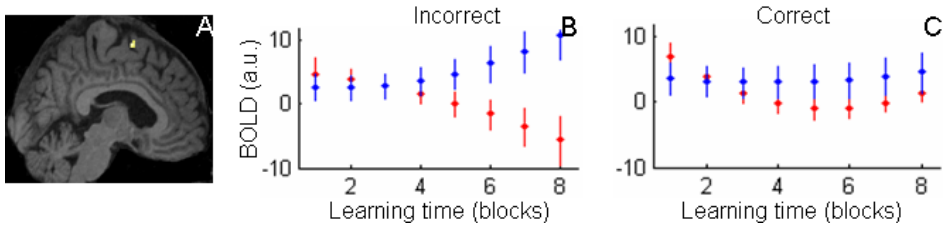

Figure 5.5: Imaging results. Anatomical localization and peak BOLD signal development during learning for both incorrect and correct trials (HL condition) for the pre-SMA (peak coordinates: 2, 4, 60). It can be seen that pre-SMA shows a response-related activation over and above the learning-related modulations of activation, both on correct and incorrect trials. Color conventions as in Fig. 5.4. For a color version of this illustration, see p. 134.

no significant activity on correct trials (Fig. 5.4D), indicating that activity in this region was specifically related to error processing. Furthermore, the time-related changes in activation on incorrect trials were stronger in the High Learning (feedback: -3.17; response: 2.60, Fig. 5.4) as compared to the Low Learning (feedback: -2.70; response: 0.15) condition, providing evidence that these changes are not simply due to time-related effects (e.g., fatigue, habituation, sensitization), but are genuinely learning-related.

There were further clusters of activity in the pre-SMA VOI, although they did not survive the additional Bonferroni correction for multiple VOIs (Table 5.1). This region showed a clear modulation of activity as a function of learning, as illustrated in Fig. 5.5, for both response (effect size: 4.20) and feedback (effect size: -3.76), and these modulations were not as strong in the LL condition (feedback: -0.04; response: 1.93). Crucially, this region did not show the same reciprocity of effects seen in the anterior cingulate clusters, as indicated by a significant main effect of response (effect size: 6.74). Furthermore, the pre-SMA revealed response-related activity during correct trials (effect size: 4.55), an indication that this region is not exclusively driven by error signals.

5.4 Discussion

The present data indicate that, over the course of learning a set of arbitrary visuomotor mappings, a region along the cingulate sulcus (RCZa) shifts its responsiveness to different sources of error information as a function of learning. Error feedback-related activation decreases as learning proceeds, while error response-related activation increases, and these effects are reciprocal (Fig. 5.4). These results show not only that the anterior cingulate cortex responds to both internal (Carter et al., 1998; Ullsperger and Von Cramon, 2001; Garavan et al., 2002) and external (Ullsperger and Von Cramon, 2003; Holroyd et al., 2004c) sources of error information, but also that this cingulate region responds to the earliest source of error information available.

Furthermore, the present data argue against a unique cognitive contribution of the vast expanse of cerebral cortex labeled 'medial frontal cortex',

confirming and detailing the functional heterogeneity of different anatomical portions of this region (Rushworth et al., 2004; Nachev et al., 2005). While the RCZa is activated in response to the first signal that an error has occurred, independent of the source of this information, pre-SMA shows response-related effects over and above learning-dependent modulations of activity on both correct and incorrect trials. These findings are consistent with the results of Akkal et al. (2002), showing that CMAr neurons are more likely to be modulated by performance feedback than pre-SMA neurons. This suggests that pre-SMA might be closer to motor aspects of the learning process rather than subserving an explicit evaluative function.

It could be argued that the the differential time-related effects seen in the RCZa for the High Learning and Low Learning conditions reflect the putative role of the anterior cingulate region in controlling arousal (Critchley et al., 2003). However, our behavioral data and post-scanning forced choice recall test indicate that participants learned the stimulus-response mappings in *both* learning conditions, although to a different extent (Fig. 5.4). This result implies that participants were evaluating stimuli and feedback during both Low and High Learning trials, although the rapid turn-over of stimuli-response mappings in the former condition prevented them from learning as effectively as during the latter condition. Moreover, the two experimental conditions evoked overlapping reaction times profiles (Fig. 5.3). These behavioral results are not immediately compatible with different arousal levels evoked by the High and Low Learning conditions.

Recently, Walton and colleagues (2004) have shown that the RCZa can be active not only on incorrect trials, but also on correct trials, provided that these trials convey behaviorally relevant information. In the current learning task, it is possible that the first correct trial associated with a specific mapping might have evoked ACC activity. Unfortunately, the current study was not designed to address this particular issue and we lack an adequate number of "first correct" trials to be able to provide a reliable estimate of ACC activity under these circumstances. This issue remains open for further investigation.

In this study, we have focused our search on RCZa on the basis of the role played by CMAr [its putative macaque-homologue (Picard and Strick, 1996)] in reward-based action selection and evaluation (Shima and Tanji, 1998). Although recent meta-analyses (Ridderinkhof et al., 2004; Ullsperger and Von Cramon, 2004) have reported that error processing within the anterior cingulate may encompass both RCZa and RCZp, the arm-subfields of these two areas are structurally and hodologically different (Picard and Strick, 1996), which suggests they have different functional properties. Indeed, an an explorative whole-brain fixed-effects analysis revealed a caudal anterior cingulate region with response-related activation, but no strong effects of feedback. Given the strong hypothesis-driven nature of this report, however, we prefer to limit the inferences of this study to those regions for which we had explicit hypotheses.

Overall, these results are consistent with a series of recent studies showing that portions of the general region labeled 'cingulate cortex' are involved in action selection based on the expected outcome of an action (Bush et al.,

2002; Hadland et al., 2003; Shima and Tanji, 1998), integrating information regarding a motor response and its potential outcome (Williams et al., 2004). Our results illustrate how a specific portion of the medial frontal cortex, the RCZa, might receive evaluative information, which can be used to adapt behavior accordingly (Holroyd et al., 2004b; Ridderinkhof et al., 2004). Conceptually, our results are also consistent with the notion that ACC activation during error trials is the result of an error in reward prediction, indicating that ongoing events are unexpectedly disadvantageous and that this information is subsequently used to guide action selection (Holroyd and Coles, 2002).

In conclusion, in this study we have illustrated the dynamic characteristics of the interplay between external and internal sources of error information, emphasizing the contribution of a specific portion of medial frontal cortex (RCZa) to the selection of appropriate behaviors.

6 Modulation of activity in the premotor cortices during error observation

This chapter is a modified version of:
Van Schie HT, Mars RB, Coles MGH, Bekkering H (2004). Modulation of activity in medial frontal and motor cortices during action observation. *Nature Neuroscience* 7:549–554 (the first two authors contributed equally to this work).

Abstract

Measures of the human event-related brain potential were used to investigate the neural mechanisms underlying error processing during action observation. Participants took part in two conditions, a task execution condition and a task observation condition. We found that activity in both the medial frontal cortex and in the motor cortices, as measured via the error-related negativity and the lateralized readiness potential respectively, was modulated by the correctness of observed behavior. These data suggest that similar neural mechanisms are involved in monitoring one's own actions and the actions of others.

6.1 Introduction

Movements are the only means we have of communicating with the outside world. Accordingly, a large body of work has been established in recent years, investigating the role of the motor system[1] in functions such as communication, action observation, and, more generally, social interaction (Frith and Wolpert, 2003). One extremely influential proposal in this field is that the actions of others are decoded by activation of one's own motor system. Empirical support for this position is thought be provided by the discovery of 'mirror neurons' in the ventral premotor cortex of macaques (Di Pellegrino et al., 1992; Gallese et al., 1996). These neurons were found to fire not only when the monkey executes a specific grasping movement, but also when the monkey observes another person executing the same action.

Neuroimaging studies on healthy human volunteers have suggested the existence of similar mechanisms, showing activation of premotor areas in observing actions performed by others (Grèzes et al., 2003a), related to imitation of another person's actions (Iacoboni et al., 1999), and when viewing objects associated with certain actions (Grèzes et al., 2003b). These studies provide evidence for a role of the motor system in a large variety of behaviors, beyond the pure preparation, execution, and evaluation of the organism's own motor actions, and have inspired a number of research lines into the neural mechanisms related to understanding the behavior of others. Consequently, a number of researchers have began to explore how computational theories of motor actions may be applied to the understanding of the behavior of others as well (Miall, 2003; Wolpert et al., 2003).

In the current study, we follow this approach by investigating, at the experimental level, whether the system underlying action monitoring during one's own task performance is similarly activated when one observes and evaluates the behavior of another person. If so, this would suggest that reinforcement learning of motor actions (Holroyd et al., 2004b) and observational learning of motor actions might rely on similar neural mechanisms. Indeed, data from non-human primates (Van Schaik, 2004) and human functional imaging (Mattar and Gribble, 2005) suggest that similar

[1] 'The motor system' in this chapter refers to the motor system at large, including not only primary motor structures (M1), but also the premotor and parietal cortices.

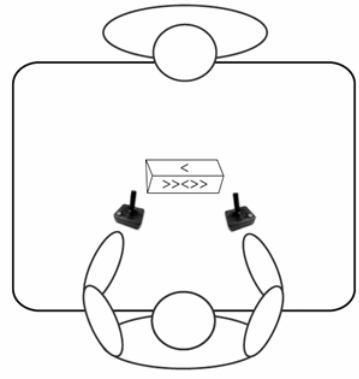

Figure 6.1: Experimental setup. Schematic overview of the experimental setup showing the actor (bottom) and the observer (top).

cognitive and neural mechanisms are involved in the learning motor behavior by execution and by observation. Moreover, a recent study has provided first evidence that systems underlying generation of the error-related negativity are also active when participants observe another person commit an error (Miltner et al., 2004). However, in this experiment, participants observed simulated rather than real task performance, and the extent of parallel activation of the motor system was not determined.

6.2 Materials and methods

Participants

Eighteen volunteers with no known neurological impairments and normal or corrected-to-normal vision participated in the experiment. Data from two participants were discarded due to recording artifacts (one participant) and excessive noise in the EEG (one participant), resulting in data from 16 participants [11 female, age ranging from 19 to 34 (M = 23.4)] that were used in the analysis. All participants were paid 6 euros per hour and provided written consent according to institutional guidelines of the local ethics committee (CMO region Arnhem-Nijmegen, Netherlands).

Apparatus and procedure

Two experimenters were continuously present during the experiment. One controlled the experimental measurements, while the second participated in the experiment. Participants were seated in front of a table facing an experimenter (Fig. 6.1). On the table were two custom-made joystick devices, positioned to the left and right of an LED stimulus device.

The LED device contained two display sides, one facing the participant, the other facing the experimenter. Both display sides contained five horizontally aligned dot matrices (13 mm wide, 18 mm high), each consisting of

a 7 by 5 LED-array. The size of the display was 77 mm by 18 mm, subtending a visual angle of 5.9° by 1.4° at an average viewing distance of 75 cm. Stimuli consisted of left and right pointing arrowheads (0.8° by 1.4° each) that were generated by turning on a selection of LED-dots.

Joysticks consisted of a 4 cm lever fitted in an electronic control box (10 cm wide and long, 3 cm high). The lever was constrained to move only in lateral directions and a pair of springs ensured that it would return to its original position after a response. Deviations of more than 5^o from the relaxed position (maximum angle 30^o) were measured as responses. Joysticks were positioned bilaterally to either side of the stimulus device, slightly in front of it (4 cm), at a viewing angle of 15.5°. Joystick movement generated no auditory cues.

Participants took part in two conditions: an execution condition in which they performed a choice reaction task, and an observation condition in which they observed an experimenter performing the same task. In this second condition the participant is referred to as the 'observer' and the experimenter as the 'actor'.

The task consisted of a modified Eriksen flanker task (Eriksen and Eriksen, 1974), in which center arrowheads were presented in conjunction with four flanker arrowheads, two on each side, which either pointed in the same direction as the center arrow (congruent trials), or in opposite direction (incongruent trials). The probability of left- and right-pointing center arrows was equal, as well as the probability of congruent and incongruent flankers. A trial sequence began with a centrally presented, diamond shaped, fixation point (0.6° by 0.6^o) that was displayed for 200 ms. Following a 200 ms stimulus-free interval, a target display was presented for 300 ms, showing the four flankers and the center arrowhead. A 600 ms stimulus-free interval completed the trial.

In the execution condition, participants were instructed to respond both quickly and accurately in the direction of the center arrowhead. Joysticks were moved with the thumb in an outward direction. Participants were instructed to give only one response per trial, and to try to avoid correcting initial errors. Also, participants were instructed to refrain from making eye movements and to reduce blinking during task performance.

The experimental session began with 40 practice trials to allow participants to familiarize themselves with the task. After this, they performed 8 runs of 100 trials of the task, each run taking approximately 2.2 minutes. Between runs, the participants were given feedback about their average response times and number of errors. One experimenter sat opposite to the participant and reported the number of observed errors after each run.

In the observation condition, which always followed the execution condition, participant and experimenter changed roles. Participants were now instructed to observe the behavior of the experimenter performing the Eriksen flanker task and to count the number of errors made by the experimenter. In this way, we could confirm that the observer was engaged in the task. The observer's display only included the center arrowhead, ensuring that error detection was not compromised by the presence of flankers. The distance between the observer and the display was held constant, but joysticks

were moved to the experimenter's side of the display (4 cm behind the LED device), resulting in a 12.4^o viewing angle for each joystick relative to the center of the display. Participants were instructed to maintain fixation on the fixation point and to identify responses without making eye movements. All participants could view the stimulus and the actor's responses without moving their eyes. A total of 8 runs of 100 trials each were completed in this condition.

Behavioral recording and analysis

The onset of the target display and behavioral responses were sampled continuously at a frequency 1000 Hz. RTs, errors, and misses were analyzed offline for individual stimulus types and conditions. Only trials with RTs in the 150 ms – 550 ms range were included for analysis. Responses with only the incorrect hand were labeled as "pure" errors. Trials with responses from two hands were not included in the analysis.

Electrophysiological recording

Brain electrical activity was recorded from 47 Ag/AgCl electrodes, referenced to linked earlobes. Electrodes were mounted in an elastic cap (Easycap, Montage 10) configured for equal arrangement of the electrodes over the scalp. Vertical and horizontal electro-oculograms were recorded from sites above and below the left eye, and 1 cm outwards to the outer cantus of each eye, respectively. The electrode common was placed on the sternum. All electrode impedances were kept below 5 kΩ. EEG recordings were amplified and digitized at 250 Hz. Data were filtered offline, using a 1–14 Hz bandpass for the ERN analyses (Nieuwenhuis et al., 2003) and a 4 Hz lowpass for the LRPs (Miller et al., 1996), using Butterworth zero phase filters. Ocular artifact was corrected (Gratton et al., 1983), whereas trials containing amplifier artifacts were discarded.

Error-related negativity

For both correct and incorrect trials in both conditions, a 600 ms epoch (baseline 100 ms – 0 ms prior to response) was extracted. To mitigate the effects of differential contribution from stimulus-related activity to the ERP we adopted a matching procedure (Coles et al., 2001). For each condition and for each participant, the data for each incorrect trial were randomly matched by RT ($\pm$ 4 ms) with the data for a corresponding correct trial. On average about 90% of all error trials and 10% of all correct trials were matched for further analysis.

Lateralized readiness potential

LRPs were calculated using signals recorded from C3 and C4 electrodes. The average asymmetry, defined as the difference between C3 and C4, was derived by averaging the asymmetries associated with trials where the left

movements were correct and those where right movements were correct according to the following equation: LRP = [left hand(C4 − C3) + right hand(C3 − C4)] / 2. Negative values of the LRP indicate relative activation of the correct response and positive values relative activation of the incorrect response (Coles, 1989). For both conditions, stimulus-locked LRPs (700 ms epoch, baseline −100 ms – 0 ms) and response-locked LRPs (−550 ms – 500 ms epoch, baseline −550 ms – −450 ms) were calculated. In the execution condition, LRPs were response-locked to the participant's own response, whereas in the observation condition the participant's (observer's) LRPs were response-locked to the actor's response.

To derive a topographical visualization of motor activation, the LRP equation was applied to all lateral electrode pairs. Lateralized effects were (arbitrarily) projected over the right hemisphere in the form of current source density (CSD) maps. These maps emphasize the difference in voltage across the scalp, and provide an indication of the loci of the underlying neural sources.

ERP statistical analyses

For both ERN and LRPs, onset latencies and onset of the difference between correct and incorrect trial waveforms were assessed via a stepwise series of one-tailed serial t-tests (step size of 4 ms). For each test, data from a time window of 40 ms (i.e., point of measure, plus and minus 20 ms) were averaged. The onset latency was defined as the first point at which five consecutive t-tests showed a significant difference ($p < .05$).

In the matching procedure, the pool of potential correct trials was larger than the pool of potential incorrect trials, resulting in an arbitrary selection of matched correct trials, which could result in variability associated with the particular set of matching correct trials chosen. In turn, this could lead to variability in the computation of the onset of the difference between correct and incorrect trial waveforms. For this reason, we used a bootstrapping procedure (Wasserman and Bockenholt, 1989) to generate a distribution of onsets over different sets of matching trials. The matching procedure was run 500 times, and the mean onset time of the distribution was taken as an indication of the time at which correct and incorrect trials started to differ.

Source localization

ERN source localization was performed on the difference between grand averaged incorrect and matched correct trial waveforms, using Brain Electric Source Analysis (MEGIS software GmbH, (Scherg and Berg, 1996). For both the execution and observation condition, source analysis was performed for the interval in which the difference between correct and incorrect trials was statistically significant (−6 ms – 146 ms and 90 ms – 318 ms respectively). A 4-shell ellipsoidal head model was used.

6.3 Results

Behavioral performance

In both execution and observation conditions the standard effects of the Eriksen flanker paradigm were observed (Eriksen and Eriksen, 1974). Incorrect responses were executed faster than correct responses (250 ms vs. 314 ms), $F(1,25) = 275.6$, $p < .001$. RTs to compatible stimuli were significantly faster (300 ms) than RTs to incompatible stimuli (328 ms), $F(1,30) = 64.6$, $p < .001$, and fewer errors were made on compatible (4.6%) than on incompatible trials (12.4%), $F(1,30) = 53.0$, $p < .001$.

Pure error trials, with only a single response of the wrong hand, were found on 8.5% of all trials. Trials with responses from both hands were recorded on 8.8% of all trials, and on 1.5% of all trials no response was registered in the 150 ms – 550 ms response interval. Reaction times were longer in the execution condition (297 ms) than in the observation condition (267 ms), but the percentage of pure errors did not differ significantly between execution and observation conditions (7.9% and 9.1% respectively), $F(1,30) = .62$, n.s.).

Error-related negativity

In the execution condition, there was a large negative deflection on (pure) incorrect trials, as compared to correct trials (Fig. 6.2, upper left). The onset latency of the negativity was 6 ms (SD: 10 ms) before the response. The peak latency of the negative difference (between incorrect and correct trials) was 80 ms after the response, maximal at medial frontal electrode sites (Fig. 6.2, lower left). These features are characteristic of the ERN observed in previous studies (Falkenstein et al., 1990; Gehring et al., 1993; Dehaene et al., 1994).

In the observation condition (Fig. 6.2, upper right), we also found a negative deflection on incorrect trials. This deflection started 90 ms (SD: 30 ms) after the observed response, and peaked at 252 ms. Scalp distribution of this negative deflection was similar to that of the ERN in the execution condition (Fig. 6.2, lower right).

Source localization

Grand average difference waveforms between ERPs to correct and incorrect responses were used for source localization to determine the possible neural generators of the negativities in the execution and observation conditions. As in previous studies, we modeled the source of the ERN using a single source (Dehaene et al., 1994; Miltner et al., 1997). In the execution condition, a single regional source (Fig. 6.3, right top), located in the medial frontal cortex (Coordinates in Talairach space (Talairach and Tournoux, 1988): x = -0.5, y = 0.6, z = 28.4), explained 97.3% of the variance in the scalp distribution for the interval where correct and incorrect waveforms differed significantly.

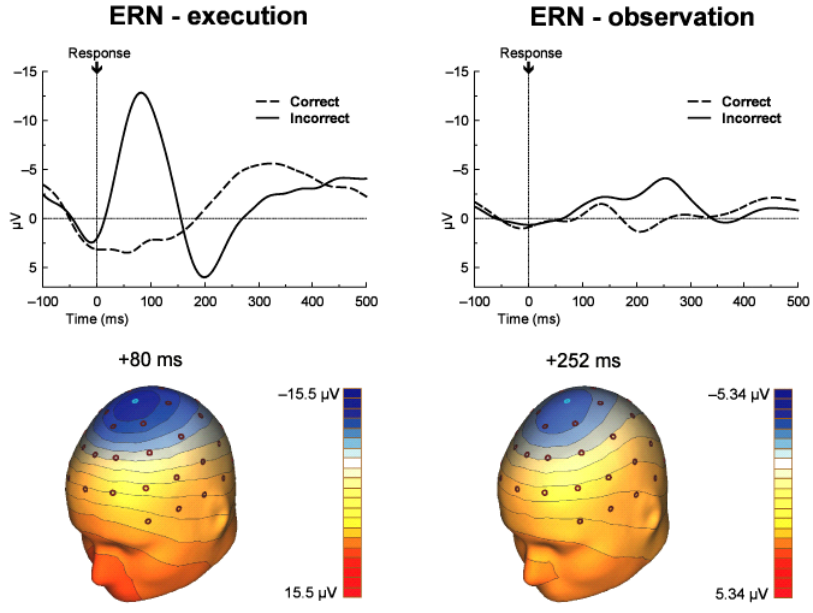

Figure 6.2: Error-related negativities. Top: Response-locked averages at electrode Cz for correct and incorrect responses in the execution condition (left) and the observation condition (right). Dashed lines indicate correct, and solid lines indicate incorrect response trials. Bottom: Spline maps showing the topography of the ERN difference wave in the execution condition and the observation condition, taken at the peak where correct and incorrect ERPs differed maximally, 80 ms and 252 ms after the response, respectively. The Cz electrode at the vertex is marked in light blue for reference. For a color version of this illustration, see p. 135.

To test the hypothesis that the negativities in the execution and observation conditions are generated in the same neural structures, we determined how well the source for the execution condition would fit as a model for the observation condition. The same source explained 92.4% of variance for the negativity in the observation condition. In a separate analysis, we modeled the data for the observation condition using an unconstrained source. This analysis yielded a source (Fig. 6.2, right bottom) that was slightly more frontal (x = 3.8, y = 4.0, z = 23.8), explaining 92.5% of variance. These data support the hypothesis that medial frontal structures involved in the processing of self-generated errors are also engaged by observing erroneous behavior in others.

Lateralized readiness potential

LRPs in the execution condition (Fig. 6.4, top left) show a pattern similar to that observed previously (Coles, 1989). For correct trials, the motor potential is more negative over the hemisphere contralateral to the correct response (indicated by negative values for the LRP), while for incorrect trials the motor potential is more negative over the hemisphere contralateral to the incorrect response (reflected by positive LRP values). LRPs for correct and incorrect responses in the execution condition shared a distribution over the lateral

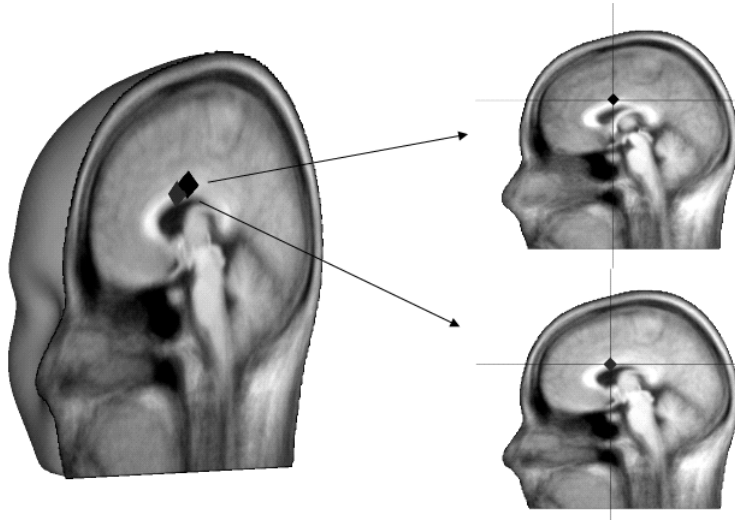

Figure 6.3: ERN source localization. Sagittal view of the brain showing the source for the ERN difference wave in the execution condition (top) and in the observation condition (bottom), displayed together within the same head model (left), and projected onto a standard MRI template (right).

motor cortex as revealed by current source density maps (CSDs, Fig. 6.4, bottom left; see Materials and methods section for further details).

In the observation condition, there is an LRP following the stimulus, which differs significantly from zero from 212 ms (t(15) = -1.8355, p = .043) until 514 ms after the stimulus. The analysis of the LRP time-locked to the response of the actor (Fig. 6.4, top right), suggests that the observer's motor cortex started to be activated before the actor's response. This activation was associated with greater negativity over the motor cortex contralateral to the correct response side, as viewed from the perspective of the observer. CSD topography also showed lateralized activation over posterior areas, probably related to processing of the preceding stimulus. This posterior activation is more prominent for incorrect trials, while motor activation is less prominent (Fig. 6.4, bottom right, +64 ms maps). This is due to a difference in response times between correct and incorrect trials (incorrect responses are faster), resulting in less time for the development of the LRP in the observer on incorrect trials

Following the observation of a correct response, the LRP continued to develop, reaching a maximum 160 ms after the actor's response was observed. However, when the actor responded incorrectly, the correct lateralization in the observer (which had began before the actor's response) rapidly decreased, and a widespread lateralized activity developed over parietal areas (Fig. 6.4, bottom right). Statistically, LRPs following observed correct and incorrect responses started to differentiate 146 ms after the actor's response (t(15) = -1.7645, p = .049).

To summarize, LRPs in the observation condition indicate that, for both correct and incorrect trials, the correct response is initially activated by

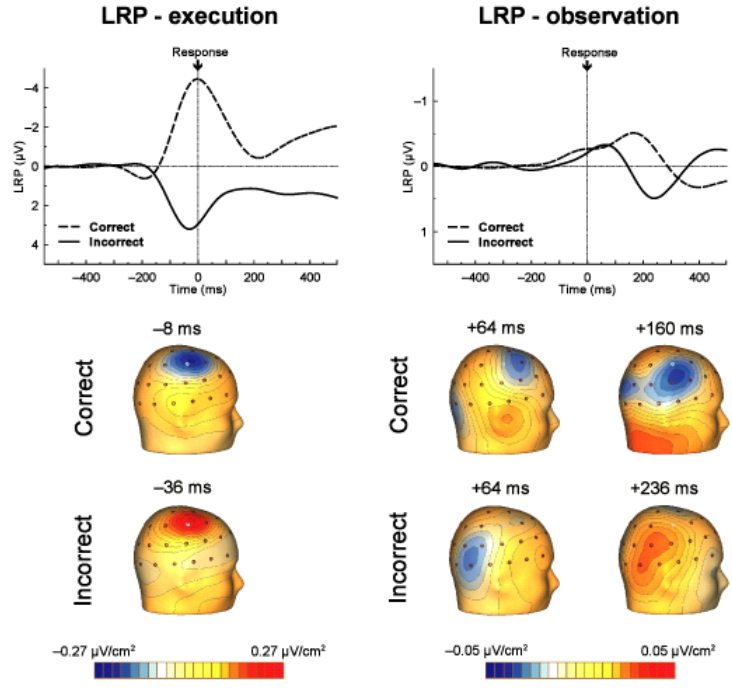

Figure 6.4: Lateralized readiness potentials. Top: Response-locked lateralized readiness potentials in the execution condition (left) and the observation condition (right). LRPs recorded to correct response trials are indicated by dashed lines, and LRPs to incorrect trials by solid lines. Bottom: CSD maps of LRP effects in the execution condition (left) and the observation condition (right), for correct and incorrect responses separately. The C3/C4 electrode over the lateral motor cortex is marked in light blue for reference. The relevant time-point (relative to the response) is indicated above each map. For a color version of this illustration, see p. 136.

the observer's motor system. Following the actor's response, the observer's motor system is differentially activated as a function of the accuracy of the observed response.

6.4 Discussion

The results of the present study provide insight into the neural mechanisms underlying action observation and error processing. Importantly, we found evidence that neural activity in both the medial frontal and the motor cortex is modulated by the correctness of both self-generated and observed responses. This suggests that similar neural mechanisms are involved in monitoring one's own actions and the actions of others.

Evidence for similar involvement of medial frontal cortex activity in both the execution and observation conditions is provided by source analysis of the negativities associated with errors. As in previous research, a medial frontal source reliably accounted for the ERN following self-generated errors and, importantly, the same source accounted for the negativity following observed errors. For this reason, we infer that an ERN is elicited by observing

errors.

The relationship between the ERN and other ERP components involving medial frontal cortex (e.g. the N2) is currently a subject of debate (Holroyd, 2004). The present data do not inform this debate. However, they do enable the critical inference that medial frontal cortex is involved in processing both self-generated and observed errors. This suggests that the brain systems associated with action selection and error processing in the medial frontal cortex are also activated under conditions of action observation.

The data from the observation condition are compatible with those obtained by the earlier study (Miltner et al., 2004). However, the extent of the ERN in the present data was longer (320 ms versus 130 ms in the earlier study) and the ERN had a shorter onset latency. These differences are most likely due to a difference in the precision with which the observer could determine when the actor responded. In the present case the observer was observing a real actor, while in the earlier study the behavior of a virtual actor was displayed in symbolic form on a computer monitor. In the latter case, the onset of the actor's movement could be precisely defined, whereas in the present case there could be ambiguity in the time at which the actor was judged to have responded. As a result, variability in the timing of the detection of the erroneous response would have occurred.

In contrast to the earlier study, data from the present study allow us to evaluate the activation of the observer's motor system when the actor executes correct and incorrect responses. LRPs in the observation condition showed that the observer's motor system was activated in two ways. First, motor cortex was active prior to the actor's response, suggesting that the observer generated a representation of the appropriate response following stimulus presentation. Then, following the actor's response, correct response activation continued to develop when the response was correct. However, following an incorrect response, differential motor activation decreased and activity lateralized over posterior areas. This lateralized activity may be associated with perceptual or attentional processing of the actor's incorrect hand movement.

The LRP results of the present study are consistent with and extend previous studies that report activation of the motor system in response to the observation of behavior (Rizzolatti and Luppino, 2001). One important study in this regard demonstrated that when participants anticipate the action of another human being, sustained activation can be seen in the ventral premotor cortex, and that this activity is absent when participants anticipate another event, such as a computer action (Ramnani and Miall, 2004). Our data extend these results, by showing participants' motor activation during action observation may reflect sub-threshold preparation of (correct) responses, and is modulated by the actually observed responses.

Noteworthy is that the initial motor lateralization following the stimulus, and the subsequent lateralization following the observation of the correct response were both found over the observer's motor cortex contralateral to the side of the correct response (from the observer's own perspective). Thus, the observer's LRP shows what the observer would have done if he/she had actively done the task him/herself, instead of maintaining a representation of

the task from the perspective of the actor. This pattern of results is consistent with studies of imitation which show that when imitating, participants mostly try to replicate the goal of the action, but tend to ignore how the actor did it [e.g., participants may use their left hand although the actor used his/her right hand (Bekkering and Wohlschläger, 2000)].

Given that activation in motor areas in the observation condition is similar to motor activation found with task execution, it is important to investigate the level at which there was covert response activation in the observer. To this end, we ran five additional participants from whom we recorded EMG in both execution and observation conditions. Response-locked averages of band-pass filtered (20-100 Hz) and rectified EMG recordings from both hands showed a strong response with task execution, but no effect in the observation condition. This indicates that the level of covert response activation in the observer does not extend to the periphery.

Data from the present study suggest that neural mechanisms used to monitor individual task performance are also activated under conditions of task observation. These mechanisms may play a central role in our ability to predict and classify the behavior of others, and thus provide a possible pathway for observational learning.

7 Discussion

7.1 Introduction

To select and perform the correct action at the appropriate moment requires substantial information. The goal of the action, the priority of this goal, the target in space of the action, the current state of the limbs, and many other factors need to be taken into account when one plans and executes any voluntary action. By monitoring the consequences of one's actions and determining how well these actions correspond to their goal, one can decide on the next course of action and learn how to respond in similar situations in the future.

The goal of the research described in the thesis is to investigate the specific role of the various subdivisions of the human premotor cortex in the control of action. To this end, the previous chapters described experiments that were designed to contribute to our understanding of the role of various subdivisions of the premotor cortex in the processes of action selection, action preparation, and action monitoring. The purpose of this final chapter is to summarize and discuss the results obtained in the experimental chapters (Chapter 2–6) in the context of current knowledge and theories of the premotor cortex and relate the results to recently published literature. Furthermore, this chapter contains some suggestions for future research.

7.2 Lateral premotor cortex

Premotor, pre-premotor, and movement preparation

The involvement of the lateral premotor cortex in the selection and preparation of voluntary actions is well established. Most proposals on the functionality of the lateral premotor cortex emphasize its role in the formation of a movement plan and in the guidance of movement based on sensory information (Passingham, 1993; Wise, 1985; Wise et al., 1997). Lesion studies (Passingham, 1993) and electrophysiological studies in monkeys (Boussaoud and Wise, 1993; Di Pellegrino and Wise, 1993) and human functional imaging studies (De Lange et al., 2004) all suggest that it is not a visual instruction per se that activates neurons in the dorsal premotor cortex (PMd), but rather the motor significance of the stimulus.

Recently, the involvement of the PMd in action selection and preparation has been further detailed in studies reporting a dissociation between the rostral and the caudal parts of the macaque PMd. Neurons in the rostral part of the PMd seem more concerned with processing stimulus attributes, while neurons in the caudal part of PMd are predominantly involved in the actual movement selection and preparation (Boussaoud, 2001). Subsequently, the rostral and caudal parts of the dorsal premotor cortex have been labeled the 'pre-premotor' and the 'premotor' cortex, respectively. A similar dissociation has been reported in humans (Picard and Strick, 2001; Chouinard and Paus, 2006; Simon et al., 2002).

The study reported in Chapter 2 further explored this dissociation in the context of the preparation of simple visuomotor actions. The study addressed the question of whether the retention of these different types of

information were associated with sustained activity in distinct cortical regions. Viewed in the context of motor preparation, this study was thus able to image sustained neuronal responses related to different stages of the visuomotor transformation (Jeannerod, 1997), from processing of the stimulus for action selection to the preparation of the movement following action selection but before action execution. In contrast to previous studies (Simon et al., 2002; Curtis et al., 2004) this was done in the context of an arbitrary visuomotor associative task (Wise et al., 1996), that allowed the characterization of mechanisms underlying the flexibility to associate abstract environmental stimuli with any form of suitable behavior, a characteristic flexibility in behavior displayed by higher organisms.

Sustained activation was found along the caudal section of the superior frontal sulcus at the border of BA6 and BA8 when participants retained visual information online during an instructed delay period. Conversely, when participants retained a motor code during the delay interval, sustained activity was found more caudally, along the precentral gyrus at the border of BAs 6 and 4. This experiment thus showed that the retention of different types of information, which can be taken to correspond to various stages of the visuomotor transformation, is indeed associated with differential activation in the rostral and caudal aspects of the dorsal premotor cortex. A similar dissociation was not found in more posterior regions, with posterior parietal cortex showing sustained delay period activity during the retention of both sensory and motor codes.

In a recent follow-up to this study, Van den Hurk and colleagues (Van den Hurk et al., 2006) endeavored to further characterize the neurophysiological mechanisms of retaining stimulus and motor codes, by investigating whether retention of stimulus or motor codes drives the motor system to different states, as indexed by cortico-spinal excitability. Although the imaging results presented in Chapter 2 suggest that the retention of stimulus and motor codes rely on partly dissociable neural structures, this study did not address the mechanisms associated with these two computational processes at a neurophysiological level within these separate clusters. Van den Hurk and colleagues took a first step in this direction by qualifying the cortico-spinal excitability during the retention of the two different informational codes. Using a similar setup to that employed in Chapter 2, cortico-spinal excitability was probed by determining the effects of a single TMS pulse over the motor cortex on the movement evoked potential (MEP). Cortico-spinal excitability was modulated compared to baseline in an effector-specific manner in the movement preparation condition. When participants retained stimulus representations online, however, cortico-spinal excitability was not modulated compared to baseline. During the preparation of motor responses, the MEP recorded from the muscle that was involved in the execution of the prepared action was increased, while there was a general attenuation of the MEP recorded from muscles unrelated to the upcoming movement.

It is important to note that, although this study probed cortico-spinal excitability over the primary motor cortex, this does not necessarily imply that primary motor cortex is the site of maintenance of the motor representation.

Rather, the excitability of primary motor cortex is likely to be a non-linear integration of influences from a spatially distributed cortical circuit, reflecting the effects of local circuitry but also distal effects from premotor and posterior parietal cortex, as indicated by the data presented in Chapter 2. These results provide further evidence for the claim that the retention of motor codes during the preparation for an upcoming movement is associated with specific neurophysiological patterns, patterns that are distinct from those that subserve the retention of sensory codes.

Precentral cortex and the likelihood of responding

A crucial aspect in labeling an action as a voluntary action is that one has the choice whether or not to execute the action. Not only can one select a specific action amongst a number of alternatives, but one can also choose to abort a previously selected action before it is executed. Two bodies of work investigating the issue of voluntary control over actions relevant to the present discussion are those investigating the effect of the probability of having to execute a response on action preparation and those investigating the inhibition of an already selected movement before it is executed.

Studies employing the first approach have shown the influence of the probability of response execution on preparatory activity. For instance, Low and Miller (1999) used lateralized readiness potentials [LRPs; see Coles (1989)] to demonstrate the effects of partial stimulus information on preparatory activity. Similarly, Schiebe and colleagues modulated the likelihood that various response alternatives in a forced-choice experiment had to be executed, showing a modulation of the contingent negative variation, and to a lesser extent the LRP, by the implicit probability that a given response would need to be executed (Scheibe et al., 2006).

Using functional imaging, Thoenissen and colleagues manipulated the probability of response execution in a delayed-response task (Thoenissen et al., 2002). Participants were presented with a visual cue instructing a specific movement. Following a variable delay interval participants were presented with a 'go' or a 'no-go' cue, instructing the participants to execute or inhibit the prepared response, respectively. Thoenissen and colleagues reported that sustained delay period activity in the precentral gyrus was modulated by the probability of responding, with different clusters showing stronger activity either following cues specifying a high or a low likelihood of responding. Preparatory activity in some frontal clusters is thus modulated by the probability of response execution. Importantly, sustained activity in the posterior parietal cortex was not modulated by response probability, consistent with the results of electrophysiological recordings in non-human primates (Kalaska and Crammond, 1995).

Consistent with the observation of precentral activity modulated by response probability, in the study reported in Chapter 2, we found a region along the left precentral gyrus that became more active during the later stages of the instructed delay period, when the probability of responding increased. This indicates that activity in various precentral regions, i.e., regions with direct connections to M1 and to the spinal cord, is modulated

by the likelihood that a certain response will be executed. Together, these results argue for the involvement of the precentral gyrus in determining which of various response alternatives will be executed in conditions of uncertainty.

A second approach for studying the volitional control over action is to investigate the inhibition of actions. Studies following this approach have predominantly focused on the inhibition of a prepotent or already initiated response (Garavan et al., 1999; Kelly et al., 2004; Nieuwenhuis et al., 2003; Aron et al., 2003) and generally have reported a network of right frontal, right parietal and medial premotor areas specifically involved in inhibition and related processes. A limitation of these studies is that they cannot distinguish between different functional properties of neural structures involved in the different motor control processes evoked by a no-go stimulus. These processes are likely to include not only inhibition of the prepared response, but also the possible selection and preparation of the new response under fierce time pressure. The results obtained in these studies may therefore not isolate activity related to the process of interest, but to a number of confounding processes due to the task design.

The study reported in Chapter 3 investigated this issue in more detail by dissociating in time processes related to programming of a motor plan independent of previous task processing from processes related to the programming of a motor plan in the context of an already existing motor plan. This study allowed us to further explore cerebral correlates of selection and inhibition of motor plans. A region in the left dorsal premotor cortex quite close to the BA6/8 locus reported in Chapter 2 was active at all moments during a trial in which a response had to be selected and prepared. However, selecting an action in the context of an already existing motor plan recruited a number of additional regions, particularly a large network of right frontal regions, including precentral gyrus, inferior frontal gyrus, and the insula. Most of these regions, however, were also activated during action selection under time pressure, indicating that they may not be related purely to the inhibition of an already present motor plan. When controlling for this potential confound, we found that only a region of the right precentral gyrus was activated specifically during the selection of actions in the context of already present motor plans. Again, we found a region located along the precentral gyrus, close to the regions identified in previous studies (Thoenissen et al., 2002). These results again illustrate the importance of the precentral cortex in determining which of various response alternatives will be executed.

Although these studies illustrate which brain regions are involved in different aspects of volitional control of action, they can only provide limited inferences concerning the underlying neuronal mechanisms mediating this control. Therefore, informed by the electrophysiological and imaging studies described above, a number of TMS studies have recently started addressing this question by examining the mechanisms underlying response preparation and cancellation at the neural level (Sohn et al., 2002; Coxon et al., 2006). An important example of this approach is provided by Strafella and Paus (2001) who investigated the neural structures involved in intra-cortical inhibition (ICI) and intra-cortical facilitation (ICF) reported in paired-pulse

paradigms (Kujirai et al., 1993). These mechanisms of ICI and ICF can illustrate how different populations of interneurons within the primary motor cortex mediate the activity underlying the maintenance of certain response alternatives. Strafella and Paus showed that ICI and ICF within the primary motor cortex are mediated by distinct neural populations in regions outside the motor cortex, specifically by regions along the precentral cortex. This study thus provides a first illustration of how the regions identified in imaging studies described above might mediate the volitional control of actions.

7.3 Medial premotor cortex: Anterior cingulate cortex

The role of different subdivisions of the medial premotor cortex in action monitoring

As discussed in Chapter 1, the ACC is not a homologous area, but consists instead of a number of distinct anatomical substructures, which can be functionally dissociated (Picard and Strick, 1996). However, the large variability of ACC architecture between individuals, and the crudeness of some experimental manipulations, make differentiation of the functional properties of each ACC substructure using functional imaging a difficult task. Illustrating this point, a recent meta-analysis by Ridderinkhof and colleagues (Ridderinkhof et al., 2004) showed that typical action monitoring tasks, such as error processing, conflict monitoring, and dealing with decision uncertainty, result in widespread activation of a region extending from the rostral ACC (BA32) up into the pre-SMA (BA6).

In Chapter 5 of this thesis, a more fine-grained experimental design was used in an attempt to differentiate the functional contributions of these regions to error processing. Participants were asked to learn stimulus-response mappings using external feedback. Earlier in the learning session, RCZa was activated in response to negative performance feedback. During the experimental session, when participants learned the appropriate stimulus-response mapping, feedback-related activity decreased, while activity related to the incorrect response increased. We concluded that RCZa is responsive to the earliest source of error information available. Activity in the pre-SMA and the RCZp followed patterns distinguishable from that in RCZa and from each other.

As discussed in Chapter 5, we do not claim that the ACC cannot be activated by performance feedback on correct trials. Indeed, Walton and colleagues (Walton et al., 2004) showed equal activation of the ACC following both positive and negative feedback when both had an equal informational content. The relationship between ACC activity and the informational value of feedback remains poorly understood and will be a valuable topic of research in the near future [see also Chapter 4 and Lemke (2003)].

Aside from the studies of 'action monitoring' such as those discussed by Ridderinkhof (Ridderinkhof et al., 2004), a number of studies have recently reported activation of the medial frontal cortex in tasks probing social cognition. Social cognition tasks here refer to tasks where one is monitoring

the mental states of others (Frith and Frith, 1999; Frith and Frith, 2001). These studies often report activation in the medial frontal cortex, mostly in the paracingulate cortex. The question arises whether these activations and those reported in action monitoring tasks are a reflection of similar processes.

The loci of activation in social cognition tasks are generally located more anterior than the loci associated with motor control. In coordinates of the Talairach atlas (Talairach and Tournoux, 1988), the social interaction foci mostly have a y-coordinate > 30 (Amodio and Frith, 2006; Frith and Frith, 2001), while motor and action monitoring tasks generally have a y-coordinate between 0 and 35. Hence, the social interaction loci have most commonly been described as located along the anterior paracingulate sulcus (Frith and Frith, 2001). Activation of the dorsal ACC during the observation of errors in others has been suggested now in three independent studies (Miltner et al., 2004; Van Schie et al., 2004; Bates et al., 2005). In each of these studies, a dorsal ACC source was reported as best fit for the 'observation-ERN'. Although it would be imprudent to make strong claims on the exact source of the component identified in these three studies because of the inverse problem in EEG dipole modeling, source localization in all studies converged on a central source. Most likely this source is located in the dorsal ACC, closer to the 'motor' loci than to the 'social interaction' loci.

Viewed from this perspective, the ACC activity elicited during the observation of erroneous behavior in others would be 'just' another source of information that can be used to bias action selection. This suggestion is compatible with the original suggestion raised in Chapter 6, where the purpose was to explore similarities between the reinforcement learning system that gives rise to the ERN and possible mechanisms of learning by observation. Research in various laboratories now focuses on the functional significance of the 'observation-ERN' and on determining its precise origin. Although the three studies to date are hardly conclusive, they do suggest that this type of research can provide an avenue for learning in a social context.

Feedback processing in the ACC

An important aspect of the functionality of the ACC in action monitoring is its responsiveness to different sources of error information. The reinforcement learning theory of the ERN especially emphasizes that the ACC is not only active in response to internally detected errors, but also in response to negative performance feedback (Holroyd and Coles, 2002; Holroyd et al., 2004c), although both sources of information might be relayed to the ACC via a single intermediate brain region such as the striatum.

The first report of error-related activity elicited in the ACC by performance feedback was the time-estimation study of Miltner and colleagues (1997). Subsequently, the functionality of this feedback-ERN has been the topic of fierce debate. In Chapter 4, it was reported that feedback-ERN amplitude was not modulated by the size of behavioral adjustments, but rather, that feedback-ERN amplitudes reflects a binary outcome of actions, i.e. it

reflects whether the goal of an action was obtained or not. These results can be reconciled with recent work on reward processing in the dopamine system, as suggested by the reinforcement learning theory of the ERN (Holroyd and Coles, 2002), but are not immediately consistent with results on the response-ERN. For instance, Hajcek and colleagues manipulated the amount of money a participant could earn on a trial-by-trial basis, and found that this reliably modulated the size of the response-ERN (Hajcak et al., 2005), replicating early results showing that response-ERN amplitude is modulated by the significance on an error (Gehring et al., 1993). The finding that error significance modulates the amplitude of the response-ERN, but not the feedback-ERN suggests at least a partial dissociation between response- and feedback-ERN.

Another important topic of debate concerns the neural source of the feedback-ERN. In a recent fMRI study, Van Veen and colleagues reported no activation of the dorsal ACC in response to negative feedback in the 'standard' time-estimation task (Van Veen et al., 2004). Since their study relied on very long delays between response and feedback in order to separate the BOLD responses associated with the different trial events, it could be argued that this negative result is merely due to the fact that the reward processing system works only on a relatively short time scale. To address this issue, Nieuwenhuis and colleagues used a shorter, variable delay between the different trial events. Their results were similar to those of Van Veen, showing no activation of the dorsal ACC in response to negative performance feedback (Nieuwenhuis et al., 2005b). Furthermore, they showed that dipoles placed in the rostral ACC, posterior cingulate and superior frontal gyrus which were activated in the fMRI study, can in principle explain the scalp topography of the feedback-ERN. These studies raise the important question of whether the feedback-ERN is really elicited in the ACC, in the same locus as the response-ERN.

A number of fMRI studies investigating the neural source of the feedback ERN did report activation of the dorsal ACC in response to negative performance feedback (Ullsperger and Von Cramon, 2003; Holroyd et al., 2004c), supporting the claims of the reinforcement learning theory of the ERN that the response- and the feedback-ERN are a manifestation of similar processes. It has been suggested that these results may be merely an 'oddball' effect, i.e., brain activation elicited by the occurrence low-frequency events. Indeed, in the studies of Ullsperger and Holroyd the negative feedback was less frequent than the positive feedback. It should be pointed out, however, that the feedback-ERN is also present when the frequencies of positive and negative feedback are equal (Miltner et al., 1997; Lemke, 2003; Mars et al., 2004), even though similar components such as the oddball N200 are strongly modulated by frequency (Holroyd, 2004). Moreover, the fMRI data reported in Chapter 5 show that activity in the RCZa elicited by negative performance feedback was strongest at the beginning of a learning session when the negative feedback was more frequent that positive feedback. Indeed, error rates were as high as 70% during the first phase of learning. Moreover, this activity in RCZa mimics the behavior of the feedback-ERN in a similar learning task (Holroyd and Coles, 2002; Nieuwenhuis et al., 2002),

suggesting that the feedback-ERN is indeed a reflection of activity in the RCZa, a region also activated by internal error detection.

The data reported in Chapter 5 thus provide evidence that the claim of the reinforcement learning theory of the ERN that activity can be elicited in the RCZa by internal error detection and negative performance feedback and that this activity has a role in the learning of action selection is accurate. The negative findings of Van Veen and Nieuwenhuis and the dissociation between some findings on the response- and the feedback-ERN, however, provide an important indication that either or both of these components reflect processes additional to those described by the reinforcement learning model. One possible explanation for the dissociation in functionality of the response- and the feedback-ERN is the fact that response-related error processing often seems to recruit a number of additional sources along the medial wall, such as the pre-SMA (Holroyd et al., 2004c). Although the results presented in Chapter 5 show that error processing is not the sole role of the pre-SMA (see also Section 7.4 below), activity from additional sources contributing to the response- but not to the feedback-ERN might account for some of the functional differences of the two components. Although not in general disagreement with the suggestions of the reinforcement learning theory of the ERN, these results do illustrate the need for caution in interpreting the results of the ERN as a direct manifestation of activity of a single cortical region.

ACC and action selection revisited

As argued in Chapter 1 (Holroyd et al., 2004b), the ACC plays an important role in the selection of motor actions. The ACC, specifically the rostral cingulate zones, respond to different types of information that can be used to bias action selection, such as response errors (Carter et al., 1998; Kiehl et al., 2000; Ullsperger and Von Cramon, 2001), negative performance feedback (Ullsperger and Von Cramon, 2003; Holroyd et al., 2004c), but also uncertainty (Volz et al., 2005; Carter et al., 1998) and social pain (Eisenberger and Lieberman, 2004; Ullsperger et al., 2004). The research presented in this thesis has contributed to this body of work by showing, crucially, how a single subregion of the ACC processes evaluative information from different sources and that the ACC has access to information derived from the behavior observed in others. Furthermore, the research presented in this thesis further illustrates the functionality of feedback-related processing in the ACC.

The research in this thesis was inspired mostly by the reinforcement learning theory of the ACC (Holroyd and Coles, 2002). However, in addition to the reinforcement learning theory and the mismatch hypothesis discussed in Chapter 1, a number of other models have been proposed concerning the function of the ACC in action monitoring (Botvinick et al., 2001; Luu and Tucker, 2003). One influential model proposes that the ACC serves to detect simultaneous activation of multiple responses in the brain's motor system (Botvinick et al., 1999; Botvinick et al., 2001; Yeung et al., 2004). According to this model, when the ACC detects this response conflict, a

signal is sent to regions in the lateral prefrontal cortex, e.g. dorsolateral prefrontal cortex, which serve to increase the attentional processing of task-relevant stimuli in order to give the correct response access to motor output system. By assuming that the ERN reflects response conflict generated by the activation of the correct or corrective response following an error, this model has been shown to adequately predict various ERN and adaptation effects, as measured by slowing in reactions times, found in speeded response tasks (Yeung et al., 2004). Furthermore, the model has the added advantage of being able to explain findings related to the N2, a negative frontocentral ERP component commonly found in speeded response tasks on correct trials when the stimulus primes a number of conflicting responses (Van Veen and Carter, 2002).

However, the conflict model does not account for findings related to performance feedback as described above and findings of reward processing in the ACC, as outlined below. Therefore, the results obtained in both Chapters 5 and 6 are inconsistent with a strict interpretation of the conflict detection theory. Moreover, the conflict detection theory would predict increased ACC activation prior to responses at the beginning of learning, since this would constitute a situation of underdetermined responding (Botvinick et al., 2001; Barch et al., 2000). In Chapter 5, we found no response-related ACC activation at the beginning of learning. Rather, we found that response-related ACC activation appeared and increased during the course of the experiment, as a function of learning.

Conversely, the reinforcement learning theory in its original formulation does not speak to pre-response ACC activations, as indexed by the N2, reported in a number of studies. Both the reinforcement learning theory and the conflict detection theory thus cannot be taken as a full description of ACC function (Rushworth et al., 2004). Currently a number of labs are working on integrative accounts of ACC function, relying on a combination of conflict and reinforcement principles (Brown and Braver, 2005; Frank et al., 2005; Holroyd et al., 2005). Furthermore, a greater emphasis is placed on the role of ACC in the larger context of motor control, integrating the results from the cognitive control and error processing literatures with those obtained in the literatures on motor learning and action selection (Holroyd et al., 2004b; Rushworth et al., 2004; Krigolson and Holroyd, 2006).

7.4 Medial premotor cortex: Pre-SMA and SMA proper

Functions of the pre-SMA in motor control

The medial part of area 6 is now recognized to contain at least two separate anatomical areas: the supplementary motor area proper (SMA), and the pre-SMA. In terms of anatomical connectivity, pre-SMA can be better described as a 'prefrontal' rather than a 'premotor' region. Similar to the distinction we observed between the rostral and caudal PMd, pre-SMA and SMA proper are active during different stages of the visuomotor transformation (Chapter 2).

Although pre-SMA is not a premotor region in the strictest sense of the word, it is often activated in tasks involving complex action selection and action monitoring. For instance, several imaging studies on action monitoring have reported not only the ACC, but also the pre-SMA as a region critically involved in error processing (Kiehl et al., 2000; Holroyd et al., 2004c). The results obtained in Chapter 5 show a more complex pattern of activation. A subtraction of response-related activation on correct trials from activation on incorrect trials would indeed have yielded activation in the pre-SMA, suggesting a role of the pre-SMA in error processing. However, a more detailed investigation of the time-related changes of activity in the pre-SMA showed that, although pre-SMA may be more activated on error as compared to correct trials, pre-SMA does have a clear role on correct trials as well. Pre-SMA shows clear response-related activation on correct trials and this activity increases during learning. Labeling pre-SMA simply as an 'error processing' region would thus be an oversimplification.

All three of the functional imaging studies reported in this thesis reported activity in the pre-SMA. In the learning study described in Chapter 5, pre-SMA was active following or during response execution and this activity increased with learning. At first glance, these results would appear to contradict the results of Sakai (Sakai et al., 1998), who reported decreasing pre-SMA activation with learning. However, it should be noted that the tasks in the two studies differed substantially. Importantly, in the Chapter 5 study, participants were pushed for speed, which might encourage response conflict. The finding that pre-SMA becomes more active with learning could be explained by the suggestion that participants are prone to pre-select a movement to be executed when they do not know which response is instructed. However, following learning, when participants have learned the appropriate response, they have to suppress competing responses. A similar suggestion was put forward by Lau, when discussing the discrepancies in the literature regarding the involvement of the pre-SMA in conflict monitoring and the free selection of actions (Lau et al., 2006).

In an attempt to provide an overarching theory of pre-SMA function, Rushworth and colleagues suggested this region to be involved in the selection of action sets, placing it at a higher hierarchical level than those regions involved in the selection of single actions (Rushworth et al., 2004). This suggestion dove-tails with a recent computational model of Nakahara and colleagues, aimed at modeling the neural mechanisms underlying the learning of visuomotor sequences (Nakahara et al., 2001). According to their model, learning of visuomotor sequences occurs in two separate neural circuits, one which learns the sequence in spatial coordinates and one which learns the sequence in motor coordinates, and at a different learning rate (Bapi et al., 2000). The pre-SMA is positioned as a 'coordinator' between the different neural circuits, coordinating which of the two neural circuits gains access to the motor output system. This suggestion is based on the findings that pre-SMA is active during the early stages of learning a visuomotor sequence, when the two circuits are hypothesized to compete (Sakai et al., 1998) and that pre-SMA neurons are especially active when a motor plan needs to be updated (Shima et al., 1996). A related 'coordinator' role for the

pre-SMA might be the suppression of undesirable output to the motor system. Such a framework would be able to explain pre-SMA activation in task switching (Rushworth et al., 2002; Crone et al., 2006) and during situations of response conflict [Ullsperger et al. (2001), but see Lau et al. (2006)].

In the studies reported in Chapters 4 and 5, pre-SMA was active when a visual stimulus was maintained online prior to the transformation from visual into motor information (Chapter 2) and during the visuomotor transformation (Chapter 3). In both studies, pre-SMA co-activated with the dorsal premotor cortex. However, a number of models [e.g., Hikosaka et al. (1999)] suggest different functions for these two anatomical structures, with PMd involved in the translation of information from visual to motor coordinates and pre-SMA involved in more higher-level aspects of motor control, such as coordination between different visuomotor streams (Nakahara et al., 2001) or task set implementation (Rushworth et al., 2004; Crone et al., 2006). However, the studies reported here were aimed at dissociating the contributions of premotor and 'pre-premotor' areas to visuomotor processing and do not speak to the dissociation of the lateral and medial premotor cortices. This remains a topic for further research.

SMA and movement preparation

Traditionally, the lateral premotor cortex has been implemented in the control of movement based on external sensory information, while the medial premotor areas, specifically SMA proper, were thought to mediate the planning of movements from memory (Goldberg, 1985).

This framework has been challenged extensively in the past decade. For example, Brett and colleagues (1997) showed that SMA activity during movement selection disappeared when participants could not prepare their response, suggesting that preparation, and not internal action selection, is the crucial factor driving SMA activity. Similar claims have been made in a number of studies (Amador and Fried, 2004; Elsinger et al., 2006). Consistent with the suggested involvement of the SMA in motor preparation, the SMA has been shown to be one of the prime generators of the Bereitschaftspotential (Cui et al., 1999). Studies in monkeys show that SMA neurons are indeed active during the preparation phase of instructed delay tasks, and also during the movement execution (Hoshi and Tanji, 2004). Furthermore, These studies showed that a number of SMA neurons responded in an effector specific matter, while very few SMA neurons were involved in action selection based on visual information. These results point to a role for the SMA in the preparation of actions after the action has been selected, when the effector can be fully specified.

Supporting this preparation viewpoint, the study reported in Chapter 2 showed sustained activation of the SMA proper when participants prepared a movement for execution. SMA thus became active only after the appropriate action had been selected. Our data thus support the view that the SMA is involved in later stages of action preparation. Amongst others, the SMA might have a role in specifying the timing of an action (Macar et al., 2004), but the studies reported in this thesis do not speak to this issue.

7.5 Integration: Premotor contributions to the control of action

As discussed in the previous chapters, the view that the generation of motor commands proceeds in a serial, hierarchical fashion, with the primary motor cortex as the final common pathway for the central control of movement has been revised. The frontal lobes contain a number of anatomically and functionally distinct premotor areas, each with direct outputs to the primary motor cortex and spinal cord. Consequently, Dum and Strick have proposed that each premotor area is a functionally distinct efferent system that differentially controls aspects of movement planning, preparation, and execution (Dum and Strick, 2005). The control of action is accomplished through parallel distributed processing in these multiple motor areas (Dum and Strick, 1991b; Dum and Strick, 2005).

Roland (Roland et al., 1980) has suggested that the "premotor areas are activated when a new motor program is established" or when a program is "changed on the basis of sensory information". The research presented in this thesis was aimed at empirically testing and further developing this statement, providing further insight into the specific contributions of the various premotor areas to the control of action. As far as the lateral surface is concerned, this thesis has concentrated on the dorsal premotor cortex, illustrating its role in the various stages of action selection (deciding which flower to pick) and preparation (waiting for the bee to leave the flower before picking it). The work on the medial premotor areas presented in this thesis has focused mostly on the role of these areas in action monitoring (learning that it is not a good idea to pick flowers when bees are present). As discussed in the Introduction and in Chapters 4 and 5, the view taken in this research is that action monitoring is part of process of response selection. The medial premotor areas, and specifically the RCZa, are thus not passive monitors, but have an active role in the selection of actions for which they use information from other, perhaps striatal, areas. The results obtained in this thesis have been generally consistent with this position.

Further research must focus on the integration of these results with other approaches, such as computational modeling and neurophysiological experimental data, as well as continuing experimental work at the system level.

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Nederlandse samenvatting

Wij mensen hebben een zeer uitgebreid repertoire aan bewegingen. We ademen, lopen in de tuin kijkend naar de bloemen, bewaren ons evenwicht tijdens het lopen, stoppen om wat bloemen te plukken, beslissen om de ene bloem weg te gooien ten gunste van een andere, trekken ons been terug als we gestoken worden door een wesp, passen ons lopen aan om het gestoken been te ontzien, en mompelen over de complexiteit van het bestaan.

Dit proefschrift gaat over motorische acties. Onze acties verschillen in de mate waarin we er vrijwillige controle over hebben en in de wijze waarop we ze aanleren. Dit proefschrift richt zich slechts op motorische acties waarover wij vrijwillige controle hebben en die we hebben leren uitvoeren.

Oorspronkelijk werd gedacht dat slechts een zeer beperkt deel van de hersenen, de primaire motorische schors, betrokken is bij het aansturen van bewegingen. De laatste 20 jaar is er echter veel aandacht voor de rol van andere hersengebieden in het regelen van motorische acties. In dit proefschrift staat de rol van een specifieke groep hersengebieden, die samen de premotorische schors vormen, centraal. Deze gebieden vormen een onderdeel van de frontale schors. Een kernmerk van deze gebieden is dat ze verbonden zijn met de primaire motorische schors en met het ruggenmerg. Het onderzoek dat de basis vormt voor dit proefschrift is gericht op de rol van de premotorische schors bij het tot stand komen van acties en het evalueren van uitgevoerde acties.

De selectie en preparatie van acties

De hoofdstukken 2 en 3 richten zich op de processen die plaatsvinden voordat een beweging wordt uitgevoerd. In het meeste onderzoek daarnaar wordt de proefpersonen geleerd om op een bepaalde visuele stimulus te reageren met een specifieke beweging. In het onderzoek beschreven in dit proefschrift wordt veelvuldig gebruik gemaakt van de zogenaamde 'delayed-response taak'. Bij deze taak wordt de proefpersonen opgedragen om, nadat ze de stimulus hebben gezien, een korte tijd, meestal enige seconden, te wachten met het uitvoeren van de bijbehorende actie. Op deze manier kunnen de hersenprocessen die betrokken zijn bij het omzetten van visuele informatie in een motorische actie worden geïsoleerd.

Het experiment dat in hoofdstuk 2 wordt beschreven, had tot doel te bepalen of er verschillende hersengebieden betrokken zijn bij het verwerken van de stimulusinformatie enerzijdse en de motorische respons anderzijds.

Daarbij werd een delayed-response taak zoals hierboven is beschreven gebruikt. Om de taak goed uit te voeren moesten de proefpersonen enige tijd wachten tussen de aanbieding van de stimulus en het uitvoeren van de bijbehorende actie. Aangezien er tijdens het interval geen stimuli werden gepresenteerd, moesten de proefpersonen taakrelevante informatie onthouden. Een conditie was zo ontworpen dat de stimulus onthouden moest worden, maar de juiste beweging nog niet kon worden geselecteerd. In de andere conditie kon de juiste beweging al wel geselecteerd worden en hoefde de proefpersoon geen visuele informatie te onthouden. Uit de resultaten van dit experiment blijkt dat andere delen van de premotorische schors betrokken zijn bij het onthouden van stimulus informatie dan bij het vasthouden van motorische informatie. Tevens is gebleken dat een ander gebied in de hersenen, de posterieure pariëtale schors, bij het onthouden van beide typen informatie betrokken is.

Bij dit type experiment wordt aangenomen dat de proefpersoon tussen de trials rustig zit te wachten tot er een stimulus wordt gepresenteerd. Het motorische systeem wordt aangenomen passief te zijn tot het moment dat de stimulus wordt aangeboden. Deze 'bottom-up' benadering bijkt een oversimplificatie te zijn. Uit de literatuur over visuele perceptie, bijvoorbeeld, blijkt dat de staat waarin het brein verkeert op het moment dat een stimulus gepresenteerd wordt, in grote mate bepalend is voor de verwerking van deze stimulus. Evenzeer is de toestand van het motorische systeem belangrijk voor de manier waarop een nieuwe actie geselecteerd wordt.

In hoofdstuk 3 staat deze stelling centraal. Opnieuwe werd aan de proefpersonen gevraagd na een stimulus een actie te selecteren en voor te bereiden en die enige tijd later uit te voeren. Uit de reactietijden bleek dat de proefpersonen het interval inderdaad gebruikten om hun actie voor te bereiden. In een klein aantal trials werd de proefpersoon opgedragen om een andere actie dan de reeds geprepareerde te selecteren en voor te bereiden. In dit geval moest de voorbereide actie dus onderdrukt worden. Op deze manier was het mogelijk hersenactiviteit te vergelijken tussen de conditie waarin het motorische systeem al bezig was met de voorbereiding van een actie en de andere conditie waarin het motorische systeem daar nog niet mee bezig was. Het blijkt dat dezelfde hersengebieden betrokken zijn bij het selecteren en voorbereiden van acties ongeacht of het motorische systeem al een andere actie aan het voorbereiden was. Indien er echter al een andere actie was voorbereid werden additionele gebieden in de inferieure parietale schors en in de frontale schors actief. Deze gebieden zijn betrokken bij het inhiberen van de reeds voorbereide actie en het selecteren van de nieuwe actie. Veel van deze gebieden waren echter ook geactiveerd tijdens het selecteren van acties onder tijdsdruk. Wanneer hiervoor gecorrigeerd werd bleef slechts één gebied over dat specifiek bij de inhibitie betrokken is: de rechter precentrale schors.

Het evalueren van acties

De hierop volgende drie experimentele hoofdstukken gaan over het evalueren van uitgevoerde acties. Nadat een actie is uitgevoerd kan bepaald worden of het beoogde doel bereikt is; deze informatie kan gebruikt worden om bij volgende acties beter te presteren. Onderzoek naar de processen die betrokken zijn bij evalueren van acties, het zogenaamde 'action monitoring', staat de laatste tien jaar zeer in de belangstelling. In dit proefschrift wordt voortgebouwd op een model van action monitoring dat is voorgesteld door Clay Holroyd en Michael Coles. Volgens dit model is een bepaald deel van de mediale premotorische schors, de anterieure cingulate cortex, betrokken bij het leren van acties op basis van de resultaten van 'action monitoring'.

Elektro-encefalografie (EEG) stelt ons in staat om de hersenactiviteit van proefpersonen met een hoge temporele resolutie te meten. In het gemiddelde EEG na een stimulus, de zogenaamde event-related potential, is een component zichtbaar wanneer proefpersonen detecteren dat ze een fout hebben gemaakt. Deze 'error-related negativity' (ERN) wordt opgewekt in een deel van de mediale premotorische schors, in de anterieure cingulate cortex. Een soortgelijke component is ook zichtbaar wanneer een proefpersoon niet zelf zijn fout detecteert, maar informatie krijgt dat het uitgevoerde gedrag fout was. Omdat deze component optreedt na de feedback die de proefpersoon informeert over zijn prestatie, wordt deze component de feedback-ERN genoemd.

In hoofdstuk 4 zijn enkele eigenschappen van de feedback-ERN nader bekeken. Aan de proefpersonen werd gevraagd om na een tijdsinterval van precies één seconde te reageren. Na elke trial kregen ze feedback over de nauwkeurigheid van hun reactie. In verschillende condities kregen proefpersonen (1) goed/fout informatie, (2) goed/fout informatie aangevuld met informatie over de richting van de fout, of (3) goed/fout informatie aangevuld met informatie over de richting en grootte van de fout. Uit het gedrag van de proefpersonen bleek dat zij gebruik maakten van deze informatie: hoe meer informatie ze kregen, hoe nauwkeuriger ze werden. Ook pasten ze in de volgende trials hun gedrag meer aan als ze te zien kregen dat ze een grotere fout hadden gemaakt. Hoewel de proefpersonen hun gedrag aanpasten bleek de amplitude van de feedback-ERN niet samen te hangen met de grootte van de gedragsaanpassing, maar wel met de hoeveelheid informatie die de proefpersonen kregen. De feedback-ERN had een kleinere amplitude in condities (2) en (3), in vergelijking met de conditie waar de minste informatie werd gegeven, conditie (1). Tevens vonden we geen verband tussen de grootte van de feedback-ERN en de aanpassing van het gedrag. Hoewel de feedback-ERN wel gevoelig was voor de hoeveelheid informatie die de feedback bevatte, konden we geen direct verband aantonen tussen de amplitude van de feedback-ERN en de gedragsaanpassingen. Dit lijkt erop dat de feedback-ERN slechts een goed/fout signaal is, maar niet de mate van informatie die zich vertaalt naar de grootte van de gedragsaanpassing.

Men kan het eigen gedrag op verschillende momenten evalueren. Soms kan een fout al gedetecteerd worden op het moment dat deze wordt gemaakt: 'Oei, dat was fout, te snel gereageerd'. Deze interne evaluatie kan echter al-

leen plaatsvinden als al bekend of aangeleerd is wat de juiste respons moet zijn. In andere gevallen, is men afhankelijk van externe informatie voor het evalueren van gedrag. Een belangrijke stelling van het Holroyd en Coles model is dat er één gebied in de anterieure cingulate cortex is dat actief is in reactie op evaluatieve informatie, ongeacht de bron van deze informatie. Dit zou ook verklaren dat een ERN gevonden wordt zowel wanneer de proefpersoon zelf een fout detecteert als na externe feedback die aangeeft dat een actie verkeerd was. Deze hypothese is getest in het experiment beschreven in hoofdstuk 5. In dit experiment, waarin niet de ERN werd gemeten maar waarin m.b.v fMRI de bij fouten actieve hersengebeiden werden opgespoord, werd proefpersonen opgedragen te proberen de associaties tussen visuele stimuli en specifieke bewegingen te leren met behulp van feedback die aangaf of een zojuist gegeven respons goed of fout was. Aan het begin van het leerproces wisten proefpersonen nog niet welke beweging bij welke stimulus hoorde en waren ze dus afhankelijk van de feedback om hun acties te evalueren. Later in het leerproces konden ze al bij het indrukken van de responseknop, dus voordat de feedback gegeven werd, bepalen of ze de juiste actie hadden uitgevoerd of niet. Hierbij moet opgemerkt worden dat proefpersonen ook als ze de associaties goed geleerd hadden toch nog fouten maakten vanwege de grote tijdsdruk.

Uit het experiment bleek dat een bepaald gebied, de anterieure rostrale cingulate zone, actief wordt als proefpersonen registreren dat een uitgevoerde actie fout is. Cruciaal is echter dat dit gebied aan het begin van leren actief was na de negatieve feedback, maar later in de experimentsessie al na de verkeerde respons zelf, dus wanneer de proefpersonen hun actie zelf konden evalueren. Hieruit kan worden geconcludeerd dat dit gebied reageert op informatie dat een actie niet goed is uitgevoerd, onafhankelijk van de bron van deze informatie. Deze bevinding is in overeenstemming met het model van Holroyd en Coles. Tevens vormt dit experiment een brug tussen het werk dat gedaan is binnen 'action monitoring' en de literatuur over het leren van motorische acties.

Het evalueren van het gedrag van anderen

Acties vormen de enige manier die we hebben om te communiceren met de buitenwereld. De laatste jaren is veel aandacht besteed aan hoe wij onze eigen acties bewaken, maar ook hoe wij de acties van anderen bekijken en begrijpen. Gebleken is dat wanneer we acties van anderen waarnemen we daarvoor niet alleen ons visuele systeem gebruiken, maar ook ons eigen motorische systeem inschakelen. Het lijkt erop alsof we de acties van de anderen mentaal 'simuleren'.

In het onderzoek dat in het laatste experimentele hoofdstuk van dit proefschrift wordt beschreven is gekeken of het systeem dat gebruikt wordt om onze eigen acties te evalueren ook actief is als we het gedrag van anderen evalueren. Twee proefpersonen werden tegenover elkaar aan een tafel gezet. De ene proefpersoon voerde een simpel snelheidstaakje uit, terwijl de andere bijhield hoeveel fouten de actor maakte. Hersenactiviteit werd ge-

meten (met behulp van EEG) zowel wanneer de proefpersonen de taak zelf uitvoerden als wanneer ze iemand anders de taak zagen uitvoeren. In overeenstemming met eerder onderzoek werd gevonden dat het maken van een fout leidde tot de al eerder besproken error-related negativity in de actor. Echter, wat we in dit experiment ook vonden was dat het detecteren van de fouten van anderen ook leidde tot een error-related negativity. Dit geeft aan dat hetzelfde systeem betrokken is bij het evalueren van ons eigen gedrag en bij het evalueren van het gedrag van anderen.

Een tweede interessant gegeven was dat het motorische systeem van de proefpersonen tijdens het observeren van het gedrag van anderen ook actief was. Tijdens dit observeren activeerden de proefpersonen de correcte respons op een subliminaal niveau. Dit resultaat geeft aan dat we ons eigen motorische systeem gebruiken om het gedrag van anderen te simuleren of zelfs te voorspellen.

Discussie

De premotorische schors bestaat uit een aantal kleinere deelgebieden die elk verbonden zijn met de primaire motorische schors en met het ruggenmerg. De activiteit van elk van deze deelgebieden samen ligt ten grondslag aan de acties die we dagelijks uitvoeren. Geen enkel gebied is alleen volledig verantwoordelijk voor een actie; elke actie is het resultaat van de gezamenlijke activiteit van meerdere gebieden. Het onderzoek dat in dit proefschrift gerapporteerd wordt heeft als doel om te komen tot een nauwkeurigere omschrijving van de bijdrage van deze verschillende deelgebieden.

De experimenten in dit proefschrift laten zien wat de rol van verschillende delen van de laterale premotorische schors is in de selectie en voorbereiding van acties en de rol van de verschillende delen van de mediale premotorische schors in de evaluatie en verbetering van de selectie van acties.

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Wouter, I think our closest contact actually started in the second half of the project, but it was great nonetheless. After reading the Introduction to this thesis you commented 'Indeed, you are more a Donders person than a NICI person'. I think our discussions have been all the more enjoyable because of our different outlooks. I also want to especially thank you for your efforts in helping me to secure a future after the Ph.D.

Apart from these two supervisors, whom I knew about when signing the contract, it turned out I had a third, bonus supervisor in Ivan Toni. Ivan, we can fairly say that your approach to research has been an eye-opener to me. At the beginning of my project I was trying to find a home at the FCDC. I think I found it in the Intention and Action group, as I think the topics of the studies in this thesis illustrate. I'm sure your style will continue to shape my work for quite some time to come. At least I hope so.

Apart from my supervisors, Ellen de Bruijn has been very important in the past four years. It was a great joy to have somebody to discuss the latest claims of certain groups. Recently, we found out that if we actually take the time to sit down together in front of a white board we can come up with some very nice ideas. I look forward to following them up in the future. More than all that, though, I am grateful for the support you gave me outside of work in recent months.

The FCDC is a great place to work and I have been fortunate to be able

to witness its growth from the opening day onwards. Thank you, all who helped me in the past years. You know who you are!

Although I was stationed at the FCDC, I have always felt as a part of the Action, Intention and Motor Control group of the NICI and there are a number of people who have been very supportive, both during work as outside of it. Thanks especially to Pin, Oliver, Aave, Ruud, Harold, Hein, Jos, Pascal, and of course Beppie.

The relationship one has with one's roommates will never cease to fascinate me: you don't necessary need to talk all the time, but being near each other day after day, you tend to know more about each other than you care to admit. Thanks, Markus, Daniel, Ben, and Giosue.

Friends are one of one's most important assets in life. A number of people outside Nijmegen have been there for me all the way. Di famili has been vital in helping me to maintain at least some of my sanity. Mostly, though, by displaying a lack of it. It is great to know there are some people out there who share a large part of your outlook on life. Thomas Gladwin thanked me in his thesis in a way that I will never be able to top, but the compliment is absolutely returned. Please don't leave experimental science, Thomas, we need you. Hubert Fonteijn, you are the only person I know who can summarize the meaning of life in a single sentence. A great gift indeed.

Els Bottema en Jan Venselaar allowed me to stay with them during the first three months of my working life in Nijmegen. This has been a great help in settling in Nijmegen and I am still very grateful to them.

A number of researchers outside Nijmegen have provided support for me during these four years in all kinds of ways. Sander Nieuwenhuis allowed me to stay at the Vrije Universiteit for some time in the summer of 2003. Although that particular project yielded no results, our subsequent collaborations have been very fruitful and very interesting. I have enjoyed these collaborations immensely and hope they will continue in the future. Clay Holroyd, whom I think still I have actually met fewer times than the number of papers we have together, was always willing to answer any question about particular aspects of dopamine, feedback, and IDL code. Wolfgang Miltner is a joy to listen to and a clear example that any topic can be studied in rigorous and interesting ways. Eveline Crone has been extremely supportive of my work and always ready to introduce me to any person I feared approaching. Matthew Rushworth's work has been a source of inspiration since the moment I found it in pubmed. I hope we will have our chance to work together in the near future.

When I was a child my parents provided all types of books for me until I found a series I liked. I have tried not to stop reading since. The love of reading, and the resulting wonder in the world around you and the will to contribute to our understanding of it, has been the real start of my scientific career. It has not always been a smooth ride, but thanks to your support I hope to have found a way. Dad also deserves a special mention for introducing me into the world of LaTeX, often under heavy deadline pressure...

No-one has had to deal with my insecurities more than Carinne. You have supported me with every step and you know this thesis is as much yours as it is mine. I know the last months have not been as you and I had

envisioned, but please know that whatever happens and whatever I will be doing in my life, there will always be a special place in my heart for you... You are wonderful...

CV and publication list

Curriculum vitae

Rogier Bertrand Mars was born on the 15th of January 1979 in the city of Hengelo in the Netherlands. He attended secondary education (VWO) at the O.S.G. Hengelo. Following a year as a student of Management and Organization at the University of Groningen, he started studying Psychology at that same university in 1998. During this time, apart from being a student, he worked as a Teaching Assistant and performed a number of representative functions in administrative bodies of the faculty. In 2002 he completed his M.Sc. on exploratory multivariate analysis of functional magnetic resonance imaging data under supervision of Berry Wijers and Henk Kiers.

Following his time in Groningen, he moved to Nijmegen for his Ph.D. research under supervision of Michael Coles, Wouter Hulstijn, and Ivan Toni. This project stimulated his interest in the neural implementation of the control of actions. Using event-related brain potentials and functional magnetic resonance imaging, he focused on the evaluation of simple motor responses and the selection and preparation of these actions. The present thesis is the result of this research.

He is currently working at the Sobell Department of Motor Neuroscience and Movement Disorders at the Institute of Neurology and the Institute of Cognitive Neuroscience at University College London. Together with Sven Bestmann, John Rothwell, and Patrick Haggard, he continues his research on the neural control of action. The main research method he uses in London is transcranial magnetic stimulation, which allows him to study these processes at a neurophysiological level.

Publication list

Manuscripts submitted/in revision

- Mars RB, Piekema C, Coles MGH, Hulstijn W, Toni I. On the programming and reprogramming of actions. *Manuscript submitted for publication.* Chapter 3 of this thesis.

- Van den Hurk P, Mars RB, Van Elswijk, Hegeman J, Pasman JW, Bloem BR, Toni I. Maintaining sensory and motor representations: Effects on cortico-spinal excitability. *Manuscript under revision.*

- Mars RB, Coles MGH, Hulstijn W, Toni I. Cerebral dynamics and topography of preparatory activity. *Manuscript under revision*. Chapter 2 of this thesis.

Articles and chapters

- Nieuwenhuis S, Scheizer TS, Mars RB, Botvinick MM, Hajcak G (in press). Error-likelihood prediction in the medial frontal cortex: A critical evaluation. *Cerebral Cortex*.

- Piekema C, Kessels RPC, Mars RB, Petersson KM, Fernàndez G (in press). The right hippocampus participates in short-term memory maintenance of object-location associations. *NeuroImage*.

- Mars RB, Coles MGH, Grol MJ, Holroyd CB, Nieuwenhuis S, Hulstijn W, Toni I (2005). Neural dynamics of error processing in medial frontal cortex. *NeuroImage*, 25:1302–1309. Chapter 5 of this thesis.

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- Mars RB, De Bruijn ERA, Hulstijn W, Miltner WHR, Coles MGH (2004). What if I told you: "You were wrong"? Brain potentials and behavioral adjustments elicited by feedback in a time-estimation task. In: *Errors, conflicts, and the brain. Current opinions on performance monitoring*, Ullsperger M, Falkenstein M, ed., pages 129–134. MPI of Cognitive Neuroscience. Chapter 4 of this thesis.

- De Bruijn ERA, Mars RB, Hulstijn W (2004). It wasn't me... or was it? How false feedback affects performance. In: *Errors, conflicts, and the brain. Current opinions on performance monitoring*, Ullsperger M, Falkenstein M, ed., pages 118–124. Leipzig: MPI of Cognitive Neuroscience.

Talks, posters, and conference proceedings

- Minelli A, Roelofs K, Mars RB, Toni I (2006, June). Neural correlates of approach-avoidance behavior. *Poster presented at the 12th Annual meeting of the Organization for Human Brain Mapping*, Florance, Italy.
- Mars RB, Piekema C, Coles MGH, Hulstijn W, Toni I (2006, June). fMRI responses related to the programming, reprogramming, and inhibition of movements *Poster presented at the 12th Annual meeting of the Organization for Human Brain Mapping*, Florance, Italy.
- Van den Hurk P, Mars RB, Van Elswijk G, Hegeman J, Bloem BR, Toni I (2006, June). Movement preparation and working memory: an electrophysiological dissociation *Poster presented at the 12th Annual meeting of the Organization for Human Brain Mapping*, Florance, Italy.
- Mars RB, Coles MGH, Toni I (2005, November). Sensory and motor delay-related responses in the human brain. *Poster presented at the 35th Annual meeting of the Society for Neuroscience*, Washington D.C., USA.
- Piekema C, Mars RB, Petersson KM, Kessels RPC, Fernàndez G (2005, November). *Poster presented at the 35th Annual meeting of the Society for Neuroscience*, Washington D.C., USA.
- Piekema C, Mars RB, Petersson KM, Kessels RPC, Fernàndez G (2005, June). Binding of spatial and non-spatial features in working memory: An fMRI study. *Poster presented at the 11th Annual meeting of the Organization for Human Brain Mapping*, Toronto, Canada.
- Mars RB, Coles MGH, Grol MJ, Holroyd CB, Nieuwenhuis S, Hulstijn W, Toni I (2005, November). Neural dynamics of error processing in medial frontal cortex *Poster presented at the 11th Annual meeting of the Organization for Human Brain Mapping*, Toronto, Canada.
- Mars RB (2005, March). Neural dynamics of error processing in medial frontal cortex. *Talk given at the EPOS/NWO Workshop Control in Attention and Action: Neurocognitive Systems and Mechanisms*, Amsterdam, The Netherlands.
- Mars RB, Van Schie HT, Coles MGH, Bekkering H (2004, June). Involvement of anterior cingulate and motor cortices in error observation: An ERP study. *Poster presented at the 10th Annual meeting of the Organization for Human Brain Mapping*, Budapest, Hungary
- Mars RB (2004, June). Temporal dynamics of error processing during learning. *Talk given at the 3rd Endo-Neuro-Psycho meeting*, Doorwerth, The Netherlands.
- Mars RB, Van Schie HT, Bekkering H, Coles MGH (2003, December). You were wrong! Medial frontal and motor cortex activation elicited by error observation. *Talk given at the Winter Conference of the Dutch Psychonomics Society*, Egmond, The Netherlands

- Nieuwenhuis S, Holroyd CB, Yeung N, Nystrom LE, Cohen JD, Mars RB, Coles MGH (2003, November). Neural correlates of reinforcement learning and error processing: A functional magnetic resonance imaging study. *Poster presented at the 33rd Annual meeting of the Society for Neuroscience*, New Orleans, USA.

- Mars RB, De Bruijn ERA, Hulstijn W, Miltner WHR, Coles MGH (2003, November). Event-related brain potentials elicited by performance feedback in a time-estimation task. *Poster presented at the 43rd Annual Meeting of the Society for Psychophysiological Research*, Chicago, USA.

- Mars RB (2003, July). Event-related brain potentials elicited by performance feedback in a time-estimation task. *Talk given at the Errors, Conflicts, and the Brain conference*, Dortmund, Germany

- Mars RB (2003, June). Event-related brain potentials elicited by performance feedback in a time-estimation task. *Talk given at the 2nd Dutch Endo-Neuro-Psycho meeting*, Doorwerth, The Netherlands.

Appendix: Color figures

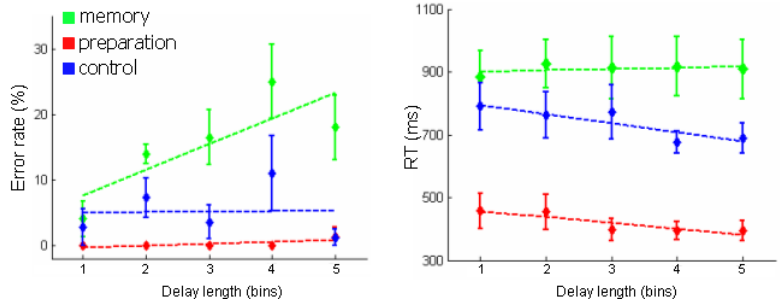

Figure 2.2. Behavioral data. Error percentages (left panel) and reaction times on correct trials (right panel) in the CONTROL, PREPARATION, and MEMORY conditions as a function of delay length, obtained during the scanning session. Curves are fitted first order polynomials; error bars indicate ±SEM.

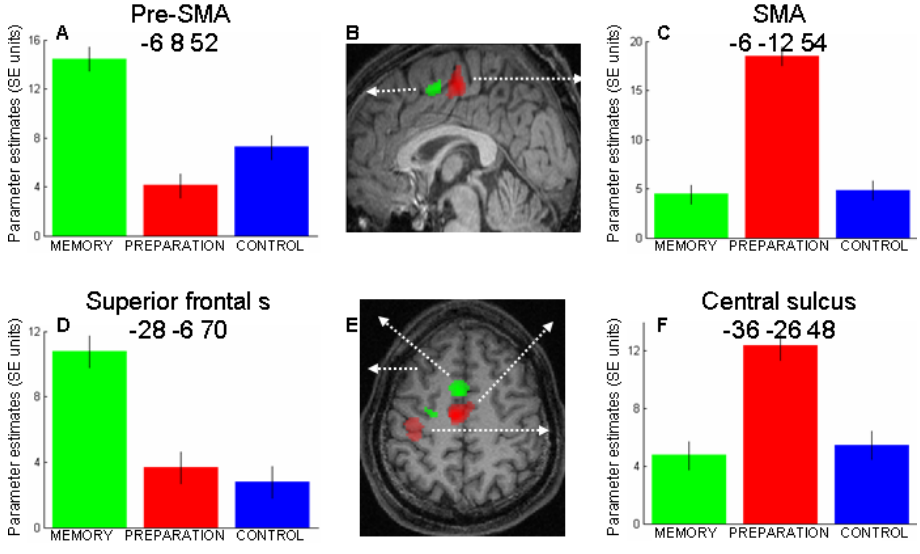

Figure 2.3. Differential delay-related sustained activity. Anatomical location (panels (B) and (E); SPM(t)s of the contrasts detailed in Table 2.1, overlaid on spatially normalized anatomical sections of one participant) and effect sizes (panels (A), (C), (D), and (F); parameter estimates of multiple regression in SEM units) of regions modulated by the task contingencies during the delay period. Regions with stronger sustained activity during delay periods of either MEMORY trials (in green) or PREPARATION trials (in red) are shown on sagittal (B) and transverse (E) anatomical sections. Clusters of delay-related activity supporting task performance during PREPARATION trials were distributed along the caudal precentral cortex (central sulcus, SMA-proper), whereas MEMORY trials evoked activity along the caudal prefrontal cortex (Brodmann area 6/8 and pre-SMA).

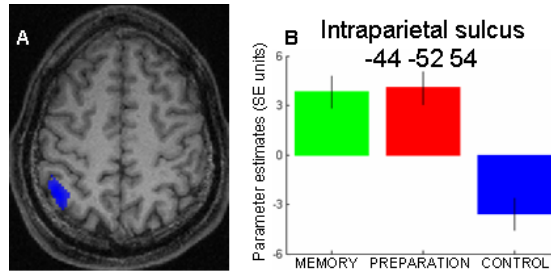

Figure 2.4. Common delay-related sustained activity. Anatomical location (A) and effect sizes (B) of a region with stronger delay-related sustained activity during PREPARATION and MEMORY trials than during CONTROL trials. Other conventions as in Fig. 2.3.

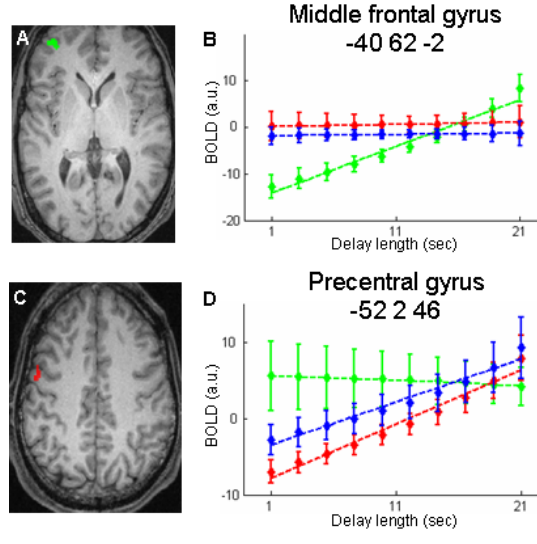

Figure 2.5. Differential delay-related time-varying activity. Anatomical location (panels (A) and (C); SPM(t)s of the contrasts detailed in Table 2.1) and effect sizes (panels (B) and (D)) of regions modulated by the task contingencies during the delay period. Regions with stronger time-varying activity during delay periods of either MEMORY trials (in green) or PREPARATION trials (in red) are shown on transverse anatomical sections. Delay-related activity increasing as a function of delay time during PREPARATION trials was found along the precentral gyrus (BA6), whereas MEMORY trials evoked activity along the middle frontal gyrus (BA10).

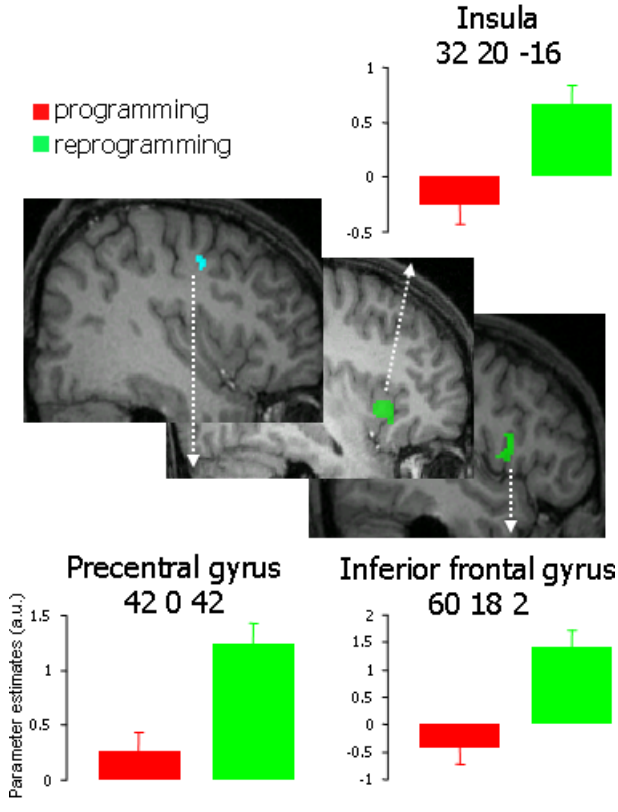

Figure 3.3. Imaging data—right frontal cortex. Anatomical location (SPM(t) of the contrasts detailed in Table 3.1, overlaid on spatially normalized anatomical sections of one participant) and parameter estimates ±90% Confidence Interval boundary) of right frontal clusters activated during action reprogramming. The cluster in cyan is the only cluster surviving a more constrained contrast (incl. masking by $IC_{SWITCH} \cap TC_{NEUTRAL}$), see main text for details.

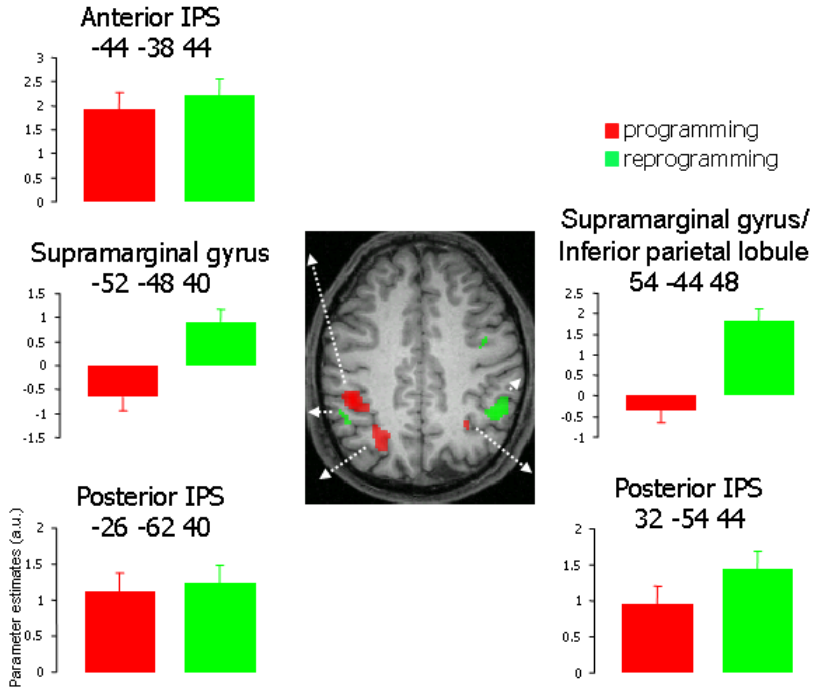

Figure 3.4. Imaging data—parietal cortex. Anatomical location (SPM(t) of the contrasts detailed in Table 3.1, overlaid on spatially normalized anatomical sections of one participants) and parameter estimates (±90 Confidence Interval boundary) of right frontal clusters activated during action programming (red) and reprogramming (green).

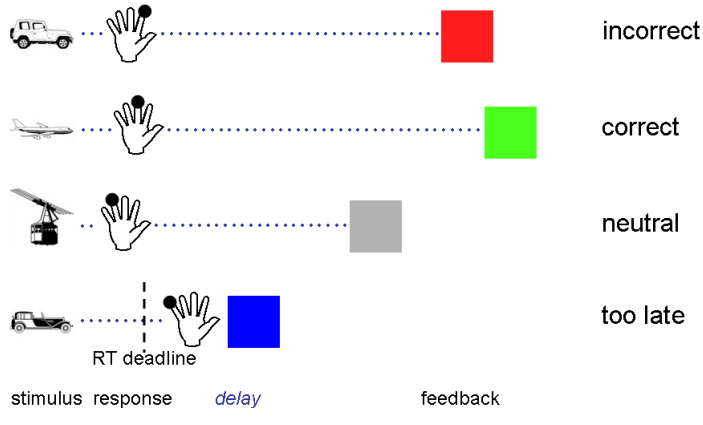

Figure 5.1. Experimental setup. Participants had to learn, by trial and error, arbitrary associations between visual stimuli and motor responses. After a variable delay, visual feedback (red/green square) was provided, indicating correct and incorrect responses. On 50% of the trials, feedback consisted of a noninformative gray square. When responses occurred after the reaction time deadline (750 ms), immediate feedback (blue square) was provided.

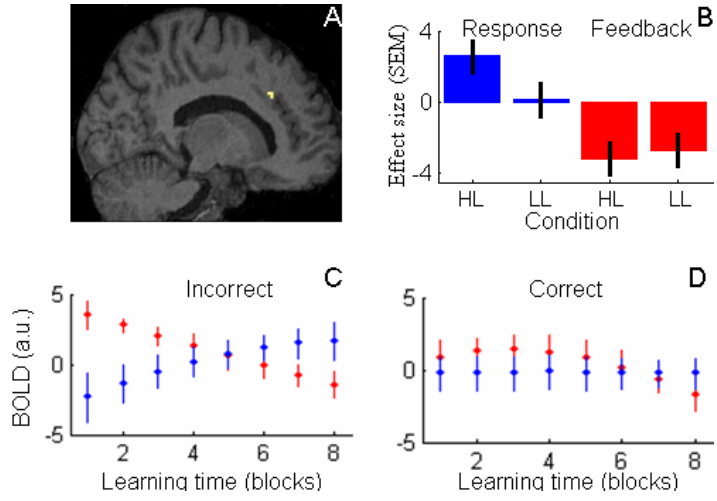

Figure 5.4. Imaging results. Anatomical localization, peak BOLD signal development during learning for both incorrect and correct trials (High Learning condition), and effect sizes for time-related modulation in BOLD response for the RCZa (top row, peak coordinates: 14, 28, 32). (A) SPM(Z) (threshold $p < 0.05$ corrected) superimposed on normalized anatomical sagittal sections of one participant. (B) Effect sizes (in SEM units) for the time-related changes in BOLD response in both the High Learning (HL) and Low Learning (LL) conditions, indicating stronger modulations of activity in the High Learning condition. (C,D) Peak BOLD signal (in arbitrary units, SEM) over the course of learning, following response (blue) and feedback (red) for incorrect (C) and correct trials (D). For display purposes, the fMRI time series of each subject were subdivided into eight blocks of equal length. The actual statistical model of the fMRI data considered time as a continuous parametric effect (see Materials and methods). It can be seen that error feedback-related activation decreases as learning proceeds, while error response-related activation increases, and these effects are reciprocal.

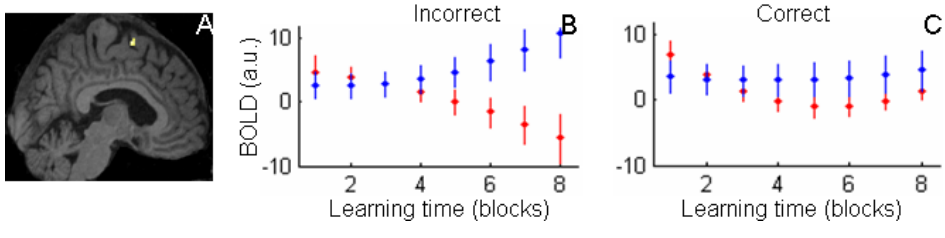

Figure 5.5. Imaging results. Anatomical localization and peak BOLD signal development during learning for both incorrect and correct trials (HL condition) for the pre-SMA (peak coordinates: 2, 4, 60). It can be seen that pre-SMA shows a response-related activation over and above the learning-related modulations of activation, both on correct and incorrect trials. Color conventions as in Fig. 5.4.

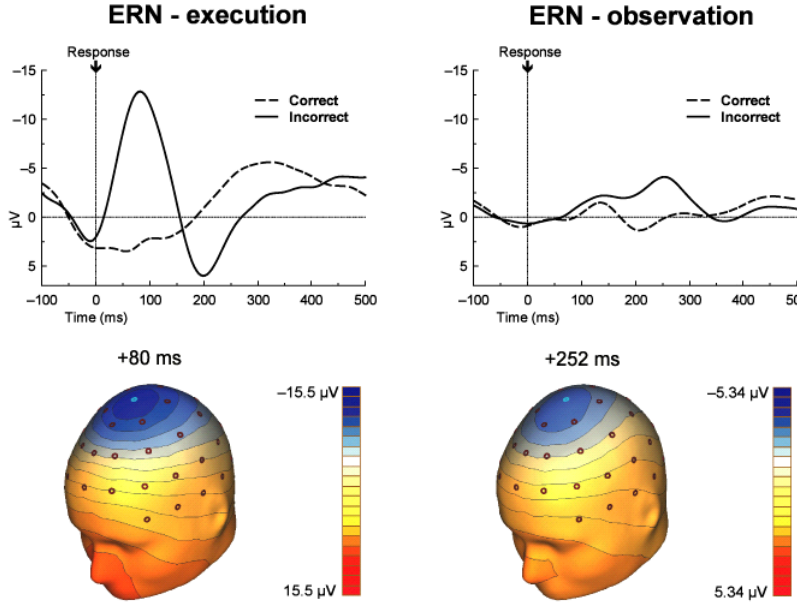

Figure 6.2. Error-related negativities. Top: Response-locked averages at electrode Cz for correct and incorrect responses in the execution condition (left) and the observation condition (right). Dashed lines indicate correct, and solid lines indicate incorrect response trials. Bottom: Spline maps showing the topography of the ERN difference wave in the execution condition and the observation condition, taken at the peak where correct and incorrect ERPs differed maximally, 80 ms and 252 ms after the response, respectively. The Cz electrode at the vertex is marked in light blue for reference.

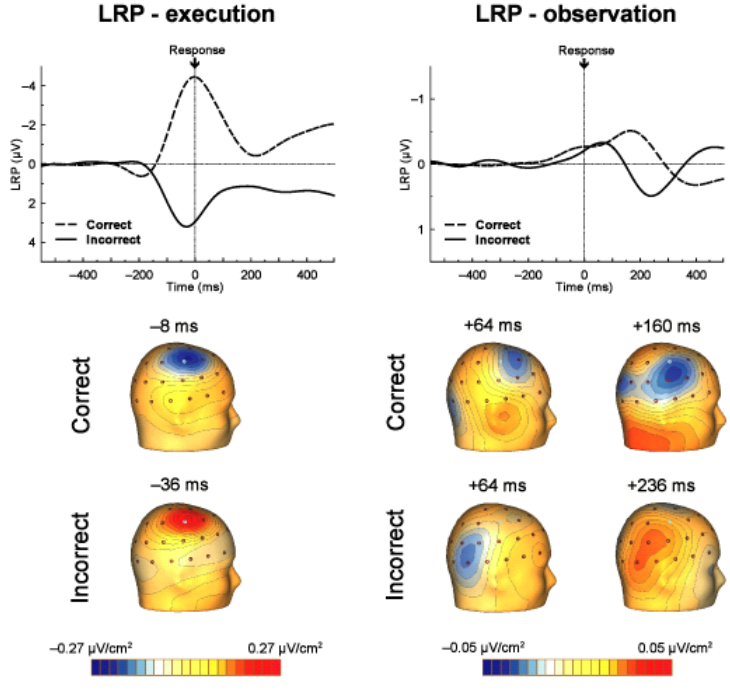

Figure 6.4. Lateralized readiness potentials. Top: Response-locked lateralized readiness potentials in the execution condition (left) and the observation condition (right). LRPs recorded to correct response trials are indicated by dashed lines, and LRPs to incorrect trials by solid lines. Bottom: CSD maps of LRP effects in the execution condition (left) and the observation condition (right), for correct and incorrect responses separately. The C3/C4 electrode over the lateral motor cortex is marked in light blue for reference. The relevant time-point (relative to the response) is indicated above each map.