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Selection and Monitoring of Actions and their Consequences

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Abstract

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Even the simplest human behavior is likely governed by the complex integration of cognitive, sensory, affective and motor factors. Yet, researchers have typically studied these factors in isolation with limited attention to the link between them. The goal of this dissertation was to investigate this link through a mixture of behavioral and neural measures. The focus was on the selection and planning of actions, as well as the subsequent monitoring and evaluation of the outcome and the consequences of the actions. These planning and evaluation processes are perhaps where the link between cognitive, sensory, affective and motor systems is most evident. Chapter 1 provides a general introduction to the topic. Chapter 2 reviews studies that emphasize multiple levels of constraints in motor control, specifically in bimanual coordination, suggesting a link between two systems (i.e., motor and cognitive) that have been generally studied separately by researchers. Chapter 3 describes two experiments on action selection showing that decision-making, which has traditionally been seen as a purely cognitive task, is directly influenced by, and in fact emerges from, the activation of the motor system. Chapter 4 provides experimental evidence that the medial prefrontal cortex (MPFC) acts to signal the need of increased resources to other brain centers and establish action-outcome contingencies that can be used to regulate future behavior. This finding, along with the anatomical connections of the MPFC, suggests that the MPFC is in a unique position to interface cognition and action and to translate intentions into behavior by modulating effort and arousal levels. Chapter 5 focuses on action observation and the role of empathy in the function of the mirror neuron system and the MPFC performance monitoring system during the observation of actions. The findings of Chapter 5 suggest that empathy plays a role in the function of the MPFC performance monitoring system but not in the activation of the mirror neuron system during action observation. These findings provide insight into how cognitive, sensory, motor and affective systems might interact to regulate behavior. Taken together the chapters of this dissertation highlight the strong link between cognitive, affective and motor systems in producing behavior. Through this work, we provide new insight into how humans plan and regulate movements and suggest that the study of the *integration* between cognitive, sensory, affective and motor systems is critical for our understanding of human cognition and behavior.

To Roberta

Chapter 1

Introduction

The ability to act upon the environment we live in is a critical aspect of human existence. This is beautifully summarized by Blaise Pascal's quote: "*Our nature lies in movement, complete calm is death*". Indeed, without the ability to act we would be mere observers deprived of the capacity to interact with the world that surrounds us.

Philosophical discussions related to the control of movement can be traced back at least as far as Plato's time (for a complete historical perspective, see Meijer, 2001). In perhaps one of the earliest references to motor control, Plato attributed control to the 'soul'. He wrote: *"… a body deriving its motion from a source within itself is animate or besouled…"*. However, it was not until the late 1800's that formal empirical investigations of how humans control and learn movements emerged (see Schmidt & Lee, 2005). The work of Bryan and Harter (1897, 1899) with telegraph workers and of Woodworth (1899) with manual aiming tasks has been particularly influential for psychologists studying motor control and the work of Sherrington (1906), particularly on the role of reflexes in motor control, has left a lasting impact in neurophysiological approaches to the study of movement.

The field of motor learning and control saw major developments during the 1960's and 1970's when researchers developed the concept of motor programs based on studies with model tasks using reaction time and simple button presses (Fitts, 1964; Henry & Rogers, 1960; Keele, 1968). This cognitivist approach described motor control as a serial process based on input/output (stimulus-response) sequences. The classical description divides the process of control into three stages: stimulus identification, response selection and response programming (Schmidt & Lee, 2005). The late 1970's saw a shift in paradigm in the area of motor learning and control with studies emphasizing that motor control could be seen as a self-organizing process based on the physical and biomechanical constraints of the body (Bernstein, 1967; Turvey, 1990; Kelso, 1995). The role of motor programs, and even of cognition, was deemphasized in the area of motor control. Notwithstanding, recent work has once again stirred the debate by showing that motor control is highly sensitive to how the action goals are represented (Mechsner, Kerzel, Knoblich, & Prinz, 2001). This has led to the suggestion of a middle ground, which sees motor control as the interaction of cognitive, sensory, affective and motor constraints (Carson & Kelso, 2004; Oliveira & Ivry, 2008).

The goal of this dissertation was to investigate this link between cognitive, sensory, affective and motor factors in human behavior. The focus of the dissertation is on aspects related to selection/planning of actions and the subsequent monitoring/evaluation of the actions. These planning and evaluation processes are perhaps where the link between cognitive, sensory, affective and motor systems is most evident.

The dissertation is composed of four chapters in addition to this introduction. Chapter 2 provides a review of representational issues in motor control and of recent behavioral and neuroscientific studies that emphasize multiple levels of constraints in motor control, specifically in bimanual coordination. Of particular relevance is the assertion that difficulties in bimanual coordination arise due to similar constraints to those observed in typical cognitive tasks. These difficulties are accompanied by the engagement of neural systems (e.g., the medial prefrontal cortex) that are also engaged in performance monitoring (chapters 4 and 5) and in action selection (chapter 4). This suggests a link between two systems (i.e., motor and cognitive) that have been generally studied separately by researchers.

Chapter 3 focuses on response selection. Specifically, we investigated how a decision is made about which hand is used to reach towards a target. Our evidence suggests that motor planning is initiated before response selection is made. This suggests that action selection does not emerge from a discrete serial process, as viewed by previous motor control theories, but can instead be viewed as a dynamic ‘embodied’ process that continuously changes as a product of the interaction with the environment. This finding also supports the view that motor and cognitive systems are intricately linked. In particular, this finding shows that decision-making, which has traditionally been seen as a purely cognitive task, is directly influenced by, and in fact emerges from, the activation of the motor system.

Chapter 4 focuses on response preparation and behavioral adaptability in response to changing environmental demands. In particular, we were interested in how the medial prefrontal cortex (MPFC) was involved in recruiting the necessary resources to deal with tasks of increasing difficulty and how this involvement relates to the MPFC’s role in performance monitoring. We propose that the medial prefrontal cortex acts to signal the need of increased resources to other brain centers and establish action-outcome contingencies that can be used to regulate future behavior. This finding along with the anatomical connections of the MPFC suggests that the MPFC is in a unique position to interface cognition and action and to translate intentions into behavior by modulating effort and arousal levels (Paus, 2001).

Chapter 5 focuses on action observation. Specifically, we were interested in the role of empathy in the function of the mirror neuron system and the MPFC performance monitoring system during the observation of actions. Our findings suggest that empathy plays a role in the function of the MPFC performance monitoring system. On the other hand, we did not find evidence to support the view that empathy plays a role in the activation of the mirror neuron system during action observation. These findings provide insight into how cognitive, sensory, motor and affective systems might interact to regulate behavior.

Taken together the chapters of this dissertation highlight the strong link between cognitive, affective and motor systems in producing behavior. Through this work, we provide new insight into how humans plan and regulate movements and suggest that the study of the *integration* between cognitive, sensory, affective and motor systems is critical for our understanding of human cognition and behavior.

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Chapter 2

The Representation of Action
Insights from Bimanual Coordination

ABSTRACT

The motor program concept, emphasizing how actions are represented, helped bring the study of motor control into the realm of cognitive psychology. However, interest in representational issues was in limbo for much of the past 30 years during which the focus was on biomechanical and abstract accounts of the constraints underlying coordinated movement. We review recent behavioral and neuroscientific evidence that highlight multiple levels of constraints in bimanual coordination, with an emphasis on work demonstrating that a primary source of constraint arises from the manner in which action goals are represented.

KEYWORDS—*bimanual coordination; action representation; motor control*

The study of bimanual coordination has played a prominent role in psychological and neuroscientific investigations of action. Motivated by ecological considerations, bimanual tasks were introduced in the late 1970's in response to a motor control literature built upon simple key-pressing tasks that focused on reaction time. Observation of daily life readily demonstrates that most actions are much more complex and require the integrative coordination of both hands.

Early studies with bimanual tasks pointed to fundamental limitations underlying the planning and execution of complex movements. This work led to models of motor control that emphasized that action planning was not disembodied, but rather occurred within a set of constraints imposed by a physical system, one with a particular biomechanical and neural architecture (Turvey, 1990). The role of representational issues, central to cognitive psychology, was de-emphasized.

This decade, however, has seen the pendulum swinging back the other direction, with a resurgence of interest on representational issues in action planning and control. This work has emphasized limitations in our ability to concurrently perform independent actions with the two hands. Indeed, many of the constraints identified in the bimanual coordination literature may arise because the tasks do not actually promote coordinated use of the two limbs; rather, these tasks are performed optimally if the two limbs are controlled independently, and it is limitations in our ability to assert independent control that is highlighted by difficulties in producing bimanual actions. Consider the childhood challenge of patting the head with one hand while simultaneously rubbing the stomach with the other. The conflict experienced here is due to cross-talk developing between the trajectory signals directed to the two hands—the trajectory of each hand becomes more like that of the other, a phenomenon called spatial coupling.

An important point to emerge from this recent work is that limitations in bimanual coordination are highly sensitive to how the action goals are represented. This has fueled a debate concerning whether bimanual coordination is constrained *purely* by factors of perceptual or motor origins (Mechsner, Kerzel, Knoblich, & Prinz, 2001). An intermediate position is developed by considering how coordination reflects the *interaction* of cognitive, sensory and motor constraints. Our goal in this paper is to highlight behavioral and neuroscientific evidence suggesting that bimanual coordination and interference depend critically on how these actions are represented at multiple levels.

The importance of action representation in understanding movement coordination

As noted above, people are quite limited in their ability to produce complex bimanual movements that require asymmetric movements of the two limbs. However, Mechsner et al. (2001) provided a compelling demonstration that people can readily learn to produce bimanual circular movements in which one hand produces four cycles to the other hand’s three cycles when the goal of the action emphasizes sensory consequences that entail a simpler representation. With vision of their arms precluded, participants rotated cranks that moved visible flags. By using a gear system, the flags rotated at the same speed when the hands maintained a 4:3 ratio. Under these conditions, participants quickly mastered a movement pattern that would be seemingly impossible if the instructions had focused on the movements of the two hands. Similarly, Rosembaum et al. (2006) reported that people are able to move the hands with relative independence under external sensory guidance. Participants tracked two objects by lightly placing their fingertips on the objects. Even though the trajectories of the objects were independent, the participants were easily able to perform this task, something that would be severely limited if participants had been asked to produce the movements without external guidance.

In a similar vein, Diedrichsen et al. (2001; also Ivry, Diedrichsen, Spencer, Hazeltine, & Semjen, 2004) observed that constraints observed in planning bimanual actions are strongly influenced by how the actions are cued. When simultaneously reaching to two targets, participants are slower to initiate movements when they require asymmetric trajectories compared to when they require symmetric trajectories (**Figure 1**). These effects have been interpreted in light of the idea that movement planning is facilitated when actions are symmetric. However, a critical difference between most laboratory studies of bimanual reaching and ecological actions is that in the former, the required actions are usually specified symbolically; for example, letters might indicate the target location for each hand or a translation is required from a space specified on the computer screen to the workspace for the actions. To evaluate these factors, a series of experiments compared symbolic and spatial cues. For spatial cues, stimuli directly specified target location. The movements themselves were essentially identical for both types of cues. Nonetheless, the reaction time cost observed on trials requiring incompatible trajectories was dramatically reduced with spatial cues, suggesting that the translation from symbolic cues to their associated responses accounts for most of the cost (Diedrichsen, Grafton, Albert, Hazeltine, & Ivry, 2006; 2001). In most studies, a small cost is evident on trials requiring incompatible trajectories, independent of the manner in which the actions are cued (Heuer & Klein, 2006). However, this effect is considerably smaller than that found when actions are symbolically cued.

These recent developments emphasize that a principle source of constraint in bimanual coordination is related to how the task goals are conceptualized. This cognitive emphasis contrasts with earlier perspectives that focused on limitations in motor programming and execution. With external sensory guidance or with spatial cues, minimal interference is evident under conditions that would lead to severe cross-talk with internally-guided or symbolic-cued movements (e.g., simultaneously drawing a U and C, see Ivry, et al., 2004). We propose that the manner by which actions are cued before movement initiation, as well as how they are guided during movement, can lead to radically different representations of the action goals. The pronounced difficulty observed when people produce non-symmetric movements reflects interference arising from how the objectives of the task goals are conceived. Indeed, this form of interference is quite similar to that observed in traditional dual-task studies, suggesting that a primary source of constraint reflects limitations in processing resources or cross-talk associated with response selection and feedback processing. By this view, response selection and online control of bimanual actions are minimally taxed when the actions are directly specified or conceptualized to focus on a simplified sensory goal.

Neuropsychological evidence of a central locus of bimanual coupling and interference

Given our argument that abstract representations of action goals are the prime source of constraint in bimanual coordination, we would expect these constraints to be operative even in extreme situations in which the actual movements or sensory consequences of the movements are absent. Studies with neurological patients have provided a unique opportunity to explore these issues, and have provided mechanistic evidence in favor of a central locus for bimanual interference and spatial coupling. Franz and Ramachandran (1998) examined "bimanual" coordination in patients with upper limb amputation. Patients had vivid phantom limbs, reporting that they not only sensed the position of the limb, but were capable of volitionally “moving” the phantom appendage. While drawing a straight line with the intact arm, patients were asked to “move” the phantom arm in a straight line or in a circular motion. As measured by the performance of the intact arm, the amputees showed interference in the spatially-incompatible condition.

More recently, Spencer et al (2005) tested functionally deafferented patients on a bimanual circle drawing task. These patients exhibit severe loss of somatosensation and proprioception. Nonetheless, their movements remained strongly coupled and exhibited increased interference when movements were asymmetric compared to when they were symmetric, even when vision was precluded. Unlike control participants, the patients exhibited large movement variability and asymmetry; for example, the two circles differed in size. However, the interactions between the abstract goals of the two movements, as expressed by the degree of spatial coupling, remained unaffected. Taken together with the amputee study, this work underscores that bimanual interference is not critically dependent on processes that arise from the periphery, an idea consistent with the representational view developed from behavioral studies with healthy individuals.

While the preceding work has focused on excluding possible mechanisms underlying spatial coupling, studies with split-brain patients have helped point to the neural locus of bimanual interference found in neurologically-healthy individuals. Remarkably, even with symbolically-cued actions, split-brain patients are able to produce spatially-incompatible trajectories with no interference (Franz, Eliassen, Ivry, & Gazzaniga, 1996). Moreover, the movements of the two hands can be essentially independent of one another (Kennerley, Diedrichsen, Hazeltine, Semjen, & Ivry, 2002). These results indicate that bimanual interference in neurologically healthy individuals arises from interactions involving callosal communication between the cerebral hemispheres.

Functional imaging insights into action representation

As reviewed above, the manipulation of task goals can produce dramatic changes in performance, suggesting that goal conceptualization can lead to qualitatively different forms of action representation. Functional imaging methods have provided converging evidence in support of this hypothesis, showing that patterns of neural activation can show marked changes as the task goals are varied, even when the actual movements are quite similar. One theme has been to compare actions that are internally generated to those that are externally guided. Debaere et al (2003) asked participants to perform coordinated flexion and extension of the wrists. Participants in the internally-generated condition performed the task with their eyes closed and participants in the externally-guided condition received online visual feedback in the form of a single cursor that indicated the degree of interlimb coordination. Externally-guided movements elicited increased activation in premotor and superior parietal areas. In contrast, internally-generated movements elicited increased activations in basal ganglia, anterior cingulate, and inferior frontal and parietal cortices. Because interference was attenuated when visual feedback was present, the different activation patterns could be related to processes associated with internal or external control, or processes underlying bimanual interference and spatial coupling.

Diedrichsen et al (2006) adopted a different approach, contrasting symbolically- and spatially-cued movements. This manipulation allowed the identification of brain activations related to: (i) the mapping of symbolic cues onto associated movements, (ii) goal-selection conflict that arises when this mapping operation requires the generation of incompatible movement trajectories, and (iii) movement-related conflict generated by incompatible movement trajectories, independent of cue type.

In comparison to conditions in which movements were cued spatially, symbolically-cued movements were associated with a large increase in activation across the extent of intraparietal sulcus (IPS), as well as increases in inferior parietal, premotor and inferior frontal cortex, all in the left hemisphere (**Figure 2**).

Interestingly, activation of the middle and posterior aspect of the left-hemisphere IPS was evident even during unimanual movements produced with the left hand. These results suggest a critical role for the left-hemisphere parietal lobe in actions that require the translation of symbolic stimuli into actions. Similar activation patterns are observed when people manipulate tools with either the left or right hand, observe other individuals using tools, or produce and comprehend abstract gestures (Johnson-Frey, 2004). Thus, the left-hemisphere role in praxis may be related to a specialization for representing action goals at an abstract level, rather than the specification of particular movement parameters.

When the symbolic cues indicated incompatible movements, the condition that leads to goal-selection conflict, an increase in activation was observed in anterior cingulate cortex and pre-supplementary motor area. Across a range of tasks, these medial frontal areas have been associated with conflict sensitivity and the modulation of cognitive and motor effort (Paus, 2001). Thus, we again see that constraints associated with bimanual coordination may reflect more general processes rather than be specific to action planning and control.

Movements requiring incompatible trajectories were associated with greater activation in posterior superior parietal lobule, a region linked to movement planning in extrinsic coordinates. Interestingly, this effect was similar for the symbolic- and spatial-cueing conditions, despite the fact that the RT increase was very small in the latter condition. Thus, the neuroimaging data point to both cognitive and motoric levels of constraint.

Motor output, where it all converges

Based on the preceding discussion, one might assume that, when the task goal is appropriately conceptualized, the motor signals themselves impose minimal constraint. However, a body of neurophysiological evidence indicates that there is a bias to simultaneously activate homologous muscles of the two limbs. For example, during unimanual movements, transcranial magnetic stimulation (TMS) of the motor cortex reveals modulation in the excitability of motor pathways of the quiescent hand (Carson et al, 2005).

The reaction time cost observed in asymmetric bimanual movements may be the sum of independent processes, one associated with low-level interactions associated with motor execution and a second associated with higher-level planning processes. Alternatively, higher-level processes associated with action planning may interact with the motor system, leading to modulations in the degree of interference and coupling. Carson et al (2005) showed that when a volitional movement with one arm was externally guided by visual feedback, the modulation of excitability of the quiescent arm was reduced compared to when the volitional movement was internally guided.

Based on the studies reviewed here, we postulate that there are two primary levels of interference underlying bimanual movements (see Carson & Kelso, 2004). In the first level, interference occurs when incompatible responses have to be planned and executed. This interference accounts for a small reaction time cost and is likely due to increased planning demands related to asymmetric target specification represented in posterior parietal cortex. The second level of interference, which accounts for the majority of the interference and spatial coupling, occurs when independent responses of each hand need to be planned and executed, and the goals of the task need to be transformed from abstract codes into movement plans. Based on the finding that the process of translation from symbolic cues to actions plans is lateralized to one (left) hemisphere, we propose that this source of interference reflects the operation of a common processor that is engaged for each of the two actions. Interestingly, it appears that split-brain patients are not subject to this constraint: for these individuals, each hemisphere is capable of performing this translation process in parallel (Hazeltine, A., & Ivry, in press). This capability either reflects a functional reorganization following callosotomy or the operation of a more conservative strategy in the intact brain, perhaps ensuring the overall behavior remains coherent (Meyer & Kieras, 1997).

Such constraints are not specific to motor control, but rather reflect general properties of our cognitive architecture. Consistent with this hypothesis, the conflict observed in many studies of bimanual coordination engage the anterior cingulate, similar to what is observed in many cognitive tasks (Bush, Luu, & Posner, 2000). Anterior cingulate activation would in turn project bilaterally to motor areas in both hemispheres, increasing the degree of bimanual coupling (Carson & Kelso, 2004; Carson, et al., 2005). This view is consistent with evidence showing that activity in the anterior cingulate during unimanual and bimanual movements is correlated with the size of the corpus callosum in healthy individuals (Stancak, Cohen, Seidler, Duong, & Kim, 2003).

Final comments

In large part, bimanual coordination emerged as a model system in the field of motor control as an ecologically-motivated alternative to the simple laboratory tasks that dominated initial forays to understand the representational basis of action planning. The work reviewed here suggests that well-studied phenomena such as spatial coupling likely reflect, in large part, more general constraints that limit our ability to perform multiple tasks simultaneously (Ivry et al., 2004). This conclusion is drawn from the integration of behavioral and neuroscientific evidence suggesting a linkage between studies of bimanual interference and dual-task performance. This has been made transparent by research manipulating how task goals are represented, even when the actual movements are held constant. Importantly, many of the model tasks employed in the motor control literature are such that optimal (i.e., constraint-free) performance requires the independent control of the two limbs. However, our everyday behavior generally entails situations in which the hands work together to achieve a common goal, even if the two gestures are quite distinct. For example, in opening a jar, one hand stabilizes the object while the other twists the lid. Tasks in which the two hands are used in a cooperative manner have not received sufficient attention in the psychological and neuroscientific literatures. The issues discussed here are likely to prove even more pertinent for these tasks given the unitary nature of the goal representation.

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FIGURE LEGENDS

Figure 1 *Symbolically- and spatially-cued reaches performed by participants in the Diedrichsen et al (2006) study*. (**A**) Movements (light gray arrows) were executed forward or sideways. The movements were cued by illuminating the target circle directly (spatial cues) or by letters indicating the movement direction (symbolic cues). Participants were tested in unimanual movements (left or right hand), bimanual movements with symmetric trajectories (both forward or both sideways), and bimanual movements with asymmetric trajectories (orthogonal movements). (**B**) Reaction Times for all of the conditions. Modified from Diedrichsen et al (2006).

Figure 1 *Brain regions activated by the execution of bimanual movements in the Diedrichsen et al (2006) study*. (A) Lateral view of the brain, and (B) Medial view of the brain. Green shaded region denotes the intraparietal sulcus (IPS). SPL: superior parietal lobule, IPC: inferior parietal cortex, IFC: inferior frontal cortex, PMC: premotor cortex, ACC: anterior cingulate cortex. When compared to spatially-cued movements, symbolically-cued movements elicited increased activity in IPS, IPC, IFC and PMC, all lateralized to the left-hemisphere. When compared with symmetric movements, movements with asymmetric trajectories elicited increased activity in SPL in both hemispheres. The combination of symbolic cue and asymmetric trajectory elicited increased activity in ACC. Figure altered from work originally produced by Patrick J. Lynch and C. Carl Jaffe, licensed through the Creative Commons Attribution 2.5 License 2006.

Figure 1

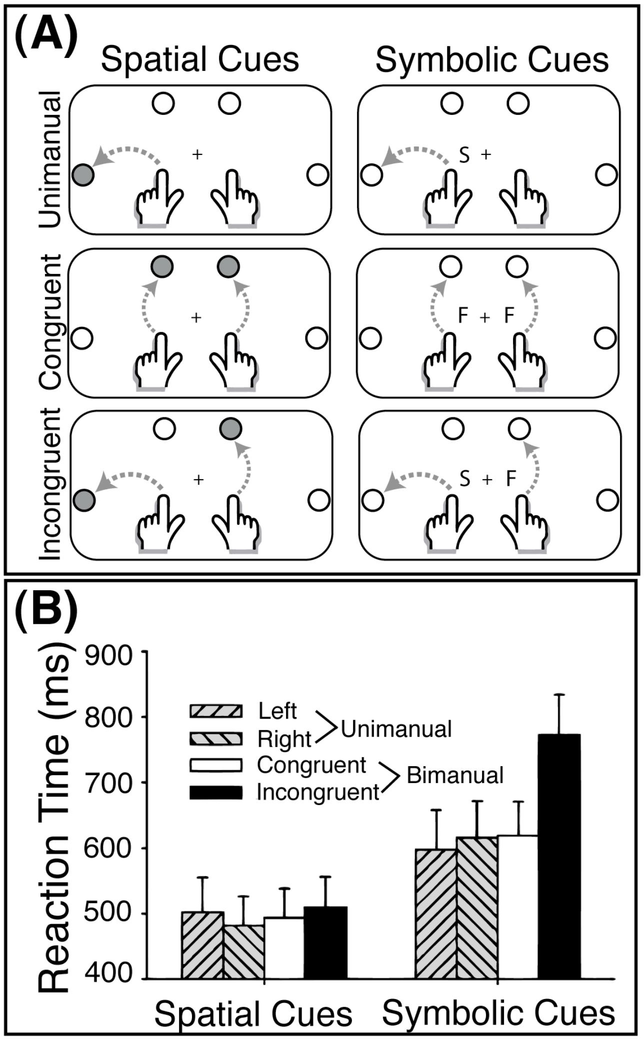
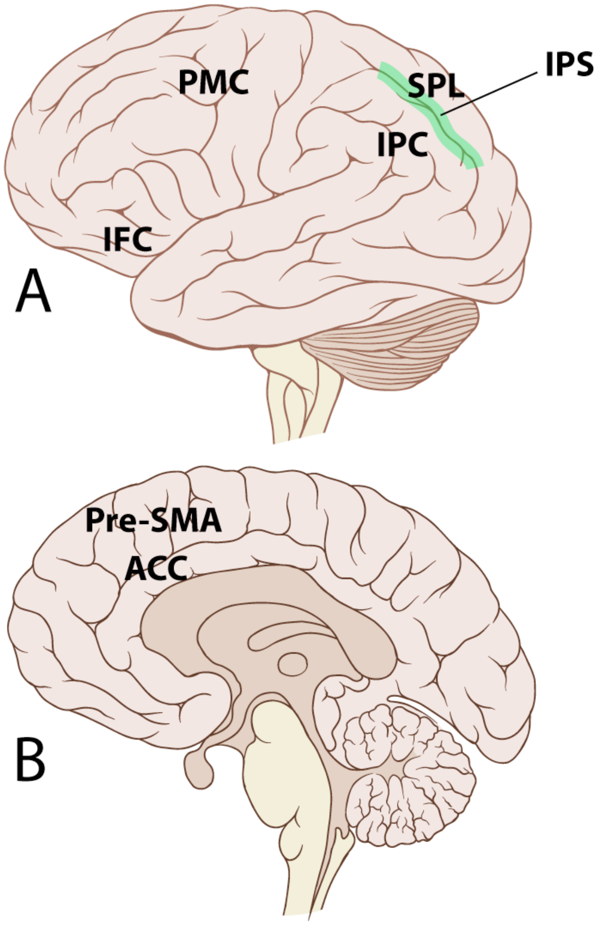

(A)
Spatial Cues
Symbolic Cues
Unimanual
Congruent
Incongruent
S +
F + F
S + F
(B)
Reaction Time (ms)
900
800
700
600
500
400
Left
Right
Unimanual
Congruent
Incongruent
Bimanual
Spatial Cues
Symbolic Cues

Figure 2



Chapter 3

Transcranial magnetic stimulation of posterior parietal cortex affects decisions of hand choice

ABSTRACT

Deciding which hand to use for an action is one of the most frequently made decisions as humans interact with the environment. Here we show behavioral and transcranial magnetic stimulation (TMS) evidence that decisions of hand choice in reaching arise through the resolution of a competitive process that involves the parallel activation of action plans for each of the hands. TMS to left posterior parietal cortex (PPC) disrupted this competitive process leading to an increase in left hand reaches in a free choice paradigm. These results provide causal evidence that the PPC is involved in decisions of hand choice and indicate that motor planning is initiated before response selection is made. This suggests that action selection does not emerge from a discrete serial process but can instead be viewed as a dynamic process that continuously changes as a product of the interaction with the environment.

Interacting with the world requires continuously making decisions about possible courses of action. While many of these decisions happen seamlessly, they are the product of complex computations that take multiple factors into account. Consider the relatively simple decision of which hand to use to press an elevator button. This decision does not require much conscious thought, but it is influenced by a host of factors such as past experience, the current context and the spatial location of the button with respect to the hands.

A central goal of psychologists and neuroscientists has been to understand decision-making. To this end, considerable attention has been given to the study of perceptual decisions. In many studies, participants decide which category best describes a perceptual stimulus while researchers record single cell activity in monkeys (Churchland, Kiani, & Shadlen, 2008; Ditterich, Mazurek, & Shadlen, 2003; Gold & Shadlen, 2007; Hanks, Ditterich, & Shadlen, 2006; Kiani, Hanks, & Shadlen, 2006; Romo, Hernandez, & Zainos, 2004; Romo, Hernandez, Zainos, Lemus, & Brody, 2002; Romo & Salinas, 2003; Yang & Shadlen, 2007) or hemodynamic responses in humans (Heekeren, Marrett, Bandettini, & Ungerleider, 2004; Heekeren, Marrett, & Ungerleider, 2008; Tosoni, Galati, Romani, & Corbetta, 2008). Other studies have looked at motor-related decisions; for example, when an animal is to reach to one of multiple targets (Cisek & Kalaska, 2005; Pesaran, Nelson, & Andersen, 2008) or when a response can be produced with either a hand or eye movement (Cui & Andersen, 2007; Quian Quiroga, Snyder, Batista, Cui, & Andersen, 2006). Notably, few studies have looked into one of the most fundamental, and indeed, commonplace decisions: which hand should be used to perform an action (Koch, et al., 2006; Taylor, Nobre, & Rushworth, 2007).

Traditional psychological theories postulate that decisions arise through a serial process in which perception, cognition and action are subserved by independent hierarchical processes (Donders, 1969; Marr, 1982; Posner, 1978; Schmidt & Lee, 2005). With respect to hand selection, this traditional approach would postulate that decisions are made at a higher cognitive level and transferred down to the motor system, activating the action plan for the selected hand without ever triggering a competitive motor process between the two hands. This framework stands in contrast to computational and neurobiological studies emphasizing that decision-making can be viewed as a bounded accumulation process (Cisek, 2006, 2007; Link & Heath, 1975; Mazurek, Roitman, Ditterich, & Shadlen, 2003; Tosoni, et al., 2008). In the context of hand selection, a bounded accumulation model would predict that information is accumulated inducing neural activity in favor of each of the hands. Once activity in favor of one of the hands reaches a threshold, this hand is selected and the accumulation of activity in favor of the competing hand is suppressed or terminated, triggering a single response. This view emphasizes that decisions are made through an integrative parallel process that binds perception, cognition and action (Cisek, 2001, 2007; McKinstry, Dale, & Spivey, 2008; Spivey & Dale, 2006; Spivey, Grosjean, & Knoblich, 2005; Tosoni, et al., 2008).

Converging lines of evidence support the idea that decisions about action selection emerge through parallel activation of competing action plans. One source of evidence comes from the 'alien hand syndrome' in which patients appear to lose conscious control over the alien limb. In some cases, patients may inadvertently produce reaching movements with both hands, even when instructed to use only one hand (Espinosa, Smith, & Berger, 2006). This syndrome may be the result of an impairment in resolving the competition between multiple action plans that have been activated in parallel; alien-hand syndrome is commonly observed in patients with lesions or resection of the corpus callosum, interrupting the major pathway of communication between the cerebral hemispheres (Scepkowski & Cronin-Golomb, 2003). Another striking evidence for parallel planning comes from a study showing the inadvertent production of multiple pre-cued movements following the presentation of an unexpected startling sound (Carlsen, et al., 2009).

Several studies point to a critical role for the posterior parietal cortex (PPC) in decision processes for hand selection, at least for reaching. Lesions of the parietal lobe can result in optic ataxia, a condition in which patients show impairments in visually-guided reaching with the contralesional hand (Karnath & Perenin, 2005; Perenin & Vighetto, 1988). Neurophysiological studies with monkeys (Buneo, Jarvis, Batista, & Andersen, 2002; Calton, Dickinson, & Snyder, 2002; Scherberger & Andersen, 2007; Snyder, Batista, & Andersen, 1997, 2000) and neuroimaging studies with humans (Astafiev, et al., 2003; Connolly, Andersen, & Goodale, 2003; Culham, Cavina-Pratesi, & Singhal, 2006; Tosoni, et al., 2008) also emphasize a critical contribution of parietal lobe in reach planning. Indeed, the functional term 'parietal reach region', has been coined to highlight the importance of a subregion of the PPC in reaching.

While the activity in the PPC is stronger in the hemisphere contralateral to the selected hand, numerous studies have also reported bilateral activations during reaching movements (Beurze, de Lange, Toni, & Medendorp, 2007; Connolly, et al., 2003; Diedrichsen, et al., 2006; Medendorp, Goltz, Crawford, & Vilis, 2005). This bilateral activation may point to parallel planning of responses or bilateral contributions to preparatory processes.

While the studies mentioned above suggest that a competitive parallel process, possibly involving PPC, supports the decision of hand choice in manual reaches, definitive evidence is lacking. Here we developed a new paradigm to investigate this decision process. Participants were asked to reach with one hand to a visual target that appeared at a variable location on a semi-circular array. In different blocks, the required hand was either pre-determined (left hand only or right hand only) or based on the participant's choice. In the latter condition, we were able to identify targets where uncertainty was minimal (i.e., the participant always used the same hand) and where uncertainty was maximal (i.e., the participant had close to an even split between using the right and left hand). Consistent with the predictions from a competitive bounded accumulation model(Churchland, et al., 2008; Gold & Shadlen, 2007; Mazurek, et al., 2003; Uchida, Kepecs, & Mainen, 2006), we found that RTs were slower under increased uncertainty.

The results from this behavioral study are consistent with neuroimaging, neurophysiology and neuropsychological evidence suggesting that hand selection might emerge through a competitive accumulation process, in which activity in PPC represents a decision variable—the quantity that reflects the likelihood of one hand being chosen over the other (Gold & Shadlen, 2007; Heekeren, et al., 2008). However, it is possible that these observations simply reflect an association between activations in bilateral PPC and hand choice. A causal role of the PPC in hand selection and the competitive nature of this process have not been directly established. To this end, we conducted a second experiment using transcranial magnetic stimulation (TMS) to disrupt the function of the PPC shortly after the presentation of the reach target. We assumed that the TMS pulse would disrupt the accumulation process associated with preparing a reach with the contralateral hand. As such, we hypothesized that if PPC activity influences hand choice, the TMS pulse would alter this decision process. Moreover, we hypothesized that if action plans for each hand go into competition with the winner triggering a response, disrupting the activity of PPC in one hemisphere should lead to an increase in the probability that the reach would be performed with the hand ipsilateral to the stimulation site. Based on evidence suggesting asymmetrical PPC activations during manual reaches, with stronger left hemisphere activations (Diedrichsen, et al., 2006; Johnson-Frey, 2004; Serrien, Ivry, & Swinnen, 2006) and evidence suggesting asymmetric functional organization between right and left PPC (Perenin & Vighetto, 1988; Vesia, Monteon, Sergio, & Crawford, 2006), we predicted that the effects of TMS might also be asymmetrical.

RESULTS

Experiment 1: The effect of hand competition on response preparation

In Experiment 1 we asked participants to perform unimanual reaches as fast and as accurately as possible under three different conditions. For two of those conditions (RIGHT-ONLY and LEFT-ONLY), the response hand was pre-determined and fixed for the entire block of trials. For the third condition (CHOICE), participants were free to use either hand on each trial, with the constraint that they were to respond as quickly as possible. Given the semi-circular array of targets (Figure 1b), it was possible to construct a psychometric function of hand preference for each participant. As is shown in Figure 2, hand choice followed a sigmoidal pattern across targets, switching from left hand preference to targets in the left side of space, to right hand preference to targets in the right side of space. Fitting this response pattern with logistic regression, we estimated the point of subjective equality (PSE)—the virtual point in target space where participants would have an equal probability of using the right or the left hand for the reach (Figure 2). The mean PSE was slightly to the left of the physical center between targets 4 and 5 (4.63), which indicates that participants more often reached with their right hand for central targets.

As a measure of response preparation, we recorded reaction time (RT). We then separately averaged the RTs for reaches to extreme targets (i.e., the two outermost targets in the target array—Targets 1 and 10 on Figure 2) and to the two targets surrounding the PSE, determined for each participant. We further separated the RTs by hand choice condition. For the analysis we combined the RIGHT-ONLY and LEFT-ONLY conditions to create a single condition for trials in which the hand was pre-determined. The results showed a main effect of condition (p = .0005). RTs were longer in the CHOICE condition (423 ms) than in the pre-determined condition (400 ms), showing an overall cost of having to choose which hand to use. For the pre-determined condition we found that RTs were faster for the targets around the PSE—which was determined in the CHOICE condition—than for the extreme targets (*p* = .019; Figure 3). This is likely due to increased deployment of attention to the center of the visual space. This attentional strategy would be optimal since it minimized the average distance from the center of attention to any of the targets, which were equally probable but randomly selected. Interestingly, this pattern of results was reversed when we looked at the RTs for the CHOICE condition. In this condition, the RTs were significantly longer for the targets around the PSE than for the extreme targets (*p* = .0024; Figure 3). We interpreted this finding as indicating that, for locations where ambiguity in hand choice is maximal, an increase in competition between action plans for each hand leads to a slow down in RT.

Experiment 2: TMS to left PPC influences hand choice

In Experiment 2 we sought to investigate the causal contribution of PPC in hand selection. Moreover, we sought to directly test the hypothesis that hand choice arises through a competitive parallel process. To this end, we applied single pulse TMS over the PPC with the goal of influencing hand selection. Participants performed unimanual reaches following the same procedures as in the CHOICE condition in Experiment 1. In separate blocks of trials, single pulse TMS was administered over the PPC of the right (TMS_RH) or left (TMS_LH) cerebral hemispheres. TMS was applied 100 ms after the target onset, with the stimulation intensity set to 120% of the passive motor threshold. We also included blocks in which TMS was not administered (noTMS). Anatomical magnetic resonance images were used to identify the target stimulation regions for each participant. The scalp location representing the caudal part of the intraparietal sulcus, just anterior to the parieto-occipital sulcus, of each hemisphere was identified using a stereotaxic localization system (Figure 4). We based our stimulation location on neuroimaging evidence showing that this region is consistently activated during reach planning (Astafiev, et al., 2003; Beurze, et al., 2007; Connolly, et al., 2003; Medendorp, et al., 2005; Tosoni, et al., 2008).

Similar to Experiment 1, we compared RTs for targets around the PSE to extreme targets, collapsing across TMS conditions. Replicating the effect found in Experiment 1, we observed longer RTs for targets around the PSE (400 ms) compared to extreme targets (388 ms, *p* = .001; Figure 5a). To further assess the effect of competition between the hands on RT, we compared RTs for each TMS condition. TMS led to marginally reliable increases in RT (TMS_LH: 392 ms, *p* = .0752; TMS_RH: 394 ms, *p* = .0703) compared to the noTMS condition (386 ms). Although this increase may be related to non-specific effects of TMS, it is also consistent with the hypothesis that disruption of PPC activity slowed down processes related to response preparation.

To test whether TMS influenced hand choice, we calculated the probability of right and left hand movements under the three TMS conditions. Collapsing over all target locations, TMS to left PPC, but not right PPC, led to an increase in the use of the hand ipsilateral to the stimulation site (Figure 6). Participants had a 4% increase in left-hand use in the TMS_LH condition relative to the noTMS condition (*p* = .0244) and a 5.7% increase relative to the

TMS_RH condition (*p* = .0137, Figure 6a). Since we expected the effect of TMS to be maximal over the location of greatest ambiguity—or hand choice competition, we used logistic regression to estimate the change in hand use at the location representing the PSE for the noTMS condition. Consistent with our expectation, the TMS_LH condition led to a 12.6% predicted increase in left-hand use relative to the noTMS condition (*p* = .0459) and a 13.9% predicted increase relative to the TMS_RH condition (*p* = .0244, Figure 6b). To further investigate the effect of TMS on hand choice, we compared the PSE location for each TMS condition. Consistent with what we found in Experiment 1 (Figure 2), the mean PSE for the noTMS condition was slightly to the left of the physical center between targets 4 and 5 (4.36). The TMS_LH condition led to a significant shift in the PSE of 0.14 target units to the right of the noTMS condition (*p* = .0371) and a shift of 0.16 target units to the right of the TMS_RH condition (*p* = .0137, Figure 6c).

Given the role of the parietal lobe in spatial attention (Desimone & Duncan, 1995), it is important to consider whether the effects of TMS were related to disruptive effects on attentional processes rather than on competitive response-related processes. If TMS produced a transient form of contralateral extinction (Walsh, Ellison, Ashbridge, & Cowey, 1999), then one would expect a selective increase in RTs for targets in the visual hemifield contralateral to the stimulated site. RTs to targets in the right visual hemifield were faster than to targets in the left visual hemifield (388 ms vs. 399 ms, *p* = .0499). This is likely due to the decreased ambiguity in hand choice for right hemifield targets, as well as the fact that a greater percentage of reaches were performed with the (right) hand ipsilateral to that hemifield, a situation in which visual input and motor output are associated with the same cerebral hemisphere (Barthelemy & Boulinguez, 2002). However, this visual field difference was not influenced by the TMS condition (*p* = .3109), arguing against an attentional account (Figure 5b).

DISCUSSION

The current results shed light on the mechanisms involved in selecting which hand to use when making a manual reach. This fundamental decision process appears to involve a competition between action plans associated with each hand. In Experiment 1, RTs were longer when participants made unimanual reaches to regions of space where ambiguity about hand choice was maximal compared to regions of space where ambiguity was minimal. This result suggests that the increased competition associated with ambiguous targets entails longer preparation processes, consistent with the predictions of bounded accumulation models (Churchland, et al., 2008; Gold & Shadlen, 2007; Mazurek, et al., 2003; Uchida, et al., 2006). According to these types of models, decisions arise through the accumulation of information associated with each candidate choice. When accumulated activity reaches a threshold, a response is elicited and terminates the accumulation process. Previous work on such models focused on perceptual decisions (Gold & Shadlen, 2007; Heekeren, et al., 2004; Heekeren, et al., 2008; Mazurek, et al., 2003; Tosoni, et al., 2008) or on decisions about which target to reach to with a pre-determined hand (Cisek, 2006, 2007). We extend this literature by showing that similar processes appear to govern decisions about hand choice.

Multiple mechanisms might lead to longer RTs under situations of increased competition between the hands. One possibility is that longer RTs are the result of mutual inhibition between the activated action plans for left and right hand reaches. Another possibility is that under situations of increased uncertainty, an accumulation process might start at a lower level of activity (Churchland, et al., 2008) and/or involve slower rates of accumulation (Gold & Shadlen, 2007; Mazurek, et al., 2003; Roitman & Shadlen, 2002). The modulation of uncertainty could reflect competitive processes or the greater distribution of neural accumulation between possible responses. A third possibility is that the threshold of activity necessary to trigger a response is elevated under situations of increased uncertainty, a mechanism that can improve the accuracy of the choices (Churchland, et al., 2008; Gold & Shadlen, 2007; Mazurek, et al., 2003). Those possibilities are not mutually exclusive. All predict that neural accumulation under increased competition should take longer to reach the threshold necessary to elicit a manual reach.

In Experiment 2 we sought to directly test the hypothesis that hand choice arises through a competitive parallel process by attempting to disrupt this process with TMS. We targeted the PPC, a region that has been frequently associated with reach planning by neuroimaging studies (Astafiev, et al., 2003; Beurze, et al., 2007; Connolly, et al., 2003; Medendorp, et al., 2005; Tosoni, et al., 2008). Previous TMS studies had implicated more anterior regions of the human PPC in reach and grasp correction (Desmurget, et al., 1999; Tunik, Frey, & Grafton, 2005), suggesting a role of PPC in *reactively* updating sensorimotor representations (Rushworth & Taylor, 2006). To the best of our knowledge, the present study is the first to provide causal evidence that the human PPC is *proactively* involved in the process of deciding which hand will be used for a manual reach. By directly affecting the decision process with TMS, we also extend to humans and to decisions of hand choice, the findings of a microstimulation study in monkeys establishing a causal role of PPC in perceptual decision-making (Hanks, et al., 2006). In the present study, TMS to left PPC changed participants' hand preference, producing an increase in left hand use.

We did not observe a change in hand use when the stimulation was directed to right PPC. At the outset, we predicted that there might be asymmetries between the two cerebral hemispheres. However, we did not specifically predict the absence of an effect with right PPC stimulation. Nevertheless, we offer three possible explanations for this result. One possibility is that right PPC is also involved in the competition process, activating the action plan for right hand reaches, but limitations in our experimental procedures led to the absence of a detectable effect. Neuroimaging studies generally show smaller reach-related activity in right PPC compared to left PPC (Diedrichsen, et al., 2006; Johnson-Frey, 2004; Serrien, et al., 2006). Assuming that these differences reflect the cortical extent of PPC areas involved in reach planning, the disruptive effects of TMS are likely to be attenuated even if this area is also involved in the competition process. It is also possible that the absence of an increase in right hand use following TMS to right PPC is due to the fact that our right-handed participants already showed a strong bias to use their dominant hand, thus leaving little room for an increase.

Another intriguing possibility is that the left PPC is involved in planning reaches for both hands (Kroliczak & Frey, 2009) but the right PPC is only involved in planning reaches for the right hand. Given such an asymmetry, TMS of right PPC would not lead to observable changes in hand preference because left PPC would be able to compensate for the deficient right PPC. This account of the asymmetry is analogous to the attention competition hypothesis for the effects of parietal lobe lesions in unilateral neglect, where it has been proposed that the right parietal lobe is involved in directing attention to both visual fields whereas the left parietal lobe is limited to directing attention to the right visual field (Mesulam, 1981).

A third more extreme possibility is that the decision process is restricted to the left PPC. According to this possibility left PPC represents the accumulation of a decisions variable by integrating the *difference* between evidence in favor of the right and left hands. A decision would emerge when activity would reach either a low or a high threshold representing a decision for a left or right hand reach, respectively. TMS to left PPC would bias the selection process in favor of left hand responses given the assumption that the TMS pulse attenuates or reduces the signal-to-noise ratio of neural activity in the targeted area.

If there is indeed a form of specialization for left PPC in decisions of hand choice, this could be mirrored in right PPC, only for a different type of decision. Recent studies with patients with PPC lesions (Coulthard, Nachev, & Husain, 2008) and TMS studies with healthy individuals (Vesia, et al., 2006; Vesia, Yan, Henriques, Sergio, & Crawford, 2008) have suggested that right PPC might have a specialized role in decisions about movement direction akin to what we found for left PPC in decisions of hand choice.

One concern with the present approach is that the baseline was based on a condition without TMS (noTMS) rather than a sham TMS condition in which the pulses are applied to a region presumed to not be involved in the task at hand. This raises the possibility that the observed shift in hand use might be related to unspecific effects of TMS. Two pieces of evidence argue against this hypothesis. First, we only found a change in hand choice in the TMS_LH condition. If unspecific TMS effects were responsible for such result, then we would have expected a similar effect in the TMS_RH condition. Indeed, the absence of any effect in the TMS_RH condition makes this condition effectively serve as a TMS control for the TMS_LH condition. Second, a separate study from our laboratory employed similar procedures but targeted TMS over premotor cortex. No changes in hand choice were observed with either left or right hemisphere stimulation (Konkle et al., 2005, *Society for Neuroscience Abstracts*).

We have also considered whether the TMS effects reflect a disruption of attentional processes rather than hand selection per se. While parietal TMS has been found to produce transient impairment in processing visual targets (Walsh, et al., 1999), an attention-based account is not consistent with the present RT results. We found no interaction between the hemisphere of stimulation and target visual hemifield, which suggests that the critical effect of TMS was on hand selection in reach planning and not on attentional or lower level perceptual processing. We recognize that one has to be careful in interpreting null results. Nonetheless, our interpretation is consistent with evidence from single cell recordings in monkeys showing that PPC activity was more predictive of movement intention than the locus of attention (Quian Quiroga, et al., 2006), from human neuroimaging showing that PPC was strongly responsive to arbitrary stimulus-response associations but only weakly responsive to the perceptual properties of stimuli (Tosoni, et al., 2008) and from TMS in humans showing that disruption of PPC function had an effect in motor but not visual coordinates in reach planning (Vesia, et al., 2006; Vesia, et al., 2008).

In summary, the current results provide strong evidence that decisions of hand choice involve a process that resolves a competition arising from the parallel activation of action plans for both hands. Serial models in which hand choice is made at a higher cognitive level without activation of action plans for both hands might have predicted an increase in RT with TMS but can not account for the shift in hand use. Rather, the results indicate that motor planning is initiated before response selection is made (Cisek, 2006, 2007), which contradicts longstanding cognitive psychology (Donders, 1969; Marr, 1982; Posner, 1978) and motor control (Schmidt & Lee, 2005) theories. This finding highlights that decisions on how to interact with the environment are not necessarily made discretely by a higher-order center (a homunculus). Instead, the emergence of decisions and actions can be viewed as a dynamic process in which many possible motor responses are competing at any one time, and the accumulation of evidence in favor of the execution of any candidate response continuously changes as a product of the interaction with the environment itself (Cisek, 2001, 2007; McKinstry, et al., 2008; Spivey & Dale, 2006; Spivey, et al., 2005; Tosoni, et al., 2008). In terms of the neural instantiation of these processes, the present results provide further evidence of the role of PPC in the representation of response specific decision variables (Gold & Shadlen, 2007; Hanks, et al., 2006). Previous studies have focused on spatial decisions related to the selection of a target (Cisek & Kalaska, 2005; Romo & Salinas, 2001; Shadlen & Newsome, 2001). Here we have shown that PPC is also involved in decisions related to the selection of an effector, even when the stimulus itself does not specify that information (Cui & Andersen, 2007). While it is likely that a broad network of cortical and subcortical areas are involved in different aspects of decision-making (Heekeren, et al., 2008; Pesaran, et al., 2008), the present results highlight the critical role that PPC has in transforming sensory information into free choices of action (Cui & Andersen, 2007; Pesaran, et al., 2008).

METHODS

Participants

Thirteen healthy members of the UC Berkeley community (6 women, mean age = 19.8 years, range = 18-21 years) participated in Experiment 1 and received course credit for their participation. Ten healthy members of the UC Berkeley community (2 women, mean age = 25 years, range: 21-33 years) participated in Experiment 2 and were paid for their participation. All participants were right-handed and experiment naïve. The protocol was approved by the UC Berkeley Institutional Review Board. Participants provided written informed consent at the start of the test session.

Procedures

Experiment 1

Participants sat in front of a table with their hands comfortably positioned on the table. A horizontal screen was positioned 48 cm above the table surface and a mirror was placed halfway between the screen and the table surface. By projecting the stimuli onto the screen, participants had the impression that the stimuli were presented on the table surface (Figure 1a). A 3D motion tracking system (miniBIRD, Ascension Technology, Burlington, VT, USA) was used to monitor the position of the hands. Sensors (8 x 8 x 18 mm) were placed on the tip of the index finger of each hand, and position information was sampled at 140 Hz. Since the mirror occluded vision of the hands, feedback in the form of two white dots indicated the current position of each hand.

Three circles (4.4 cm diameter) were always visible to participants. Two of these circles indicated the starting location for the hands and were symmetrically positioned 11 cm lateral to the midline. At the start of each trial, participants were instructed to move their fingertips into these circles. A "+" symbol was displayed within the third circle, indicating the visual fixation location. This circle was positioned 11.4 cm from the starting circles.

After the participants had maintained the starting position for a variable period, they were presented with one of three types of trials (Figure 1c). On unimanual trials, a single target circle (4.4 cm) was presented in one of 10 possible locations. These locations were arranged in a semi-circular array at an average distance of 29 cm from the starting circles (Figure 1b). The participant was instructed to reach as quickly as possible to the target location, using one hand. The instructions emphasized that the responses should be initiated and completed as fast as possible in one, smooth movement, and that endpoint errors need not be corrected. In addition to the unimanual reach trials, we also included two types of catch trials. On bimanual-catch trials, two target circles were presented and the participant had to reach to both targets simultaneously, one with each hand. These trials were included to ensure that participants remained ready to respond with both hands, reducing the likelihood that participants might adopt a strategy of always using a single hand. For fixation-catch trials, the "+" in the center of the fixation circle changed to an "x". Participants were required to move both hands into the fixation circle on these trials. The fixation-catch trials were included to ensure that fixation was maintained at the start of each trial. We instructed participants that they were free to move their eyes once a target had been displayed.

Participants were tested in three different conditions: RIGHT-ONLY, LEFT-ONLY, and CHOICE. For the RIGHT-ONLY and LEFT-ONLY conditions, participants were instructed to reach to the targets using only the right or the left hand, respectively (pre-determined conditions). For the CHOICE condition, participants were free to reach with either the left or right hand. Each participant completed 14 blocks of 48 trials each (6 CHOICE, 4 RIGHT-ONLY and 4 LEFT-ONLY), with the order pseudo-randomly assigned. Each block included four unimanual trials for each of the 10 target locations. CHOICE blocks also had four fixation-catch trials and four bimanual-catch trials. RIGHT-ONLY and LEFT-ONLY blocks had eight fixation-catch trials and no bimanual-catch trials.

To increase participants' motivation, we set the experiment up as a game in which participants earned points based on how fast and accurately they performed the reaches and lost points for missing the catch trials. During the rest periods between blocks, we provided participants with feedback indicating their mean movement times during the block, as well as the number of points earned.

Before the start of the test blocks, participants completed two practice blocks of 24 trials each. One of the practice blocks was always assigned to the CHOICE condition and the other practice block was randomly assigned to either the RIGHT-ONLY or the LEFT-ONLY conditions. The order of the practice blocks was randomly assigned.

Experiment 2

At the start of the testing session, the target scalp locations for TMS of the left hemisphere and right hemisphere PPC, as well as the stimulation level were established on an individual basis. We used anatomical magnetic resonance images (MRI) acquired on a 4T Varian scanner to identify the target stimulation location. Using a frameless stereotaxic localization system (Brainsight, Rogue-Research Inc., Montreal, Canada), we identified the scalp location over the caudal part of the intraparietal sulcus (IPS), just anterior to the parieto-occiptal sulcus (Figure 4). This location was marked on a tight-fitting elastic cap for each hemisphere. For setting the stimulation level, we opted to use a criterion based on the motor threshold for the left hand at rest. The motor threshold value was set to the stimulation level that elicited visible movements of the fingers in four of eight TMS pulses. TMS was given with a rapid stimulator configured with an air-cooled figure-8 70 mm coil (The Magstim Company Ltd., Carmathenshire, UK).

For the reaching part of the experiment, the procedures were similar to that of Experiment 1, with the following exceptions. Targets were slightly closer to the starting circles (average distance = 27.8 cm) and only the CHOICE condition was tested. Each participant completed two practice blocks of 36 trials and 12 test blocks of 72 trials each. A test block included six unimanual trials per target location (60 total unimanual trials), six bimanual catch-trials and six fixation-catch trials.

There were three types of blocks: TMS_LH, TMS_RH and noTMS. In the TMS_LH and the TMS_RH blocks, participants received a single TMS pulse at 120% of the motor threshold on every trial. The pulse was applied 100 ms after the onset of the reach target. The timing of the TMS stimulation was based on pilot data. The orientation of the coil was rostro-caudal with the handle pointing caudally. In the noTMS condition and in the practice blocks, participants did not receive TMS. Block order was pseudo-randomly determined such that each of the three conditions occurred once every three blocks.

To increase participants' motivation we used the same point procedures as in Experiment 1 but participants received financial bonuses based on the points they earned.

Analysis and statistics

As a measure of hand preference, we calculated, for each condition, the participants' probability of using the right and left hand for each target. The psychometric function derived from these probabilities was used to calculate the point of subjective equality (PSE), the estimated location at which participants were equally likely to use the right or left hand (Figure 2). We calculated the PSE by fitting a logistic regression curve to the psychometric functions. For Experiment 2, separate functions were fit for each of the three conditions. To assess the effect of TMS on hand choice in Experiment 2, we calculated the percent change in ipsilateral hand use by dividing the probability of using the ipsilateral hand over all locations in the TMS_LH and TMS_RH conditions by the probability in the noTMS condition. We also directly compared the TMS_LH and TMS_RH conditions.

As a measure of response preparation, we calculated Reaction time (RT) as the time from the onset of the target to the time the cursor moved outside the starting circle. Median RT was determined for each condition (Experiment 1: LEFT-ONLY, RIGHT-ONLY, CHOICE; Experiment 2: TMS_LH, TMS_RH, noTMS). To assess the effect of hand choice, we combined the data for the two extreme targets (the outermost right and left targets in the target array) as the locations of least ambiguity and combined the data for the two targets around the PSE as the locations of most ambiguity. An additional analysis in Experiment 1 combined the data from the RIGHT-ONLY and LEFT-ONLY conditions to represent trials in which hand choice was pre-determined to compare it to the CHOICE condition. Trials in which both hands moved, or in which none of the hands moved, were excluded from all analyses.

Dependent variables were analyzed using permutation tests. For all pairwise comparisons we performed one-tailed paired permutation tests based on all possible permutations of the data (2^{13} for Experiment 1 and 2^{10} for Experiment 2). To look at the effect of target location and hand choice condition in Experiment 1, we performed a 2 (target location: Extreme, PSE) by 2 (hand choice condition: pre-determined, CHOICE) repeated measures permutational analysis of variance (ANOVA). To look at the effect of TMS condition by which visual hemifield the target was displayed on (Experiment 2), we performed a 2 (visual hemifield: right, left) by 3 (TMS condition: TMS_LH, TMS_RH, noTMS) repeated measures permutational ANOVA (Manley, 2007). Permutational ANOVAs were based on 10,000 permutations of the data.

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FIGURE LEGENDS

Figure 1 *Schematic illustration of the experimental setup and stimuli:* **(a)** An LCD projector presented the stimuli on the top screen. By viewing the stimuli on a mirrored surface placed halfway between the screen and the table surface, participants had the impression that the stimuli were in the same plane as their hands. The position of the hands was indicated by two white dots (not displayed). **(b)** Starting circles (bottom two circles), fixation circle (center circle) and the 10 possible target locations. (**c**) Start position (top) and the three types of trials. On unimanual trials, the participant reached with one hand towards the target. This hand was either pre-determined (RIGHT-ONLY and LEFT-ONLY conditions) or was selected by the participant after the onset of the target (CHOICE condition). For bimanual-catch trials, two target circles were presented and the participant reached to each target concurrently using both hands. For fixation-catch trials, the "+" at the center of the fixation circle changed to an "x" and the participants moved both hands to the fixation circle.

Figure 2 *Psychometric function of hand choice for the CHOICE condition***.** Mean probability of right hand use is plotted as a function of target location. Targets are listed relative to their location (1=leftmost target, 10=rightmost). The dashed vertical line indicates the physical center of the target array. The solid vertical line represents the mean PSE. Circles represent individual participants' PSE.

Figure 3 *Effect of target location and hand choice condition on reaction time*. **(a)** Mean RTs for the two targets around the PSE and the two extreme targets (pre-determined combines the RIGHT-ONLY and LEFT-ONLY conditions). Error bars represent standard error (S.E.M.). **(b)** RTs for each participant separated by condition. Each point displays median RT for extreme (vertical axis) and for PSE (horizontal axis) targets. The dashed line represents points in which RTs are the same for extreme and PSE targets. All but 3 triangles fall above this equality line showing that RTs for extreme targets were slower (403 ms) than for PSE targets (398 ms) in the pre-determined condition (p = .019). All but 2 circles fall below the equality line showing that for the choice condition, the RTs for PSE targets were slower (429 ms) than for extreme targets (418 ms; p = .0024). **(c)** RT difference in milliseconds between PSE and extreme targets. These data were derived by subtracting the RT for the PSE targets from the RT for the extreme targets. Circles represent individual participant data. All but 2 circles fall above the equality (dashed) line showing a target location by condition interaction (p = .0029). Eight out of the 13 circles fall in quadrant one showing a negative difference (RTs were larger for extreme than for PSE targets) in the pre-determined conditions and a positive difference (RTs were larger for PSE than for extreme targets) in the CHOICE condition.

Figure 4 *Three-dimensional reconstructions of participants' brains*. White dots indicate target stimulation area, defined as caudal part of the intraparietal sulcus.

Figure 5 *Effect of target location and TMS condition on reaction time*. (**a**) RTs for targets around the PSE and extreme targets collapsed over TMS conditions. **(b)** RTs separated by visual hemifield and TMS condition. Visual hemifield refers to the location where targets were presented. Error bars represent S.E.M.

Figure 6 *Effect of TMS on hand choice*. (**a**) Change in hand use over all target locations. Change is expressed as percent change in ipsilateral hand. Circles represent individual participant data. (**b**) Estimated change in hand use at the PSE. We calculated the estimated probability of ipsilateral hand use for each condition at the point in target space representing the PSE in the noTMS (baseline) condition. We did this by fitting a logistic regression curve to the data in each condition. (**c**) PSE change. Positive numbers represent more left hand use.

Figure 1

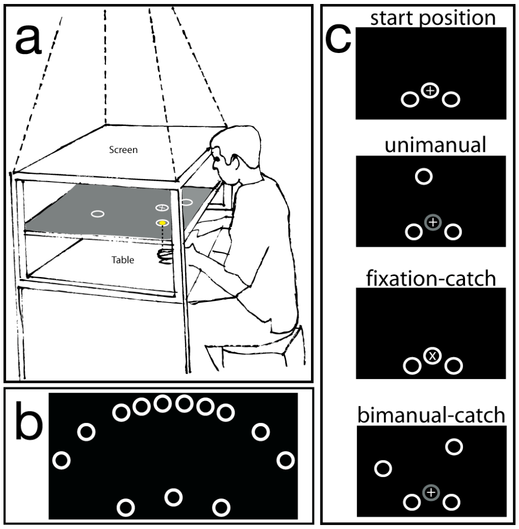

a
Screen
Table
b
c
start position
unimanual
fixation-catch
bimanual-catch

Figure 2

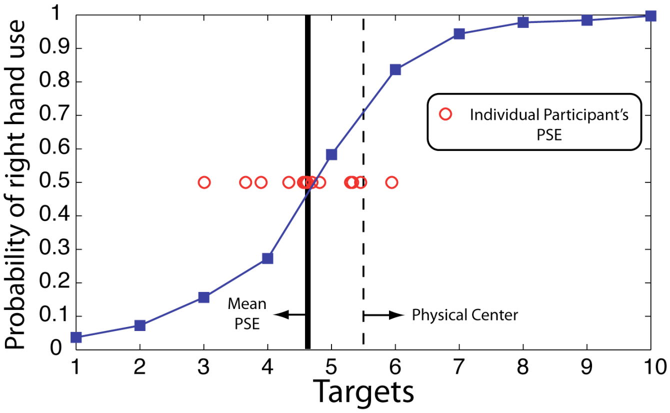

Probability of right hand use
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1
2
3
4
5
6
7
8
9
10
Targets
○ Individual Participant's PSE
Mean PSE
Physical Center

Figure 3

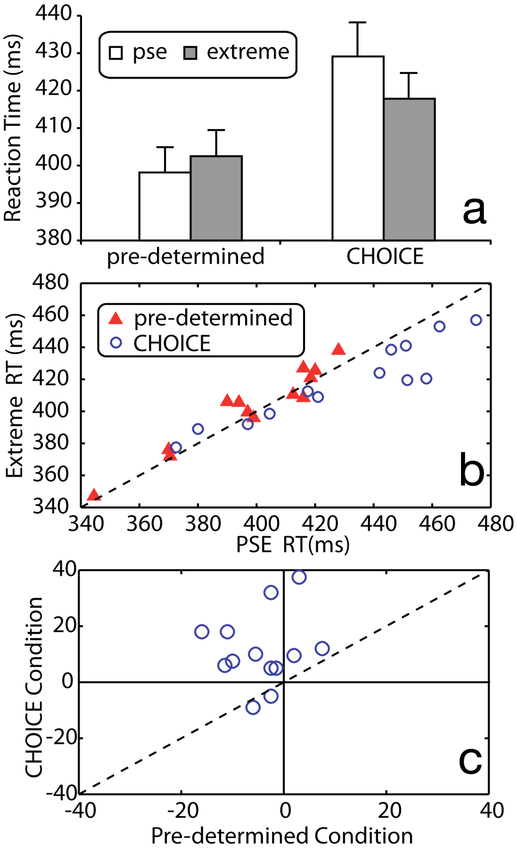

440
430
420
410
400
390
380
Reaction Time (ms)
□ pse ▨ extreme
pre-determined
CHOICE
a
480
460
440
420
400
380
360
340
Extreme RT (ms)
▲ pre-determined
○ CHOICE
340 360 380 400 420 440 460 480
PSE RT(ms)
b
40
20
0
-20
-40
CHOICE Condition
-40 -20 0 20 40
Pre-determined Condition
c

Figure 4

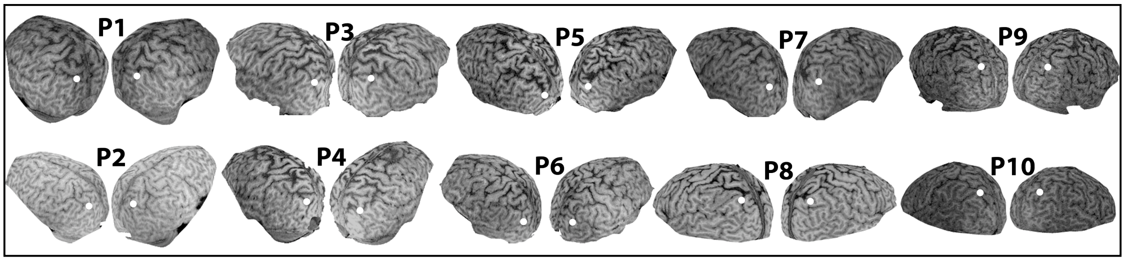


Figure 5

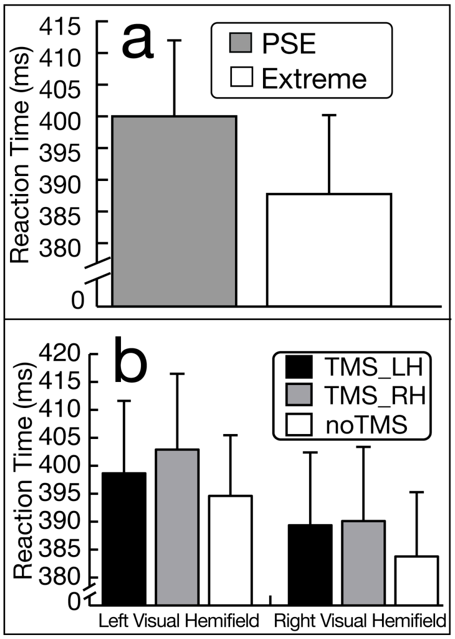
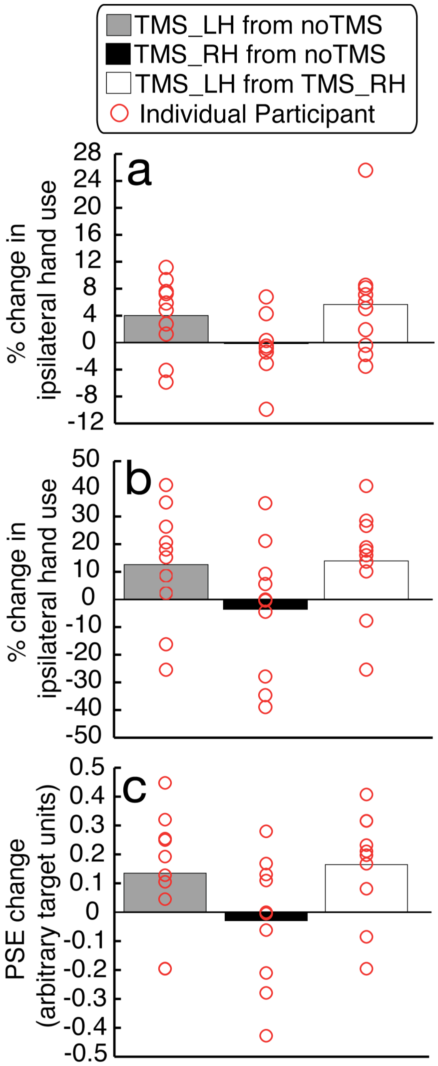

a
PSE
Extreme
Reaction Time (ms)
415
410
405
400
395
390
385
380
0
b
TMS_LH
TMS_RH
noTMS
Reaction Time (ms)
420
415
410
405
400
395
390
385
380
0
Left Visual Hemifield
Right Visual Hemifield

Figure 6


TMS_LH from noTMS
TMS_RH from noTMS
TMS_LH from TMS_RH
Individual Participant
a
% change in ipsilateral hand use
28
24
20
16
12
8
4
0
-4
-8
-12
b
% change in ipsilateral hand use
50
40
30
20
10
0
-10
-20
-30
-40
-50
c
PSE change (arbitrary target units)
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
-0.5

Chapter 4

Effort allocation, action selection and exploratory behavior: A unifying role of the medial frontal cortex in response preparation, conflict and errors

ABSTRACT

The medial frontal cortex (MFC) is thought to play a role in adaptive goal-directed behavior. The specific function of the MFC, however, has been a matter of debate. Two influential theories have suggested that the MFC is involved in performance monitoring, reacting to errors and situations involving conflict. This is inconsistent with recent evidence that the MFC is also activated in an anticipatory, predictive manner. We attempted to bring together the performance monitoring and anticipatory functions of the MFC by testing the idea that the MFC is generally sensitive to cues that indicate the need for increased cognitive or physical effort. We recorded event-related potentials (ERPs) to the presentation of cues indicating whether a subsequent task required low or high effort. The high effort cue elicited a fronto-central negativity with an estimated source in MFC. We also recorded ERPs elicited by errors and conflict and found similar MFC neural generators. We propose that conflict, errors and effort-related cues all activate the MFC because they serve as cues that indicate the need for increased effort to maintain successful task performance. We suggest that a unifying function for the MFC might be to build and utilize action-outcome contingencies based on effort-benefit analysis.

An important feature of human behavior is the ability to modify strategies and allocate resources in accordance with goals and expectations as well as differing environmental conditions and internal states. This ability allows human behavior to be flexible and adaptive.

Evidence from cognitive neuroscience suggests that the posterior medial frontal cortex (pMFC), an area that encompasses the anterior cingulate cortex (ACC) and the pre-supplementary motor area (pre-SMA), is involved in the processes that subserve adaptive goal-directed behavior (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). This view is supported by studies of psychiatric disorders affecting pMFC function (Ullsperger, 2006) and by studies with non-human species (Hadland, Rushworth, Gaffan, & Passingham, 2003; Schweimer, Saft, & Hauber, 2005; Shima & Tanji, 1998; Thaler, Chen, Nixon, Stern, & Passingham, 1995; Walton, Bannerman, Alterescu, & Rushworth, 2003) and human patients with lesions to pMFC (R. A. Cohen, Kaplan, Moser, Jenkins, & Wilkinson, 1999; R. A. Cohen, Kaplan, Zuffante, et al., 1999; Ochsner, et al., 2001), showing that pMFC dysfunction leads to deficits in voluntary goal-directed actions.

Determining the precise function of the pMFC, however, has been complicated by the fact that the neuroimaging evidence shows that pMFC activation is increased by a diverse set of experimental manipulations (Duncan & Owen, 2000; Paus, Koski, Caramanos, & Westbury, 1998). This has led researchers to ascribe different functions to the pMFC, including response selection (Badgaiyan & Posner, 1998; Posner, Petersen, Fox, & Raichle, 1988), and the processing of pain (Vogt, Derbyshire, & Jones, 1996) and novelty (Berns, Cohen, & Mintun, 1997). However, the most prominent theories of pMFC function center on the idea that pMFC is involved in performance monitoring. In particular, two theories have been highly influential. The first suggests that the pMFC is activated by information indicating errors in performance or when events are worse than expected (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000; Gehring, Goss, Coles, Meyer, & Donchin, 1993; Holroyd & Coles, 2002; Miltner, Braun, & Coles, 1997). The second suggests that the pMFC is sensitive to response conflict occurring when two competing responses are co-activated (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Botvinick, Braver, et al., 2004; Botvinick, Cohen, & Carter, 2004; Carter, et al., 1998; Carter, et al., 2000; Yeung, Cohen, & Botvinick, 2004). Both of these theories suggest that the pMFC responds in a *reactive* manner during or after the performance of tasks.

Recent theories have challenged the notion that the pMFC acts in a reactive manner in performance monitoring, suggesting that the pMFC can act in a proactive, anticipatory or predictive manner even prior to performance (Aarts, Roelofs, & van Turennout, 2008; Brown & Braver, 2005, 2007). Brown and Braver (2005) proposed an elegant hypothesis suggesting that the pMFC “learns” to predict the likelihood of errors in a particular task. However, this error-likelihood hypothesis has encountered some opposition with studies failing to replicate the finding of increased pMFC activity in response to cues that indicated high likelihood of errors (Nieuwenhuis, Schweizer, Mars, Botvinick, & Hajcak, 2007). The error-likelihood hypothesis (along with the error processing and conflict monitoring theories) is also unable to explain evidence that the pMFC is responsive to rewards and positive feedback (Akkal, Bioulac, Audin, & Burbaud, 2002; Ito, Stuphorn, Brown, & Schall, 2003; Niki & Watanabe, 1979; Oliveira, McDonald, & Goodman, 2007; Walton, Devlin, & Rushworth, 2004).

A potentially unifying account of pMFC function posits that the pMFC is sensitive to cues that signal situations that demand increases in cognitive or physical effort (Oliveira, et al., 2007; Ridderinkhof, et al., 2004; Rushworth, Walton, Kennerley, & Bannerman, 2004). According to this account, pMFC might be involved in representing and updating action-outcome contingencies based on the amount of effort required by the actions and the potential benefit that these actions might generate. The pMFC might be further involved in allocating the necessary effort to select and produce actions that lead to favorable consequences (Oliveira, et al., 2007; Rushworth, Buckley, Behrens, Walton, & Bannerman, 2007). We therefore refer to this account as the 'effort allocation hypothesis'. This hypothesis suggests that negative events and response conflict represent instances of a broader class of stimuli that the pMFC is sensitive to, namely stimuli that signal the need for increased effort to update action-outcome contingencies or to select and produce actions with favorable consequences. In other words, response conflict and error information are sufficient but not necessary to activate the pMFC. The effort allocation hypothesis also explains the pMFC response to unexpected positive feedback by suggesting that feedback (of any valence), which violates an expectation, signals the need to recruit cognitive effort to update action-outcome associations (Oliveira et al., 2007). This is necessary to improve the chances of producing behavior that leads to favorable consequences in the future.

Importantly, the effort allocation hypothesis also predicts that the pMFC should be similarly activated by information that signal the need for increased effort regardless of whether this information is presented before, during or after task performance. While this prediction, at first glance, may be similar to that of the error-likelihood hypothesis since situations with high error-likelihood in general also require increased effort, an important distinction is that according to the effort allocation hypothesis, the pMFC is only responsive to information that can guide a change in behavior or a change in action-outcome associations. Cues indicating error-likelihood can, but do not necessarily, carry this type of information. They may only carry information about the probability of reward without providing information that can be used to favorably change this probability. This may be the reason for the mixed evidence regarding the error-likelihood hypothesis (Nieuwenhuis, et al., 2007).

Here we developed a novel task to test the effort allocation hypothesis by investigating the proactive role of the pMFC prior to task performance. Participants performed a maze-tracing task that varied in the degree of effort required to solve it. Prior to the display of a Go or a NoGo signal for each trial, participants were presented with a maze. The maze provided a perceptual cue, indicating whether the task required high or low effort. An important difference between the motor task we employed and the cognitive tasks previously employed to test the error-likelihood hypothesis (Brown & Braver, 2005; Nieuwenhuis, et al., 2007) is that our task provided information that could directly guide the selection of action and lead to preparatory adjustments in behavior before participants could begin to solve the task.

We recorded event-related potentials (ERPs) to investigate differences in brain activation evoked in response to the presentation of each of the figures. With the high temporal resolution of ERPs we were also able to record the brain responses to Go/NoGo signals and to correct responses and errors. This allowed us to compare the activity occurring in response to the cues indicating the amount of effort needed to solve the task, to the activity elicited by paradigms that have been used to show the pMFC's sensitivity to response conflict (Braver, Barch, Gray, Molfese, & Snyder, 2001; Donkers & van Boxtel, 2004; Nieuwenhuis, Yeung, van den Wildenberg, & Ridderinkhof, 2003) and to errors (Kiehl, Liddle, & Hopfinger, 2000; Luu, Tucker, Derryberry, Reed, & Poulsen, 2003), respectively. We predicted that if the pMFC is sensitive to cues that signal the effort required to ensure immediate or future success, the evoked response should be modulated prior to performance and the distribution of this response would be similar to the ERP components elicited by NoGo stimuli and by response errors.

METHODS

Participants

Sixteen healthy university students participated in the study. Data from two participants were excluded from all analyses because of excessive noise in the electroencephalogram (EEG). The remaining 14 participants (6 women, 1 left-handed, mean age: 21.6 years, range: 18-26 years) provided written informed consent prior to the start of the experiment and received course credit for their participation.

Task and Procedures

Participants sat comfortably in an electrically shielded and sound attenuated chamber at a distance of 65 cm to a 19-inch CRT monitor with the screen resolution set to 800x600 pixels. The task was to navigate a cursor through a single-path maze using a standard computer mouse with the right-hand (Figure 1). Each trial started with the presentation of a white fixation cross (5 mm x 5 mm) at the center of the screen on a grey background for 1250 ms. Following this, one of 8 possible mazes was pseudo-randomly selected and added to the fixation display. The 8 mazes were green and differed according to four spatial configurations (Figure 1A) and two path widths (Figure 1B). The narrow-path maze (9 mm width) represented the LOW-EFFORT condition and the wide-path maze (18mm width) represented the HIGH-EFFORT condition (Figure 1B). The LOW-EFFORT and the HIGH-EFFORT mazes provided participants with a salient perceptual cue to the amount of effort needed to complete each maze and also with information (e.g., direction and width of the path) that allowed them to prepare for the tracing task. After 1,500 ms, the fixation cross changed color to indicate equally likely Go (green fixation cross) or NoGo (red fixation cross) trials. The red or green fixation crosses remained on the screen for 1,000 ms. In the case of a NoGo trial, the fixation cross changed to white to indicate the start of the following trial. In the case of a Go trial, the fixation cross was replaced by a square cursor that was under the control of the computer mouse. Trials were considered successful if the participant was able to navigate the entire maze without letting the cursor leave the maze path. Upon successful completion of the task, the maze changed color to yellow. If the cursor left the maze path, the maze changed color to red and the trial ended (Figure 1C).

On the first trial, participants had a limit of 13 seconds to complete the task, after which the maze turned red representing a timed-out trial. This time limit varied according to an adaptive procedure. After each unsuccessful trial, the time limit was increased by 250 ms and after each successful trial the time limit was decreased by 250 ms. Immediately after the maze changed color to red or yellow, the screen froze for 1,000 ms. All displays and colored stimuli were physically isoluminant at 6.00 cd/m^2. To increase motivation, participants were instructed that the experiment was set up as a game. Participants earned points for each successfully completed task and lost points for time-outs and errors. At the end of each block participants received feedback about their score. Each block consisted of 16 trials. The full experimental session was composed of 30 blocks.

Behavioral measures and analysis

As indirect measures of the effort needed to complete the task, we calculated the percentage of trials that were correct, incorrect and that resulted in time-outs separated by effort condition. We further calculated the amount of time it took for participants to successfully complete the HIGH EFFORT and LOW EFFORT MAZES.

We were also interested in obtaining a measure of the behavioral adjustments made in response to increased recruitment of control. In performance monitoring studies, a commonly used measure of monitoring is post-error or post-conflict slowing of reaction times (RTs; Kerns, et al., 2004; Klein, et al., 2007). Since in this experiment we were interested in anticipatory behavioral adjustments, we compared RTs in the two effort conditions immediately following the presentation of the respective mazes. This allowed us to assess the proactive recruitment of control and behavioral adjustments generated by the presentation of the cue indicating the amount of effort necessary to solve the task (i.e., the mazes). RT was measured as the time it took for participants to start moving the mouse after the GO signal. All behavioral results were analyzed by one-tailed paired permutation tests based on all possible (2^{14}) permutations of the data.

Electrophysiological recording and pre-processing

EEG was recorded from 63 tin electrodes attached to an elastic-fabric cap (Electro-Cap International, Inc). All but 5 of these electrodes were positioned according to the 10-10 system (FPz, FP1, FP2, AF3, AF4, Fz, F1, F2, F3, F4, F5, F6, F7, F8, FCz, FC1, FC2, FC3, FC4, FC5, FC6, Cz, C1, C2, C3, C4, C5, C6, T7, T8, CPz, CP1, CP2, CP3, CP4, CP5, CP6, Pz, P1, P2, P3, P4, P5, P6, P7, P8, P9, P10, POz, PO3, PO4, PO7, PO8, Oz, O1, O2, Iz, and M1). The remaining 5 electrodes were positioned inferior to the standard row of occipital electrodes. Horizontal electrooculographic (EOG) signals were recorded bipolarly at both external canthi. All electrodes from scalp sites were referenced to an electrode placed on the right mastoid (M2). Electrode impedances were kept below 10 kΩ for all electrodes. EEG signals were amplified by a gain of 20,000 and a band pass of 0.1-100 Hz, digitized at 500 Hz and stored on a microcomputer for offline averaging. Offline analysis was performed with EEGLAB (Delorme & Makeig, 2004). The data were down-sampled to 250 Hz, re-referenced to an average reference, epoched and filtered offline with a bandpass of 0.5-30 Hz. We then used blind source separation based on second order blind identification (SOBI) to remove EOG (Gómez-Herrero, et al., 2006) and based on canonical correlational analysis (CCA) to remove electromyographic (EMG) artifacts from the data (De Clercq, Vergult, Vanrumste, Van Paesschen, & Van Huffel, 2006). An automated procedure was used to exclude trials with activity deviating by 6 standard deviations or more from the probability distribution of all trials for each participant and also trials with activity greater than 100 μV or smaller than -100 μV. Excluded trials accounted for an average of 4.7% of the total trials.

Event-related potential (ERP) analysis

After pre-processing the data, we extracted ERPs by averaging the epochs for 6 conditions of interest. An initial analysis compared ERPs elicited by the presentation of the LOW EFFORT and the HIGH EFFORT mazes. A second analysis compared ERPs elicited by the presentation of the Go and NoGo signals. A third analysis compared ERPs elicited by the successful completion of the task and by errors. For all ERP analysis, data were baselined to the average amplitude of the 200 ms period preceding stimulus onset. All statistical comparisons were performed on the mean amplitude of the waveforms for the FCz electrode during the time windows of interest. The comparisons were performed through one-tailed paired permutation tests based on all possible permutations of the data (2^{14}).

Source analysis

We used a two-step procedure for source analysis. First we used BESA 5.2 software (Megis software) to generate a distributed linear solution based on a local autoregressive average (LAURA) model (Grave de Peralta Menendez, Andino, Lantz, Michel, & Landis, 2001; Grech, et al., 2008). We plotted the activation foci from the LAURA model on the Colin brain—a high resolution average of 27 MRI scans of one brain (Van Essen, 2002). On the second step, we used the location of the foci of activity found in the LAURA analysis to create a dipole model. We fixed dipoles to the center of the foci of activity and started a fit of the orientation of the dipoles for the time window of interest. This two-step procedure allowed us to calculate the amount of variance explained by a dipole model informed by the LAURA analysis. This provided a data-driven method to estimate the number and location of dipoles. While LAURA requires no a priori assumption of the number and location of activity foci, dipole models are highly sensitive to such assumptions (Grech, et al., 2008).

RESULTS

Behavioral results

The behavioral results showed that the HIGH EFFORT condition was considerably harder than the LOW EFFORT conditions. Participants made errors in a larger percentage of trials in the HIGH EFFORT condition (71%) than in the LOW EFFORT condition (25%, *p* = .0001, Figure 2), committed more time-outs (HIGH EFFORT: 1.7% of trials; LOW EFFORT: 0.2% of trials, *p* = .016, Figure 2) and took more time to complete the task (HIGH EFFORT: 12.7 seconds; LOW EFFORT: 7.9 seconds; *p* = .0001, Figure 3). The results also showed that participants adjusted to the different control requirements in a proactive, anticipatory manner. RTs were significantly longer for the HIGH EFFORT (245 ms) than the LOW EFFORT (206 ms; *p* = .0002, Figure 4) conditions.

Event related potentials (ERPs)

In our main contrast of interest, we compared the ERPs elicited by the onset of the LOW EFFORT and HIGH EFFORT mazes. Figure 5A shows the ERP waveforms for the two conditions at electrode FCz. A pronounced difference between the two conditions emerged around 400 ms, peaked around 480 ms and lasted until 800 ms after the onset of the mazes. This difference led to a reliably larger negative-going deflection in the ERP waveform for the HIGH EFFORT condition compared to the LOW EFFORT condition (420-500 ms, Figure 5A; *p* = .0017). This negativity was maximal at fronto-central electrode sites (Figure 5B), consistent with previously reported ERP components attributed to pMFC activity (Luu, et al., 2003; Nieuwenhuis, et al., 2003; Van Veen & Carter, 2002).

In the second contrast of interest, we compared ERPs elicited by the onset of the Go and NoGo signals. Figure 6A shows the ERP waveforms for the two conditions at electrode FCz. The ERP waveforms elicited by both the NoGo and the Go signals showed a positive-going deflection starting at around 150 ms after the onset of the signals. This positive-going deflection peaked at around 250 ms in the Go waveform. At around 200 ms, the NoGo waveform showed the start of a negative-going deflection that peaked at around 300 ms. This deflection is consistent with the NoGo N2 (Falkenstein, Hoormann, & Hohnsbein, 1999, 2002; Nieuwenhuis, et al., 2003) and was absent from the Go waveform generating a reliable difference between the two conditions (240-280 ms, Figure 5A; *p* = .00006). Consistent with previous reports of the NoGo N2, this negative-going peak was maximal at fronto-central electrode sites (Figure 5B; Falkenstein, et al., 2002; Nieuwenhuis, et al., 2003). After the peak of the N2, the NoGo waveform showed a positive-going deflection, which generated a reliable difference between the two conditions during the time window analyzed (360-412 ms, *p* = 0.00006). This difference was consistent with a NoGo P3 (Falkenstein, et al., 1999, 2002) and was also maximal at fronto-central electrode sites (Figure 5D; Falkenstein, et al., 2002).

In the third contrast of interest, we compared ERPs elicited by errors and correct task performance. We time-locked the ERPs to the moment the errors occurred (i.e., the cursor left the maze path) and the moment the task was successfully completed (i.e., the cursor reached the end of the maze path). These times were also marked by a change of maze color to indicate the end of a correct trial or an error. Figure 6A shows the ERP waveforms for the two conditions at electrode FCz. The error waveform showed an early negative-going deflection that peaked at around 90 ms after the onset of the errors. This negative-going deflection was absent from correct trials generating a reliable difference between the two conditions (68-108 ms, Figure 6A; *p* = .0005). This negativity is consistent with previous reports of the error negativity (Ne) or error-related negativity (ERN) (Falkenstein, et al., 2000; Gehring, et al., 1993). Analysis of the scalp topography of this negativity revealed that it was maximal at central electrode sites, slightly posterior to what we found for the effort-related and NoGo-related components (Figure 6B). Previous reports have frequently found the ERN to be maximal at fronto-central sites, but the central maximum that we found is also consistent with several studies investigating the ERN (Allain, Carbonnell, Falkenstein, Burle, & Vidal, 2004; Mathalon, Whitfield, & Ford, 2003; Van Veen & Carter, 2002). After the ERN, the error waveform showed a large positive-going deflection that peaked at around 350 ms after the onset of the error. This positivity is consistent with previous reports of the error positivity (Pe; Falkenstein, et al., 2000) and was reliably larger than the positivity for the correct waveform during the time window we analyzed it (300-400 ms, Figure 6A, p = .00006). Analysis of the scalp topography of this negativity revealed that it was maximal at fronto-central electrode sites (Figure 6D), which is consistent with previous reports of the Pe (Luu, Tucker, & Makeig, 2004; Mathalon, Bennett, et al., 2003; Overbeek, Nieuwenhuis, & Ridderinkhof, 2005).

Neural source estimations

Neural sources were estimated using LAURA at the time of peak activation for each of the 5 contrasts of interest. Consistent with our predictions, the LAURA analysis showed increased activation in the pMFC in response to the presentation of the HIGH EFFORT maze compared to the presentation of the LOW EFFORT maze. This activity was estimated to be in the dorsal-rostral ACC and was accompanied by increased activation in bilateral lingual gyrus (Figure 5C). The dipole model we created based on these activation foci had 3 dipoles: one in the ACC and one in each hemisphere's lingual gyrus. We fitted the orientation of these dipoles during the same time window in which we performed the ERP analysis (420-500 ms). The dipole model showed a good fit, accounting for 95.7% of the variance in this time window.

We followed similar procedures with the source analysis for the two ERP components identified for the NoGo minus Go contrast. Similar to what we found for the HIGH EFFORT minus LOW EFFORT contrast, the LAURA analysis estimated that the dorsal ACC and bilateral lingual gyri were involved in the generation of the NoGo N2 (Figure 6C). In addition to those sources, a focus of activity was also estimated in the right lateral prefrontal cortex extending from dorsal- to ventral-lateral prefrontal cortex (Figure 6C). This is consistent with previous studies implicating the right lateral prefrontal cortex in inhibitory control (Bunge, Ochsner, Desmond, Glover, & Gabrieli, 2001; Garavan, Ross, Murphy, Roche, & Stein, 2002; Konishi, et al., 1999; Xue, Aron, & Poldrack, 2008). The dipole model we created based on these activation foci had 4 dipoles: one in ACC, one in each hemisphere's lingual gyrus and one in right lateral prefrontal cortex close to the middle frontal gyrus. We fitted the orientation of these dipoles during the same time window in which we performed the ERP analysis (240-280 ms). The dipole model showed a good fit, accounting for 96.5% of the variance during this time window. The LAURA-estimated sources for the NoGo P3 were similar to those of the NoGo N2 but without the right lateral prefrontal focus (Figure 6E). The dipole model with 3 dipoles (one in ACC and one in each hemisphere's lingual gyrus) accounted for 94.5% of the variance during the 360-412 ms time window.

The LAURA neural source estimations for the ERN and Pe were similar to each other with foci in the ACC and posterior cingulate cortex along with activations in lingual gyri, but had slight differences in the exact location of each of the foci (Figures 7C and 7E). The ACC source for the ERN was located just rostral to the genu of the corpus callosum, which was more rostral and ventral than the ACC source for the Pe and the ACC sources for the effort-related and NoGo-related components. Also, the posterior cingulate cortex source for the Pe was more dorsal than the posterior cingulate source for the ERN and extended into the precuneus. The foci in ACC and posterior cingulate for the ERN (Badgaiyan & Posner, 1998; Luu, et al., 2003; Luu, et al., 2004) and Pe (O'Connell, et al., 2007) are consistent with previous studies performing source estimation. Both of the 4-dipole models for the ERN and Pe had good fits, explaining 95.4% and 96.2% of the variance in their respective time-windows of interest (ERN: 68-108 ms Figure 7C, Pe: 300-400 ms, Figure 7E).

DISCUSSION

In the present study we developed a new paradigm to investigate the effort allocation hypothesis. Consistent with the predictions of this hypothesis, the data showed that the presentation of the HIGH EFFORT maze elicited a negative-going ERP component that peaked at around 480 ms after the onset of the maze and was estimated to involve a pMFC source. This finding adds to the growing body of literature showing pMFC activity elicited proactively in anticipation of task performance (Aarts, et al., 2008; Brown & Braver, 2005, 2007; Johnston, Levin, Koval, & Everling, 2007).

Effort allocation and error-likelihood

The present result are also compatible with the error-likelihood hypothesis (Brown & Braver, 2005) as the HIGH EFFORT maze predicted increased error-likelihood in addition to providing participants with information about the amount of effort necessary to successfully solve the task. A question that arises is what differentiates our task from the recent studies that have failed to observe increased pMFC activity in response to cues indicating high error-likelihood (Nieuwenhuis, et al., 2007). An important difference is that in those studies, the error-likelihood cues were arbitrary and provided little information that could be used to guide behavioral changes to improve task performance (Nieuwenhuis, et al., 2007). In contrast, we used a motor task in which participants were provided with information that could directly guide performance and adjustments in behavior prior to the initiation of their movements. Cognitive tasks make it challenging to provide these types of cues because in most cases it becomes impossible to prevent participants from starting to solve the task prior to the onset of an imperative.

While the goal of our study was not to test the error-likelihood hypothesis directly, or to pit the effort allocation hypothesis against the error-likelihood hypothesis, we suggest that what critically activates the pMFC is the information about the need for increased effort to improve performance, and not high error-likelihood per se. Although the present data cannot disambiguate between these two possibilities, this conjecture finds support in an elegant study that showed that cues informing participants about the presence or absence of conflict in a subsequent Stroop-like task activated the pMFC independent of conflict and error-likelihood (Aarts, et al., 2008).

Do conflict, errors and effort-related cues generate the same ERP component?

Another goal of our study was to compare the ERP component elicited by the HIGH EFFORT maze to the ERP components elicited by conflict and errors. Early definitions of ERP components were based on common latency, polarity and scalp distribution, but more recent views suggest that a more appropriate definition is based on common computational operations and neuro-anatomical generators (Luck, 2004). The effort allocation hypothesis postulates that errors, conflict and effort-related cues are all instances of a broad category of stimuli that indicate the need for increased effort to improve the performance of a task immediately or in the future. Accordingly, they could all trigger a common computational operation aimed at recruiting the effort necessary to achieve positive outcomes from immediate or future actions. The results from our neural source estimations showed that the pMFC was a common neural generator for all of the components analyzed, which is consistent with the idea that the components elicited by conflict, errors and effort-related cues could all represent different forms of the same ERP component.

A potential problem with the idea that conflict, errors and effort-related cues elicited similar ERP components was the fact that there were slight differences in the precise location of the pMFC activation foci for each component. Also, the additional foci that were activated in conjunction with the pMFC differed between the components. Despite these differences, it is still plausible that these components represent the same broad computations by the pMFC. The differences in location of the pMFC activation foci could be due to the relatively coarse precision of LAURA source estimations.

A more likely explanation, however, is that the pMFC has different functional units that have the same general function of influencing other task-relevant brain areas, but are specialized anatomically and functionally to recruit different kinds of physical or cognitive resources (Bush, et al., 2000; Naito, et al., 2000; Paus, Petrides, Evans, & Meyer, 1993). The different functional units in the pMFC may be specialized but organized such that they all act as a network that integrates information from different modalities to influence attention allocation, motor preparation and motor responses (Bush, 2004; Bush, et al., 2002). Indeed, under different task demands it appears that the pMFC might act in modulating different task-related processing units. In auditory discrimination, instructions emphasizing increased speed and accuracy demands lead to pMFC activation and increases in early auditory potentials presumably by an up-modulation of task-relevant brain areas by the pMFC (Mulert, et al., 2007; Mulert, Menzinger, Leicht, Pogarell, & Hegerl, 2005; Mulert, et al., 2008). Similarly, in motor tasks the pMFC appears to up-modulate the gain of task-relevant units and down-modulate the gain of task-irrelevant units under situations requiring increased cognitive and physical effort (Isoda & Hikosaka, 2007; Taylor, et al., 2007). Thus, despite the differences in the activation foci that accompanied the pMFC activation, it is possible that the ERP components we analyzed all represent the activation of the pMFC to subserve a common general function, namely allocating the necessary effort to improve the chances of successful task performance.

Effort allocation, action selection and exploratory behavior

Recent evidence has suggested that the role of the pMFC in allocating effort may be through a role in action selection involving effort-based cost benefit analysis (Walton, et al., 2003; Walton, Bannerman, & Rushworth, 2002; Walton, Kennerley, Bannerman, Phillips, & Rushworth, 2006). In a T-maze paradigm where one arm of the maze is associated with high effort (i.e., climbing a barrier) and high reward and the other arm with low effort and low reward, healthy rats consistently chose the high effort and high reward arm. After lesions to pMFC, however, this pattern changed with rats choosing the arm with low effort and low reward. This deficit does not appear to be due to an inability to represent reward or to make the effort to climb the barrier. Rats returned to choosing the high reward option if a second barrier was placed in the low effort arm, equating the amount of effort for both arms (Walton, et al., 2003; Walton, et al., 2002). Instead it appears that pMFC lesions caused an inability to integrate the effort-cost with the reward information to select and carry on actions that had a high effort cost but a favorable effort to reward ratio.

It possible that in our experiment the increased pMFC activation in response to the HIGH EFFORT maze, at least partially reflected this role of the pMFC in integrating effort and reward to guide decisions about actions (Rushworth, et al., 2004). In the HIGH EFFORT condition, participants were faced with the decision of whether or not it was worth to dispend the effort necessary to successfully solve the task. In other words, they had to evaluate if the effort to reward ratio was favorable for them. This was not a decision of whether or not the participants should act during the HIGH EFFORT task, but instead whether or not it was worth the effort required to give themselves a real chance of succeeding.

Another aspect of action selection that the pMFC has been recently linked to is free choice during exploratory behavior (Aston-Jones & Cohen, 2005; J. D. Cohen, McClure, & Yu, 2007; Quilodran, Rothe, & Procyk, 2008; Rushworth, 2008). This may have also played role in the increased pMFC activation in response to the HIGH EFFORT maze. It appears that the pMFC is not involved simply in holding action-outcome contingencies that take into account the ratio of effort to reward. The pMFC also appears to be involved in exploratory behavior to build these action-outcome contingencies. Previous studies have shown that the pMFC is more strongly activated during early than late phases of learning (Jueptner, et al., 1997; Milham, Banich, Claus, & Cohen, 2003; Raichle, et al., 1994). Early in learning behavior is variable and involves the selection of potentially better actions on each trial. Late in learning exploitative behavior dominates and is expressed through the repetition of actions already known to produce the desired outcome. Most of the experimental paradigms used to test the role of the pMFC in decision-making and action selection have involved decisions between alternative options of 'what to do'; for example pressing a button with the right or left hand. Outside of the laboratory, however, many if not most selections of action do not involve a decision of 'what to do' but rather a decision of 'how to do it'. Most action goals can be achieved by many different actions or variants of the same action. In the present experiment, for example, participants did not have a choice of action, but could choose between different ways to produce the same action. One example was how participants decided to deal with the speed-accuracy tradeoff. Due to the time pressure, participants were forced to speed up their responses in the HIGH EFFORT task to avoid time-outs. However, the accuracy requirement of the task made it such that faster responses had a higher likelihood of leading to an error. Since participants did not achieve a high level of accuracy in the task during the experiment, they likely engaged in a trial-by-trial exploration of this speed-accuracy tradeoff to find the optimal way of solving the task. In the case of the LOW EFFORT task, participants maintained a high level of accuracy from early in the testing session, which presumably permitted them to simply exploit the same successful strategy by repetition. If the pMFC is indeed involved in guiding action-selection during exploratory behavior, this may have been reflected in the increased pMFC activation in response to the HIGH EFFORT maze.

CONCLUSION

The present results show that a cue indicating increased effort needed to solve a subsequent task activates the pMFC prior to the execution of the task. This result is inconsistent with theories that ascribe performance-monitoring functions to the pMFC (Botvinick, et al., 2001; Botvinick, Cohen, et al., 2004; Carter, et al., 1998; Carter, et al., 2000; Falkenstein, et al., 2000; Gehring, et al., 1993; Holroyd & Coles, 2002; Miltner, et al., 1997; Yeung, et al., 2004). We suggest that a unifying role for the pMFC in response preparation and performance monitoring might be to build and utilize action-outcome contingencies based on effort benefit analysis to support behaviors that lead to positive outcomes (Rushworth, 2008; Rushworth, et al., 2004). According to this view, the pMFC supports decisions to increase cognitive or physical effort by modulating the gain in task-related processing units in the brain (Aston-Jones & Cohen, 2005), thereby adjusting behavior to seek positive consequences or avoid negative consequences immediately or to improve the chances of favorable outcomes in the future (Oliveira, et al., 2007). This idea is well supported by patient studies showing that, in general, lesions to pMFC do not lead to deficits in error processing or conflict monitoring, but instead lead to apathy and failure to exert effort and control arousal states (Baird, et al., 2006; Critchley, et al., 2003; Fellows & Farah, 2005). It is also consistent with the broad anatomical connections that pMFC has with motor, limbic and cognitive areas (Devinsky, Morrell, & Vogt, 1995; Paus, 2001), suggesting that pMFC might be particularly fit to mediate the translation of information about the past history of reinforcement and the current environmental and internal states to changes in behavior that improve the chances of positive performance outcomes.

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Figure Captions

Figure 2 *Stimuli and Task*. (**A**) The four different spatial configurations for the maze. (**B**) Examples of LOW EFFORT and HIGH EFFORT mazes. (**C**) Schematic representation of the events on each trial. The trial started with a white central fixation presented for 1,250 ms. Following, one of the eight possible mazes was added to the fixation display. The presentation of the maze provided participants with a perceptual cue about how much effort the task was going to require. The fixation cross then changed color to either red or light green to indicate a NoGo or a Go trial respectively. In Go trials, the fixation cross was replaced by a square cursor after 1,000 ms and the participants gained cursor control. Upon successful completion of the task, the maze turned yellow. In case of errors or time-outs the maze turned red.

Figure 3 *Mean percentage of trials that were successful or ended in an error or time-out.*

Figure 4 *Mean task completion time in seconds for the two effort conditions.*

Figure 5 *Mean reaction time in milliseconds for the two different effort conditions.*

Figure 5 *ERPs and source analysis for the LOW EFFORT and HIGH EFFORT mazes*. (**A**) Grand averaged (n = 14) ERP waveforms time-locked to the presentation of the LOW EFFORT and HIGH EFFORT mazes for the FCz electrode. Time zero represents the onset of the mazes. The grey shaded region represents the time window used for the statistical analysis. Negative voltages are plotted up by convention. (**B**) Scalp topography of the difference between the HIGH EFFORT and LOW EFFORT conditions during the time window (420-500 ms) represented by the grey shaded region. Black dots represent the location of the electrodes. The large white dot represents the location of the FCz electrode. (**C**) LAURA neural source estimations for the difference between the HIGH EFFORT and LOW EFFORT conditions at 484 ms.

Figure 6 *ERPs and source analysis for the Go and NoGo signals*. (**A**) Grand averaged (n = 14) ERP waveforms time-locked to the presentation of the Go and NoGo signals for the FCz electrode. Time zero represents the onset of the signal. The grey shaded regions represents the time windows used for the statistical analysis. Negative voltages are plotted up by convention. (**B**) Scalp topography of the NoGo N2—the difference between the NoGo and Go signals during the time window (240-280 ms) represented by the earlier grey shaded region. Black dots represent the location of the electrodes. The large white dot represents the location of the FCz electrode. (**C**) LAURA neural source estimations for the NoGo N2 at 260 ms. The activation shown in the Right Lateral view is overlaid on a white matter surface reconstruction to show activity in the sulci. (**D**) Scalp topography of the NoGo P3—the difference between the NoGo and Go signals during the later grey shaded region (360-412 ms). (**E**) LAURA neural source estimations for the NoGo P3 at 396 ms.

Figure 7 *ERPs and source analysis for errors and correct responses*. (**A**) Grand averaged (n = 14) ERP waveforms time-locked to the onset of errors or successful completion of the task for the FCz electrode. Time zero represents the moment the cursor left the maze path (error) or reached the end of the maze path (correct). The grey shaded regions represents the time windows used for the statistical analysis. Negative voltages are plotted up by convention. (**B**) Scalp topography of the ERN—the difference between errors and correct responses during the time window (68-108 ms) represented by the earlier grey shaded region. Black dots represent the location of the electrodes. The large white dot represents the location of the FCz electrode. (**C**) LAURA neural source estimations for the ERN at 88 ms. (**D**) Scalp topography of the Pe—the difference between errors and correct responses during the later grey shaded region (300-400 ms). (**E**) LAURA neural source estimations for the Pe at 348 ms.

Figure 1

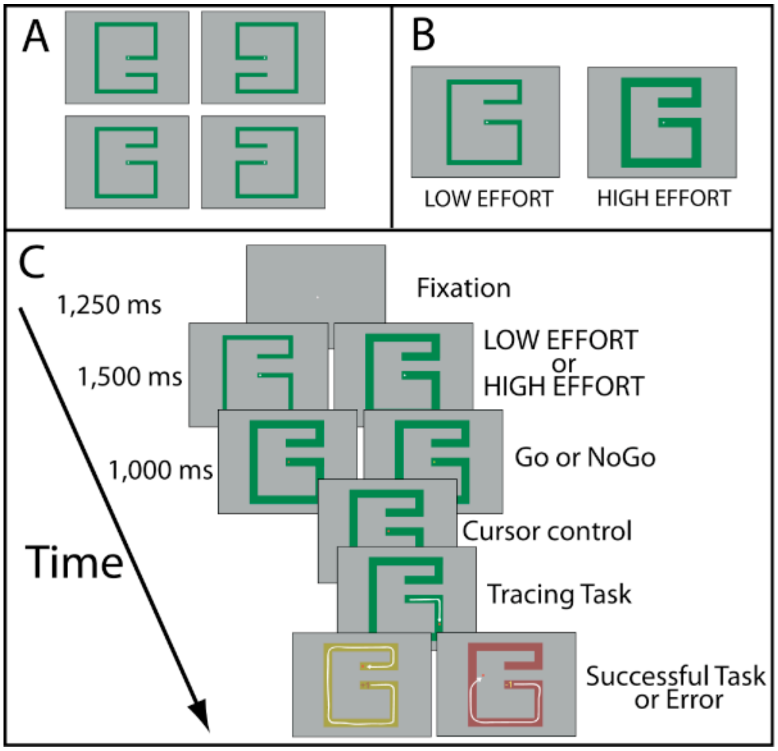

A
B
LOW EFFORT
HIGH EFFORT
C
1,250 ms
Fixation
1,500 ms
LOW EFFORT
or
HIGH EFFORT
1,000 ms
Go or NoGo
Cursor control
Time
Tracing Task
Successful Task
or Error

Figure 2

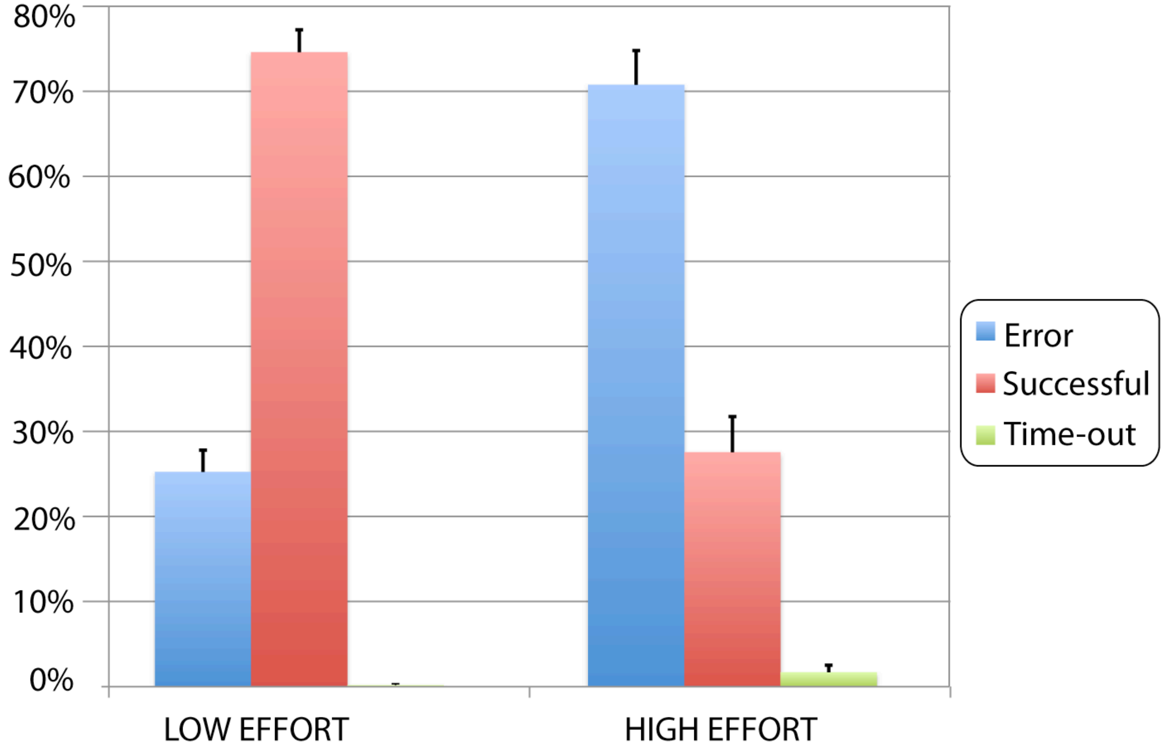

80%
70%
60%
50%
40%
30%
20%
10%
0%
LOW EFFORT
HIGH EFFORT
Error
Successful
Time-out

Figure 3

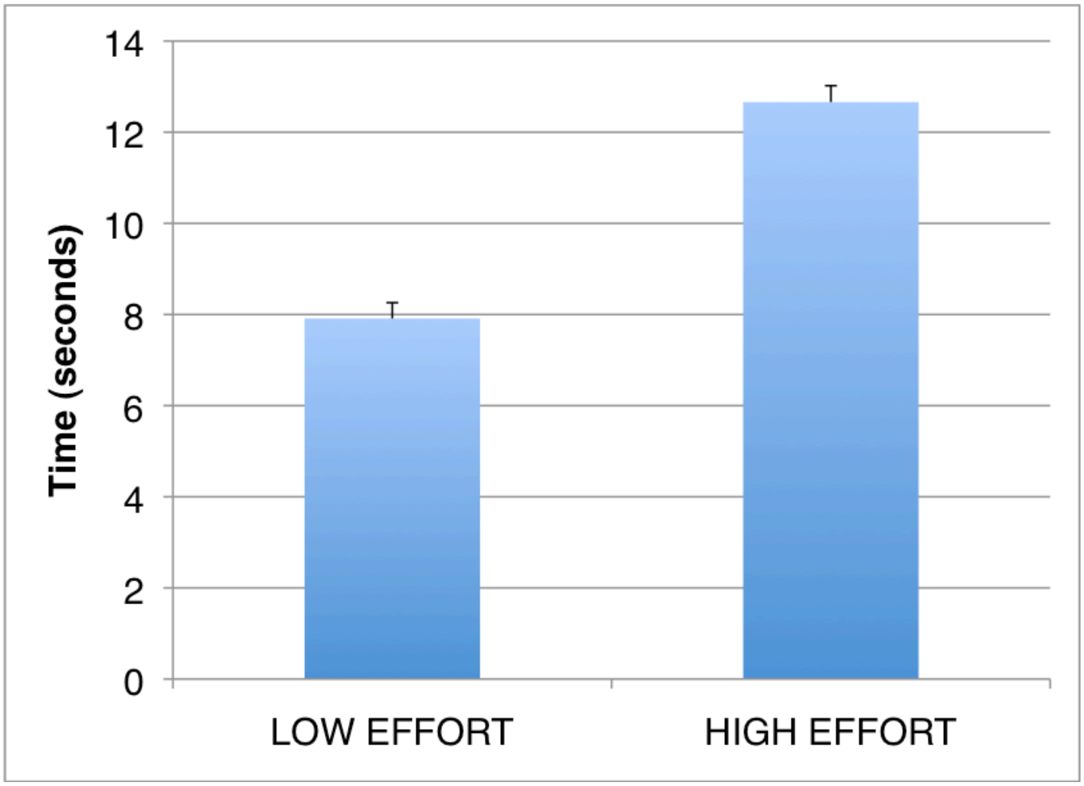


Figure 4

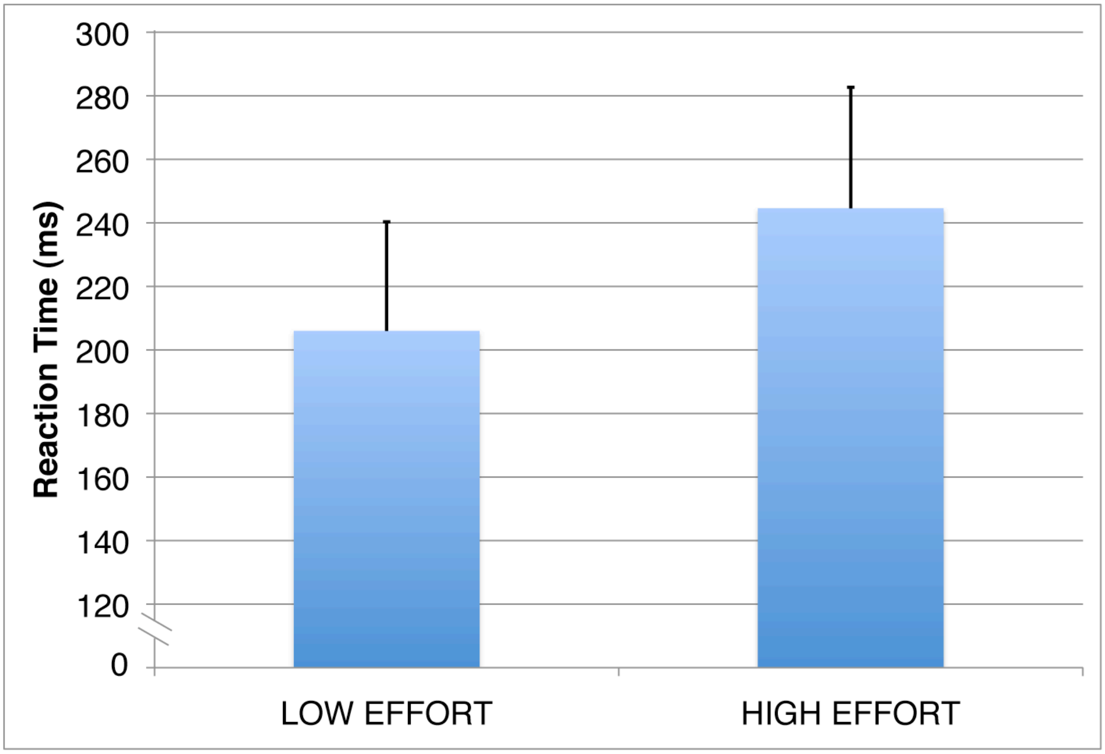

300
280
260
240
220
200
180
160
140
120
0
Reaction Time (ms)
LOW EFFORT
HIGH EFFORT

Figure 5

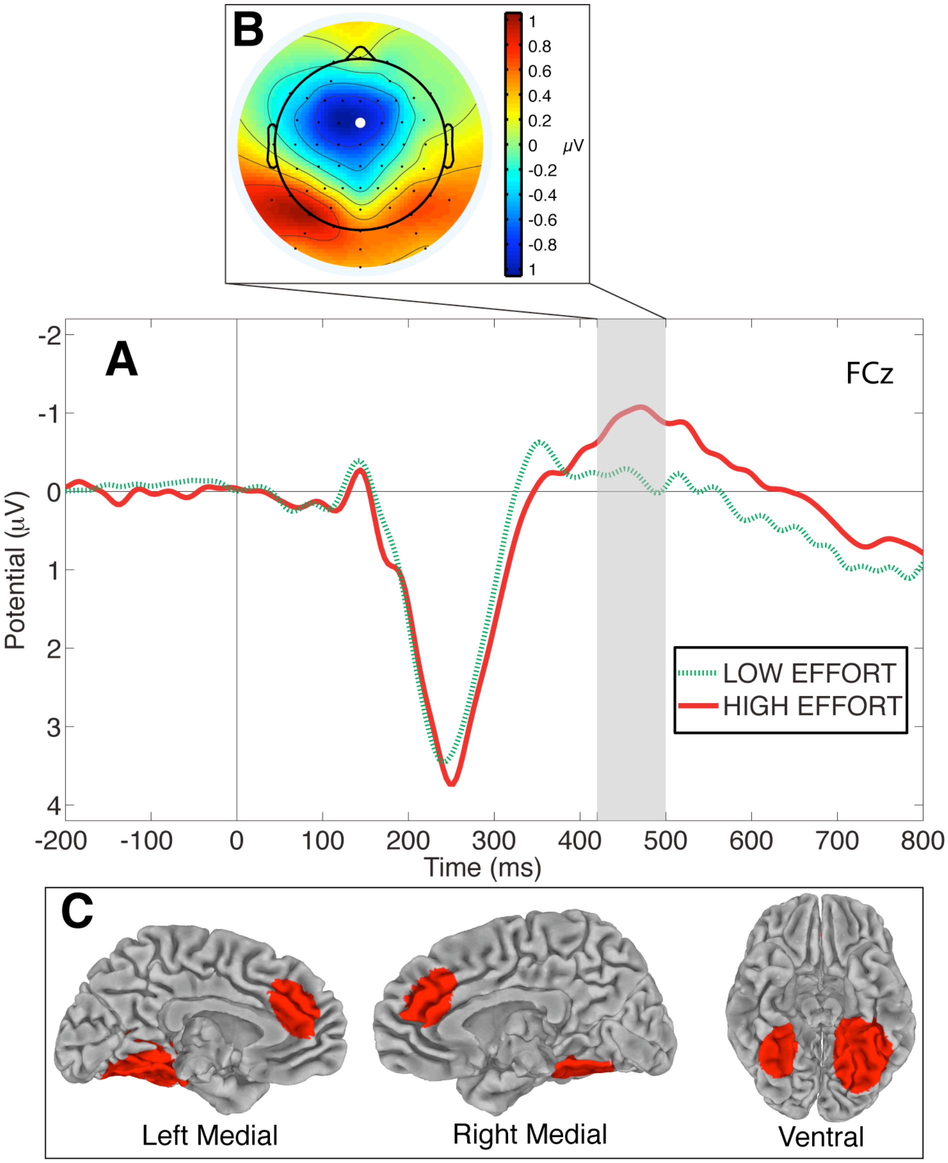
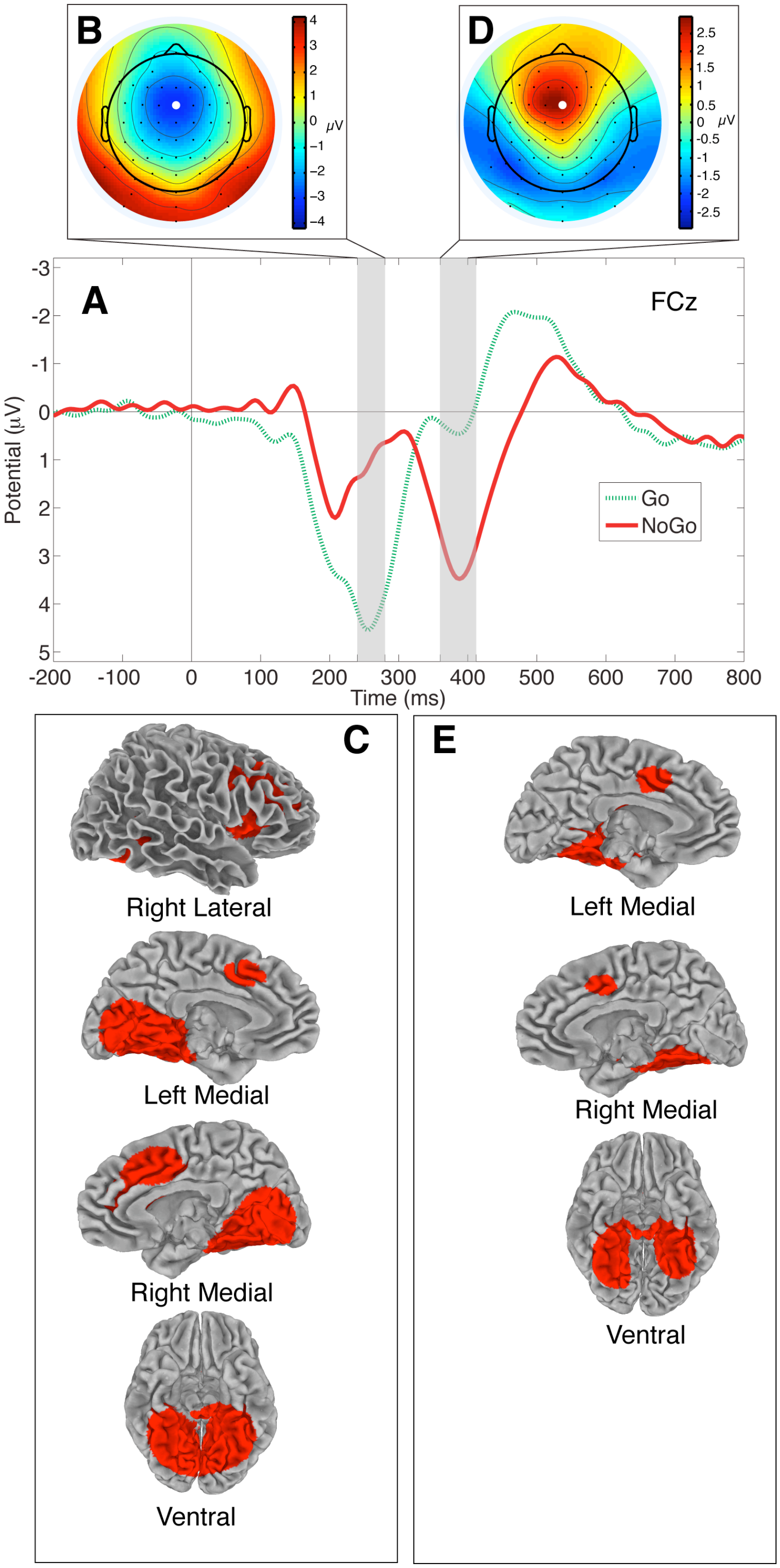
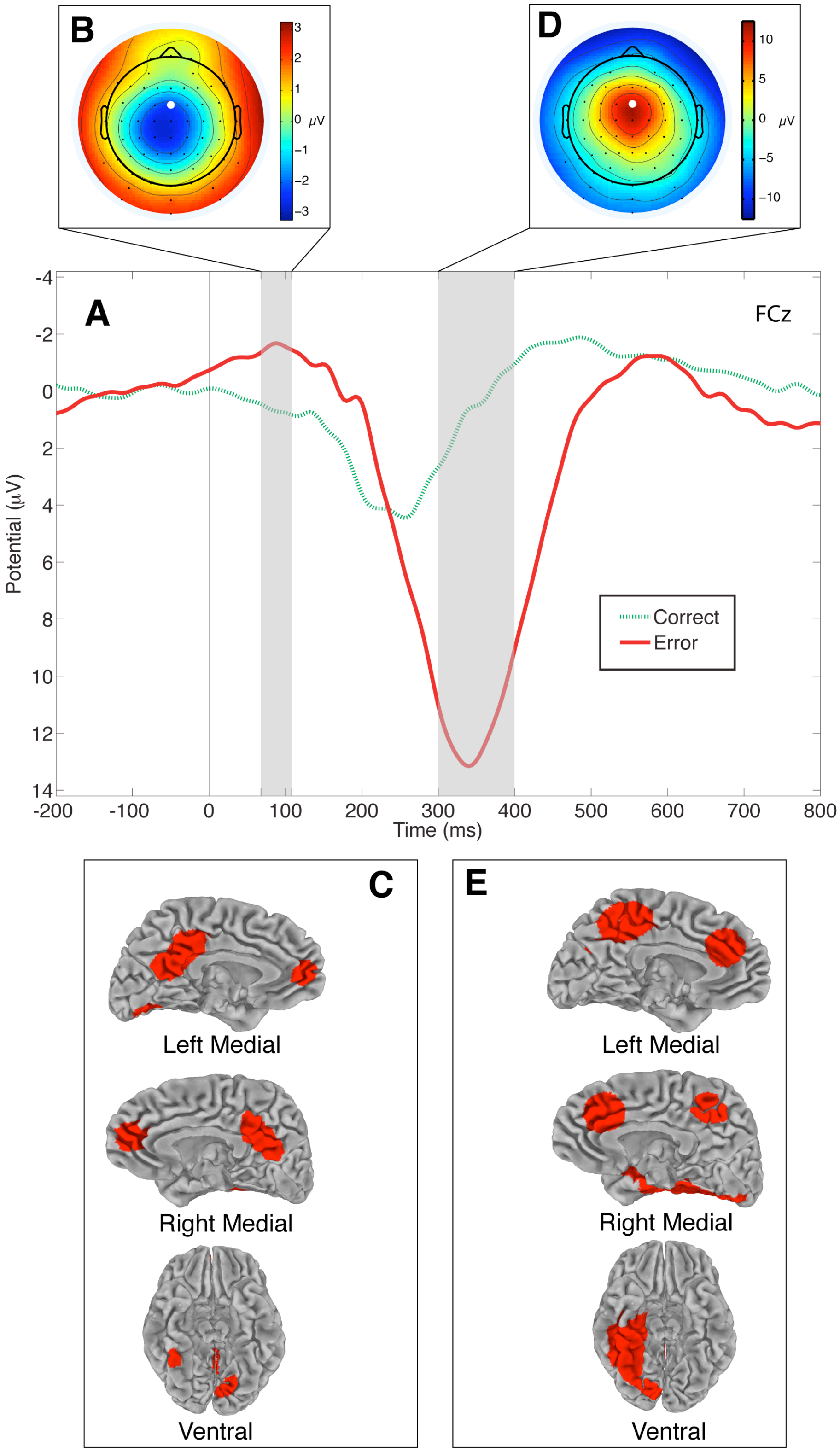

B
1
0.8
0.6
0.4
0.2
0
μV
-0.2
-0.4
-0.6
-0.8
1
A
FCz
-2
-1
0
1
2
3
4
Potential (μV)
-200
-100
0
100
200
300
400
500
600
700
800
Time (ms)
LOW EFFORT
HIGH EFFORT
C
Left Medial
Right Medial
Ventral

Figure 6



B
4
3
2
1
0
−1
−2
−3
−4
µV
D
2.5
2
1.5
1
0.5
0
-0.5
-1
-1.5
-2
-2.5
µV
A
FCz
Potential (µV)
-3
-2
-1
0
1
2
3
4
5
-200
-100
0
100
200
300
400
500
600
700
800
Time (ms)
Go
NoGo
C
Right Lateral
Left Medial
Right Medial
Ventral
E
Left Medial
Right Medial
Ventral

Figure 7


B
3
2
1
0 μV
−1
−2
−3
D
10
5
0 μV
−5
−10
A
FCz
Potential (μV)
-4
-2
0
2
4
6
8
10
12
14
-200
-100
0
100
200
300
400
500
600
700
800
Time (ms)
Correct
Error
C
Left Medial
Right Medial
Ventral
E
Left Medial
Right Medial
Ventral

Chapter 5

The role of empathy in the observation of actions and action errors

ABSTRACT

The recent discovery of mirror neurons, cells in the primate brain that respond to both the execution and observation of actions, has led to a surge in interest in how humans understand the actions of others and learn from them. An analogous system has also been proposed for performance monitoring, suggesting that the medial frontal cortex (MFC) in the human brain responds to one's own action errors as well as the observation of action errors by others. Here we investigated whether empathy for the observed actor plays a role in the function of the human mirror neuron system (MNS) and the MFC performance monitoring system during the observation of actions. Participants played a gambling game in which they chose one of two actors to be their partner, while the unselected actor became their opponent, on a basketball "shootout" competition. Participants observed partner and opponent actions while electroencephalography (EEG) was recorded. The results showed that the observation of partner errors led to an increased observation-related negativity, which was estimated to originate from a MFC source, relative to the observation of opponent errors. This finding suggests that empathy modulates the gain of the MFC performance monitoring system during the observation of action. We found that the human MNS, as indexed by mu rhythm suppression, was activated during the observation of both partner and opponent actions. This activation was stronger in the left hemisphere, suggesting that there may be a left-hemisphere dominance in the MNS during the observation of whole-body movements. We found no difference in mu rhythm suppression between the observation of partner and opponent actions, which suggests that the sensorimotor MNS is insensitive to the amount of empathy the observer has for the observed actor.

It takes a smart man to learn from his mistakes, but a wise man to learn from the mistakes of others.

An important feature of human cognition is the ability to understand the actions and intentions of others. This enables us to regulate our actions when their outcome is influenced by or dependent on others. It also enables us to learn from the actions of others to improve the chances of favorable outcomes when carrying out similar actions ourselves. The discovery of cells known as 'mirror neurons' in the primate brain has offered a neurophysiological mechanism that appears to play a fundamental role in observational learning and action understanding (Cattaneo & Rizzolatti, 2009; di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992; Rizzolatti & Craighero, 2004). Mirror neurons are activated when performing actions but also when observing actions of others. They were first identified in area F5 of the monkey premotor cortex (di Pellegrino, et al., 1992; Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996) and later found in the rostral inferior parietal cortex (Gallese, Fogassi, Fadiga, & Rizzolatti, 2002; Rozzi, Ferrari, Bonini, Rizzolatti, & Fogassi, 2008), which led researchers to propose a parieto-frontal mirror neuron circuit (Iacoboni & Dapretto, 2006; Rizzolatti & Craighero, 2004). Since then, neuroimaging studies have found evidence of a human analog to the monkey mirror neuron system (MNS; Aziz-Zadeh, Koski, Zaidel, Mazziotta, & Iacoboni, 2006; Buccino, et al., 2001; Gazzola & Keysers, 2009; Iacoboni, et al., 2005) and have suggested that it is expressed electrophysiologically through the desynchronization, or suppression, of the mu rhythm—a cortical rhythm in the 8-13 Hz frequency range[1] originating in sensorimotor cortex (Muthukumaraswamy & Johnson, 2004; Muthukumaraswamy, Johnson, & McNair, 2004; Pineda, 2005, 2008).

Two main theories have been advanced to explain the function of the MNS. The first theory, which we refer to as action understanding theory, centers on the idea that the MNS provides the basis for action understanding (Rizzolatti & Craighero, 2004; Rizzolatti, Fogassi, & Gallese, 2001). According to this theory, the observation of an action activates the same parts of the motor system that are activated to perform the action and, as a consequence, allows the observer access to knowledge about the goal of the action (Fogassi & Ferrari, 2007). This theory further suggests that the MNS may be linked to language and its evolution with the understanding of communicative gestures coming from the activation of embodied representations of these gestures (Fogassi & Ferrari, 2007; Rizzolatti & Arbib, 1998).

The second theory, which we refer to as the empathy theory, centers on the idea that the MNS provides the basis for imitation, which in turn allows action understanding (Iacoboni, 2009; Jeannerod, 1994). According to this view, action and intention understanding arise from an observer placing oneself empathetically in the position of the observed actor (Kaplan & Iacoboni, 2006).

These two theories are not mutually exclusive, and in fact the empathy theory can be viewed as an extension of the action understanding theory that links the process of imitation to

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[1] The mu rhythm also includes another component in the 14-25 Hz range (Hari, 2006; Pineda, 2008), which has been studied less frequently.

action understanding and to the MNS. However, the two theories suggest a subtle but important difference in how the MNS might be involved in action understanding and observational learning. For the empathy theory intention is inferred by empathetically placing oneself in the position of others, therefore experiencing similar inner states as the observed actor. In other words, this view suggests that the MNS is not only involved in 'reading' actions but also in reading the mind of whom we observe (Gallese, 2005). On the other hand, the action understanding theory suggests that intention may be inferred by activating an embodied representation of the action without the need to empathetically imitate or place oneself in the position of the observed actor. The two theories therefore place different emphasis on the importance of who the actor is.

Evidence in favor of the action understanding and the empathy theory is mixed. Studies showing that mirror neurons are multimodal and respond to the sounds of actions, such as breaking peanuts and ripping paper, suggest that information conveying the concept of action, even in the absence of an observable actor, is enough to activate the MNS (Gazzola, Aziz-Zadeh, & Keysers, 2006; Kohler, et al., 2002). This evidence seems to support the action understanding theory. On the other hand, studies of patient populations that appear to have deficits in MNS function, such as individuals with autism, appear to favor the empathy view. Individuals with autism have their ability to identify and understand actions relatively unimpaired (Hamilton, Brindley, & Frith, 2007). However, they show impairments positioning themselves in the place of others and inferring by observation the inner states that others may experience (Bernier & Dawson, 2009). Recent studies show that not only do individuals with autism have anatomical (Hadjikhani, Joseph, Snyder, & Tager-Flusberg, 2006) and functional (Oberman, et al., 2005) deficits in the MNS, but the functional deficit is correlated with autism symptom severity (Dapretto, et al., 2006).

One possible unifying account is that, particularly in humans, a large-scale mirror-like neural system extends beyond the sensorimotor system and is composed of the traditional MNS along with the limbic system and the insula (Cattaneo & Rizzolatti, 2009; Iacoboni, 2009). This account suggests that this extended mirror-like system is responsible for the experience of emotional states by observation (Goldman, 2009). This could suggest that the deficits associated with autism may not be of the traditional sensorimotor MNS per se, but rather of the extended mirror-like system with which it interacts (Hamilton, et al., 2007; Southgate, Gergely, & Csibra, 2009; Southgate & Hamilton, 2008). Further investigation of the role of empathy in the activation of both the traditional sensorimotor MNS and the extended limbic mirror-like system is therefore critical to understanding observational learning, action comprehension, and imitation, as well as pathologies that appear to involve these psychological processes.

Recent studies investigating the mirror proprieties of other neural systems have led researchers to propose that the role of the medial frontal cortex in performance monitoring is analogous to the role of the MNS in action observation (Miltner, Brauer, Hecht, Trippe, & Coles, 2004; Newman-Norlund, Ganesh, van Schie, De Bruijn, & Bekkering, 2009; van Schie, Mars, Coles, & Bekkering, 2004). The posterior medial frontal cortex (pMFC), which is part of the limbic system and includes the anterior cingulate cortex (ACC) and the pre-supplementary motor area (preSMA), has been extensively linked to performance monitoring (Luu, Flaisch, & Tucker, 2000; Oliveira, McDonald, & Goodman, 2007; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). This idea has been largely advanced by studies of the error-related negativity or error negativity (ERN/Ne), a negative-going deflection in the event-related potential (ERP) elicited by the commission of errors (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000; Gehring, Goss, Coles, Meyer, & Donchin, 1993) and also by feedback indicating errors (Miltner, Braun, & Coles, 1997). The role of the pMFC in performance monitoring has also received support from single cell recordings in monkeys (Niki & Watanabe, 1979; Wang, Ulbert, Schomer, Marinkovic, & Halgren, 2005) and humans (Williams, Bush, Rauch, Cosgrove, & Eskandar, 2004), as well as from functional neuroimaging showing error-related pMFC activations (Holroyd, et al., 2004; Kiehl, Liddle, & Hopfinger, 2000). Interestingly, the observation of third party errors also elicits an ERN/Ne-like component (van Schie, et al., 2004), which we refer to as observation-related negativity. This finding converges with functional neuroimaging studies suggesting that the pMFC may have mirror properties (Newman-Norlund, et al., 2009).

The function of the pMFC in performance monitoring is a matter of debate with different views ascribing dedicated error processing (Falkenstein, et al., 2000; Miltner, et al., 1997), reinforcement learning (Holroyd & Coles, 2002; Nieuwenhuis, Holroyd, Mol, & Coles, 2004) and more recently the establishment and representation of action-outcome associations (Oliveira, et al., 2007; Oliveira, Hickey & McDonald, unpublished data; Rushworth, 2008; Rushworth, Walton, Kennerley, & Bannerman, 2004) as possible pMFC functions. Similar to the theories of MNS function, the theories of pMFC function have different predictions with respect to the importance of who the observed actor is. Take for example a situation in which a basketball fan watches the last seconds of a tied game and one of the teams is awarded a pair of free-throws that can decide the game. A question that arises is whether the basketball fan's pMFC responds differently upon the observation of a missed free-throw in this situation if the player shooting the free-throws is part of the team that the fan supports or if the player is part of the opposing team. The dedicated error processing theory would predict that the pMFC would be similarly activated regardless of who the observed actor was. This is because understanding the concept of an error should be insensitive to the consequences of the error to the observer and to the amount of empathy the observer has for the observed actor. On the other hand, the reinforcement learning and the action-outcome association theories would predict that the pMFC would be differently activated in situations where the actor was part of the team being supported compared to situations where the actor was part of the opposing team. Despite the fact that these two situations represent an action error, the consequences of the action error would be different for the observer leading to the differential pMFC activation.

Here we created a naturalistic task to investigate the effect of empathy on the activity of the sensorimotor MNS and on the activity of the pMFC performance monitoring system. We recorded electroencephalography (EEG) while participants played a game in which they selected one of two basketball players to be their partner—effectively gambling on this player—and then watched videos of this partner and an opponent shooting basketball free-throws in a shootout competition.

We predicted that if the sensorimotor MNS, as indexed by mu rhythm suppression, is modulated by empathy and imitation, than observing the partner—a person the participants would have more empathy for—would lead to greater activation of the sensorimotor MNS compared to when observing the opponent. On the other hand, we predicted that if the sensorimotor MNS is not based on empathy and imitation but rather reflects action understanding by the activation of embodied representations of the action, than the sensorimotor MNS would show similar activity in response to the observation of partners and opponents.

With respect to the pMFC performance monitoring system, we predicted that if it reflects a dedicated error processing system, than activity in the pMFC, as indexed by the observation-related negativity, would be similar for the observation of partner and opponent errors. On the other hand, we predicted that if the pMFC reflects a system that takes into account the consequences of the observed action to the self—such as what is proposed by the reinforcement learning and action-outcome association theories—then the pMFC would be differently activated by the observation of partner and opponent errors. This could be reflected by increased pMFC activity elicited to partner errors relative to opponent errors and partner hits, and possibly also by increased pMFC activity elicited to opponent hits—which are unfavorable to the participants—relative to opponent misses—which are favorable to the participants.

METHODS

Participants

Ten healthy right-handed experiment naïve men (mean age 21.7 years, range: 18-27 years) participated in the study. We screened potential participants for basketball experience and only selected those who played basketball at least once a month. On average participants estimated that they played 6.1 times per month (range: 2-20 times per month). Participants provided written informed consent prior to the start of the experiment and were paid for their participation.

Task and Procedures

Participants sat comfortably in an electrically shielded and sound attenuated chamber in front of a window immediately facing the screen of a CRT monitor that was placed outside of the chamber. The task was to play a series of games in which participants selected virtual partners for a basketball shootout. Participants were instructed that they would receive additional money depending on how well they performed in the game; thus, they were effectively betting that their selected player would outperform the non-selected player. Each game was composed of two halves and started with the presentation of two side-by-side pictures of male basketball players (Figure 1). Participants selected one of the two players to be their partners by pressing the right or left arrow keys on a computer keypad. Following the selection, participants saw a screen that lasted 2,000 ms and indicated that the selected player was their partner and the unselected player was their opponent. Participants then saw a single picture of either their partner or opponent—with the order pseudo-randomly assigned—for 2,000 ms. This was followed by a series of 6 videos of this player shooting basketball free-throws. Each video was 3,000 ms long and the last frame of the video was frozen for an additional 800 ms. A blank screen was presented between videos for a variable period lasting 750 to 2,750 ms. After watching the first series of videos, participants saw a single picture of the other player (i.e., the partner if the first series of videos was for the opponent and the opponent if the first series of videos was for the partner) followed by a series of 6 videos of this player shooting. After the end of the second series of videos, participants were asked a question about the score of the game (e.g., Is your partner winning by two baskets?) and responded by pressing the right (yes) or left (no) arrow keys on a computer keypad. These questions were used to ensure that participants were paying attention to the videos. Participants then saw a feedback screen for 2,500 ms indicating the score of the game and whether they had correctly or incorrectly answered the question. Following the feedback screen, participants saw a video of visual white noise for 5,000 ms. This corresponded to the halftime of a game. The score from the first half of the game carried over to the second half, which followed similar procedures as the first half but started with participants selecting a partner from a new pair of players. At the end of the second half participants received an additional feedback screen indicating the overall score of the game, as well as how much money they had earned on that game. Participants were instructed that earnings were based both on the score of the game as well as on whether they responded the questions correctly or incorrectly. Unbeknownst to the participants, the frequency of hits and misses for partners and opponents was pre-determined across the experiment and fixed at one third misses and two thirds hits for both partners and opponents, irrespective of participant choices. None of the participants reported noticing this during debriefing. Each testing session was composed of 22 games (44 halves).

Electrophysiological recording and pre-processing

We recorded EEG from 64 silver/silver chloride active electrodes attached to an elastic-fabric cap (Biosemi B.V., Amsterdam) and positioned in standard locations according to the 10-10 system (Fpz, Fp1,Fp2, AFz, AF3, AF4, AF7, AF8, FCz, FC,1 FC2, FC3, FC4, FC5, FC6, Fz, F1, F2, F3, F4, F5, F6, F7, F8, FT7, FT8, Cz, C1, C2, C3, C4, C5, C6, T7, T8, CPz, CP1, CP2, CP3, CP4, CP5, CP6, Pz, P1, P2, P3, P4, P5, P6, P7, P8, P9, P10, TP7, TP8, POz, PO3, PO4, PO7, PO8, Oz, O1, O2 and Iz). An additional 6 electrodes were used in the recordings. We placed one of these electrodes on the right mastoid (M1) and one on the left mastoid (M2). We also placed electrodes lateral to both external canthi to record horizontal electrooculography (EOG) and an electrode below the left eye to record vertical EOG. EEG signals were digitized at 512 Hz and stored for offline averaging. Offline analysis was performed with EEGLAB (Delorme & Makeig, 2004). The data were down-sampled to 256 Hz, re-referenced to an average reference and filtered offline. For the ERP analysis we filtered the data with a lowpass filter of 20 Hz and a highpass filter of 1 Hz. For the time-frequency analysis we filtered the data with a lowpass filter of 20 Hz and a highpass filter of 0.1 Hz. The data were then epoched and trials with artifacts were excluded by visual inspection. For the ERP analysis we then used blind source separation based on second order blind identification (SOBI) to remove EOG artifacts from the data (Gómez-Herrero, et al., 2006). Following, we used an automated procedure to exclude trials with activity deviating by 6 standard deviations or more from the probability distribution of all trials for each participant and also trials with activity greater than 100 µV or smaller than -100 µV. Excluded trials accounted for an average of 15.8% (3.2% S.E.M) of the total trials.

Event-related potential (ERP) analysis

With the ERP analysis we were interested in comparing the differences in brain responses to the observation of hits and misses between videos of partners and opponents. After pre-processing the data, we extracted ERPs for 4 conditions of interest: partner hits (P_HIT), partner misses (P_MISS), opponent hits (O_HIT) and opponent misses (O_MISS). ERPs were calculated by averaging the epochs time-locked to the last frame of each movie. For all ERP analyses, data were baselined to the average amplitude of the 100 ms period preceding the last frame of the videos.

Neural source analysis

Neural sources were estimated by creating dipole models using BESA 5.2 software (Megis software) for each of the contrasts of interest: [P_MISS – P_HIT], [O_MISS – O_HIT] and [(P_MISS – P_HIT) – (O_MISS – O_HIT)]. For all three contrasts we created free-fit models with two symmetrical regional sources to account for activity in extrastriate cortex and an additional unconstrained dipole.

Time-Frequency Analysis

With the time-frequency analysis we were interested in comparing mu rhythm suppression in response to the observation of videos of partners and opponents shooting. We also included videos of white noise in the analysis as a baseline for mu rhythm activity. We calculated event-related spectral perturbations (ERSP) for the C3 and C4 electrodes, which lie approximately over sensorimotor cortex where the mu rhythm is generated (Pineda, 2005, 2008). To calculate the ERSP we used a sinusoidal wavelet transform with 2 cycles in length at the lowest frequency (4 Hz), increasing linearly to 9 cycles in length for the highest frequency (18 Hz). The ERSP was calculated on epochs time-locked to the onset of individual videos relative to a baseline spanning the 500 ms preceding the onset of the videos (Delorme & Makeig, 2004).

Statistical analysis

For all pairwise comparisons, we conducted one-tailed paired permutation tests based on all possible permutations of the data (2^{10}). For all multi-factor comparisons, we conducted repeated measures permutational analyses of variance (pANOVAs) based on 10,000 permutations of the data. We calculated bias corrected and accelerated bootstrap confidence intervals (C.I.) by creating a paired-sample bootstrap distribution of 10,000 resamples of the data.

RESULTS

Behavioral results

The behavioral results showed that participants paid attention to the outcome of the videos responding correctly to 90.5% (95% C.I: 86.7% - 93.6%) of the questions about the scores.

Event-related potentials (ERPs)

Figure 2a displays ERP waveforms elicited by P_MISS, P_HIT, O_MISS and O_HIT videos. Videos of missed shots, irrespective of whether they were of partners or opponents, elicited a negative-going deflection that peaked at around 220 ms after the onset of the last frame of the video (Figure 2a). This negativity had a fronto-central maximum (Figure 2c) and was virtually absent from the ERP waveforms elicited by videos of hits, irrespective of whether the videos were of partners or opponents. Instead, hits showed a positive-going deflection that peaked at around 110 ms after the onset of the last frame of the video (Figure 2a) and had a central-posterior / left-posterior maximum (Figure 2c). We conducted two planned pairwise comparisons on the mean amplitude of the waveforms during the 82-242 ms time window at electrode Cz to test the significance of the difference between hits and misses for partner and opponent videos. The P_MISS and the O_MISS waveforms were significantly more negative than the P_HIT ($p = .001$) and O_HIT waveforms ($p = .002$), respectively. Figure 2b displays the difference waveforms for [P_MISS – P_HIT] and [O_MISS – O_HIT]. The difference between the negative-going deflection for the misses and the positive-going deflection for the hits was expressed as a negativity peaking at around 125 ms after the onset of the last frame of the partner and opponent videos. These negativities both had a central maximum, but extended posteriorly and laterally to the left (Figure 2d). To test the interaction between the outcome of the videos (hits or misses) and which players were shooting (partners or opponents), we compared the mean amplitude of the two difference waveforms during the 109-137 ms time window at electrode Cz. We found that the difference waveform for partner videos was significantly more negative than the difference waveform for opponent videos during this time window ($p = .0029$). The difference of the differences (i.e., [(P_MISS – P_HIT) – (O_MISS – O_HIT)]) peaked at 125 ms and had a central maximum (Figure 2d).

Neural source estimations

Figure 3 displays the source estimations from the dipole models for the [P_MISS – P_HIT], [O_MISS – O_HIT] and [(P_MISS – P_HIT) – (O_MISS – O_HIT)] contrasts. All three free-fit models were similar with an estimated dipole in caudal ACC (Figures 3a and 3b) and the symmetric sources estimated in extrastriate cortex (Figures 3c and 3d). The three models provided good fits to the data: the model for the [P_MISS – P_HIT] contrast accounted for 96.9% of the variance in the 82-242 ms time window, the model for the [O_MISS – O_HIT] contrast accounted for 93% of the variance in the 82-242 ms time window and the [(P_MISS –

P_HIT) – (O_MISS – O_HIT)] contrast accounted for 92.4% of the variance in the 109-137 ms time window.

Mu rhythm suppression

Figure 4 displays the ERSP at electrodes C3 and C4 induced by videos of partners, opponents and visual white noise. Videos of partners and opponents induced suppression in the 8-13 Hz range starting at around 200 ms and lasting for the entire video duration. In contrast, videos of visual white noise did not show mu rhythm suppression. We tested the difference in the ERSP in the 8-13 Hz range between videos of partners, opponents and visual white noise by conducting three separate 2 (video) by 2 (electrode) pANOVAs on the mean power in this frequency range during the 500-3000 ms time window. All three pANOVAs had C3 and C4 as the two levels for the electrode factor. The pANOVA with partner and white noise as the two levels for the video factor showed video (p = .0278) and electrode (p = .0254) main effects and no interaction (p = .7427). The pANOVA with opponent and white noise as the two levels for the video factor showed a similar result with a video main effect (p = .0282) and a marginally reliable electrode main effect (p = .0532) and no interaction (p = .9334). The pANOVA with partner and opponent as the two levels for the video factor showed an electrode main effect (p = .0358) but no video main effect (p = .748) and no interaction (p = .5324). Figure 5a displays the mean power in the 8-13 Hz range for the 500-3000 ms time window. The 95% confidence intervals show that the mu suppression induced by the partner and opponent videos was reliably different from zero for both the C3 and C4 electrodes. On the other hand, visual white noise induced small mu suppression at electrode C3 and enhancement at electrode C4 but none of these effects were reliably different from zero.

To evaluate whether the observation of partner and opponents had an effect on the gain of mu suppression, we conducted simple linear regression analysis with zero intercept by least squares method. Figures 5b and 5c show the individual data and the regression line for electrodes C3 and C4, respectively. The model was a good fit for the data with 78% (C.I. = 32% to 98%) and 94% (C.I. = 52% to 99%) of the variance in opponent mu suppression explained by partner mu suppression for electrodes C3 and C4, respectively. The slope of the regression line indicates the relation between mu suppression for observation of partner actions and opponent actions. A slope greater than one indicates increased mu suppression gain for the observation of opponent actions relative to partner actions. A slope smaller than one indicates decreased mu suppression gain for the observation of opponent actions relative to partner actions, and a slope of one suggests no difference in mu suppression gain between partner and opponents. The slope for the regression line was close to one for both electrodes (C3 = 0.93, C.I. = 0.81 to 1.19; C4 = 0.99, C.I. = 0.88 to 1.03), adding to the results of the pANOVA in suggesting that there was no difference in the gain of mu suppression between the observation of partners and opponents.

DISCUSSION

In the present study we used a naturalistic task to investigate the role of empathy on the function of the pMFC performance monitoring system and the MNS in action observation. We made different predictions based on the main theories that attempt to explain the function of these two neural systems.

Empathy and the pMFC performance monitoring system

At the outset, we predicted that if the pMFC performance monitoring system is only related to the comprehension of an error and is not sensitive to the consequences of the action to the self, then empathy would not affect the activity of the pMFC during the observation of partner and opponent actions. On the other hand, we predicted that if the pMFC performance monitoring system is sensitive to the consequences of the action to the self, than empathy would modulate the activity of the pMFC during the observation of partner and opponent actions. This could be expressed in two ways. The most extreme result would be the combination of an increased activation of the pMFC in response to partner misses relative to partner hits and the opposite result for the observation of opponents with increased activation of the pMFC in response to opponent hits relative to opponent misses. A less extreme result would be increased activation of the pMFC in response to misses relative to hits for both partners and opponents, but an increase in the gain of this difference in the case of partners.

The results favored the view that empathy influences the pMFC performance monitoring system, matching the less extreme version of the predicted results for this view. The findings extended the results of previous studies (Miltner, et al., 2004; van Schie, et al., 2004) showing that the observation of missed shots elicited an observation-related negativity that was absent from the observation of hits for both the observation of partners and opponents (Figure 2). This observation-related negativity was estimated to come from a pMFC generator in caudal ACC for both the observation of partners and opponents (Figure 3). Interestingly, the observation-related negativity was larger for the observation of partners than opponents (Figures 2c and 2d). This difference appears to reflect a modulation of the gain in the activity of the same neural generators as those responsible for the difference between hits and misses. The neural source of this activity was estimated to come from approximately the same caudal ACC and extrastriate sources (Figure 3). This result suggests that the consequences of the observed action to the participants, and therefore the amount of empathy the participants had for the observed players, took part in the modulation of the pMFC activity in performance monitoring. This could be explained in three ways.

The first possibility is that participants increased their attention to the outcome of partner shots, which in turn increased the gain of the observation-related negativity. This attention-based explanation is consistent with evidence showing that instructions or different task demands that require participants to attend to an aspect of the task (e.g., accuracy or speed), can modulate the gain of the response elicited ERN/Ne (Gehring, et al., 1993; Rüsseler, Kuhlicke, Heldmann, & Münte, 2004; Ullsperger & Szymanowski, 2004). This possibility suggests that the role of empathy was increasing the attentional focus directed to partners, whom the participants presumably had more empathy for, relative to opponents.

Another possibility is that in the case of partner shots, participants developed stronger and more frequent expectations of hits. This is consistent with data suggesting that humans are overoptimistic about self-affecting future events (Miller & Ross, 1975; Oliveira, et al., 2007; Sharot, Riccardi, Raio, & Phelps, 2007) and also that humans evaluate outcomes in a biased manner when gambling (Gilovich, 1983). A more optimistic expectation of partner outcomes than opponent outcomes would lead to a larger percentage of partner misses reflecting a violation of expectancy, which has been shown to relate to pMFC activity more closely than errors (Oliveira, et al., 2007). This is because when expectations are violated, the pMFC is presumably involved in updating the internal model that is used to generate the expectations (Oliveira, et al., 2007 ; Oliveira, Hickey & McDonald, unpublished data).

A third possibility is that two types of errors played a role in the generation of the observation-related negativity. Since participants were playing a gambling game in which their goal was to choose the players who would score the most to be their partners, it is possible that the observation-related negativity was a superposition of negative-going deflections elicited in response to both errors of choice and missed shots.

These three different possible explanations for the observation-related negativity results are not mutually exclusive. These results therefore cannot disambiguate between the different theories that attempt to explain the role of the pMFC in performance monitoring at a process level. Nevertheless, the observation-related negativity results showed that the pMFC was more strongly activated in response to partner misses than opponent misses, consistent with the results of a recent fMRI study (Newman-Norlund, et al., 2009). This suggests that, independent of the psychological processes underlying these results, the pMFC performance monitoring system is differentially responsive to the observation of actors for whom the observers have more or less empathy.

Empathy and the sensorimotor MNS

At the outset, we predicted that if empathy plays an important role in the activity of the sensorimotor MNS, than the observation of partner actions would lead to greater activation of the MNS than the observation of opponent actions. On the other hand, we predicted that if empathy does not play an important role in the activation of the sensorimotor MNS, than the activation of the MNS would not differ between the observation of partner and opponent actions.

The results favored the view that empathy does not play an important role in the activation of the sensorimotor MNS. Consistent with previous studies, we found that the observation of action induced mu suppression at the C3 and C4 electrodes, which lie over sensorimotor cortex (Muthukumaraswamy & Johnson, 2004; Muthukumaraswamy, et al., 2004; Neuper, Wortz, & Pfurtscheller, 2006; Oberman, et al., 2005; Oberman, Ramachandran, & Pineda, 2008; Pineda, Allison, & Vankov, 2000). However, we found no reliable difference in mu suppression during the observation of partners and opponents (Figure 5). The two conditions led to nearly identical mu suppression in both the C3 and C4 electrodes (Figure 5). It is important to note that one has to be careful when interpreting null results. Nevertheless, this finding supports the idea that empathy and theory of mind may rely on neural systems separate from the sensorimotor MNS (Southgate & Hamilton, 2008; Völlm, et al., 2006). One possibility that cannot be discarded, however, is that mu suppression does not in fact represent the activation of the MNS, given that the MNS is traditionally associated with inferior frontal and parietal cortices. Mu rhythm suppression appears to originate in sensorimotor cortex (Caetano, Jousmaki, & Hari, 2007) and reflect the effect of the frontal and parietal MNS areas in sensorimotor cortex (Hari, 2006; Pineda, 2005, 2008). However, it may not directly reflect the activity of the core parieto-frontal MNS. Still, independent of whether mu suppression reflects the activity of the core parieto-frontal MNS or not, our results show that activity in sensorimotor cortex during the observation of action does not appear to be sensitive to the amount of empathy that observers have for the actors.

Lateralization of the MNS

An important question related to the MNS is whether or not it displays any hemispheric specialization. This is particularly relevant for theories that advocate that the MNS is linked to language (Aziz-Zadeh & Ivry, 2009; Aziz-Zadeh, Wilson, Rizzolatti, & Iacoboni, 2006; Corballis, 2009a, 2009b; Fogassi & Ferrari, 2007; Rizzolatti & Arbib, 1998), since language is largely lateralized to the left-hemisphere (Gazzaniga, 2000). The existing evidence is mixed with some authors suggesting that the MNS is lateralized to the left hemisphere (Corballis, 2009a; Fecteau, Lassonde, & Theoret, 2005) and some arguing that it does not display any sort of lateralization (Aziz-Zadeh, Koski, et al., 2006; Iacoboni & Dapretto, 2006). Our results favor the view of a left-hemisphere dominant MNS. Mu suppression was significantly stronger in the left hemisphere compared to the right hemisphere for both the observation of partners and opponents. This is consistent with evidence suggesting a left-hemisphere specialization for praxis (Frey, 2008; Oliveira & Ivry, 2008).

Are the present results ecologically valid?

When designing the experiment, one of our goals was to develop a task that was naturalistic and ecologically valid. To this end, we used whole-body videos of a multi-joint action (i.e., basketball shot). One major constraint, however, was the need to have a substantial number of trials to deal with the relatively low signal-to-noise ratio of EEG recordings. An important question that arises is whether the large number of trials in the experiment created an artificial situation. While we are confident that our results reliably represent the effect that observing partner and opponent actions had on our participant's neural activity, it is possible that our results do not represent the most extreme cases of observing actors for whom the observers may have high or low empathy. In other words, if we were able to extract the brain responses to a single observation of an important action such as a game-deciding basketball free-throw, would our results have been different? We find this conjecture possible and even likely. Nevertheless, in our daily lives such extreme situations are rare. Thus, we believe that while our results might not provide a complete picture of how empathy for the observed actor influences the pMFC performance monitoring system and the sensorimotor MNS, it still provides an understanding of how this may work for the majority of situations we face. Whether or not empathy plays a different role in more extreme situations is a question that warrants future work.

CONCLUSION

In summary, our data show that the observation of missed free-throws by both partners and opponents led to a larger observation-related negativity relative to the observation of made free-throws. The difference between misses and hits was larger for partner videos than opponent videos. This finding suggests that empathy for observed actors plays a role in modulating the gain of pMFC activity elicited by the observation of action errors. With respect to the MNS, we found mu rhythm suppression during the observation of both partner and opponent actions. Mu rhythm suppression was larger in the left hemisphere, which suggests that activity in the MNS might be left-hemisphere dominant during the observation of whole-body actions. We found no difference in mu rhythm suppression between the observation of partner and opponent actions. This finding suggests that the activity in the sensorimotor MNS is insensitive to the amount of empathy the observer has for the observed actor.

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FIGURE CAPTIONS

Figure 1. *Schematic representation of a game half.*

Figure 2. *Grand averaged ERP waveforms and scalp voltage distribution maps*. (**a**) ERP waveforms for electrode Cz, time-locked to the last frame of the videos for the four conditions of interest. The grey shaded area represents the time window used for the statistical analysis. Negative voltages are plotted upward by convention. (**b**) Difference waveforms calculated by subtracting hit waveforms from miss waveforms separately for partner and opponent videos. Waveforms are time-locked to the last frame of the videos. The yellow shaded area represents the time window used for the statistical analysis. Negative voltages are plotted upward by convention. (**c**) Scalp voltage maps for the four conditions of interest. Squares surrounding each map match the corresponding ERP waveforms in [a]. Colors represent the mean voltage for the 82-242 ms time window (the grey shaded area in [a]). The small black dots in each scalp map represent the location of each electrode and the larger grey dot represents the location of the Cz electrode. (**d**) Scalp voltage maps for the two difference waveforms ([P_MISS – P_HIT] and [O_MISS – O_HIT]) and the difference of the differences waveform ([(P_MISS – P_HIT) – (O_MISS – O_HIT)]). Squares surrounding maps match the corresponding ERP waveforms in [b]. Colors represent the mean voltage for the 82-242 ms time window (the grey shaded area in [a]) for the difference waveforms and for the 109-137 ms time window (the yellow shaded area in [b]) for the difference of the differences waveform. The small black dots in each scalp map represent the location of each electrode and the larger grey dot represents the location of the Cz electrode.

Figure 3. *Neural source estimations*. Dipole models for [P_MISS – P_HIT], [O_MISS – O_HIT] and [(P_MISS – P_HIT) – (O_MISS – O_HIT)] are overlaid an anatomical magnetic resonance image as green, red and blue sources, respectively. (**a**) Sagital view displaying the caudal ACC sources. (**b**) Axial view displaying the caudal ACC sources plotted on a 3D reconstruction of the head. (**c**) Sagital view displaying the extrastriate sources. (**d**) Axial view displaying the extrastriate sources.

Figure 4. *Grand averaged ERSP time-locked to the onset of the videos for the three conditions of interest plotted separately for the C3 and C4 electrodes*. Red dots on the sphere head model display the position of the C3 and C4 electrodes. Rectangular boxes represent the time/frequency window used for the statistical analysis (500-3000 ms / 8-13 Hz).

Figure 5. *Mu suppression and enhancement*. (**a**) Mu rhythm suppression and enhancement at electrodes C3 and C4 for partner (Part.), opponent (Opp.) and visual white noise (W.N.) videos. Data plotted represent mean power at the 8-13 Hz frequency band from 500 to 3000 ms after the onset of the videos (this time-frequency window is displayed as the rectangular boxes in Figure 4). Positive values indicate enhancement and negative values indicate suppression. MNS activity is associated with mu suppression. Error bars display 95% confidence intervals. Grey dots on the sphere head model display the position of the C3 and C4 electrodes. (**b**) Partner and opponent mu suppression at electrode C3. Black dots represent individual participant data. The dashed line represents the regression line for the simple linear regression model with zero intercept. The

slope of the regression line represents the modulation of the mu suppression gain by the observation of opponent actions relative to partner actions. A slope greater than one suggests that the observation of opponent actions led to an increase in mu suppression gain relative to the observation of partner actions. A slope smaller than one suggests that the observation of opponent actions led to a decrease in mu suppression gain relative to the observation of partner actions, and a slope of one suggests no difference in mu suppression gain between partner and opponents. (**c**) Partner and opponent mu suppression at electrode C3. Details as in [**b**].

Figure 1

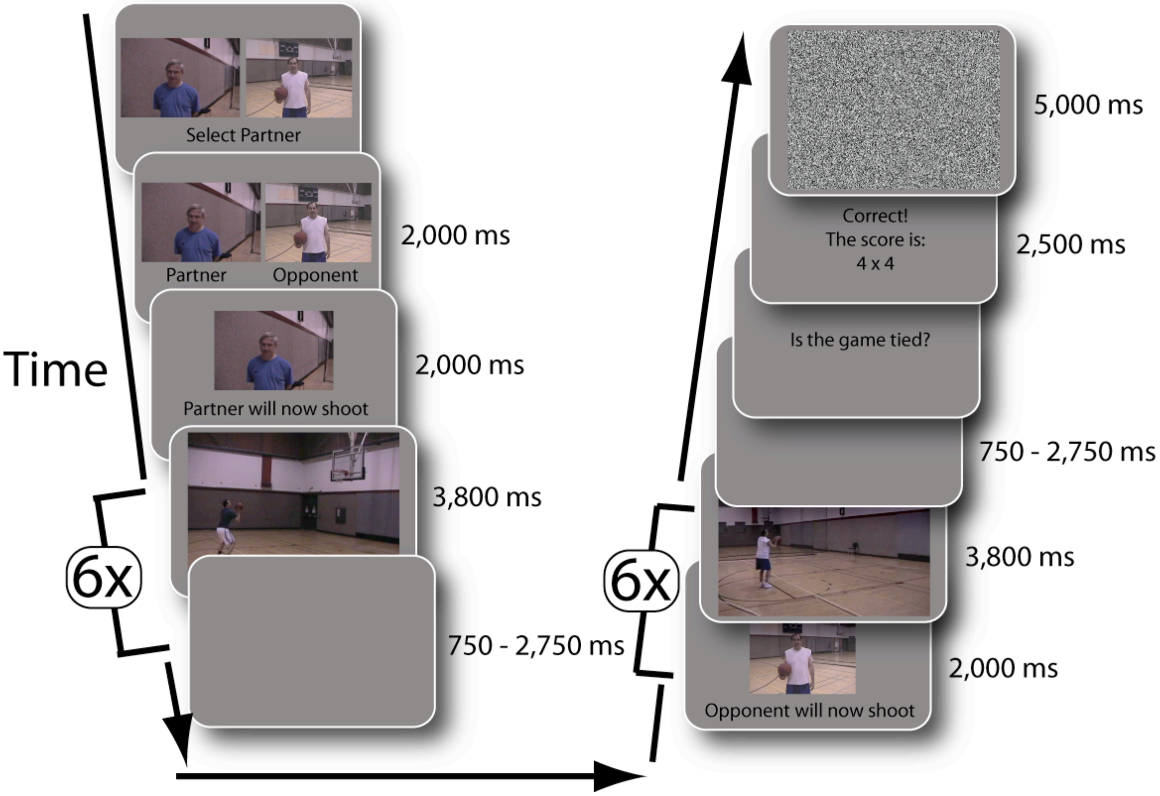

Time
Select Partner
Partner
Opponent
2,000 ms
Partner will now shoot
2,000 ms
3,800 ms
6x
750 - 2,750 ms
5,000 ms
Correct!
The score is:
4 x 4
2,500 ms
Is the game tied?
750 - 2,750 ms
6x
3,800 ms
Opponent will now shoot
2,000 ms

Figure 2

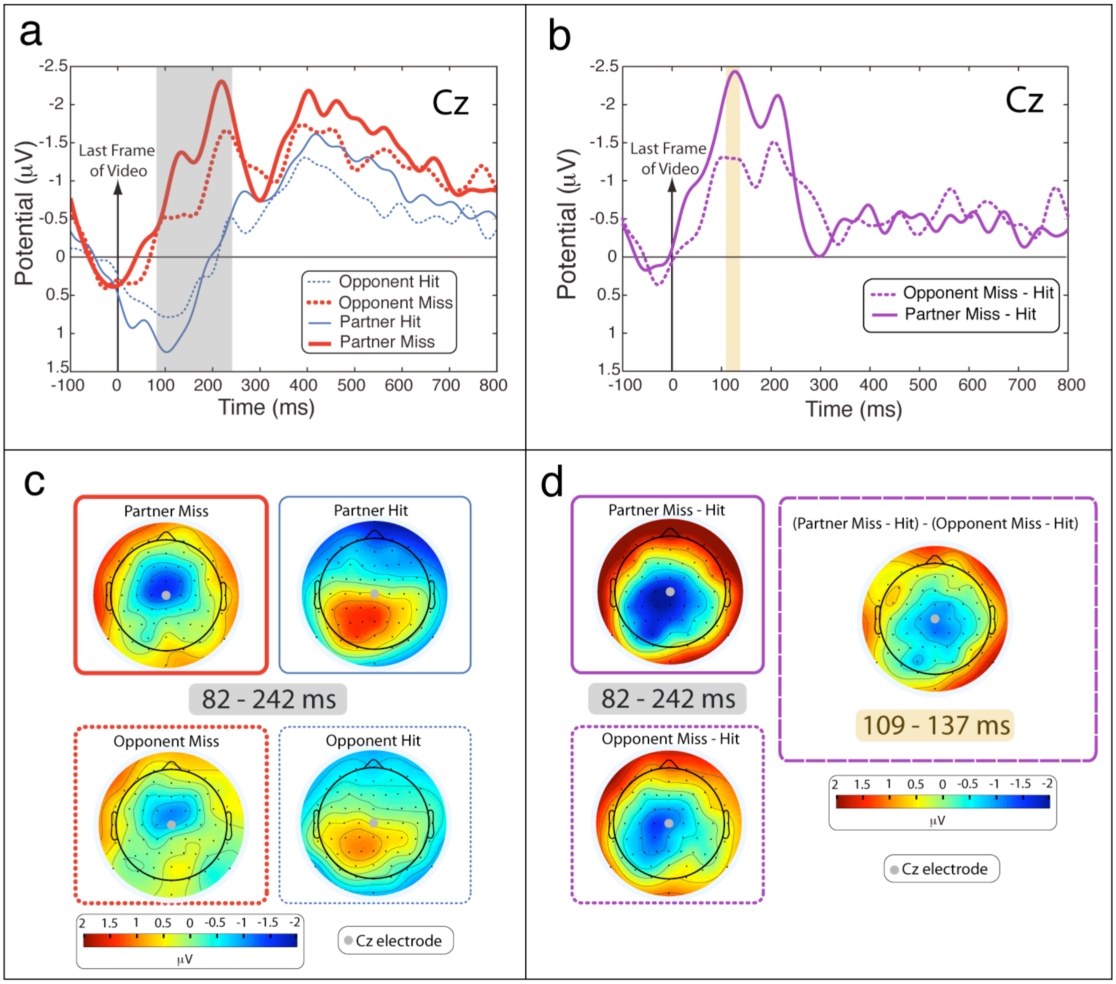

a
Cz
Potential (µV)
-2.5
-2
-1.5
-1
-0.5
0
0.5
1
1.5
Last Frame of Video
-100
0
100
200
300
400
500
600
700
800
Time (ms)
Opponent Hit
Opponent Miss
Partner Hit
Partner Miss
b
Cz
Opponent Miss - Hit
Partner Miss - Hit
c
Partner Miss
Partner Hit
82 - 242 ms
Opponent Miss
Opponent Hit
2 1.5 1 0.5 0 -0.5 -1 -1.5 -2
µV
Cz electrode
d
Partner Miss - Hit
82 - 242 ms
Opponent Miss - Hit
(Partner Miss - Hit) - (Opponent Miss - Hit)
109 - 137 ms
2 1.5 1 0.5 0 -0.5 -1 -1.5 -2
µV
Cz electrode

Figure 3

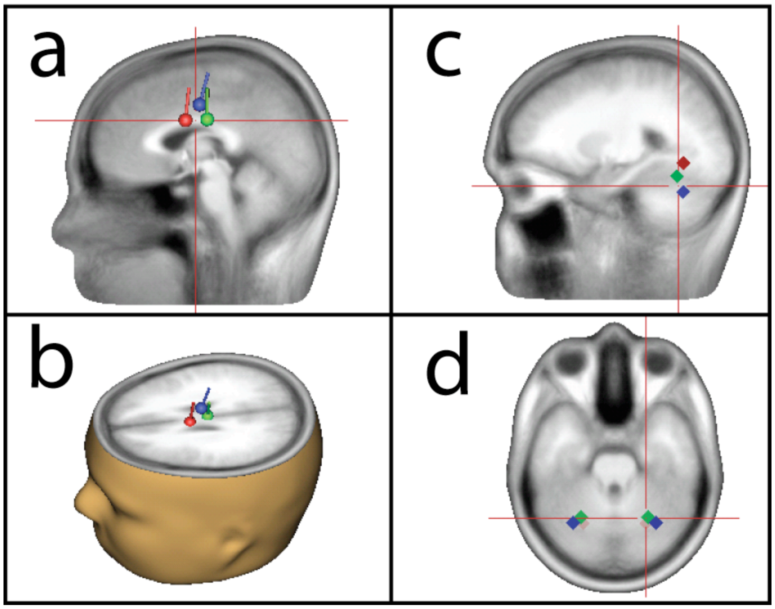


Figure 4

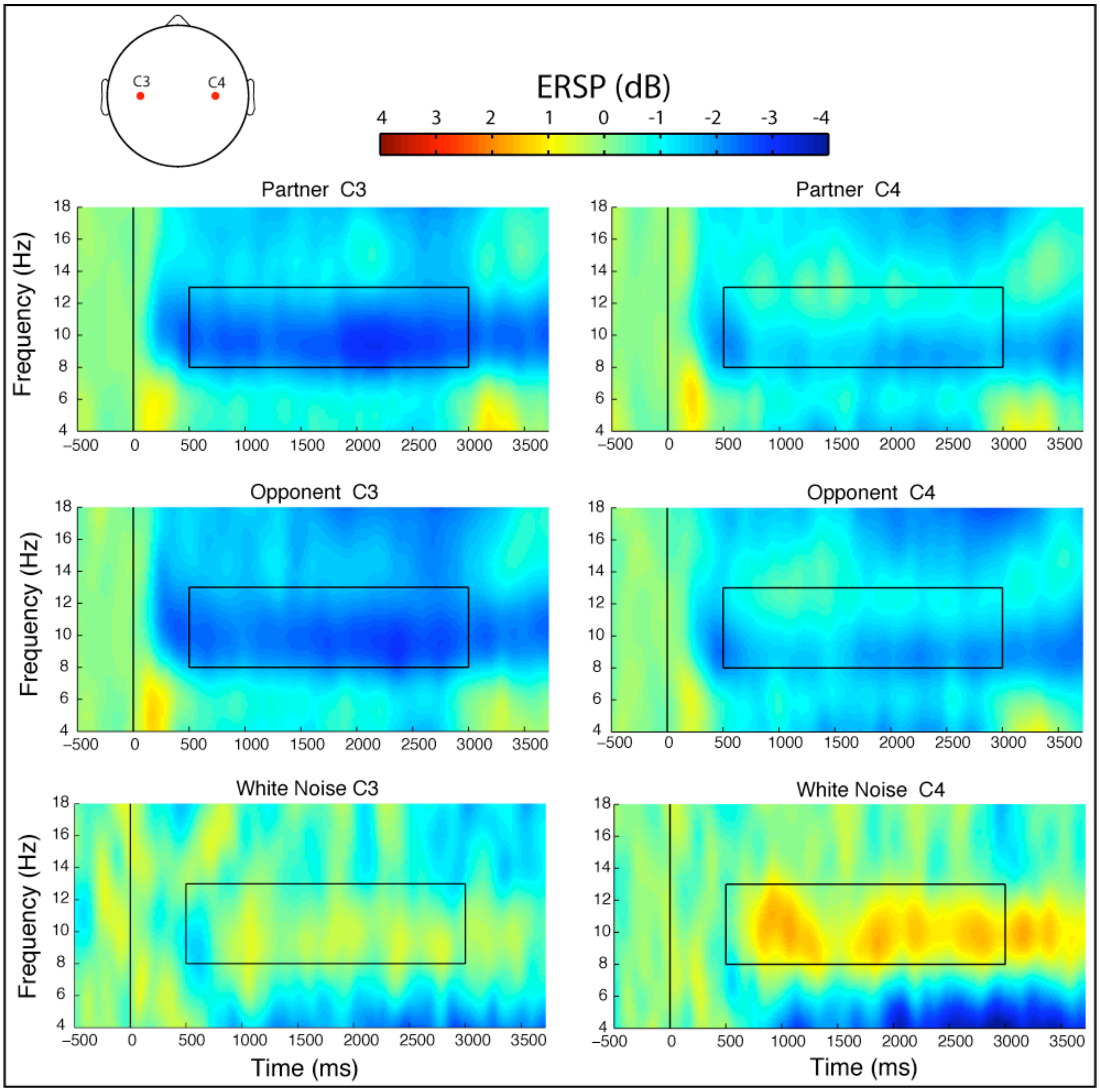
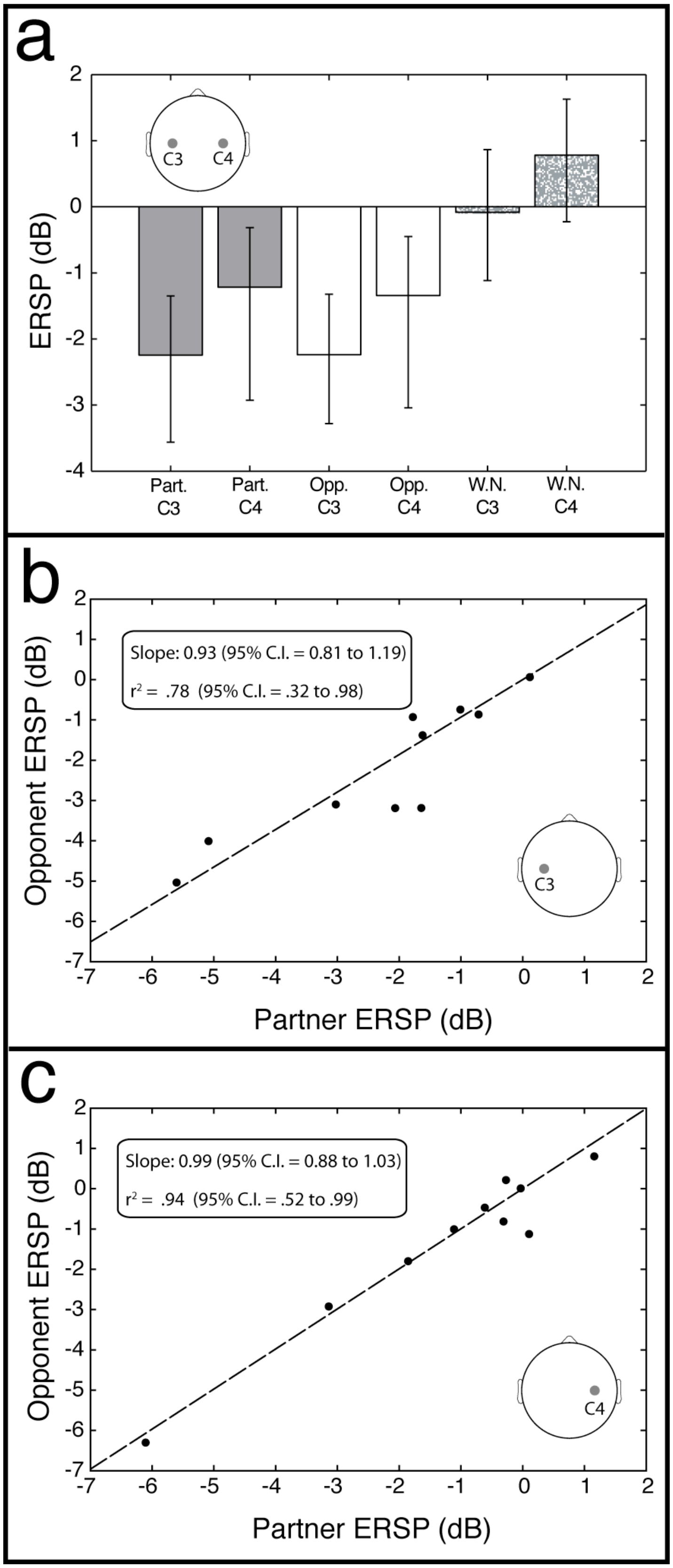

C3
C4
ERSP (dB)
4 3 2 1 0 -1 -2 -3 -4
Partner C3
Partner C4
Opponent C3
Opponent C4
White Noise C3
White Noise C4
Frequency (Hz)
18 16 14 12 10 8 6 4
–500 0 500 1000 1500 2000 2500 3000 3500
Time (ms)

Figure 5



a
ERSP (dB)
2
1
0
-1
-2
-3
-4
C3
C4
Part. C3
Part. C4
Opp. C3
Opp. C4
W.N. C3
W.N. C4
b
Slope: 0.93 (95% C.I. = 0.81 to 1.19)
r² = .78 (95% C.I. = .32 to .98)
C3
Opponent ERSP (dB)
Partner ERSP (dB)
-7
-6
-5
-4
-3
-2
-1
0
1
2
c
Slope: 0.99 (95% C.I. = 0.88 to 1.03)
r² = .94 (95% C.I. = .52 to .99)
C4
Opponent ERSP (dB)
Partner ERSP (dB)
-7
-6
-5
-4
-3
-2
-1
0
1
2