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Neural Systems for Preparatory and Reactive Imitation Control

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by

Kathryn Amy Cross

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ABSTRACT OF THE DISSERTATION

Neural Systems for Reactive and Preparatory Imitation Control

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Humans have an automatic tendency to imitate, as illustrated by unconscious mimicry during social interactions and behavioral interference effects in the laboratory. Automatic imitation is thought to arise from activation of the imitative motor representation during action observation, which is likely mediated by the overlapping representation of observed and executed actions in the mirror neuron system. In contrast to mechanisms of automatic imitation, models attempting to explain how automatic imitative tendencies are brought under intentional control are incomplete. In this dissertation, I use functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS) to measure and disrupt neural activity during imitation interference tasks to expand current models of imitation control. In particular, I focus on dissociating imitation control from control over a related prepotent response tendency—spatial compatibility—to determine (1) whether control mechanisms involved in overcoming automatic response tendencies evoked by action observation utilize a dedicated mechanism and (2) whether imitation control involves modulation of the mirror neuron system. In addition, I explore the hypothesis that imitative control mechanisms may differ depending on whether control is exerted in reaction to a stimulus (after the automatic response tendency has been evoked) or in advance of a stimulus (reducing the degree of automatic response activation in the first place).

Results indicate that neural systems involved in reactive control of imitation are dissociable from those involved in controlling spatially compatible response tendencies. I propose a model of reactive imitation control involving interactions between prefrontal control regions and the mirror neuron system. In contrast to reactive control, I found no evidence of a dissociable preparatory imitation control mechanism in an fMRI study. However, TMS results suggest that preparatory control of imitation involves suppression of MNS activity, which can be reconciled with neuroimaging results through a general control that reduces the influence of visual input on the motor system. Thus, regardless of the timing, imitation control seems to involve modulation of MNS activity through interactions between general cognitive control systems and the more specific imitation circuits.

The dissertation of Kathryn Amy Cross is approved.

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Chapter 1

Introduction

Imitation plays an integral role in social and language development, learning and the transmission of culture. While we often imitate after consciously deciding to do so, such as in imitating a teacher to learn a new skill, there is now a substantial body of work demonstrating that imitation can also occur relatively automatically. Here, automatic refers to intentionality and awareness—humans often imitate without an explicit decision to do so and without realizing it. In everyday life, automatic imitation takes the form of motor mimicry as we assume the postures and gestures of social counterparts (Chartrand and Bargh, 1999). Recent work indicates that this kind of mimicry benefits social interactions. For example, being mimicked has been associated with increased liking, prosocial behavior, affiliation, and feelings of closeness (Chartrand and Bargh, 1999; Van Baaren et al., 2004; van Baaren et al., 2009). Nonetheless, we clearly do not want to be imitating all the time and the automatic tendency to imitate must be controlled in some situations. Indeed, accumulating evidence indicates that mimicry during social interactions is modulated by various factors. People mimic others they like or people of the same social group with higher frequency (Likowski et al., 2008) and mimicry is modulated by social priming (i.e. interdependent words such as “together” and “cooperate” increase mimicry, while independent words such as “alone” decrease mimicry; van Baaren et al., 2003). Thus, in real world interactions imitation frequently occurs unintentionally and without awareness, but the tendency to imitate can be modulated.

In line with these observations of the modulation of imitative behavior in naturalistic settings, there is evidence that an active control mechanism inhibits the automatic tendency to imitate. This is demonstrated most strikingly when the control mechanism is disrupted in disease states, releasing imitative behavior. Rare patients with frontal lobe damage compulsively imitate observed actions, continuing to do so even when told not to and when imitating the observed actions is irrational (for example, putting on glasses when already wearing a pair) (Lhermitte et al., 1986; De Renzi et al., 1996). More commonly, patients with neuropsychiatric and neurodegenerative disorders exhibit excessive imitation in the form of echolalia (mimicry of speech) and echopraxia (mimicry of movements) (Ganos et al., 2012; Bathgate et al., 2001; Roberts, 1989; Ford, 1989). The existence of an active control mechanism is also supported by data from healthy subjects showing that automatic imitation in a behavioral task increases when executive function resources are occupied by another task (van Leeuwen et al., 2009).

Although the neural underpinnings of imitation have received substantial attention in the past several decades, neural mechanisms involved in modulating automatic imitation remain poorly understood. Given the importance of automatic imitation in social interactions, elucidating imitative control mechanisms could prove a fruitful new avenue to understand social deficits in various psychiatric disorders, as well as provide insights into potential treatment targets. For example, in autism it has been proposed that deficits in imitation lead to poor language and social development, the core features of the disease (Williams et al., 2001). Furthermore, recent data suggest autism is associated with abnormal mirror neuron system (MNS) function (Oberman et al., 2005; Bernier et al., 2007; Theoret et al., 2005; Dapretto et al., 2006), which (as detailed below) is important for imitation. Yet, the view that mirror neuron dysfunction is a primary cause of imitative deficits in autism is disputed by the fact that some functions attributed to the mirror neuron system remain intact (McIntosh et al., 2006; Oberman et al., 2008). Thus, an alternative emerging theory posits that instead of a primary MNS deficit, the MNS

dysfunction detected in specific situations may be related to improper modulation of the MNS (Hamilton, 2008; Cook and Bird, 2012). An understanding of the normal mechanisms of imitative control is an integral first step to pursuing this theory. Yet, even if imitation control does not turn to be abnormal in autism, understanding factors that modulate imitative tendencies could improve intervention efficacy, as interventions aimed at increasing imitation have shown promise in improving language development (Ingersoll, 2008; Ingersoll and Lalonde, 2010).

With these broader implications in mind, the goal of this dissertation is to understand neural mechanisms of imitation control using functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS). Drawing on what we already know about the neural mechanisms of automatic imitation, as well as previous work on sensorimotor integration and control, I focus on whether brain systems involved in modulating imitative tendencies are distinct from other forms of cognitive control and whether control systems interact with the mirror neuron system.

1.1 Automatic imitation in the laboratory

Stimulus response compatibility paradigms provide a tightly controlled laboratory parallel to the mimicry observed in naturalistic social interactions (reviewed in Heyes, 2011). In these paradigms, the participant is instructed to make a particular response during the visual presentation of either a similar (congruent) action or a dissimilar (incongruent) action. In many variations of the task, the observed action is task-irrelevant—the response is performed to some other stimulus and the subject need not pay attention to the observed action to perform correctly. Nonetheless, the content of the observed action affects reaction times; responses are slower during observation of an incongruent action than during observation of a congruent action (congruency effect). Given that the action stimulus does not need to be processed to perform the task successfully, and that it interferes with the *intended* action on incongruent

trials, it is inferred that the processing of the action stimulus is not volitional—i.e. it is automatic—and that slower incongruent responses are due to the need to overcome automatic activation of the incorrect imitative response.

This “automatic imitation” effect is very robust and has been replicated across a variety of tasks and effectors. In the first study of its kind, participants performed hand opening and closing (grasping) actions in response to the color of a hand stimulus, which depicted either a static opened or closed hand, or a video of a hand opening or closing. Although the subjects had to look at the hand, the nature of the observed action was irrelevant since the appropriate response was dictated by the *color* of the hand. Congruency effects—faster responses when the observed and performed actions were the same compared to when they were different—were detected in both static and dynamic conditions (Stürmer et al., 2000).

Brass and colleagues extended this work in an experiment in which subjects lifted their index or middle finger in response to a number cue (i.e. 1=index, 2=middle) while a video in the background depicted a congruent action, an incongruent action or a static relaxed hand (Brass et al., 2000). By adding the relaxed hand neutral condition, they were able to demonstrate that differences between congruent and incongruent reaction times result from a combination of facilitation on congruent trials and interference on incongruent trials (Brass et al., 2000). In other words, as would be expected from automatic response activation, action observation both speeds performance of an imitative response *and* slows performance of a non-imitative response.

The same group subsequently extended the work to a simple response paradigm (in contrast to the previous two-alternative forced choice tasks), where the same video stimuli were used but the required response was predefined. The onset of movement in the action video acted as a “go” signal to perform the predefined response. Again, even though the nature of the observed action was irrelevant and the required response could be planned well in advance of the observed action, a congruency effect was observed (Brass et al., 2001a). This suggests that

the observed action interferes with a relatively late stage of motor processing—after response selection has already occurred—in keeping with the view that interference occurs due to automatic activation of the imitative response representation.

Since these seminal studies, imitative interference effects have been replicated many times. They are observed for a variety of finger (Bertenthal et al., 2006; Brass et al., 2000; Brass et al., 2001a), hand (Heyes et al., 2005; Press et al., 2008), arm (Kilner et al., 2007; Kilner et al., 2003), mouth (Leighton and Heyes, 2010) and foot (Gillmeister et al., 2008) actions; for transitive (Vainio et al., 2007; Boyer et al., 2012; Jiménez et al., 2012) and intransitive actions (Bertenthal et al., 2006; Kilner et al., 2007; Kilner et al., 2003; Press et al., 2008; Brass et al., 2000; Brass et al., 2001a; Catmur and Heyes, 2011); in choice (Brass et al., 2000; Brass et al., 2005; Bertenthal et al., 2006) and simple response tasks (Press et al., 2008; Press et al., 2006; Brass et al., 2001a); when attention must be directed at the observed action or at an alternative stimulus; and, most relevant to the studies described in the dissertation, when the observed action is spatially compatible with the response (Brass et al., 2000; Brass et al., 2001a; Press et al., 2008; Stürmer et al., 2000) and when it is not (Jiménez et al., 2012; Catmur and Heyes, 2011; Bertenthal et al., 2006; Brass et al., 2001a; Press et al., 2008).

Importantly, recent work has begun to support the presumption that these behavioral interference effects are related to the social mimicry previously described. Factors that affect the degree of mimicry during social interactions (e.g. independent and interdependent priming) have been shown to affect interference effects in a parallel way (Leighton et al., 2010; Cook and Bird, 2012), providing indirect evidence that the interference in compatibility studies and naturalistic mimicry may reflect similar processes.

1.2 Neural mechanisms of automatic imitation

The prevailing neural explanation for automatic imitation is the tight link between the observed and executed actions mediated by the MNS. Mirror neurons, recorded in macaque ventral premotor area F5 (di Pellegrino et al., 1992; Gallese et al., 1996) and in the rostral portion of the inferior parietal lobule (area PF) (Fogassi et al., 2005), are defined by their coexisting motor and sensory properties. They discharge when the monkey performs an action (e.g. grasping an object) and when the monkey observes a similar action being performed by another individual. Soon after their discovery, it was proposed that the properties of mirror neurons provide a parsimonious solution to the long-standing "correspondence problem" of imitation: How do we translate visual information into the motor representation of a visually similar action so rapidly and effortlessly? The fact that both visual and motor representations of an action might be coded for by a single neuron (or neuronal population) would mitigate the need for a complex mapping process—mirror neurons could provide a simple and fast "direct matching" mechanism between observed and performed actions allowing for efficient imitation (Iacoboni et al., 1999).

It is difficult to record mirror neurons directly in humans, as was done in monkeys, for obvious ethical reasons (though see Mukamel et al., 2010). Nonetheless, a number of findings in humans using TMS and functional imaging have providing converging evidence for an MNS-mediated direct-matching mechanism for imitation. To start with, positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies provided evidence supporting the existence of a mirror neuron system in humans. Action observation in the absence of movement was shown to activate areas that correspond closely to the regions containing mirror neurons in monkeys: the ventral part of the precentral gyrus along with the most posterior part of the inferior frontal gyrus and the rostral inferior parietal lobule (Buccino et al., 2001; Grafton et

al., 1996; Iacoboni et al., 1999; Rizzolatti et al., 1996). The same areas were shown to have motor properties as well (Grèzes et al., 2003; Iacoboni et al., 1999).

Perhaps the strongest evidence of mirroring in humans came from a study that also suggests a role for the MNS in imitation. Based on the strength of neuronal responses measured in monkeys, Iacoboni and colleagues (1999) hypothesized that areas with mirroring properties should be less active for observation compared to execution of actions, and that during imitation, which involves both processes, activity should be greater than during each in isolation. In a study of simple finger movements, both the ventral premotor cortex and the anterior part of the parietal lobe showed this predicted activity pattern (Iacoboni et al., 1999). Thus, neuroimaging studies have identified regions in the human brain that (1) have similar functional properties to mirror neurons, (2) are in similar locations to macaque mirror neuron regions, and (3) are highly active during imitation. In addition, a causal role of the ventral premotor mirror neuron region in imitation is supported by a study demonstrating that disruption of the region with TMS impairs imitation (Heiser et al., 2003).

The most relevant data with regard to mechanisms of *automatic* imitation come from parallel investigations of the human mirror neuron system using single pulse transcranial magnetic stimulation (TMS). This technique can be used to measure the corticospinal excitability of particular motor representations. The primary motor cortex is stimulated with a brief magnetic pulse, which induces a current in the underlying neural tissue that excites motor neurons. If the stimulation intensity is high enough to induce action potentials in those neurons, a peripheral muscle twitch (motor-evoked potential, MEP) can be measured from the innervated muscle with electromyography (EMG). When the stimulus intensity is held constant, the amplitude of the MEP provides a measure of the corticospinal excitability during different cognitive states. Using this technique, many studies have now demonstrated that during the passive observation of actions, corticospinal excitability increases in a specific way: MEP facilitation occurs specifically in the muscles that would be used to perform the observed action

(Gangitano et al., 2001; Borroni and Baldissera, 2008; Baldissera et al., 2001; Montagna et al., 2005; Gangitano et al., 2004; Clark et al., 2004; D'Ausilio et al., 2009; Borroni et al., 2005; Fadiga et al., 1995). Since the MEPs provide a measure of cortical motor output—and imitation is by definition a motor response that matches an observed action—this "motor resonance" phenomenon demonstrates that the imitative response is activated by action observation even in the absence of any intention to act (i.e. automatically).

Motor resonance provides a plausible neurophysiological explanation for the behavioral automatic imitation interference effects described in the previous section, and the properties of mirror neurons map well onto both phenomena. As such, a relationship between the three (motor resonance, mirror neurons and automatic imitation) has been suggested for some time, and more direct evidence for this view continues to emerge. First, the fact that motor resonance is mediated by the MNS is suggested by a study that used repetitive TMS (rTMS) to temporarily disrupt activity in ventral premotor cortex (PMv; the human homologue of monkey F5 that was activated in the previously described neuroimaging studies). Disruption of PMv eliminated the motor resonance phenomenon (Avenanti et al., 2007)—there was no longer evidence of muscle-specific facilitation in response to action observation—suggesting intact function of the region is required for motor resonance to occur. TMS disruption of the same premotor region also reduced automatic imitation in a recent behavioral study (Catmur and Heyes, 2011), providing indirect evidence that mirror neurons and the motor resonance phenomenon are related to automatic imitation. Further evidence linking motor resonance and automatic imitation has come from recent studies demonstrating that manipulations modulating automatic imitation modulate motor resonance in a parallel fashion. As already mentioned, people mimic more after being primed with pro-social or interdependent words (i.e. "together", "cooperate") and less with independent or anti-social words (i.e. "individual", "alone") (Leighton et al., 2010; van Baaren et al., 2003). Similar priming also increases action observation-induced MEP facilitation (Hogeveen and Obhi, 2012). A converse relationship between mimicry and motor resonance

has also been observed: People who imitated more in a natural interaction showed greater action observation-induced motor facilitation (Obhi et al., 2011). Thus, converging evidence now provides strong footing for the argument that action observation activates a corresponding imitative response that can be measured with motor resonance; and that this motor resonance is likely to be mediated by the mirror neuron system and underlie automatic imitative tendencies.

The data summarized support a model of imitation proposed by Iacoboni (Iacoboni, 2005) that can be extended as well to automatic imitative tendencies (Ferrari et al., 2009). According to the model, parietal mirror neurons receive visual information about actions via inputs from posterior superior temporal sulcus (STS), a region involved in visual processing of biological motion (Perrett et al., 1989; Puce and Perrett, 2003). Parietal mirror neurons are reciprocally connected to premotor mirror neuron regions, which project to primary motor cortex. Therefore, action observation results in a flow of information from visual regions, through the mirror neuron system, and finally to primary motor cortex (Nishitani and Hari, 2000), causing excitation of the motor representation for observed actions.

1.3 Neural mechanisms of imitation control

The fact that action observation causes motor excitation of the imitative response raises the question of how this motor activation is modulated. It is clear from the work already described that some modulation of imitative tendencies occurs, allowing subconscious mimicry in some circumstances while avoiding perpetual imitation. Furthermore, the fact that brain damage can release imitative behavior, suggests that this modulation occurs via an active inhibitory mechanism that normally keeps unwanted imitation at bay.

The neural mechanisms involved in inhibiting automatic imitative tendencies have only recently been studied. This work has utilized the automatic imitation interference paradigms

described in the previous section. As already mentioned, slower responses when an observed action is incongruent with the required response are attributed to the fact that the incorrect imitative response is automatically activated, causing conflict between intended and automatically activated responses. In line with the broader cognitive control literature (Miller and Cohen, 2001), slower reaction times associated with this conflict are attributed in particular to the recruitment of 'control' processes required to overcome the automatically evoked response in favor of the less automatic response. Innumerable models delineating control over prepotent response tendencies have been proposed (Miller and Cohen, 2001; Kornblum et al., 1990; Ridderinkhof et al., 2004; Botvinick et al., 2004), with many of them incorporating a mechanism that detects the presence of conflict and a mechanism to select between competing response representations, often through top-down inhibition of the unwanted response representation. The neural correlates of these control processes are identified through a comparison of incongruent trials (when the automatically evoked response is incorrect and therefore must be controlled) with congruent trials (when the automatically evoked imitative response is correct and need not be controlled).

Brass and colleagues were the first to apply this strategy to the study of imitation control a decade ago. During fMRI scanning, participants performed a simple response task—lifting or tapping the index finger upon the detection of movement in videos depicting the same two actions (Brass et al., 2001b). Greater activity during incongruent compared to congruent trials was observed in dorsolateral prefrontal cortex, a region commonly identified in interference paradigms (Derrfuss et al., 2004; Egner and Hirsch, 2005; Liu et al., 2004; Nee et al., 2007; Wager et al., 2005), as well as in the anterior medial prefrontal cortex (mPFC), a region more commonly associated with social-cognitive processes such as theory of mind and agency attribution (Amodio and Frith, 2006).

The involvement of mPFC—in addition to the view that imitation is supported by a specialized action-observation matching mechanism (the MNS) and the fact that patients can

have relatively specific imitation control deficits (Lhermitte et al., 1986; De Renzi et al., 1996)—led the authors to propose a distinct mechanism for imitative control as compared to control over other non-imitative response tendencies. They went on to test this hypothesis by comparing imitation control to control in a Stroop task, which requires avoidance of the automatic tendency to read a written word and report instead the ink color (Stroop, 1935). Dissociations between control processes employed in the imitation and Stroop interference tasks were demonstrated in two ways. First, a subset of patients with frontal lobe damage had large congruency effects in the imitation interference task (suggesting impaired imitation control), but did not show substantial deficits in a Stroop task compared to controls (Brass et al., 2003). Furthermore, patients' performance on imitation and Stroop interference tasks was not correlated. Thus, impairment in imitation control need not be related to impairment in control in the Stroop task, suggesting distinct control mechanisms. In a related fMRI study of healthy participants, the authors argue for a dissociation between control mechanisms based on qualitatively different patterns of activation for the imitative and Stroop congruency effects (Brass et al., 2005). This study replicated the involvement of mPFC in imitation control. Furthremore, the region was not activated for incongruent trials on the Stroop task, suggesting a selective involvement in imitation control. In addition to replicating this previous finding, they found involvement of the temporo-parietal junction (TPJ), a region involved in higher social-cognitive functions (Amodio and Frith, 2006).

Following these early studies implicating two regions (mPFC and TPJ) that have previously been observed in more complex social tasks involving mentalizing, self-referential processing and determining agency (Ruby and Decety, 2001; Farrer et al., 2003; Farrer and Frith, 2002; Nahab et al., 2011; Amodio and Frith, 2006), Brass and colleagues proposed the "control of shared representations" theory (Brass et al., 2009). They proposed that a central process in imitation control involves distinguishing between motor activity generated by one's own intentions and motor activity generated by action observation. This process is required

because both perceived and internally planned actions are represented in the same neural system (the MNS; Rizzolatti and Craighero, 2004), yet the system itself does not distinguish between the source of the representations (Jeannerod, 1999). Therefore, an imperative first step to carrying out an intentional action in a situation where a conflicting motor representation is activated by action observation is to attribute each motor representation to self or other. This process (the need to distinguish between self and other), they argue, shares features with other higher social-cognitive functions such as theory of mind and therefore, explains involvement of similar brain systems (Brass et al., 2009).

Since the first evidence of similar functional anatomy, more direct evidence for a relationship between social-cognitive processes and imitation control has emerged. First, within-subject designs demonstrated overlapping activity in the TPJ during imitative control, theory of mind and agency attribution tasks; and in mPFC for imitation control, theory of mind and self-referential tasks (Spengler et al., 2009). Furthermore, behavioral congruency effects in the imitative control task were correlated with fMRI responses in the mPFC not only during the imitation task, but also during the theory of mind task (Spengler et al., 2009). Parallel neuropsychological data were also reported: participants with autism who had poor theory of mind showed greater deficits in imitation control (larger behavioral interference effects) and imitation interference effects were correlated with activity in the TPJ and mPFC during the theory of mind task (Spengler et al., 2010). In yet another study examining this relationship, imitative control deficits were correlated with deficits in perspective-taking in patients with TPJ lesions and with theory of mind deficits in patients with frontal lesions, but not with performance on a Stroop task (Spengler et al., 2010). Thus, to date there is substantial evidence for a relationship between performance and neural correlates in tasks requiring self-other distinction, agency attribution and imitation control.

The specific roles of the TPJ and mPFC in imitative control are proposed to parallel their roles in social cognition. The TPJ was primarily observed in agency attribution tasks and the

mPFC is associated with self-referential processing. Thus, in imitation control the TPJ is proposed to contribute to the distinction between self and other by signaling that an observed action is related to another agent (regardless of the presence of conflict). In contrast, the mPFC indicates activity is related to one's own motor intention, and by extension, is responsible for enforcing this intention in situations of conflict (Brass et al., 2009). How this conflict resolution occurs, however, has received little attention in the imitation control literature to date, aside from scarce evidence and some speculation about interactions with the mirror neuron system (Spengler et al., 2009; Spengler et al., 2010; Wang et al., 2011).

The development of the shared representations theory has been very targeted in its approach—since the very first neuroimaging studies of imitation control (Brass et al., 2001b; Brass et al., 2005), region of interest analysis have restricted examination strictly to the mPFC and TPJ, even though multiple additional brain systems were activated by imitative congruency. Thus, although the shared representations theory provides an intriguing link between imitation control and social cognition, it does not investigate mechanisms of imitation control beyond the early step of distinguishing between externally and internally driven motor activation.

1.4 Goals of the dissertation

To summarize, behavioral studies in laboratory and naturalistic settings demonstrate that humans have an automatic tendency to imitate observed actions. Neurophysiological data suggest that these tendencies arise from automatic activation of the motor representation of imitative responses by action observation, a phenomenon that is likely to be mediated by the MNS. Early work attempting to examine how imitative tendencies are controlled—preventing the excessive imitation observed after brain damage—indicates that imitation control is related to social cognition, insofar as they draw on similar processes related to self/other distinction and agency attribution.

In this dissertation I describe studies using fMRI and TMS to extend models of imitation control and begin to address three questions. First, I explore whether imitation control involves distinct neural circuitry compared to control over other types of automatic response tendencies. This is a precursor to the second, more interesting hypothesis that imitation control involves modulation of the MNS. A link between imitation control and MNS system activity would provide a starting point to test the hypothesis that the MNS and imitation abnormalities observed in autism are related to dysfunctional MNS modulation rather than an intrinsic MNS deficit. Finally, I test a third hypothesis that imitation control mechanisms differ depending on whether they detect and resolve conflict after it occurs (reactive control) or prevent conflict by biasing processing before it arises (preparatory control).

As a first step in addressing these questions, in Chapter 2 I test the hypothesis that control over imitative and spatially compatible response tendencies recruit distinct neural circuitry. The hypothesis that imitation control involves interactions with the MNS rests partially on the assumption that imitation control is distinct from control over response tendencies evoked by non-imitative stimuli, since MNS activity is relevant only for conflict related to action observation. The current evidence that imitation control is distinct from other commonly studied control processes rests almost entirely on the dissociations demonstrated between imitation control and Stroop tasks, a dissociation that could be explained by task differences that have nothing to do with imitation per se. As such, I performed two fMRI studies comparing imitation control to control of spatially compatible response tendencies, a more appropriate task for comparison than the Stroop task.

Based on substantial differences between the results discussed in Chapter 2 and previous studies of imitative control, I hypothesized that there may be differences between preparatory and reactive imitative control mechanisms. The subsequent chapters examine potential interactions between mirror neuron and control systems while disentangling

preparatory and reactive mechanisms of control. Chapter 3 describes two experiments examining reactive control of imitation. The first uses fMRI to identify imitation-specific control regions and examine their functional connectivity. The second attempts to disrupt processing in these regions with TMS to modulate imitation control.

Chapter 4 describes two experiments examining preparatory control mechanisms using a paradigm with preparatory cuing so that imitative conflict is predictable. The first study uses fMRI to examine the neural correlates of preparatory control and the second uses TMS to measure motor resonance, a putative measure of mirror neuron activity, during preparation.

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Chapter 2

Imitation & spatial compatibility: Two sides of the same coin?

2.1 Neural systems for imitative and spatial compatibility are similar in a block design task

2.1.1 Introduction

The shared representations model of imitation control holds that control over imitative tendencies is distinct from other cognitive control processes and involves a mechanism related to self-other distinction and higher social cognitive functions (Brass et al., 2009; Spengler et al., 2009). However, at present the only direct evidence for a dedicated imitation control mechanism comes from patient and neuroimaging data suggesting a dissociation between conflict resolution in imitation interference and Stroop tasks (Brass et al., 2003; Brass et al., 2005). Given that commonly employed conflict taxonomy schemes attribute conflict in these tasks to different processing stages (Kornblum et al., 1990; Hommel, 2011), a dissociation between control in automatic imitation and Stroop tasks could be explained without the need to invoke a special mechanism for imitation.

In the imitation interference task, participants are instructed to perform one of two simple finger movements while a video stimulus displays either the same (congruent) or the opposite (incongruent) action. The appropriate response is either pre-specified, with the video serving only as a "go signal," or specified by a symbolic cue (i.e. "1" for index finger, "2" for middle

finger). In both circumstances the action content of the video is irrelevant to successful task performance. Nonetheless, responses are slower when the observed and executed movement conflict, presumably due to an automatic activation of the observed action that has to be controlled to allow the appropriate incongruent response. Thus, increased response time or brain activation on incongruent compared to congruent trials is attributed to the processes required to inhibit the automatic imitative response (Brass et al., 2000; Brass et al., 2001b; Brass et al., 2003; Brass et al., 2005).

In the Stroop task, subjects must overcome the automatic tendency to read, and instead report the font color of a written word. According to feature overlap models (Kornblum et al., 1990) Stroop conflict results primarily from overlapping *stimulus* features—the word meaning and color represented in the stimulus conflict. This framework is consistent with evidence that resolution of Stroop interference occurs largely at the stimulus rather than response level (i.e. through selective visual attention) (Egner and Hirsch, 2005; Egner et al., 2007; Nee et al., 2007). In contrast, in the imitation interference paradigms conflict arises from overlap between features of the stimulus and the response—the *stimulus* finger conflicts with the *response* finger. Given evidence for distinct mechanisms involved in stimulus-stimulus and stimulus-response conflict resolution (Egner et al., 2007), it would not be surprising for control mechanisms to differ for automatic imitation and Stroop tasks even if control of automatic imitation relied on a general conflict resolution mechanisms employed at the response stage.

The aim of the present study is to provide a more definitive test of the hypothesis that overcoming imitative tendencies relies on a specialized imitation control mechanism by contrasting more similar types of conflict. Spatial compatibility provides an ideal task for comparison because, similar to automatic imitation, interference effects stem from stimulus-response overlap (Hommel, 2011). Furthermore, the two tasks can be equated on all dimensions except for the presence or absence of action observation.

In the compatibility task employed here, subjects performed one of two finger movements (lifting the index or middle finger of the right hand) in response to a dynamic stimulus depicting either a finger (imitative) or dot (spatial). For compatible blocks subjects lifted the same finger as the stimulus (in the case of imitative cues) or the finger that corresponded to the location of the moving dot (for spatial cues). For incompatible blocks subjects lifted the non-corresponding finger. Dual route models describing two parallel response selection processes have commonly been invoked to explain the slowing observed on incompatible trials in compatibility tasks like this one (Kornblum et al., 1990; De Jong et al., 1994). A direct (fast and automatic) route links long-term, overlearned stimulus-response pairs; an indirect (slow) route applies short-term task-relevant rules required for arbitrary stimulus-response pairs. For compatible mappings, the rule-based mapping and the overlearned automatically activated response are the same. In contrast, for incompatible mappings, the rule-based mapping and automatically activated response are in conflict. Thus, for incompatible mappings, correct responding requires selection between the two responses through increased reliance on the rule-based sensorimotor mapping, suppression of the automatically activated (incorrect) response, or both.

Thus, if a unique imitation control mechanism exists (Brass et al., 2005; Brass et al., 2009), we would expect to observe a dissociation for imitative and spatial stimuli when the automatic response has to be suppressed, even under these highly similar task demands. To test this hypothesis, we examined brain regions that are more active for incompatible than compatible trials for each cue type. These activations are then directly compared between cue types to examine areas of overlap as well as differences in regional brain activity.

2.1.2 Methods

Participants

28 adult participants were recruited from UCLA and the surrounding community through advertisements in the university newspaper and free online bulletins. 4 subjects were excluded from analysis due to scanner equipment technical failure (1 subject) and failure to meet inclusion criteria discovered after enrollment (3 subjects). The remaining 24 participants (12 female) were 18-33 years old (mean=22.4, standard deviation=3.5), right-handed, had normal or corrected-to-normal vision and reported no history of neurologic or psychiatric disorders and no current use of psychoactive medication. The study was approved by the UCLA Institutional Review Board. Written informed consent was obtained from all subjects and subjects were paid $25/hour for participating.

Behavioral Paradigm

We used a choice response task to compare imitation and spatial compatibility during fMRI. Subjects were instructed to extend the index or middle finger of their right hand in response to videos depicting similar finger movements, or dots moving with similar trajectory (Figure 2.1). In compatible blocks, a green border designated that subjects should lift the finger on the same side as the video (i.e. index finger in response to index finger extension, or to upward motion of dot over index finger). In incompatible blocks, a red border indicated that subjects should lift the finger on the opposite side from the video (i.e. index finger in response to middle finger extension, or to upward motion of dot over middle finger). The result is a 2 (Cue type: imitation, spatial) x 2 (Compatibility: compatible, incompatible) design consisting of a total of four conditions: Imitate compatible (ImC), imitate incompatible (ImI), spatial compatible (SpC) and spatial incompatible (SpI).

Video stimuli comprised five frames. The first frame was always the same, showing a left hand resting on a surface in a relaxed position with the palm down and fingers facing the

subject, as in previous studies (Brass et al., 2000; Iacoboni et al., 1999; Iacoboni et al., 2001; Koski et al., 2003). Two black dots were superimposed over the index and middle fingernails. After 750 ms, the video depicted upward movement (4 frames shown at a rate of 34ms/frame) of either a finger or a dot. In imitative trials, the index or middle finger was extended, moving upward from the resting position, while the dots remained stationary; in spatial trials, one of the dots moved upward while the fingers remained stationary. The trajectory of the dot was determined based on the fingernail in the imitation videos, such that the primary difference between imitation and spatial trials was the presence or absence of action observation. The final frame remained on the screen for 900ms, providing the response window. Trials were separated by a 500ms intertrial interval (ITI) consisting of a blank blue background.

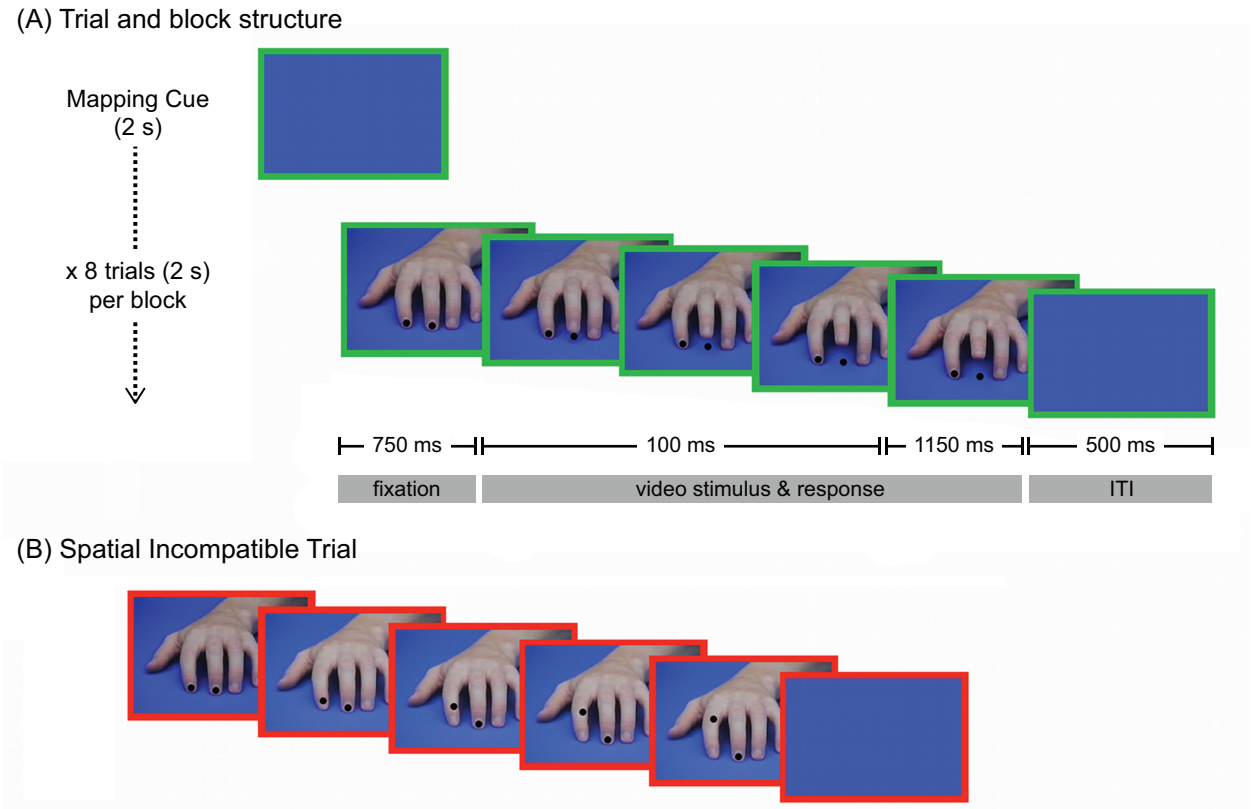

Figure 2.1: Behavioral paradigm. (A) Block and trial structure (imitate compatible condition). (B) Example of spatial ncompatible trial. Border color denotes task instructions for 2 seconds at the onset of and throughout each block (green = compatible; red = incompatible). Both examples shown require a middle finger response.

Task blocks were preceded by a 2 second mapping cue (blank blue background with red or green border), giving subjects time to process the mapping rule before beginning the block. The mapping cue was followed by eight 2-second trials (separated by 0.5 second ITI) comprising a 20 second task block. Task blocks alternated with 20-second rest blocks (blank blue screen, no border). The stimulus-response mapping rule (compatible, incompatible) was alternated every two blocks (to minimize the frequency of task set changes and maximize compatibility effects) and the cue type alternated every block. Four possible stimulus orders were created within these constraints, each beginning with a different condition. Each subject performed all four possible orders (in 4 runs), with the order of runs counterbalanced across subjects.

Procedure

Immediately prior to scanning, each subject was familiarized with the task during a brief practice session. Subjects subsequently performed a total of 8 blocks of each of the four conditions [spatial compatible (SpC), spatial incompatible (SpI), imitation compatible (ImC), imitation incompatible (ImI)] during fMRI scanning. The session was divided into four runs each 5:56 minutes long, between which the subjects were allowed a short break. Each run was preceded by a reminder of the instructions.

MRI data acquisition & processing

Images were acquired on a Siemens 3T (Erlangen, Germany) Trio MRI scanner. For functional runs we acquired 178 T2*-weighted echoplanar images (EPIs) [repetition time (TR) 2000ms; echo time (TE) 28ms; flip angle=90°; 34 slices; slice thickness 4mm; matrix 64 x 64; FOV 192mm]. To allow for T1 equilibrium the first two volumes of each functional scan were automatically discarded before data collection began. Two sets of structural images were also acquired for registration of functional data: a T2-weighted matched-bandwidth high-resolution scan with the same slice prescription as the EPI [repetition time (TR) 5000ms; echo time (TE)

34ms; flip angle=90°; 34 slices; slice thickness 4mm; matrix 128 x 128; FOV 192mm]; and a T1 weighted magnetization prepared rapid-acquisition gradient echo image (MPRAGE) [TR, 1900ms; TE 2.26ms; flip angle = 9°; 176 sagittal slices; slice thickness 1mm; matrix 256 x 256; FOV 250mm]. Visual stimuli were timed and presented with Presentation software (Neurobehavioral Systems, Albany, CA) through magnet-compatible LCD goggles. Responses were recorded with a magnet-compatible response box (Current Designs, Philadelphia, PA).

Image preprocessing and data analysis were performed with FSL version 4.1.4 (Centre for Functional Magnetic Resonance Imaging of the Brain software library, www.fmrib.ox.ac.uk/fsl; Smith et al., 2004). Images were realigned to the middle volume to compensate for any head motion using MCFLIRT (Jenkinson et al., 2002). Images were then examined visually for gross motion artifacts that cannot be corrected with simple realignment. When motion artifacts were detected, a nuisance regressor for each affected volume (mean=2 vols/run, SD=3.6) was included in the general linear model. In addition 1 run for each of 2 subjects was excluded for excessive motion (>10% volumes exhibiting motion artifacts). Data were temporally filtered with a high-pass filter cutoff of 100s and spatially smoothed with a 6mm full width half maximum Gaussian kernel in three dimensions.

fMRI analysis

Statistical analyses were performed at the single subject level using a general linear model (GLM) with fMRI Expert Analysis Tool (FEAT). After convolution with a canonical double-gamma hemodynamic response function, each block type (ImC, ImI, SpC, SpI) was included as a regressor in the GLM. In addition, the mapping cue beginning each block and the reaction time for each trial (orthogonalized with respect to EVs of interest) were included in the model as nuisance regressors. Temporal derivatives were included for each regressor to account for variability in the hemodynamic response. To identify control regions estimated the following contrasts: Incompatible-Compatible separately for both spatial and imitative cues (ImI-ImC and

SpI-SpC); and the interaction between cue type and compatibility [(ImI-ImC)-(SpI-SpC) and (SpI-SpC)-(ImI-ImC)]. In addition, to determine whether the cue types were processed differently, we examined the cue type main effect [(ImI+ImC)-(SpI+SpC) and (SpI+SpC)-(ImI+ImC)].

First level contrast estimates were computed for each run and then registered to standard space (Montreal Neurological Institute, MNI) in three stages. The middle volume of each run of individual EPI data was registered first to the co-planar matched-bandwidth high-resolution T2-weighted image and subsequently, the co-planar volume was registered to the T1-weighted MPRAGE. Both of these steps were carried out using FLIRT (affine transformations: EPI to co-planar, 6 degrees of freedom; co-planar to MPRAGE, 6 degrees of freedom) (Jenkinson et al., 2002). Finally registration of the MPRAGE to standard space (FSL's MNI Avg152, T1 2x2x2mm) was carried out with FLIRT (affine transformation, 12 degrees of freedom) and refined using FNIRT (non-linear transformation) (Jenkinson and Smith, 2001; Jenkinson et al., 2002).

Contrast estimates for each subject were then computed treating each run as a fixed effect. Finally, a group level analysis was performed to calculate a group mean for each contrast treating each subject as a random effect using FSL's FLAME (FMRIB's local analysis of mixed effects) stage 1 and stage 2 to maximize sensitivity (Beckmann et al., 2003; Woolrich, 2008; Woolrich et al., 2004). Group images were thresholded at $z > 3.1$ ($p<0.001$), corrected for multiple comparisons using cluster-based Gaussian random field theory controlling family-wise error across the whole-brain at $p < 0.05$. Common areas of activation for spatial and imitative cues were examined with a simple conjunction overlay analysis, which includes all areas that show significant activation for Incompatible > Compatible ($z>3.1$, corrected) for both spatial and imitative cues.

2.1.3 Results

Behavioral Data

Mean reaction time (RT) was calculated for correct responses in each condition. Trials with RT greater than 2 standard deviations from the mean were considered outliers and excluded from analysis (0.6-3.4% of trials for each subject). Reaction time analysis was carried out using a Cue type (spatial, imitation) x Compatibility (compatible, incompatible) repeated measures ANOVA. This revealed only a main effect of compatibility [$F(1,23)=61.7$, $p<0.001$], indicating that responses on incompatible trials (mean=415ms, SD=67.4ms) were slower than compatible trials (mean=338ms, SD=36.2ms) regardless of the cue type. Accuracy data showed an identical pattern when subjected to the same ANOVA, with a small but significant main effect of compatibility [$F(1,23)=21.7$, $p<0.001$); compatible: mean=99.4%, SD=0.9%; incompatible: mean=98.2%, SD=1.9%] (Figure 2.2A).

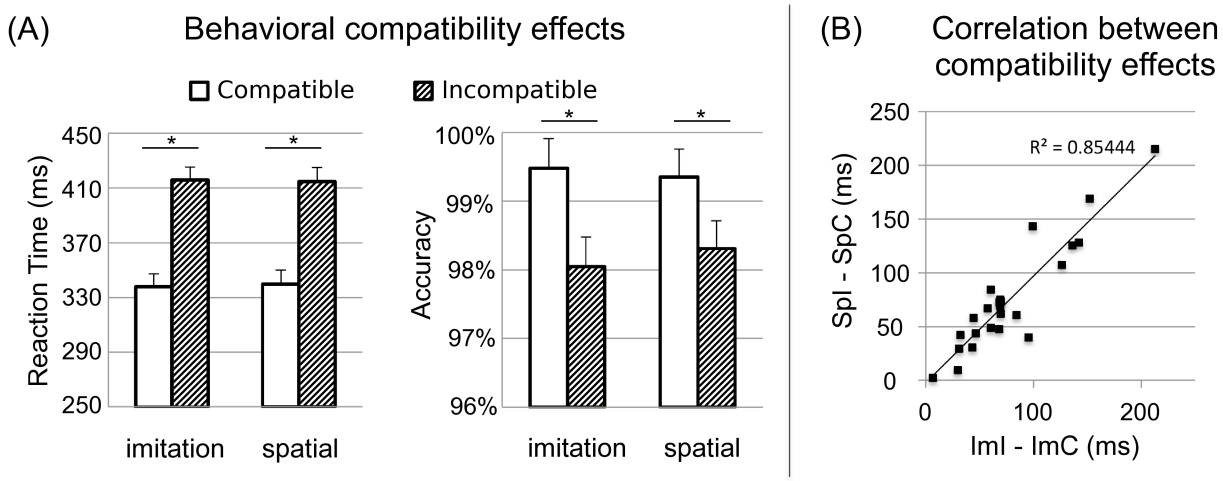

Figure 2.2: Behavioral Results. (A) Compatibility effects for each cue type for reaction time (left) and accuracy (right). (B) Scatterplot showing reaction time compatibility effects for imitative (x-axis) and spatial (y-axis) cue types.

In addition, we computed a correlation between compatibility effects (Incompatible – Compatible reaction time) for the two cue types. If similar cognitive and neural mechanisms are involved for spatial and imitative cues, one might expect a high correlation between behavioral measures. Indeed, we observed an extremely high correlation between spatial and imitation

compatibility effects (r=0.92, p<0.00; Figure 2.2B). A similar correlation did not exist for accuracy effects, likely due to lack of variability in error rates across subjects.

fMRI Data

The Incompatible > Compatible contrast revealed extremely similar patterns of activation for spatial and imitative cues. Activation was observed in bilateral superior parietal lobule (SPL), dorsal premotor cortex (PMd), and pre-supplementary motor (pre-SMA) area, as well as the anterior insula and cerebellum. To identify activation specific to one or the other cue type, we examined the Cue type x Compatibility interaction [(ImI-ImC)-(SpI-SpC) and (SpI-SpC)-(ImI-ImC)]. Paralleling the similarity between compatibility effects, there were no areas showing significant interactions, even uncorrected or at a more liberal threshold (z > 1.7, corrected). The overlay conjunction illustrates the significant overlap between compatibility effects for the two cue types in all activated regions (Figure 2.3A and Table 2.1).

Table 2.1 Peaks of activity for Incompatible > Compatible for each cue type.

	Imitation				Spatial			
Anatomical Region	*Z*	x	y	z	*Z*	x	y	z
R LOC/SPL	4.72	16	-64	58	5	16	-66	58
L LOC/SPL	4.97	-16	-62	64	3.97	-24	-60	56
R PMd	5.01	32	0	62	4.96	24	0	56
L PMd	4.49	-24	-10	50	4.78	-26	-4	52
R Insula	4.54	34	16	4	4.71	42	18	2
L Insula	4.16	-32	14	2	4.61	-32	14	-10
R PMv	*4.14**	56	10	38	4.28	52	8	30
R IPL	4.2	42	-46	36	4.66	40	-38	50
preSMA	4.39	-8	16	42	4.36	4	18	52
ACC	4.23	12	22	24	4.33	8	22	32
R cerebellum	4.32	28	-56	-34	4.48	44	-56	-30
L cerebellum	4.31	-28	-60	-32	4.33	-32	-46	46

*Does not survive correction for multiple comparisons
x, y & z refer to MNI coordinates; R=right; L=left; SPL=superior parietal lobule; PMd=dorsal premotor cortex; PMv=ventral premotor cortex; IPL=inferior parietal lobule; preSMA=presupplementary motor area; ACC=anterior cingulate cortex.

To rule out the possibility that imitative and spatial cues were being processed identically (for example, that the hand in the background or the similar trajectory of both cue types biased subjects towards mental imagery of finger movement even when stimuli depicted dot movement) we contrasted the imitation and spatial cues (collapsed across compatibility). In addition to more robust activation in visual areas, there was increased activation in fronto-parietal areas known to activate during imitation (ventral premotor cortex and superior parietal lobule/anterior intraparietal sulcus; Iacoboni et al., 1999; Caspers et al., 2010) in imitation blocks compared to spatial blocks (z>3.1, uncorrected; Figure 2.3B). No areas showed significantly more activation for spatial than imitative cues.

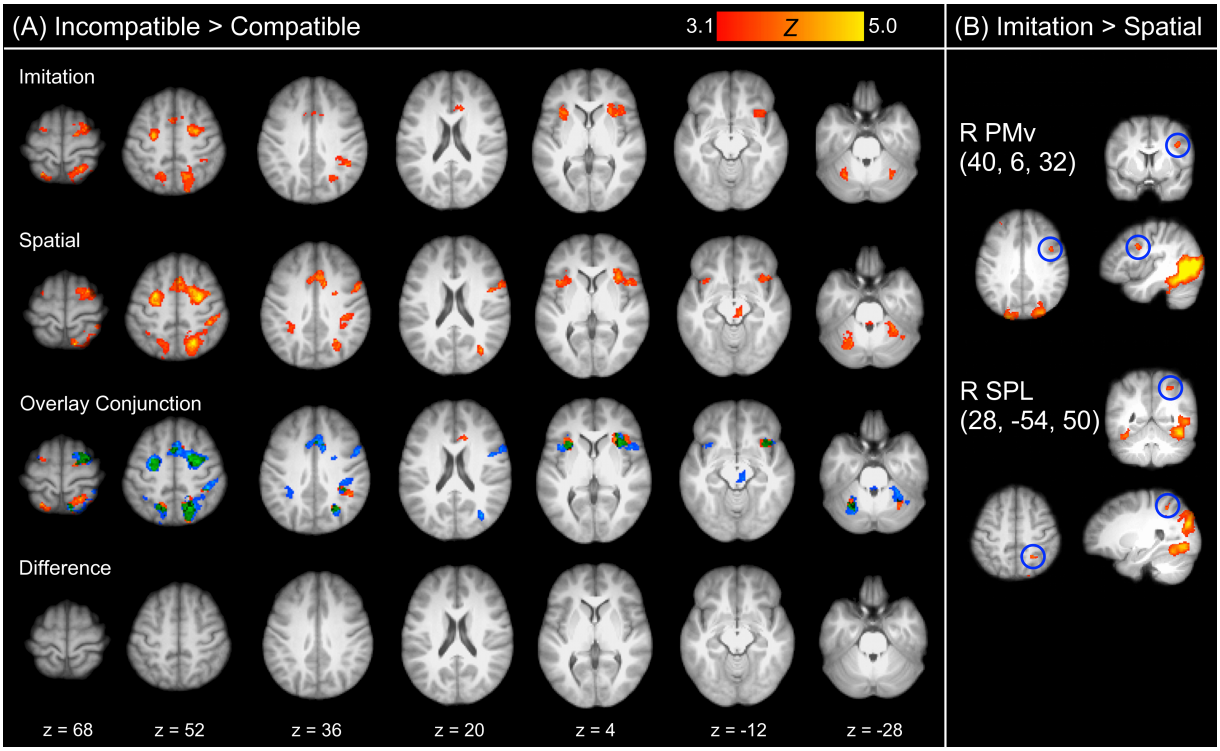

Figure 2.3: Activation analysis results. (A) Incompatible > Compatible contrasts for imitative (1st row) and spatial (2nd row) cues are very similar. Conjunction overlay of imitation and spatial compatibility effects (3rd row) illustrate significant overlap. Orange = Imitation; Blue = Spatial; Green = Overlap. Difference of imitation and spatial cues (4th row) depicts lack of Cue x Compatibility interaction (even when threshold is lowered to z > 1.7, corrected). Maps are thresholded at Z > 3.1, corrected. (B) Imitation > Spatial contrast (collapsed across compatibility), depicting activation in frontoparietal areas previously associated with imitation. L=left; R=right; coordinates refer to the MNI; PMv=ventral premotor; SPL=superior parietal lobe. Maps are thresholded at Z > 3.1, uncorrected.

2.1.4 Discussion

We aimed to examine the neural mechanisms involved in overcoming automatic responses induced by spatial and imitative stimuli. To do this we used two stimulus-response compatibility tasks that were identical except for the presence or absence of biological motion. The similarity between the two tasks was made possible by the use of simplistic actions for the imitative stimuli. While the imitative stimuli are somewhat removed from real world imitation, they allowed us to compare imitative and spatial cues in a well-controlled task in which inferences regarding differences can be attributed specifically to the presence of action observation.

Within each cue type, both compatible and incompatible blocks consisted of identical motor responses and stimuli, such that differences in activation between incompatible and compatible mappings should not be due to low level perceptual or motor processes. Instead, they should reflect increased demands on visuomotor integration systems: During incompatible mappings, the required response conflicts with the automatically activated compatible response, whereas this conflict is absent for compatible mappings (Eimer et al., 1995; Stürmer and Leuthold, 2003). As a result, compared to compatible mappings, incompatible mappings require: (1) increased reliance on the rule-based mapping and/or (2) inhibition of the automatically activated response (Kornblum et al., 1990).

Comparison of incompatible and compatible mappings for each cue type revealed activation of a network similar to previous studies of spatial compatibility (Dassonville et al., 2001; Iacoboni et al., 1996; Iacoboni et al., 1997; Matsumoto et al., 2004; Wager et al., 2005). Activation was detected in bilateral PMd, SPL, preSMA, cerebellum and insula, all areas known to be involved in planning and execution of motor responses to sensory stimuli (Andersen and Cui, 2009; Iacoboni et al., 1996; Iacoboni et al., 1998; Kurata et al., 2000; Nachev et al., 2008; Passingham, 1993; Picard and Strick, 2001). Furthermore, a similar parieto-frontal network is recruited in motor tasks requiring responses to spatial (Iacoboni et al., 1996; Iacoboni et al.,

1998) and non-spatial cues (Grafton et al., 1998; Kurata et al., 2000), as well as both visual (Grafton et al., 1998; Iacoboni et al., 1998) and auditory (Iacoboni et al., 1998; Kurata et al., 2000) cues, suggesting that this set of co-activated regions is involved in sensorimotor mapping regardless of the input modality or spatial relationship between stimuli and responses. Thus, in the present task similar activation of this network for incompatible mappings for both spatial and imitative cues is consistent with increased demands on a general sensorimotor integration process when the correct incompatible response conflicts with the automatically activated compatible response.

Because a general mechanism for arbitrary stimulus-response mapping is not surprising in the context of the previous work described above, we did expect to observe some overlap in activation for imitative and spatial compatibility effects. However, we also expected differences in the compatibility effects reflecting distinct mechanisms for inhibition of the automatically activated compatible response for imitative and spatial cues (Brass et al., 2000; Brass et al., 2009; Catmur and Heyes, 2011), which were not observed. This would suggest that in the present task, a single shared process underlies inhibition of compatible responses for both stimulus types. For example, a common inhibitory mechanism for the two cue types involving the insula (Nee et al., 2007) and/or PMd (Praamstra et al., 1999; Koski et al., 2005) might explain the identical activation patterns observed.

This view is in line with the argument that imitation represents just a special case of spatial compatibility, where the stimuli happen to represent human actions (Aicken et al., 2007; Jansson et al., 2007; Stürmer et al., 2000). Yet, since this argument was first put forth numerous studies have shown that, although in some tasks spatial compatibility contributes to imitative interference effects (Brass et al., 2001a), automatic imitation is not entirely reducible to spatial compatibility. Automatic imitation effects are observed even when spatial compatibility between the observed action and imitative responses is removed by changing the orientation of the stimulus (Bertenthal et al., 2006; Brass et al., 2001a; Jiménez et al., 2012; Press et al., 2008). In

addition, the time course of automatic imitation and spatial compatibility effects have been dissociated in a task showing that automatic imitation interference effects increased for slower responses whereas spatial compatibility effects decreased for slower responses (Catmur and Heyes, 2011).

While behavioral dissociations between automatic imitation and spatial compatibility by no means indicate that control mechanisms for the two stimulus types rely on distinct neural mechanisms—indeed, behavioral dissociations could result from distinct routes to automatic activation even in the context of a similar top-down control mechanism acting to avoid the automatic response—the negative effect observed here has several potential alternative explanations. In the next section we describe a follow-up study to rule out the possibility that the data might be explained by attention reorienting processes that are applied regardless of stimulus type, rather than the response selection and inhibition account that motivated the present study design.

2.2 Minimizing attention reorienting does not change neural systems for imitative and spatial compatibility.

2.2.1 Introduction

Although commonly employed dual route models explain spatial compatibility effects primarily in terms of automatic response activation and response selection (De Jong et al., 1994; Kornblum et al., 1990), an alternative account of results from the previous experiment is that behavioral and fMRI compatibility effects may be related to attention reorienting processes (Cieslik et al., 2010; Cieslik et al., 2011). According to this account, the salience of the stimulus causes a “bottom-up” or exogenously driven shift of attention toward the stimulus on all trials. For incompatible trials, spatial attention is then reoriented to the opposite (response) side in concert with the motor response. In contrast, for compatible trials the side of the stimulus and

response are the same so the additional reorientation of attention is not necessary. Thus, according to this view, incompatible trials involve an additional attentional orienting process relative to compatible trials.

While it is well-established that neurons in dorsal premotor and parietal regions similar to those activated in the compatibility paradigm are involved in action planning and selection, it is difficult to distinguish those regions from the nearby frontal and parietal eye fields, which are involved in the planning and selection of eye movements and intimately related to shifts of attention. Indeed, the regions activated comprise the nodes of Corbetta and Shulman's (Corbetta et al., 2008) dorsal and ventral attention networks which are involved in endogenously and exogenously driven attention shifts. As such, one possibility for identical activated networks in the previous experiment might be that attentional shifts dominate the task and a single mechanism related to attentional control is applied for both stimulus types.

To minimize the influence of attention reorienting, we ran an identical task with new stimuli aimed at reducing directional shifts of attention. Instead of using movement of one of two fingers that are horizontally arranged, imitative stimuli consisted of a hand opening or closing from a relaxed starting position (half-way between open and closed). Instead of dots, spatial stimuli depicted a circle expanding or contracting. Since there is still spatial and imitative overlap between stimuli and responses, we expect to observe similar compatibility effects. However, because the stimuli and responses are expanding and contracting movements around a stable central focus rather than a movement in a single spatial location, we assume that directional attention shifts are minimized and results should be attributable to response selection demands.

2.2.2 Methods

Participants

20 adult participants (4/16 M/F) were recruited from the UCLA and surrounding community through advertisements in the university newspaper and free online bulletins.

Participants were 18-31 years old (mean=21.3, standard deviation=3.4), right-handed, had normal or corrected-to-normal vision and reported no history of neurologic or psychiatric disorders and no current use of psychoactive medication. The study was approved by the UCLA Institutional Review Board. Written informed consent was obtained from all subjects and subjects were paid $25/hour for participating.

Behavioral Paradigm

The instructions and task were identical to the previous experiment (Section 2.1), with the exception that stimuli represented hands opening and closing instead of index and middle finger movements (Figure 2.4). In addition, imitative and spatial stimuli were not superimposed (this was intended to minimize visual differences between stimuli, however large main effects of cue type in visual regions in the previous study suggest this was not accomplished and so the strategy was abandoned).

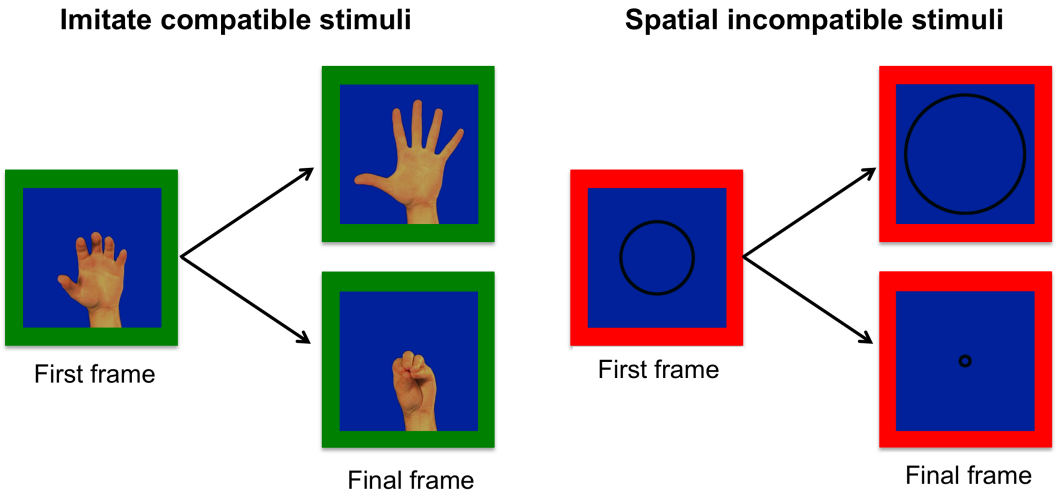

Figure 2.4: Stimuli. The first frame and the two final frames (open and close) are shown for each cue type. Both cues were shown with both border colors, representing compatible (green) and incompatible (red) mappings.

Timing was identical, except that the new stimulus videos consisted of 12 frames in total rather than 5 frames for the finger stimuli. Videos again began with a 750ms static first frame,

followed by the 10 movement frames displayed at a rate of 16.7ms/frame and subsequently by a final static frame, which was presented for the remainder of the 2-second trial.

Because the action was no longer conducible to reaction time recording with a button box, after the fMRI experiment participants performed a shortened version of the task (4 blocks per condition; 128 trials total) outside the scanner while muscle activity in the forearm finger flexors and extensors was recorded with electromyography (EMG). Surface electrodes were placed on flexor digitorum superficialis (FDS) and extensor digitorum communis (EDC) muscles and EMG signals were amplified (x1000), bandpass filtered online (50-450 Hz; Delsys, Inc., Boston, MA) and digitized at 5000 Hz for offline analysis. EMG onsets were determined offline according to the following procedure (implemented in Matlab): The signal was rectified after removing DC shift by subtracting the mean; EMG onsets were defined as the time at which the EMG voltage exceeds 2.5 times the standard deviation of the baseline window (defined as the 200ms before stimulus onset) for at least 35 out of 50ms (Lidierth, 1986); EMG onsets were inspected visually and adjusted by hand when necessary (visual inspection has been shown to be stable across raters; Van Boxtel et al., 1993). Statistical analyses revealed similar results when data were analyzed with and without adjustment. Reaction time was then calculated as the difference between EMG onset and stimulus movement onset.

MRI data acquisition, processing & analysis

All MRI acquisition and processing procedures were identical to the previous study except that responses were not recorded during scanning. However, an experimenter monitored subjects through the console room window to ensure they were performing the task.

2.2.3 Results

Behavioral Data

Reaction time analyses were carried out with a Cue Type (Spatial, Imitation) x Compatibility (Compatible, Incompatible) repeated measures ANOVA as in the previous study. The main effect of compatibility was again significant ($F_{(1,19)}$=39.8, p<0.001), indicating that responses on incompatible trials (mean=212ms, SD=36.5ms) were slower than compatible trials (mean=299.1, SD=79.6ms). There was also a significant cue type x compatibility interaction ($F_{(1,19)}$=8.8, p=0.007) reflecting a larger compatibility effect for imitative cues (mean=89.9ms, SD=61) compared to spatial cues (mean=74.7ms, SD=57.6). Post-hoc paired t-tests indicate this stems from small but significant benefit for ImC trials (mean=212ms) compared to SpC trials (mean=221ms; $t_{(19)}$=3.0, p<0.01). Accuracy data showed only a main effect of compatibility ($F_{(1,19)}$=12.25 p=0.002; compatible: mean=97.0%, SD=3.8%; incompatible: mean=82.8%, SD=5.8%; Figure 2.5A). The correlation between compatibility effects (Incompatible – Compatible reaction time) for the two cue types was again highly significant (r=0.93, p<0.001; Figure 2.5B).

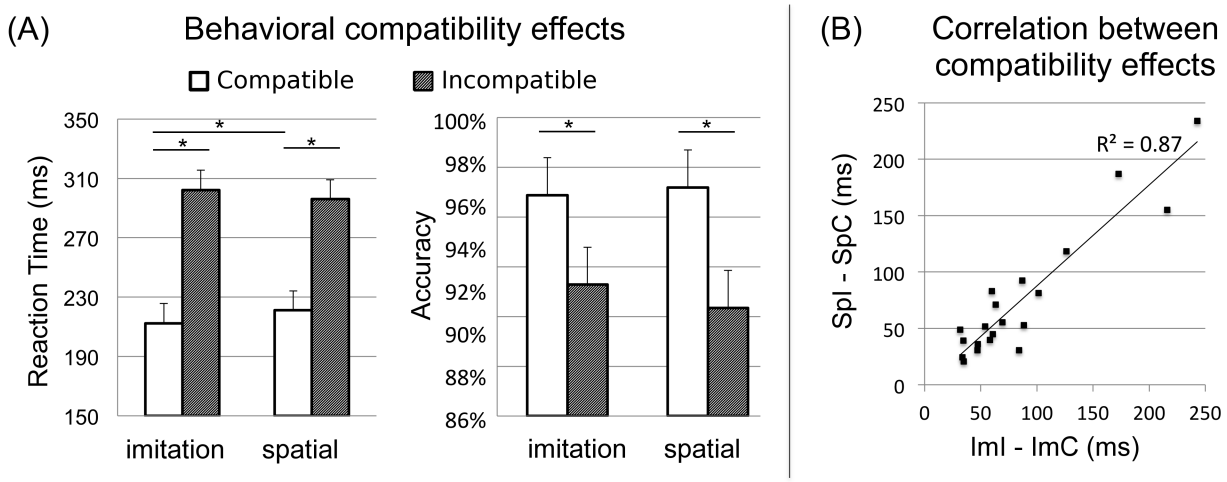

Figure 2.5: Behavioral Results. (A) Compatibility effects for each cue type for reaction time (left) and accuracy (right). (B) Scatterplot showing reaction time compatibility effects for imitative (x-axis) and spatial (y-axis) cue types.

Neuroimaging Data

The Incompatible > Compatible contrast revealed similar patterns of activation for spatial and imitative cues. Activity was observed in bilateral superior parietal lobule (SPL), dorsal premotor cortex (PMd), and pre-supplementary motor area (pre-SMA), as well as insula and cerebellum. The overlay conjunction illustrates the significant overlap between compatibility effects for the two cue types in nearly all activated regions and strongly resembles the results of the previous study (Figure 2.6). The Cue type x Compatibility interaction [(ImI-ImC)-(SpI-SpC) and (SpI-SpC)-(ImI-ImC)] showed no significant clusters until the threshold was lowered to z > 2.3 (corrected). In that case, the anterior cingulate demonstrated a larger compatibility effect for spatial than imitative cues, the activity in the ACC was present for both cue types when examined separately.

An examination of the difference between compatibility effects across this and the previous study (fingers vs. hands; not shown) demonstrated activity only in early visual regions, indicating that activity in the parietal/premotor visuomotor integration network did not differ depending on stimuli.

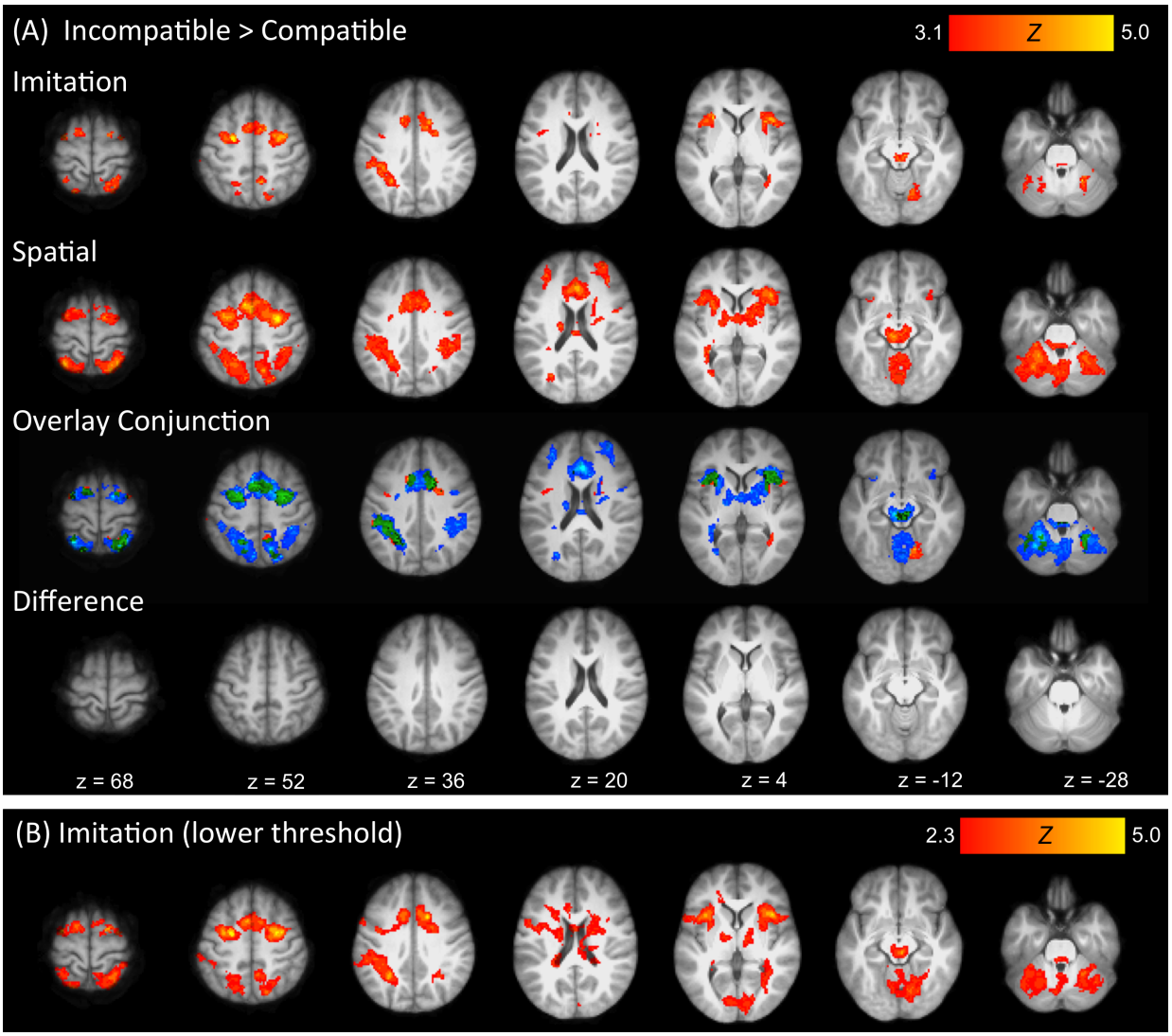

Figure 2.6: FMRI Results. (A) Incompatible > Compatible contrasts for imitative (1st row) and spatial (2nd row) cues are very similar, although activation for spatial cues had a greater extent. Conjunction overlay of imitation and spatial results (3rd row) illustrate significant overlap. Orange = Imitation; Blue = Spatial; Green = Overlap. Difference of imitation and spatial cues (4th row) depicts lack of Cue x Compatibility interaction when thresholded at z > 3.1, however anterior cingulate region survived when the threshold was lowered to z>2.3 (B) Imitation compatibility effect (same as A, first row) depicted at lower threshold better demonstrates similar pattern to spatial cues.

2.2.4 Discussion

This was a replication of the previous study, except that stimuli were altered with the goal of minimizing spatial attention shifts. The aim of this manipulation was to rule out the possibility that fronto-parietal activity associated with the compatibility effect was related to attention-shifting rather than increased demands in sensorimotor integration due to response conflict. Assuming the manipulation was successful, results from the Incompatible > Compatible

contrast should reflect neural correlates of enforcing the desired stimulus-response rule and inhibiting the automatically activated compatible action. Given that the activation pattern was extremely similar to the previous study, the present data is consistent with the original conclusion that the fronto-parietal circuit reflects response selection and inhibition processes. There was again very little difference in compatibility effects between cue types. One exception here is that the ACC showed a stronger compatibility for spatial than imitative cues. In fact, the network as a whole was qualitatively more robustly activated spatial than imitative cues, perhaps due to difference in salience of the visual stimuli. Nonetheless, given that the patterns are extremely similar this seems likely to reflect different magnitudes of engagement of the same process, rather than different neural mechanisms for the two cue types; indeed greater activation magnitudes for spatial cue may have contributed to the slightly smaller behavioral compatibility effects observed for spatial cues.

2.3 Conclusions

Taking the results of the two studies together, there was no evidence of distinct control mechanisms for imitative and spatial cues. Furthermore, the regions previously implicated in imitation control—the mPFC and TPJ—were not observed. Most previous studies reporting these regions used tasks in which the observed action is irrelevant, as a separate number cue determines the appropriate response (Brass et al., 2001b; Brass et al., 2005). However, the mPFC and TPJ are reported in a compatibility study similar to this one, where the observed action is relevant and either imitated or counter-imitated based on a mapping cue (Brass et al., 2009). This suggests that the particular task instruction and the relevance of the observed action is unlikely to be the cause of differences between this and previous imitation control studies.

Instead, a significant difference from previous studies of imitation control is the use of a block design, where each condition is presented many times in a row (previous studies presented congruent and incongruent trials in a mixed random order). The block design approach was chosen here because it maximizes power to detect activation differences (Henson, 2006), increasing the probability of detecting small differences likely to be associated with higher cognitive functions. However, it seems likely that in an effort to increase power to detect differences between imitative and spatial cues, we in fact also changed the imitation control processes being observed.

How might the block design have changed the control processes? In these two studies, the conflict between the observed and performed action is completely predictable. The mapping cue provided at the beginning of each block (before any stimuli are presented) indicates whether the automatic imitative response will be beneficial or disruptive to performance. As such, it is possible that processes associated with controlling the automatic response tendency are employed in advance of any conflict, in a preparatory way. This contrasts with previous paradigms that randomized congruent and incongruent trials, so that it was not possible to predict whether the imitative response would interfere. While there is surely some preparation or task set involved in those tasks as well, the preparation will be the same for both congruent and incongruent trials since they are randomly presented. Therefore, in previous studies of unpredictable imitative conflict, differences between congruent and incongruent trials must reflect only processes occurring in response to the stimulus ("reactive" processes).

Until recently (Braver, 2012; Boy et al., 2010; Aron, 2011) relatively little attention had been paid to how control mechanisms evolve over time in the cognitive control literature generally, as well as in imitation control. This is problematic, given that many tasks used to study cognitive control and interference resolution vary in the time at which control can be implemented relative to the experience of conflict. For example, the influential conflict monitoring theory (Botvinick et al., 2004) has been based on the phenomenon of "conflict

adaptation" in which cognitive control is engaged as a result of previous conflict in order to avoid subsequent conflict. This type of strategic adjustment in control ("adaptive control") is likely to be different from mechanisms employed to select between competing response representations after they have already reached motor cortex; it may also differ from strategic control mechanisms used to prepare for upcoming conflict based on knowledge about the task structure rather than based on the level of immediately preceding conflict. These differences are not commonly addressed when different control tasks and mechanisms are compared (i.e. Wager et al., 2005; Nee et al., 2007). Nonetheless, emerging evidence suggests they may be important.

Braver and colleagues (Braver et al., 2007; Braver, 2012) have recently described a model distinguishing between proactive (preparatory) and reactive control mechanisms. According to their dual mechanisms of control theory, in preparatory control, information about upcoming conflict can be used to bias perception and action processing before conflict arises, thus reducing the magnitude of subsequent conflict. This contrasts with reactive control, which is required to resolve conflict after it is detected in situations where proactive control is not sufficient to prevent conflict altogether. The importance of distinguishing between different preparatory and reactive control mechanisms is highlighted by several recent studies showing dissociations between various preparatory and reactive conflict resolution mechanisms. For example, preparatory control based on explicit cues and adaptive control based on previous conflict have been dissociated behaviorally (Alpay et al., 2009) and with MEG (Correa et al., 2009). In addition, adaptive control and reactive control have also been shown to be behaviorally dissociable (Boy et al., 2010), as have adaptive control and proactive control based on the proportion of high conflict trials (Funes et al., 2010). Not only do these studies underscore the importance of carefully defining conflict situations across time, but they also suggest that there may be distinctions between various types of preparatory and reactive control.

In light of these observations in tasks dealing with non-imitative conflict, it is plausible that differences between the block design compatibility task described here and previous imitation control studies by Brass and colleagues (Brass et al., 2001b; Brass et al., 2005; Brass et al., 2009), result from the use of preparatory and reactive control mechanisms, respectively. Indeed, it may be the case that preparatory control mechanisms are similar regardless of the cue type, whereas reactive mechanisms differ. It is also possible that preparatory control differences do exist, but were not detectible because the BOLD signal is overwhelmed by variance associated with the motor response. Because the BOLD response is slow, in the block design used here it is not possible to separate potential preparatory control mechanisms from processes involved in motor planning, execution and conflict resolution that occur after the onset of the stimulus. Therefore, in the subsequent chapters we continue to explore stimulus specificity in imitation control, but we do so in two new paradigms: one aimed at examining reactive control mechanisms similar to previously described work; and one aimed at examining preparatory control mechanisms, which have not been investigated previously in the context of imitation.

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Chapter 3

Reactive control of imitation

3.1 Dissociation between reactive control of imitation and spatial compatibility.

3.1.1 Introduction

Previous work on imitation control suggests that a central process in imitation control involves distinguishing between motor activity generated by one's own intentions and motor activity generated by action observation (Brass et al., 2005; Brass et al., 2009; Spengler et al., 2009). While this shared representations theory has gained traction, it does not describe mechanisms of imitation control beyond the role of mPFC and TPJ. For example, it is not yet clear how the mPFC might be involved in resolving conflict between observed and intended actions after self-other distinctions are made. Furthermore, the mPFC and TPJ are not the only regions associated with imitative control tasks, suggesting that additional regions are involved in resolving imitative conflict. The frontal operculum (Bien et al., 2009; Wang 2011) and ventral premotor cortex (Brass et al., 2005; Spengler et al., 2009) are two potentially relevant regions that have also been associated with imitation control. Involvement of these inferior frontal regions, led to the hypothesis that imitation control involves modulation of the MNS (Spengler et al., 2009; Wang 2011). However, to date this hypothesis has only received indirect support.

To build on previous models of imitative control we used fMRI and dynamic causal modeling (DCM) to examine functional interactions between regions involved in reactive

imitative control and to test the hypothesis that resolving imitative conflict involves MNS modulation. In an imitation interference task, subjects performed a finger-lifting action while simultaneously watching a video depicting either the same action or a different action. Numerous studies have demonstrated that subjects are slower to respond on incongruent trials—when the observed and performed action differ—compared to congruent trials in similar interference tasks (Bertenthal et al., 2006; Bird et al., 2007; Brass et al., 2000; Brass et al., 2001a; Catmur and Heyes, 2011; Gillmeister et al., 2008; Kilner et al., 2003; Longo et al., 2008; Press et al., 2008; Stürmer et al., 2000; Wang et al., 2011a). This slowing is attributed to the recruitment of additional control processes on incongruent trials: Since the prepotent imitative response is incorrect on these trials, it needs to be inhibited to allow execution of the correct response. Therefore, regions more active during incongruent compared to congruent trials are likely involved in imitation control. In addition, because the congruency was randomized and therefore unpredictable, any differences between congruent and incongruent trials must be due to differences in processing after the stimulus is presented.

For comparison, we included a spatial interference paradigm that was identical to the imitation task except that stimuli depicted moving dots instead of moving fingers (as in Chapter 2.1). The rationale for including the spatial compatibility task was twofold. It allowed us to identify regions that are involved specifically when conflict arises from action observation, in line with an imitation control mechanism that is distinct from those involved in overcoming prepotent responses evoked by non-social, symbolic stimuli. In addition, comparing the imitation and spatial compatibility tasks provided a way to localize regions activated selectively for action observation so that we could identify putative mirror neuron regions within the same paradigm and subjects (Friston et al., 2006).

With a standard activation analysis based on the General Linear Model (GLM), we initially identified a specific imitation control network that was consistent with previous studies and included the frontal node of the MNS. Following this, we built on previous work using

dynamic causal modeling (DCM), a method of modeling effective connectivity, to examine interactions between the imitation control regions and the MNS. DCM provides a way to test a set of alternative hypotheses about causal interactions within a group of task-relevant regions. Here, we tested a number of models to determine (1) which prefrontal region acts as a modulator of the MNS and (2) whether conflict processing in the network is consistent with the shared representations hypothesis.

3.1.2 Methods

Participants

25 adult subjects (15 female; age 19-39) were recruited through advertisement in the university newspaper and free online bulletins. All subjects were right-handed, had normal or corrected-to-normal vision, no history of neurologic or psychiatric disorders and were not taking psychoactive medications. Subjects were compensated for their participation and the study was approved by the UCLA Institutional Review Board. One subject was excluded from analyses for a structural abnormality and four additional subjects were excluded based on quality control criteria: two reported falling asleep during scanning and failed to respond on more than 15% of trials in two or more runs and two had excessive head motion (more than 10% of volumes with motion artifacts detectable by visual inspection in 2 or more runs). The remaining 20 subjects were included in data analysis, with 17 subjects entering the DCM analysis (3 did not show reliable activation maxima in one or more of the 4 ROIs).

Behavioral Paradigm

Participants performed a simple reaction time task modified from Brass et al., (2001) to include both automatic imitation and spatial compatibility components (Figure 3.1A). Subjects lifted their index or middle finger as soon as they detected movement in a video stimulus. The required response (index or middle finger) was indicated by a written instruction before each

block of videos. For the automatic imitation blocks, videos depicted a hand lifting either the index or middle finger, such that the video was either imitatively congruent with respect to the predefined response finger (e.g. index finger video on a trial where the subject was instructed to lift their index finger) or incongruent (e.g. middle finger video on a trial where the subject was instructed to lift their index finger).

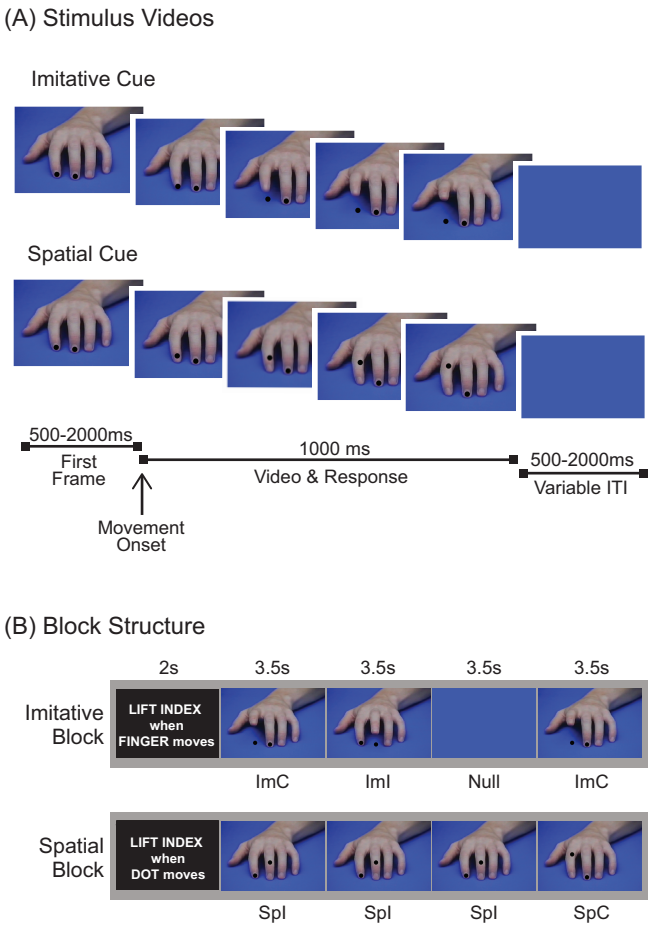


Figure 3.1: Behavioral paradigm. (A) Example video stimuli and timing of one trial for imitative (top) and spatial (bottom) interference tasks. (B) Two example blocks are shown with time progressing from left to right and images depicting the last frame of the video for each trial. Conditions are listed under each frame (ImC = Imitate congruent; ImI = Imitate incongruent; SpC = Spatial congruent; SpI = Spatial incongruent). The congruency is defined with respect to the instructed action (lift index finger, in these examples).

Spatial compatibility blocks were identical except that videos depicted a moving black dot instead of a finger. The trajectory of the dot was similar to the trajectory of the fingertip in the

imitative stimuli. Thus, the action was congruent or incongruent with respect to the left-right spatial location of the dot, but no action observation or imitation was involved.

The resulting 2 x 2 design (cue type x congruency) consists of four conditions: Imitative Congruent (ImC), Imitative Incongruent (ImI), Spatial Congruent (SpC), and Spatial Incongruent (SpI). The first frame of all four trial types was the same, and the duration was jittered between 500 and 2000ms in 500ms steps so that participants could not anticipate movement onset (i.e. the go signal). Then, the movement of either a finger or dot was presented as three 34ms frames, followed by a final frame showing the finger or dot in the raised position for 900ms. A blank blue screen marked the end of the response window and trial. This blue inter-trial interval (ITI) was between 500 and 2000 ms (again in 500ms steps) depending on the length of the first frame, so that trial duration was always 3.5 seconds. In addition to the 4 task conditions, “null” trials were included for measurement of a passive baseline and to improve detection power by jittering the interval between successive trial onsets. Null trials were the same length as task trials (3.5 s) and identical to the blue ITI. Therefore, they were perceived simply as longer ITIs and were not explicitly signaled to subjects. The trial order was optimized using a genetic algorithm (Wager and Nichols, 2003) for the efficiency of Incongruent > Congruent contrasts for each cue type (simple effects of congruency) with the following constraints: Within each cue type, each trial type followed every other type with equal probability and no more than 3 trials of the same condition occurred in a row.

Trials were presented in a mixed block/event-related design (Figure 3.1B). Each 16-second block began with a 2 second instruction screen (“Lift your INDEX FINGER when the FINGER[DOT] moves” or “Lift your MIDDLE FINGER when the FINGER[DOT] moves”) followed by four 3.5-second trials. Blocks consisted of all imitative or all spatial cues, but middle and index stimuli were presented randomly within a block so that the congruency (i.e. the need for control) was unpredictable. Imitation and spatial blocks alternated and the instructed finger movement changed every two blocks, so that subjects lifted the same finger for an imitative and

a spatial block and then switched fingers for the next two blocks. The response finger and cue type for the first block in each run were counterbalanced across runs and subjects.

Response times for each condition were measured with respect to the onset of movement in the video. Subjects held down two buttons on a response box with the index and middle fingers whenever they were not responding. A button was released when subjects performed the finger lifting response, and the stimulus presentation computer recorded button release times.

Procedure

Immediately prior to scanning, each subject was familiarized with the task in a brief practice session. The experiment comprised 80 trials of each of the four conditions as well as 80 null trials during a single scanning session. The session was divided into 5 runs lasting 5 minutes 20 seconds each, between which the subjects were allowed a short break. Each scan was preceded by a reminder of the instructions: “Remember, as soon as you see movement of either the fingers or dots in the video, lift the designated finger as quickly as you can.”

MRI data acquisition

Images were acquired on a Siemens 3-T Trio MRI scanner (Erlangen, Germany). The five functional runs consisted of 160 T2*-weighted echoplanar images (EPIs) [repetition time (TR) 2000ms; echo time (TE) 28ms; flip angle=90°; 34 slices; slice thickness 4mm; interleaved slice acquisition; matrix 64 x 64; FOV 192mm]. To allow for T1 equilibrium, the first 2 volumes of each run were automatically discarded by the scanner before task initiation. Two sets of structural images were also acquired for registration of functional data: a T2-weighted matched-bandwidth high-resolution scan with the same slice prescription as the EPI [repetition time (TR) 5000ms; echo time (TE) 34ms; flip angle=90°; 34 slices; slice thickness 4mm; matrix 128 x 128; FOV 192mm]; and a T1 weighted magnetization prepared rapid-acquisition gradient echo image (MPRAGE) [TR, 1900ms; TE 2.26ms; flip angle = 9°; 176 sagittal slices; slice thickness 1mm;

matrix 256 x 256; FOV 250mm]. Visual stimuli were timed and presented with Presentation software (Neurobehavioral Systems, Albany, CA) through magnet-compatible LCD goggles.

FMRI Activation: General Linear Model (GLM)

In the first stage of analysis, a conventional GLM was performed to identify regions involved specifically in controlling automatic imitation. Image preprocessing and data analysis were performed with FSL version 4.1.4 (Centre for Functional Magnetic Resonance Imaging of the Brain software library, www.fmrib.ox.ac.uk/fsl; Smith et al., 2004). Functional images were realigned to the middle volume to compensate for any head motion using MCFLIRT (Jenkinson et al., 2002). After motion correction, volumes were visually inspected for motion artifacts. Runs in which greater than 10% of volumes displayed striping artifacts were excluded from analysis. As previously mentioned, 2 subjects who had 2 runs meeting this criteria were excluded from analysis. In three subjects only one run met exclusion criteria; the remaining 4 runs for these subjects were included in analysis. After motion correction, data were temporally filtered with a high-pass filter cutoff of 50s and spatially smoothed with a 6mm full width half maximum Gaussian kernel in three dimensions.

Statistical analyses were performed separately for each run using a general linear model (GLM) with fMRI Expert Analysis Tool (FEAT). Each trial type, convolved with a canonical double-gamma hemodynamic response function, was included as a regressor in the GLM. In addition, nuisance regressors were included for error trials, block instructions and the reaction time for each trial. The reaction time regressor was demeaned and orthogonalized with respect to EVs of interest. Trials for each condition were modeled as one-second events starting at video movement onset. Temporal derivatives were included for each regressor to account for variability in the hemodynamic response.

To identify regions involved in controlling automatic response tendencies for the two cue types we specified 3 contrasts. The simple effects of congruency (ImI-ImC and SpI-SpC)

identified regions involved in overcoming the automatic response tendency evoked by each stimulus type. The cue type by congruency interaction, [i.e. the difference between congruency effects (ImI-ImC)-(SpI-SpC)], identified regions involved specifically in control of imitation, since this would subtract out the activation of any non-specific control regions involved in overcoming the spatially-compatible response tendency. Finally, we examined the main effect of cue type (Imitate - Spatial) for regions sensitive to action observation, regardless of congruency, to identify the MNS.

After contrast estimates were computed for each run in native subject space, they were registered to standard space (Montreal Neurological Institute, MNI) in three stages. The middle volume of each run of individual EPI data was registered first to the co-planar matched-bandwidth high-resolution T2-weighted image and subsequently, the co-planar volume was registered to the T1-weighted MPRAGE. Both of these steps were carried out using FLIRT (affine transformations: EPI to co-planar, 6 degrees of freedom; co-planar to MPRAGE, 6 degrees of freedom) (Jenkinson et al., 2002). Registration of the MPRAGE to MNI space (FSL's MNI Avg152, T1 2x2x2mm) was carried out with FLIRT (affine transformation, 12 degrees of freedom) and refined using FNIRT (non-linear transformation) (Jenkinson and Smith, 2001; Jenkinson et al., 2002). Contrast estimates for each subject were then computed by averaging over runs, treating runs as fixed effects.

The group level analysis was performed with a one sample t-test for each contrast using FSL's FLAME (FMRIB's local analysis of mixed effects) stage 1 and stage 2 with outlier de-weighting (Beckmann et al., 2003; Woolrich et al., 2004; Woolrich, 2008). Group images were thresholded at $Z > 2.3$ corrected for multiple comparisons using cluster-based Gaussian random field theory controlling for familywise error across the whole brain at $p = 0.05$. All analyses were performed across the whole-brain. However for the interaction analysis, discussion is limited to regions showing a significant simple effect of congruency, so that only regions showing a robust congruency effect for at least one cue type are considered control regions. This was

accomplished by inclusively masking the interaction contrast by both simple effects of congruency after whole-brain statistical inference.

FMRI Effective Connectivity: Dynamic Causal Modeling (DCM)

With the cue type x congruency interaction contrast [(ImI-ImC)-(SpI-SpC)] (see Results section) we identified 4 regions specifically involved in imitation control (medial prefrontal cortex, mPFC, anterior cingulate cortex, ACC, anterior insula, aINS, and inferior frontal gyrus, pars opercularis, IFGpo). We used DCM to examine effective connectivity between these regions and test a number of different models of imitative control. In DCM, the brain is treated as a deterministic dynamic system. Models of causal interactions between task-relevant brain regions are compared within a Bayesian statistical framework to identify the most likely model out of those examined (Friston et al., 2003; Stephan et al., 2010). A bilinear state equation models neuronal population activity in each region of interest. Activity in a region is influenced by neuronal inputs from one or more connected regions and/or by exogenous, experimentally controlled inputs (i.e. task stimuli). Experimental inputs can influence the system in two ways: as "driving" inputs that elicit responses by directly affecting activity in a region (i.e. stimulus-evoked responses); or as "modulatory inputs" that change the strength of connections between regions (i.e. task-related changes in effective connectivity). Thus, with DCM one can compare a set of models differing in (1) which regions receive driving inputs (stimulus-evoked activity), (2) which regions are connected with one another and how they are connected (the endogenous connectivity structure) and (3) which of these connections receive modulating inputs (task-related changes in effective connectivity). Multiple models (hypotheses) are compared within a Bayesian statistical framework to identify the most likely model out of those examined given the observed data (Friston et al., 2003; Stephan et al., 2010).

Because DCM is not implemented in FSL, we used DCM10 within SPM8. To ensure that preprocessing of the data was consistent with the modeling procedures, we re-processed the

data using a standard SPM processing stream and used this new preprocessed data for all DCM analysis steps. Although the SPM analysis showed very similar patterns to the FSL-derived GLM described above, it was not as sensitive, especially in the interaction contrast. Nonetheless, based on similarities with previous imitation control studies discussed in detail below, it is unlikely that this difference reflects false positives in the FSL analysis. While stronger group effects less sensitive to small differences in processing streams would be ideal, we did not have trouble locating individual subject peaks in our regions of interest using typical methods, so we proceeded with the DCM analysis even though SPM group effects were not as robust as FSL group effects. Several differences in FSL and SPM processing streams may have contributed to the difference in sensitivities. The methods for estimating autocorrelation differ between the packages, and differences in the estimation and success in modeling autocorrelation can affect variance and therefore t-value estimates. In addition, we employed a 2-stage model estimation analysis (Flame 1&2) in FSL, which increases sensitivity by refining variance estimates for all near-threshold voxels in the second stage (Beckmann et al., 2003; Woolrich, 2008).

For the DCM analysis data were preprocessed as follows: functional images were slice-time corrected (Kiebel et al., 2007), motion corrected with spatial realignment to the mean volume of the first run and coregistered to the MPRAGE structural scan. The MPRAGE was processed using a procedure that combines grey and white matter segmentation, bias field correction and spatial normalization. The normalization parameters were then applied to the functional images. Finally the images were smoothed with a 6mm full-width half-maximum Gaussian kernel and resampled to 3x3x3mm voxels. In order to identify individual subject regions of interest in the reprocessed data, we again fit a GLM using SPM8 for each subject with separate regressors for each condition, errors, block instructions and reaction time. Temporal derivatives and motion parameters were also included in the model. An F-test across

all conditions and temporal derivatives was specified to correct extracted timeseries, effectively removing variance associated with motion parameters.

Hypotheses and Model Specification

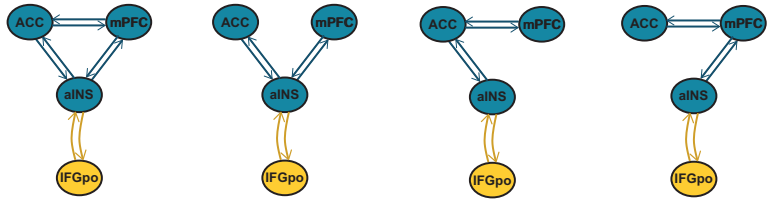
We constructed models defining exogenous inputs to, and endogenous connections between, four regions of interest (ROI) identified to be involved specifically in imitation control. As described in detail in the Results section, these ROIs included a "prefrontal control network"—medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC) and left anterior insula/frontal operculum (aINS)—and the frontal node of the MNS—left inferior frontal gyrus, pars opercularis (IFGpo; see Results Figure 3.4). The construction of our model space was motivated by three central questions: (1) Which prefrontal control region interacts with the MNS? (2) Does conflict detection occur in the mPFC (consistent with the shared representations hypothesis), in the ACC (consistent with the conflict monitoring hypothesis) or in the MNS? (3) Is coupling between the control network and MNS node stronger when control is required than when it is not?

In all models, the MNS node (IFGpo) received action observation (i.e. imitative trials) as a driving input consistent with the response of this region and functional properties of the MNS and IFGpo (di Pellegrino et al., 1992; Iacoboni et al., 1999). In addition, the three regions comprising the control network were connected to one another with all combinations of either 2 or 3 bidirectional connections consistent with anatomical evidence for connections between these regions in primates (Augustine 1996; Petrides and Pandya 2007; Yeterian et al., 2012). This allowed identification of the most likely functional connectivity structure within the prefrontal control network before turning to questions about imitative conflict detection and resolution. Thus, there were 4 base models (Figure 3.2A), across which we varied which prefrontal region was connected to the IFGpo, and which regions and connections were affected by imitative conflict, to answer our three questions (Figure 3.2B).

First, endogenous connectivity structures were defined to determine which of the prefrontal control regions interacts with the MNS. Three separate variations were created in which each one of the three control regions was connected directly to the IFGpo (Figure 3.2B, rows). When crossed with the 4 prefrontal control structures detailed above, this yielded a total of 12 possible endogenous connectivity structures in the full model space.

Next, we varied which node detects (i.e. which region is responsive to) imitative conflict (defined as the difference between incongruent and congruent trials; Figure 3.2B, columns). To test the shared representations theory, conflict drove activity in mPFC, because this region is thought to be engaged when observed and executed actions activate conflicting motor representations (Brass et al., 2009b). In a variation of this model, conflict acted as a driver of the ACC. This was based on the influential conflict monitoring theory from the broader cognitive control literature in which the ACC is proposed to detect response conflict (Botvinick et al., 2004; Carter and Van Veen, 2007) and provide a signal to lateral prefrontal regions to implement conflict resolution. In addition, we included models in which conflict drove both the mPFC and ACC to test the possibility that these regions act in concert in the detection of imitative conflict. This would be consistent with a scenario in which the mPFC detects imitative conflict specifically, whereas the ACC is a more general response conflict detector and therefore contributes across a variety of tasks. Finally, we tested a fourth alternative hypothesis in which conflict is detected in the MNS. Since the MNS represents both observed and executed actions, it is possible that conflict between planned and observed actions is detected where conflicting representations first arise. The presence of this conflict could then signal prefrontal cortex to reinforce the intended action or inhibit the externally-evoked action. These 4 variations in the location of conflict as a driving input (mPFC, ACC, mPFC+ACC, IFGpo) were crossed with the 12 endogenous connectivity structures creating 48 models.

(A) 4 prefrontal connectivity structures.



(B) Model space of fully connected prefrontal family.

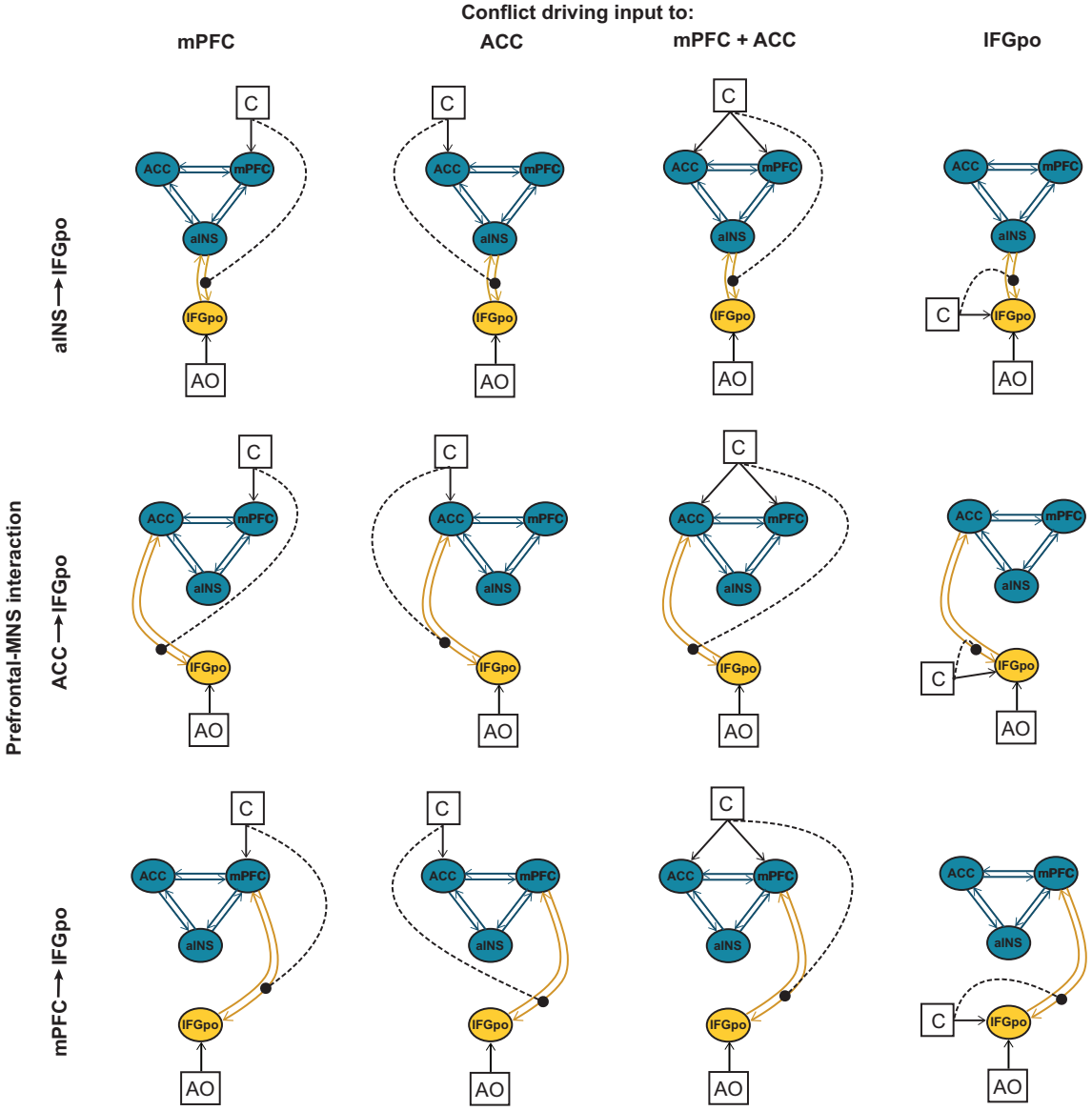


Figure 3.2: DCM Model Space. (A) 4 prefrontal connectivity families were tested first to identify the most plausible structure (only aINS→IFGpo models depicted). (B) Models in the fully connected prefrontal family are shown. Rows depict 3 possible prefrontal→MNS connections. These were fully crossed 4 potential targets for conflict as driving input (columns) and the presence or absence of conflict as a modulator of prefrontal→MNS connectivity (dotted lines). Inputs in all models are depicted in boxes (C=conflict; AO=action observation). The frontal node of the mirror neuron system is depicted in yellow (IFGpo=inferior frontal gyrus, pars opercularis) and prefrontal control network in blue (ACC=anterior cingulate; aINS=anterior insula; mPFC=medial prefrontal cortex).

Finally, we included another set of the identical 48 models but with the addition of conflict as a modulator of the connection from the prefrontal control network to the IFGpo. This allowed us to determine whether the influence of prefrontal control regions on the frontal node of the MNS is greater when imitative control is implemented, as would be expected if prefrontal-MNS interactions relate to resolving the imitative conflict. Thus, the total model space was comprised of 96 models built as a factorial combination of 12 connectivity structures, 4 locations of conflict driving input, and 2 modulating inputs (i.e. the presence or absence of conflict as a modulator).

Time series extraction

The selection of subject-specific ROIs in the mPFC, ACC, aINS and IFGpo was based on local maxima of the relevant contrasts from the GLM analysis (Stephan et al., 2010). For the prefrontal control network we identified the local maxima in the imitative congruency contrast (ImI-ImC) nearest the interaction peaks (mPFC: -3 44 22; ACC: -3, 14 34; aINS: -39, 17 -5). Although guided by the interaction, we used the simple effect of imitative congruency for localization of individual subject ROIs so that control nodes were defined by their contribution to imitative control and not influenced by any effect of spatial congruency. For the IFGpo we used the main effect of cue type to define the node by its mirror properties, again locating the local maxima nearest the interaction peak (MNI -39, 14, 25). Nonetheless, parameter estimates from the resulting IFGpo individual subject ROIs still showed the imitative congruency effect as expected based on the GLM [$t(16)=2.5$, $p = 0.02$].

Individual subject ROIs were defined for each region as all supra-threshold voxels ($p<0.05$, uncorrected) within a 6mm sphere centered on the peak nearest to the group coordinate. Peaks were required to be within 16mm of the group coordinate and the four peaks for each subject were separated by at least twice the smoothing kernel (12mm). Finally, peaks were also within the following anatomical regions as defined by the Harvard-Oxford

Probabalistic Atlas: mPFC – cingulate or paracingulate gyrus; ACC – anterior cingulate gyrus (more posterior than mPFC peaks); IFGpo – inferior frontal gyrus, pars opercularis; aINS – anterior insula or frontal operculum. Using this procedure, one or more peaks could not be identified for 3 of the 20 subjects, so these subjects were excluded from the DCM analysis. This number is typical (e.g. Wang et al., 2011b) for a study including several ROIs. The resulting mean coordinates for each ROI were: mPFC (-2,42,23); ACC (-3, 15, 34); aINS (-35, 16, -4); and IFGpo (-39, 15, 25). Regional timeseries were extracted from each ROI as the first eigenvariate of responses and adjusted for effects of interest F-test (variance due to motion removed).

Model Selection

We used Bayesian model selection (BMS) amongst individual models (Stephan et al., 2009; Stephan et al., 2010) with inference over families of models (Penny et al., 2010) to identify the most likely model structure from the model space described above. This was done in two stages. First, for each subject the model evidence was computed for each model and each run using the negative free-energy approximation to the log-model evidence. The free-energy metric for model evidence balances model fit and complexity taking into account interdependencies amongst parameters and has been found to outperform other more conventional methods of model scoring for model comparison (Penny et al., 2012). The subject-specific sums of log evidences across runs (equivalent to a fixed effects analysis across runs) were entered into group random effects (RFX) BMS to identify the most likely model across subjects (Stephan et al., 2009). This procedure requires that all subjects have the same number of runs (c.f. SPM DCM manual), so only the first four runs were used for DCM for all subjects (as mentioned previously, three subjects had only four usable runs due to motion artifacts).

The RFX approach to group model selection was preferred over fixed effects because it does not assume that the optimal model is the same for all subjects. This is appropriate in

studies of higher cognitive functions where there may be heterogeneity in strategy or neural implementations of task performance (Stephan et al., 2010). Results from random effects model comparisons are understood in terms of the exceedance probability (the probability that a particular model is more likely than any other model tested) and the expected posterior probability (the likelihood of obtaining the model for a random subject from the population) (Stephan et al., 2009). Both measures sum to 1, so the exceedance and expected posterior probabilities are reduced as the model space increases. As such, including multiple models makes it less likely that a single model will dominate the RFX analysis. Family level inference has been introduced as a technique to deal with this issue of dilution from a large number of models, which is particularly problematic when different models have many shared parameters and when different subjects use slightly different models (Penny et al., 2010). With this technique, models are divided into groups (families) according to the presence of shared features, which allows inference about these general features and can be used narrow the search for a best model.

Here, we divided models into families based on the intrinsic connectivity structure in a stepwise manner. First, we identified the family with the preferred prefrontal connectivity structure, limiting further inference about MNS interactions and conflict detection to the set of most plausible models. Next, we entered models from the winning family (fully connected prefrontal network; Figure 3.2B) into a second set of BMS analyses to answer the questions outlined previously. The remaining models were divided into 3 families, each of which included models sharing the same prefrontal→MNS connection (aINS→IFGpo, ACC→IFGpo, or mPFC→IFGpo; rows in Figure 3.2B), but differing in the location of conflict driving and modulatory inputs. This allowed us to determine which prefrontal control region is most likely interacting with the MNS, removing uncertainty about the influence of conflict on the system. Models in the winning family were then compared to examine conflict processing in the system. To summarize individual parameters of the winning model, we computed the mean and

standard deviation of the maximum a posteriori parameter estimates across subjects and performed one-sample t-tests to determine whether the parameters were significantly different from zero.

3.1.3 Results

Behavioral Results

Mean reaction time (RT) and accuracy were calculated for correct responses in each condition for each subject, and then averaged across subjects. Trials with RT greater than 2 standard deviations above the mean were considered outliers and excluded from analysis (1.1-3.8% of trials per subject). RT analysis was carried out using a 2 (Cue type: imitative, spatial) x 2 (Congruency: congruent, incongruent) repeated measures ANOVA. This revealed a main effect of congruency ($F_{(1,19)}$=38.1, p<0.001), demonstrating that responses for incongruent trials (mean=317ms, SD=32) were slower than congruent trials (mean=304ms, SD=41; Figure 3.3).

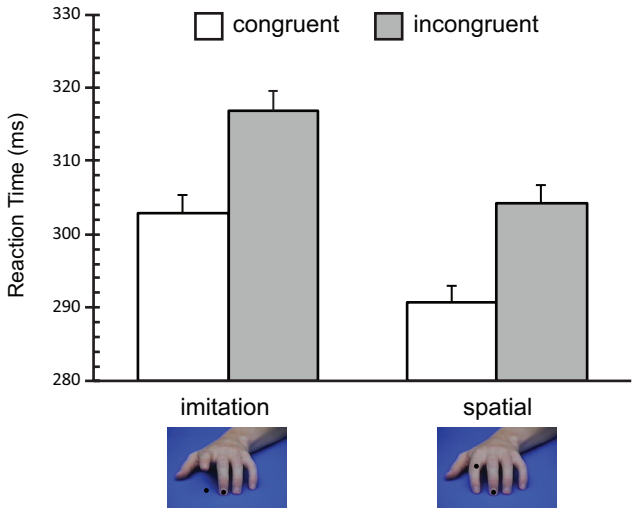


Figure 3.3: Behavioral Results. Mean reaction time for each condition. Error bars represent within subject standard error of the mean, calculated with Cousineau's adaptation of Loftus & Masson's method {Cousineau 2005, Loftus 1994}. Main effects of congruency and cue type were significant (p < 0.01), but the interaction between cue type and congruency was not.

There was also a main effect of cue type ($F_{(1,19)}$=36.0, p<0.001), with responses being slightly faster for spatial (mean=292ms, SD=33) than imitative cues (mean=304ms, SD=40ms). Earlier detection of movement onset may have occurred for the dots due to greater contrast between the dot and background. Importantly, there was no interaction between cue type and congruency ($F_{(1,19)}$=0.27, p=0.6), confirming that congruency effects were of similar size regardless of the cue type (spatial: 12ms; imitative: 13ms). As such, differences in congruency effects in brain activation cannot be attributed to differences in the presence or magnitude of the interference effect. In a similar ANOVA on accuracy data, no significant effects were observed as accuracy was near ceiling in all four conditions (>97%).

GLM Results

Neuroimaging data revealed a dissociation between congruency effects for the two cue types. For imitative stimuli, the simple effect of congruency (ImI - ImC) showed activation in frontal and parietal regions, as well as the cerebellum and caudate (Figure 3.4A, Table 3.1). Consistent with previous studies of imitation control (Brass et al., 2001b; Brass et al., 2005; Brass et al., 2009a; Bien et al., 2009b; Spengler et al., 2009; Wang et al., 2011b), large clusters in the frontal lobes were observed in medial prefrontal cortex (mPFC) extending into the frontal pole, anterior cingulate cortex (ACC) and bilateral anterior insula (aINS) extending into the frontal operculum and orbito-frontal cortex. In addition there was bilateral activation in the IFG pars opercularis (IFGpo) extending posteriorly into precentral gyrus. In contrast to findings for imitative cues, no regions showed a significant congruency effect for spatial cues. This was true even when the threshold was lowered to z > 1.7 to be more sensitive to small differences and when using a most liberal post-hoc ROI approach: One-sample t-tests on the parameter estimates for the contrast (SpI-SpC) were extracted from each of the regions showing an imitative congruency effect. No regions approached significance for spatial congruency effects even by this liberal method (all p-values greater than 0.2).

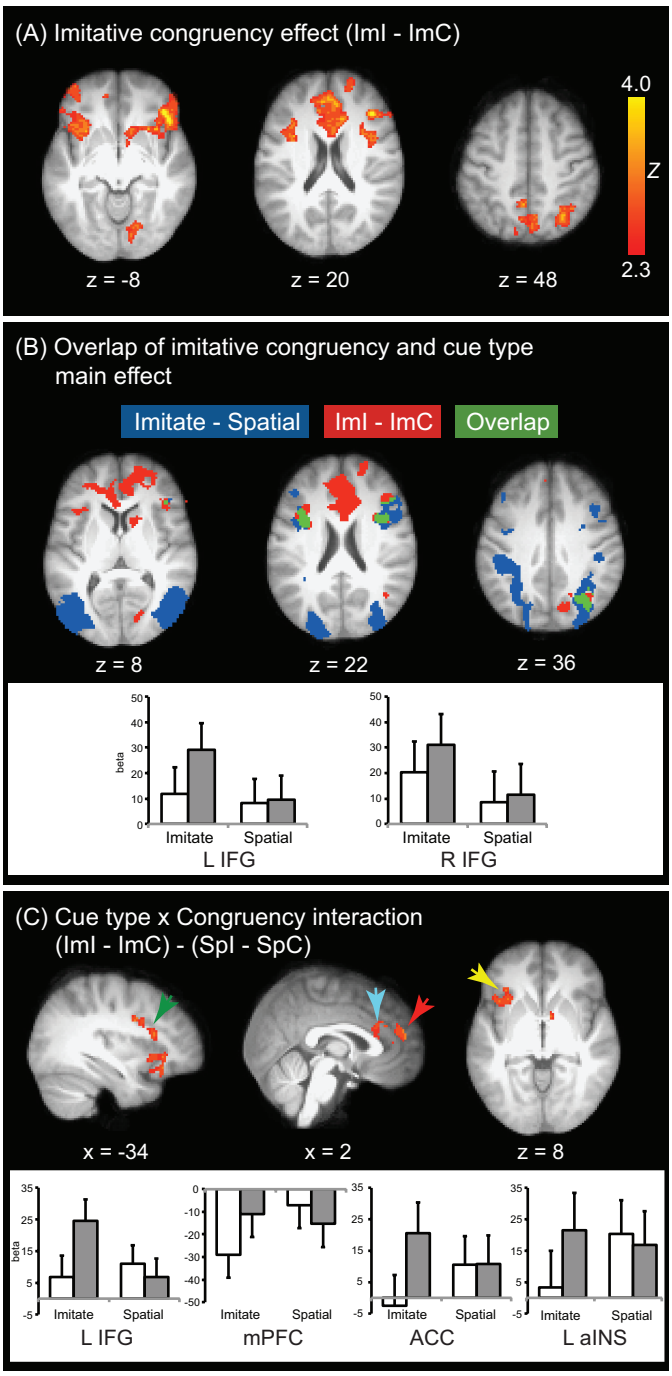


Figure 3.4: GLM Results. (A) Regions with greater activation for incongruent than congruent trials for imitative cues. No regions showed a significant congruency effect for spatial cues. (B) Overlap (green) of imitative congruency effect (red) and main effect of cue type (blue) demonstrate the IFGpo is both modulated by congruency and more active during action observation than observation of moving dots (C) Interaction effect showing regions where congruency effect is significantly greater for imitative than spatial cues. These regions represent the regions of interest in the DCM analysis (Green = IFGpo; Blue = ACC; Red = mPFC; Yellow = aINS). Bar graphs depict parameter estimates extracted from significant clusters, with error bars representing standard error of the mean across subjects. All contrasts are thresholded at z>2.3 corrected across the whole brain for multiple comparisons ($p < 0.05$ FWE).

To localize potential mirror neuron regions, we examined the cue type main effect (Imitate - Spatial). As expected, a fronto-parietal network commonly observed during action observation and imitation tasks was more active for imitative cues compared to spatial cues (Iacoboni et al., 1999). The network involved bilateral inferior frontal gyrus, pars opercularis (IFGpo) extending into ventral premotor cortex (PMv) and the superior parietal lobes (Figure 3.4B, Table 3.1). To determine whether these mirror neuron regions were modulated during resolution of imitative conflict, we compared the cue type main effect with the imitative congruency effect. An overlay of the two contrasts demonstrates that the right parietal and bilateral IFGpo regions were sensitive to action observation and also modulated by conflict. The main effect of cue type strongly suggests that IFGpo represents the frontal node of the human MNS, especially in the context of previous work. The IFGpo is causally involved in both automatic imitation (Catmur et al., 2009) and motor resonance phenomena (Avenanti et al., 2007) and this region is also likely to be a human homologue of monkey area F5 where mirror neurons have been recorded in monkeys (Rizzolatti and Arbib, 1998). The imitative congruency effect observed in the same region suggests that this frontal MNS node is modulated during imitation control.

Consistent with the qualitative difference between imitative and spatial congruency effects, a direct comparison of the congruency effects confirmed a dissociation between control processes depending on the cue type. Significantly greater congruency effects for imitative compared to spatial cues [assessed with the Cue Type x Congruency interaction contrast (ImI-ImC) - (SpI-SpC)] were detected in multiple frontal regions: the ACC, mPFC extending into the frontal pole, left IFGpo and left aINS extending into the frontal operculum and OFC (Figure 3.4C, Table 3.1).

Table 3.1. Local maxima from significant clusters identified by GLM.

Region	*Z*	MNI Coordinates x	y	z
Imitative congruency effect (ImI > ImC)				
Frontal Orbital Cortex	3.81	42	34	-8
Middle Frontal Gyrus	3.73	40	32	20
Frontal Pole	3.56	32	46	-2
Cingulate Gyrus, anterior division	3.51	10	38	6
Frontal Orbital Cortex	3.57	-30	22	-16
Inferior Frontal Gyrus	3.44	-34	18	22
Insular Cortex	3.83	-38	16	-2
Precentral Gyrus	3.49	-30	8	26
Superior Parietal Lobule	3.39	32	-62	48
Precuneus Cortex	3.32	-2	-64	56
Lingual Gyrus	3.40	12	-82	-6
Intracalcarine Cortex	3.37	10	-82	0
Cerebellum	3.71	-2	-84	-32
Cue Type Main Effect (Imitate > Spatial)				
R Middle Frontal Gyrus	3.60	42	24	26
R Inferior Frontal Gyrus, pars opercularis	3.92	36	12	26
L Inferior Frontal Gyrus, pars opercularis	3.56	-38	20	20
R Precentral Gyrus	3.32	40	4	24
L Precentral Gyrus	3.46	-40	2	28
L Lateral Occipital Cortex	6.25	-46	-84	10
R Lateral Occipital Cortex	6.06	50	-72	0
Cue type x Congruency Interaction (congruency effect (ImI - ImC) > (SpI - SpC)				
Frontal Pole	3.48	20	58	16
Paracingulate Gyrus	3.47	-4	48	28
Cingulate Gyrus, anterior division	3.04	6	28	22
Inferior Frontal Gyrus, pars opercularis	3.16	-36	20	18
Frontal Orbital Cortex	3.12	-30	24	-16
Insular Cortex	3.18	-32	18	-6

Regions surviving z>2.3, cluster corrected (FWE z<0.05) are reported. MNI refers to Montreal Neurological Institute x, y and z coordinates and the highest probability region according to the Harvard-Oxford probabilistic atlas was used for anatomical localization. Only one maximum per anatomical region is reported.

DCM Results

We sequentially partitioned the model space into families (groups of models which shared common features) to zero in on a winning model via bayesian model comparisons. We

first used family level inference to find the preferred prefrontal connectivity structure by partitioning models into four families with each family sharing the same set of prefrontal connections. Results indicated that the fully connected prefrontal control network was more likely than the more sparsely connected prefrontal networks (exceedance probability= 0.88; expected posterior probability = 0.48; Table 3.2). An exceedance probability more than 10 times higher than the next highest family provides strong evidence that the fully-connected prefrontal network is better than other prefrontal connectivity structures.

Next, we entered models from the winning family—those with fully connected prefrontal nodes—into a second family-level comparison to determine which of the 3 prefrontal control regions (mPFC, ACC and aINS) interacted with the frontal MNS node (IFGpo). Models in each family shared the same prefrontal→MNS connection (aINS→IFGpo, ACC→IFGpo or mPFC→IFGpo). Results demonstrated that the IFGpo is substantially more likely to be connected to the aINS (exceedance probability p=0.82; expected posterior probability = 0.50) than either the ACC (exceedance probability = 0.14; expected posterior probability = 0.30) or the mPFC (exceedance probability p=0.03; expected posterior probability = 0.20; Figure 5; Table 3.2).

Finally, we performed BMS on the 8 models in the winning family—models with the aINS to IFGpo connection—to determine more specifically how conflict processing occurs within the system. The models varied according to which region is driven by conflict (IFGpo, ACC, mPFC or ACC+mPFC) and whether top-down influence of the prefrontal control network on the IFGpo is modulated by conflict. Model 8 (Figure 3.5) clearly out-performed the other 7 models, with an exceedance probability of 0.88 and expected posterior probability of 0.40 (Table 3.2). In this model both the ACC and mPFC are driven by conflict. Furthermore, the connection between the aINS and IFGpo is modulated by conflict, with greater connectivity when conflict resolution is required than when there is no conflict. This model is more likely than any of the alternatives, however it is interesting to note that the second highest model was identical except conflict

drove only the ACC (model 7). The total exceedance probability of these two models together was greater than 0.99 with an expected posterior probability together of 0.73, providing strong evidence that conflict detection occurs in the medial frontal regions rather than first being detected in the MNS and then propagating to the frontal cortex. Similarly, these models both include conflict modulation of the aINS to IFGpo connection whereas the identical models without this modulation have exceedance probabilities much lower than 0.01.

Table 3.2: DCM model selection results

	Exp. Posterior Probability	Exceedance Probability
Prefrontal Family Inference		
Fully connected prefrontal nodes	0.48	0.88
mPFC-aINS & ACC-aINS connections	0.14	0.02
mPFC-ACC & ACC-aINS connection	0.24	0.08
mPFCACC & mPFC-aINS connections	0.14	0.02
Prefrontal → IFGpo Family Inference		
aINS → IFGpo	0.50	0.82
ACC → IFGpo	0.30	0.14
mPFC → IFGpo	0.20	0.03
Fully connected/aINS→IFGpo BMS (top 3)		
mPFC + ACC detection, with modulation	0.40	0.88
ACC detection, with modulation	0.22	0.11
mPFC detection, with modulation	0.09	0.005
IFGpo detection, with modulation	0.08	0.005
mPFC + ACC detection, no modulation	0.08	0.004
ACC detection, no modulation	0.04	< 0.001
mPFC detection, no modulation	0.04	< 0.001
IFGpo detection, no modulation	0.04	< 0.001

Averages of posterior parameter estimates across subjects for the winning model are depicted in Figure 3.5. The endogenous connections from the mPFC→aINS and ACC→aINS were significantly greater than zero ($p < 0.05$). In addition, all driving inputs were significant: conflict driving input to the ACC ($p = 0.001$); conflict to the mPFC ($p<0.001$); and action observation to the IFGpo ($p = 0.048$). Conflict modulation of the aINS→IFGpo connection also

approached significance (p=0.073). Other individual parameters did not reach significance, including the aINS→IFGpo connection.

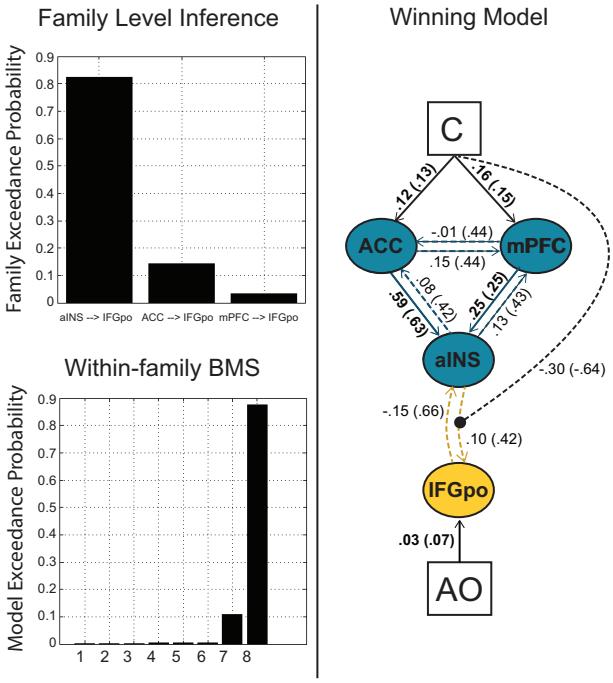


Figure 3.5: DCM Results. Results from family level inference performed on models within the fully-connected prefrontal family demonstrate exceedance probability of 0.82 for models including the aINS→IFGpo connection (top left). Model selection comparing models within this family shows only 2 models receiving any evidence (bottom left). The winning model (model 8) is shown at right. Values next to each connection or input show the mean and standard deviation (in parentheses) of the parameters across subjects. Parameters significantly different from 0 ($p<0.05$) are depicted with solid lines and bold parameter values. The modulation of aINS→IFGpo connection by conflict also approached significance (p=0.07).

3.1.4 Discussion

Subjects performed a predefined finger movement in response to video stimuli depicting either an action (finger movement) or a dynamic spatial stimulus (a moving dot). As expected, for both cue types people were slower to respond when the stimulus and response were imitatively or spatially incongruent compared to when they were congruent, presumably due to the recruitment of additional resources to control the automatic response tendency on incongruent trials. In contrast to the very similar behavioral congruency effects, neural activity demonstrated a dissociation between imitative and spatial congruency effects, revealing a set of regions involved specifically in imitation control. We used dynamic causal modeling to explore

interactions between these regions and test several hypotheses about mechanisms of imitation control. Our results suggest that the mPFC and ACC detect conflict between observed and planned actions and the anterior insula interacts with the MNS, with some evidence for stronger coupling in the face of imitative conflict. Below, we begin by discussing results from the GLM analyses in the context of previous literature and then propose an expansion of the shared representations model of imitation control to incorporate the DCM findings.

Four regions—the ACC, mPFC, aINS and IFGpo—showed a significant interaction between congruency and cue type, demonstrating a congruency effect for imitative cues but not for symbolic spatial cues that moved with a similar trajectory. This cannot be attributed to an absence of response conflict altogether for the spatial cues. Congruency effects for the two cue types were intentionally equated to rule out the possibility that differences in neural correlates of the congruency effects are due to different degrees of conflict and control (Aicken, 2007). Instead, similar behavioral manifestations of conflict suggest that similar degrees of automatic response tendencies were evoked by the two stimulus types, and therefore, neural correlates of this conflict are likely related to the particular content of the stimuli rather than to the degree of conflict. Thus, the role of these regions in imitation control is distinct from any potential role in controlling prepotent response tendencies induced by the non-social, symbolic stimuli used in the spatial task.

This dissociation between imitation and spatial compatibility is in line with previous behavioral work demonstrating distinctions between imitative and spatial compatibility (Brass et al., 2001a; Heyes et al., 2005; Bertenthal et al., 2006; Catmur and Heyes, 2011; Jiménez et al., 2012). However, previous neuroimaging support of these findings has been mixed. Crescentini and colleagues (Crescentini et al., 2011) compared imitation and spatial congruency effects in similar tasks. However, they did not find behavioral congruency effects for half of responses and also did not observe fMRI congruency effects for either cue type. This may have been due to the task instructions, which required that participants withhold their response until the end of the

video stimulus rather than responding immediately. In this situation, it is possible that inhibition of the prepotent response occurred on both congruent and incongruent trials, as subjects waited for the appropriate time to respond. In another study comparing imitative and spatial compatibility (Bien et al., 2009) only the frontal operculum was demonstrated to show a greater imitative than spatial congruency effect. The relevant interaction contrast, however, was not performed across the whole brain so it is possible that a wider network similar to the present study showed similar effects.

The regions identified here as specifically involved in imitation control are consistent with previous studies that did not control for spatial compatibility. Although the mPFC has received the most attention (Brass et al., 2001b; Brass et al., 2005; Brass et al., 2009; Spengler et al., 2009; Wang et al., 2011b), the other regions have also been implicated in studies reporting whole brain imitation congruency effects (Brass et al., 2001b; Brass et al., 2005; Bien et al., 2009; Wang et al., 2011b). The anterior insula/frontal operculum region observed here is similar to that found in multiple previous studies (Brass et al., 2005; Bien et al., 2009; Wang et al., 2011b) despite receiving relatively little attention in theories of imitation control. The consistency of involvement of this region in imitation control may have been obscured by differences in nomenclature. For example, a cluster with MNI coordinates (45, 26, -7) falls within our aINS cluster, but was hypothesized to be part of the MNS and thus labeled the IFG (Wang et al., 2011b). Similarly, Brass and colleagues reported activation in Talairach (41 5 3), which is slightly posterior to the anterior insula cluster we observed. Bien and colleagues (2009) also identified a region in the frontal operculum, however coordinates are not reported. Thus, activity around the junction of the anterior insula and frontal operculum seems relatively consistent across a variety of imitation control tasks.

The observation of IFGpo involvement in imitative control is especially intriguing in the context of previous literature on imitation and the MNS. The anatomical location of the congruency effect—the very posterior part of the inferior frontal gyrus and extending into the

ventral premotor cortex—is one of the proposed human homologues of the frontal node of the monkey MNS (Rizzolatti and Arbib, 1998) and the region is commonly activated in studies of action observation and imitation in humans (Caspers et al., 2010). However, even more importantly, in our task the same region showed a main effect of cue type, indicating sensitivity to action observation as one would expect of a mirror neuron region. This finding is consistent with several previous imitation control studies that have argued for modulation of the MNS (Spengler et al., 2009; Wang et al., 2011b). However, previous claims were based on anatomical parallels to the literature rather than identifying the MNS in the same study. The inclusion of a spatial compatibility task that was very similar to the imitation task except for the absence of action observation, allowed us to test the hypothesis that the MNS is involved in imitation control more directly. Our results support this hypothesis, and led us to explore functional interactions between the prefrontal control regions and the frontal node of the MNS using dynamic causal modeling.

We were interested specifically in how the set of 3 prefrontal control regions (mPFC, ACC, aINS) interacts with the MNS during imitation control and how conflict processing occurs in the network. In the winning model the aINS interacted with the IFGpo, this connection was modulated by imitative congruency, and activity in the mPFC and ACC was driven by imitative conflict. This model of imitative control is consistent with the shared representations theory in that the mPFC is involved in detecting conflict between self-generated and other-generated motor activity (Brass et al., 2000). However the DCM suggests an extension of the shared representations model, which has not provided a detailed account of how conflict between the observed and intended action is subsequently resolved.

In the winning model the aINS input to the MNS is modulated by conflict. Although a univariate test of the parameter did not quite reach significance, the fact that the top models all included this modulation parameter suggests that it does contribute to model fit, and provides at least some support for the hypothesis that this interaction is involved in resolving conflict. A

closer look at the aINS→IFGpo interaction provides some insight into potential prefrontal-MNS interactions in conflict resolution. The endogenous connectivity between aINS and IFGpo was not different from zero, but a modulation of this connection occured in response to conflict. This provides at least tentative evidence that the aINS interacts with the MNS activity only when conflict occurs. Furthermore, the direction of modulating input was negative, suggesting that aINS suppresses MNS activity in response to conflict. Although further support is desirable given that we observed only a trend in the parameter, this pattern is consistent with models of conflict processing which often argue for inhibitory mechanisms, both in the context of automatic imitation (Brass et al., 2009b) and in more general response conflict tasks (Kornblum et al., 1990; de Jong, 1995; Miller and Cohen, 2001; Burle et al., 2004; Ridderinkhof et al., 2004).

Within the prefrontal control network, both the ACC and mPFC were driven by conflict in the winning model. In the next best model, the ACC alone was driven by conflict. Thus, both medial prefrontal regions seem to play some role in detecting imitative conflict. While mPFC seems to be involved only for the more specific case of imitation in which conflict is related to agency (Brass et al., 2001b; Brass et al., 2005; Brass et al., 2009a; Spengler et al., 2009; Wang et al., 2011b), previous studies suggest the ACC is activated by a wide range of conflict tasks (Van Veen et al., 2001; Bunge et al., 2002; Egner and Hirsch, 2005; Wendelken et al., 2009; Botvinick et al., 2004; Carter and Van Veen, 2007) and therefore may represent a more multi-modal and general conflict detector. In addition, the aINS region could also represent a more domain-general node of the network, as this region is also implicated in both response inhibition and conflict resolution, including stop-signal, go/no-go, Stroop and flanker tasks (Wager et al., 2005; Nee et al., 2007; Levy and Wagner, 2011, Swick et al., 2011).

Based on these similarities, control of imitation may involve interactions between general cognitive control mechanisms and a more specific imitation-relevant network. The ACC and aINS may be involved in detecting and resolving conflict regardless of the source of the conflict, but interact with different networks depending on the nature of conflict. In the context of imitation

and action observation, the mPFC would be responsible for determining agency and thereby indicate to the aINS which representation reflects the intended action; the MNS—where conflict first arises—would be the target of top-down mechanisms of conflict resolution. This model is in line with a parsimonious and generalizable framework whereby a general conflict resolution system interacts with the system in which the conflicting representations occur. Indeed this is consistent with several previous studies aiming to dissociate conflict processes. Egner and others have demonstrated modulation of the visual system in tasks involving stimulus conflict (Egner and Hirsch, 2005; Egner et al., 2007), modulation of the amygdala in tasks with emotional conflict (Etkin et al., 2006; Egner et al., 2008), and motor modulation in tasks with response conflict (Egner et al., 2007; Stürmer et al., 2002).

Finally, we should note that our model of imitation control differs somewhat from a recent study that also used DCM to examine imitation control mechanisms, albeit in the context of direct and averted gaze (Wang et al., 2011b). That study was motivated by the observation that imitation interference effects were reduced when video showed someone looking at the participant as compared to when someone was looking away from the participant. This behavioral effect was proposed to reflect reduced top-down control on automatic imitation in response to the social gaze stimulus (Wang et al., 2011a). Results from their DCM suggested that the interaction between imitation control and gaze was due to mPFC-mediated modulation of visual inputs to the frontal node of the MNS. The interpretation of MNS involvement in this study is tenuous, given that an inferior frontal region assumed to be the frontal MNS was identified in an interaction between imitative congruency and eye gaze and was quite far anterior. However, a more interesting explanation for potentially different control mechanisms in the two studies is the difference in the timing of imitative control. In the gaze experiment, gaze was directed toward or away from the participant before the imitative task. Thus, the effect of gaze on imitative control is likely to occur in advance of the imitative stimulus, in a preparatory manner. In contrast, in the current study congruency effects must reflect control exerted in

response to the imitative conflict rather than in preparation for conflict, since the need for control was unpredictable. Differences between preparatory and reactive control mechanisms have been observed in other domains (Braver et al., 2007; Boy et al., 2010; Braver, 2012) and are plausible in this context as well. For example, in a situation where imitation control can be implemented in advance, it could occur by changing motor system sensitivity to action observation through modulation of input to the MNS (as described by Wang et al., 2011b; see also Heyes, 2011; Chapter 4). However, when preparation to avoid imitation is not possible or is incomplete then some reactive control mechanism must deal with the unwanted motor activation that arises in response to action observation—in this case it may be too late to modulate the visual input, and instead the motor output of the MNS may be modulated as described in the current study.

Conclusions

In summary, our results support the view that imitative control relies on neural mechanisms that are at least partially distinct from those involved in overcoming automatic response tendencies evoked by non-social stimuli. In addition, we propose an extension of the shared representations hypothesis of imitation control (Brass et al., 2009): Once the mPFC and ACC detect conflict between the planned and the observed actions, enforcing the intended action involves interactions between the anterior insula and frontal node of the human MNS.

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3.2 Theta-burst stimulation fails to modulate imitation control.

3.2.1 Introduction

In Experiment 1 we identified several frontal regions showing a Cue type x Congruency interaction: the mPFC, IFGpo, ACC and aINS. This suggests a role in imitative control, however

fMRI cannot provide evidence of causation. In a follow-up study, we used repetitive transcranial magnetic stimulation (TMS) to determine whether transiently disrupting function of involved regions reduces imitation control abilities. Larger reaction time or accuracy interference effects from worse performance on incongruent trials after stimulation, would demonstrate that the stimulated region is required for imitation control.

In addition, results may provide converging evidence for a dissociation between control mechanisms for automatic imitation and spatial compatibility. While I have argued that the fMRI dissociation between spatial compatibility and automatic imitation provides evidence for a dissociation, the lack of any congruency effect in brain activation for spatial cues could indicate that there was simply not enough power to detect activation in the same regions identified for imitative cues. As noted, this seems unlikely, given the similarity of behavioral congruency effects for the two cue types. Nonetheless, effects of TMS that are specific to control of automatic response activation by imitative cues would provide more definitive evidence that interaction effects observed in fMRI reflect a true dissociation between control mechanisms employed in response to imitative and non-imitative conflict.

3.2.2 Methods

Participants

30 participants (18-30 years old; 18 female) were recruited from the UCLA community through fliers and free internet bulletin boards. All participants were right-handed, had normal or corrected-to-normal vision, were not taking psychoactive medications and had no history of neuropsychiatric disorder. Participants also completed safety screening for both MRI and TMS to rule out risks such as metal implants and increased likelihood of seizure. All experimental protocols were approved by the UCLA Institutional Review Board and participants were compensated for their time.

Behavioral Paradigm

Participants performed a simple response imitation control task with and without theta-burst TMS. The stimuli and task instructions were identical to the fMRI study just described (Section 3.1): participants lifted the index or middle finger of their right hand in response to index and middle finger and dot videos, according to a predefined instruction. However, there were slight modifications to better accommodate TMS and remove the constraints of fMRI. Rather than null trials, which provided resting baseline for fMRI, we included catch trials in which there was no movement in the video stimulus to minimize anticipation errors (Press et al., 2006; Press et al., 2005; Press et al., 2008). Trial timing was the same except that the ITI was fixed at 2500ms (as opposed to the variable 500-2000ms in the fMRI experiment). 200 trials (40 trials per condition: ImC, ImI, SpC, SpI, catch) were presented in blocks of 10 trials of a single cue type. Between blocks the instruction screen indicating the cue type and response finger was presented for 2 seconds. Response finger alternated every block and stimulus type alternated every two blocks. Congruent, incongruent and catch trials were presented pseudorandomly, within the constraint that congruent and incongruent trials followed each other with the same frequency. The total duration of the task was less than 17 minutes, which is short enough to be well within the window of effects of theta burst TMS (Huang et al., 2005).

Participants performed the task twice, once immediately following theta burst stimulation (experimental task) and once without stimulation (baseline task). Reaction time and error rate were compared within subjects across the two performances. To avoid learning effects, the order of tasks was counterbalanced: Half the subjects performed the baseline task before stimulation, and half performed it after the experimental task. When the baseline task was performed second, it followed stimulation by an hour and 15 minutes, outside the window in which theta-burst effects on cortical excitability are evident in primary motor cortex (Huang et al., 2005).

TMS Procedures

TMS was delivered immediately prior to experimental task performance with a Magstim Super Rapid stimulator using a hand-held figure of eight coil (70mm standard coil, Magstim Co., Whitland, Dyfed, UK) that was placed tangential to the scalp. A 40-second train of theta burst stimulation (3 pulses at 50Hz, repeated at 5 Hz; 600 pulses total) was delivered to a single cortical site with an intensity of 80% of active motor threshold. This protocol has been shown to decrease cortico-spinal excitability when delivered over primary motor cortex for nearly 1 hour (Huang et al., 2005) and has been used subsequently to disrupt social-cognitive functions (e.g. Volman et al., 2011; Verschuere et al., 2012; Banissy et al., 2010).

Motor threshold was determined at the beginning of the session by stimulating over the hand area of primary motor cortex. Active motor threshold was defined as the minimum intensity required to elicit a motor evoked potential in the first dorsal interosseus with peak-to-peak amplitude of at least 100 microvolts in at least 5 of 10 trials while the participant maintained voluntary contraction of about 20% maximum force using visual feedback.

The location of stimulation was determined by the group coordinates of the imitation congruency effect described in the previous experiment (Section 3.1; frontal operculum: -44, 22, 0; mPFC: -4 48 32; premotor cortex: -38, 2, 32; Figure 3.6A). The ACC was not stimulated because it was too deep. The precise coordinate location was limited by accessibility, rather than being the maximum of the cluster. Specifically, a posterior local maximum was chosen from ventral premotor cortex to maximize comfort as well as distance from the frontal operculum site; and the most superficial parts of the mPFC and anterior insula clusters (located in the frontal operculum) were selected. For each subject the location corresponding to the group standard space coordinates was identified by registering their previously acquired high resolution structural MRI (MPRAGE: TR, 1900ms; TE 2.26ms; flip angle = 9°; 176 sagittal slices; slice thickness 1mm; matrix 256 x 256; FOV 250mm) to MNI space and applying the calculated transform to the group coordinate to obtain the subject-specific coordinate. The scalp

location for coil positioning to target that subject-specific coordinate was then determined with a frameless stereotaxy system (Brainsight, RogueResearch, Montreal, Canada). Landmarks on the subject's head were coregsseristered with the structural MRI to allow tracking of the TMS coil position with respect to the cortex (Figure 3.6B).

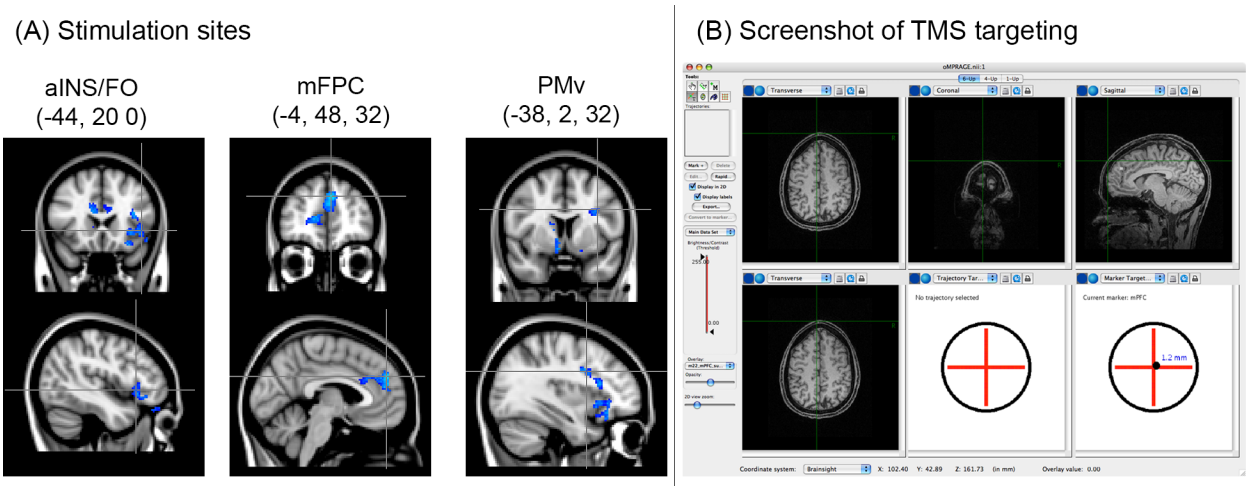

Figure 3.6: TMS targeting. (A) Stimulation sites indicated with crosshairs are shown on a standard brain showing Cue type x Congruency activation map. (B) Screenshot from Brainsight software during stimulation of mPFC. Target is marked on the image by white dot. The red crosses (bottom right) indicate the position of the coil relative the target (black dot) during stimulation. aINS=anterior insula; mPFC=medial prefrontal cortex; PMv=ventral premotor cortex; coordinates represent MNI coordinates of target.

3.2.3 Results

An ANOVA with site (mPFC, IFGpo, aINS) as a between-group factor and TMS (No, Yes), Cue Type (Imitation, Spatial) and Congruency (Congruent, Incongruent) as repeated measures was performed on reaction time to determine whether stimulation had a site-specific effect on behavior. The main effect of congruency ($F_{(2,27)}$=36.9, p<0.001) was the only significant effect (all other p > 0.10; Figure 3.7).

A 3-way ANOVA was performed within each site to determine whether a negative effect was due to a lack of power for the between-group factor. This appeared not to be the case: the main effect of congruency was the only significant effect for all three sites (p<0.05; all other p>0.10). Thus, there was no effect of TMS on reaction time. To examine the possibility that we failed to detect effects of TMS because they dissipated before the end of the task we split the

task into 4 blocks and examined the effect of block. Including block in the ANOVA did not change results. Similarly, there was no effect of task order (i.e. TMS or No TMS session first) when this was included in the model.

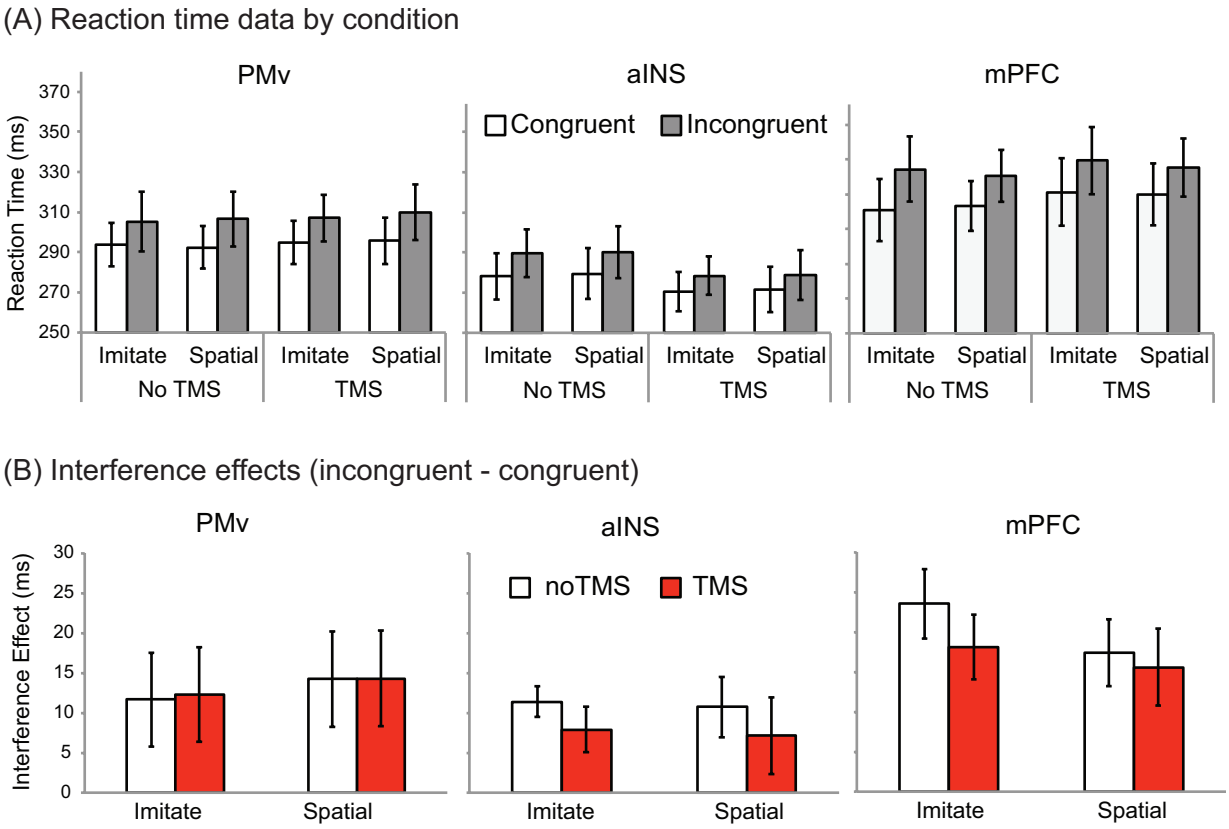

Figure 3.7: Results. (A) Reaction time data for all conditions for each stimulation site (group). (B) Interference effects with and without TMS for each cue type and stimulation site (group). Interference effects are evident for all conditions, and there was no difference between interference effects. Error bars reflect standard error of the mean across subjects.

Participants performed with very high accuracy (99% or above in all conditions). Many of those errors were anticipation or omission errors, which are not attributable to a failure in imitation control. Excluding those errors, mean accuracy was 99.5% (SD 1.5)—no participant made more than 3 errors in which they lifted the incorrect finger. As a result of this ceiling effect, errors did not provide a useful measure of imitative control.

3.2.4 Discussion

We were unable to modulate interference effects in the reactive control task by applying theta burst TMS to the 3 sites identified in the fMRI study. There are several potential explanations for this negative result, some methodological and others related to brain function. First, it is possible that the targeted brain areas were not actually disrupted by TMS. This is plausible because the targeted regions, which were located based on the fMRI study, were below the cortical surface. While rare studies have successfully affected behavior when targeting regions below the surface (Klucharev et al., 2011; Sohn, 2004), targeting deeper regions is problematic. The strength of the magnetic field declines rapidly with distance from the coil limiting stimulation to 2-3cm below the skull surface (Sandrini et al., 2010). Depending on the thickness of the skull and other membranes, this substantially limits the accessibility of regions below the cortical surface.

It is also possible that individual differences in functional anatomy contributed to the lack of effects. Although we used a stereotaxy system for targeting using individual subject anatomy, the regions were functionally located based on a group average. The most activated region for individual subjects likely varied around the group peak, so that optimal targeting would be done using individual subject functional data obtained during task performance. Indeed, targeting with individual functional data has been shown to result in greater behavioral effect sizes (Sack et al., 2009).

Methodological issues aside, if one assumes that the targeted regions were in fact adequately stimulated there are several potential conclusions. Perhaps none of the stimulated regions are causally involved in producing the interference effect, though this would be a far from parsimonious interpretation of the fMRI data. Alternatively, it is possible that disruption of an individual region of the identified cortical network is not sufficient to interfere with imitative control—that is, other regions compensated adequately for the previously involved but currently disrupted region. Indeed, the imitative congruency effect showed relatively bilateral activation of

the LIFG and aINS so one possibility is that the contralateral un-stimulated homologue is sufficient to support successful reactive imitation control.

3.2.5 References

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Chapter 4

Preparatory control of imitation

4.1 Neural systems involved in preparatory control of automatic imitation

4.1.1 Introduction

There is now a substantial body of work demonstrating that humans have an automatic tendency to imitate others. Recent work examining how these imitative tendencies are controlled suggests that higher social-cognitive processes related to self-other distinction are involved (Spengler et al., 2010; Brass et al., 2009) and that control may occur through interactions with the human mirror neuron system (Wang et al., 2011; Spengler et al., 2009; Chapter 3.1). However, this work has focused on situations where imitative control processes occur in a reactive manner: In these studies, the need for control is unpredictable so control mechanisms must be exerted in response to experienced conflict between an intended and imitative response. In the present study, we aim to extend work on imitation control to include situations in which the need for control is predictable and strategic preparation is possible. In this situation, a preparatory control mechanism may be able to bias sensory or motor systems to be less sensitive to interference prior to any stimulus that would otherwise evoke conflict. In other words, reactive control mechanisms previously studied detect and resolve conflict after it occurs, whereas preparatory mechanisms studied here may prevent or reduce conflict before it arises. Given increasing evidence from the broader cognitive control literature that preparatory

and reactive forms of control may involve at least partially distinct mechanisms (Funes et al., 2010; Boy et al., 2010; Braver, 2012), it is plausible that preparatory control of imitation involves mechanisms distinct from those previously studied in reactive control paradigms.

To explore preparatory control of imitation, we draw on dual route frameworks that have been widely applied to stimulus-response compatibility effects similar to those observed in automatic imitation paradigms (Proctor and Vu, 2006; Kornblum et al., 1990; Heyes, 2011). Automatic imitation refers to the observation that performance of an action is more efficient when it is accompanied by observation of the same (compatible) action and less efficient when accompanied by observation of a different (incompatible) action. Dual route models explaining such stimulus-response compatibility effects propose two parallel routes to response activation. An intentional route (often called the "short-term" or "indirect" route) links stimuli and responses according to task rules—this route can accommodate any stimulus-response pair by applying the relevant stimulus-response rule held in short term memory. At the same time, a parallel automatic route (often called the "long-term" or "direct" route) activates a compatible response due to long-term stimulus-response associations or similarities between the stimulus and response. When the required response is compatible, both the rule-based and automatic routes activate the correct response and therefore performance is fast and accurate. In contrast, when the task requires an incompatible response the two routes lead to different responses. The automatic route activates the incorrect compatible response, which must be inhibited in favor of the slower rule-based incompatible response.

An important feature of stimulus-response compatibility effects relevant to the present question of preparatory control is that they are observed primarily when preparation is possible. When the required stimulus-response mapping (compatible or incompatible) is not known in advance of the imperative stimulus, compatibility effects are reduced (Stoffels, 1996; Ehrenstein and Proctor, 1998; De Jong, 1995; Vu and Proctor, 2004), or abolished altogether (Shaffer, 1965; Heister and Schroeder-Heister, 1994; Vu and Proctor, 2004). The preferred explanation

for this finding involves preparatory suppression of the automatic response (Shaffer, 1965; De Jong, 1995; Proctor and Vu, 2006; Vu and Proctor, 2004). When the required mapping is unknown and compatible and incompatible trials are randomly presented, the automatic response route is strategically suppressed because it would lead to the incorrect response on half of trials (the incompatible trials). As a result of this suppression, the slower rule-based indirect route must be utilized for both compatible and incompatible trials, making reaction times equivalent—compatible trials no longer benefit from the automatic route. In contrast, when the required response mapping is known in advance, the automatic response route can be suppressed selectively for incompatible trials (when it would lead to the incorrect response) so that the compatible trials still benefit from the fast automatic response route. According to this framework, preparatory suppression of automatic response activation (henceforth referred to as "direct route suppression") can be examined by comparing preparatory activity on incompatible trials and trials in which the mapping is unknown (when there is preparatory suppression) compared compatible trials, when the automatic response route is utilized and there is no preparatory suppression.

Here we examine preparatory suppression of imitation in a stimulus-response compatibility task with preparatory cueing. Previous compatibility studies have provided substantial insight into neural systems implementing the indirect route—rule based stimulus-response mapping—by identifying regions that are more active for incompatible compared to compatible responses (Cieslik et al., 2010; Dassonville et al., 2001; Iacoboni et al., 1996, 1998; Cavina-Pratesi et al., 2006; Schumacher et al., 2007). However, in these studies where compatible and incompatible mappings are separated into different task blocks, it is not possible to disentangle activity related to implementation of stimulus-response rules from activity related to suppression of the automatic response tendency. The preparatory effects described above allow us to disentangle preparatory suppression from indirect route preparation and implementation. We also use a novel strategy to examine neural correlates of automatic

response activation. In contrast to the rule-based stimulus-response mapping (the indirect route), the neural systems underlying automatic response activation (the direct route) have remained elusive: Examination of the reverse contrast (compatible > incompatible) tends not to reveal any above-baseline activity. Here, we capitalize on trial-by-trial variability in direct route activity by identifying regions in which greater activity during preparation for a compatible response is related to faster subsequent responses.

Using these strategies, we aim to (1) identify neural correlates of preparatory suppression of automatic imitation to determine whether they are similar to previously described reactive imitation control mechanisms (Brass et al., 2001b, 2005, 2009; Spengler et al., 2009, 2010); and (2) compare biological and non-biological stimuli to determine whether neural correlates of automatic response activation and suppression are stimulus-specific. This second aim is motivated by the fact that automatic imitation is thought to result from activity in the mirror neuron system (MNS). The MNS is active during both the performance of actions and the observation of actions, and is proposed to provide a direct matching mechanism for imitation (Iacoboni et al., 1999; Heyes, 2011). This view suggests the direct route differs for biological and non-biological stimuli and raises the possibility that mechanisms involved in suppression of the direct route also differ.

4.1.2 Methods

Participants

37 participants (20 female; 18-34 years old) were recruited from the UCLA community through posted fliers and undergraduate subject pools. All subjects were right-handed, had normal or corrected-to-normal vision, no history of neuropsychiatric disorders and were not taking psychoactive medication. 3 subjects were excluded due to technical failure preventing response recording and two were excluded for poor performance (one failed to respond on >10% of trials and reported falling asleep; the second performed with less than chance-

accuracy on one condition and below 3 standard deviations from the mean across conditions). Data from the remaining 32 participants was included in analyses. Written informed consent was obtained from all participants and they received monetary compensation or course credit for their time. The study was approved by the UCLA Institutional Review Board.

Behavioral Paradigm

Subjects performed compatible or incompatible finger lifting responses to either biological (finger) or non-biological (dot) stimuli. In the biological condition videos depicted a left hand lifting either the index finger or the middle finger. In the non-biological condition, one of two small black dots moved upwards. The dots were arranged based on the index and middle fingertips in the hand videos, with similar initial and final positions and trajectories. The appropriate response was determined by a mapping rule, which changed from trial to trial and was indicated by the color of a thick border around the video. When the border was green, participants performed the compatible response: they imitated the hand videos (i.e. lift index finger in response to index finger video and middle finger in response to middle finger video) and performed the left/right spatially compatible response for the dot videos (i.e. lifted index finger in response to left upward moving dot video and middle finger in response to the right dot). When the border was red, participants performed the incompatible response, counter-imitating the hand videos (e.g. middle finger response to index finger video) and performing the spatially incompatible response for the dot videos (middle finger response to left dot stimulus)

The first frame of the video, which depicted the finger/dots in the static starting position, was presented for 2, 5, 7 or 10 seconds and represented the preparatory period. This was followed by 4 movement frames representing the response period. The ability for participants to prepare for the upcoming stimulus-response mapping was manipulated by varying the time at which the mapping cue (green or red border) was provided. Sometimes the mapping cue was provided during the preparatory period (2/3 of trials; half compatible, PrepC, and half

incompatible, PrepI). In the remaining trials (NoPrep condition), the preparatory period had a gray border and the border turned green or red at the same time as the target movement occurred. As a result, the mapping rule was not known before the response period. The resulting 3 by 2 design included 6 different preparatory conditions: 3 conditions each (PrepC, PrepI and NoPrep) for biological and non-biological cues (Figure 4.1)

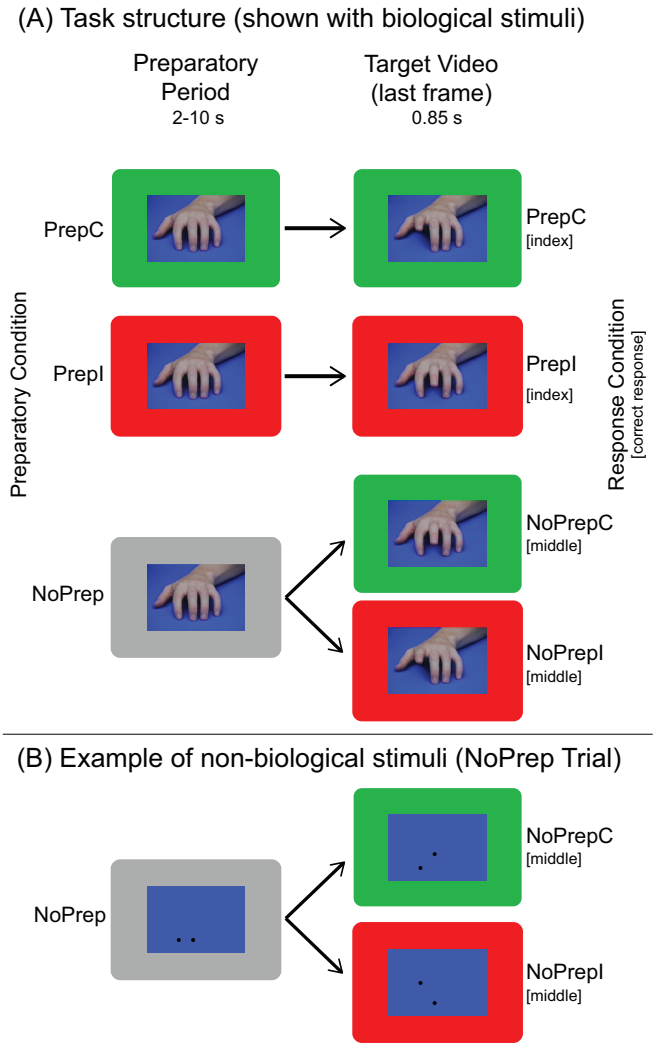

Figure 4.1: Task design. (A) Example trials for each condition are shown with biological stimuli. The first video frame (left column) remains on the screen for the entire preparatory period. The right column depicts the last frame of the target video. The onset of the target video represents the end of preparation and beginning of the response period. Left and right margin labels indicate preparatory and response conditions as modeled by separate regressors in the GLM. The correct response for each example trial is indicated in square brackets. (B) Example of non-biological stimuli. (Prep = Stimulus-response mapping rule provided during preparation; NoPrep = Stimulus-response mapping rule not provided during preparation; C = compatible; I = incompatible).

The target period was short (850ms) to encourage preparation, and participants were instructed to prepare as much as possible for the upcoming response while waiting for the target movement. Trials were separated by a variable inter-stimulus interval (4, 6 or 8 seconds). Preparatory conditions were pseudo-randomized within a block that contained only one stimulus type (fingers or dots) so that each preparatory condition followed each other condition with equal probability and compatible and incompatible targets followed one another with equal probability.

Procedure

Immediately prior to scanning, subjects were familiarized with the task during a brief practice session. During each of 4 scanning runs that lasted 11 minutes, participants performed 2 blocks with imitative cues and 2 blocks with spatial cues. Participants held down two buttons with their index and middle fingers and responded by lifting a finger to release one of the buttons. Response times were recorded as the time of button release relative to the onset of movement in the video. Subjects were allowed a short break between runs. Each run was preceded by a reminder of the instructions.

MRI data acquisition & preprocessing

Images were acquired on a Siemens 3T (Erlangen, Germany) Trio MRI scanner. Functional runs comprised 330 T2*-weighted echoplanar images (EPIs) [repetition time (TR) 2000ms; echo time (TE) 28ms; flip angle=90°; 34 slices; slice thickness 4mm; matrix 64 x 64; FOV 192mm]. To allow for T1 equilibrium the first two volumes of each functional scan were automatically discarded before data collection began. Two sets of structural images were also acquired for registration of functional data: a T2-weighted matched-bandwidth high-resolution scan with the same slice prescription as the EPI [repetition time (TR) 5000ms; echo time (TE) 34ms; flip angle=90°; 34 slices; slice thickness 4mm; matrix 128 x 128; FOV 192mm]; and a T1 weighted magnetization prepared rapid-acquisition gradient echo image (MPRAGE) [TR,

1900ms; TE 2.26ms; flip angle = 9°; 176 sagittal slices; slice thickness 1mm; matrix 256 x 256; FOV 250mm]. Visual stimuli were timed and presented with Presentation software (Neurobehavioral Systems, Albany, CA) through magnet-compatible LCD goggles. Responses were recorded with a magnet-compatible response box (Current Designs, Philadelphia, PA).

Image preprocessing and data analysis were performed with FSL version 4.1.4 (Centre for Functional Magnetic Resonance Imaging of the Brain software library, www.fmrib.ox.ac.uk/fsl; Smith et al., 2004). Images were realigned to the middle volume to compensate for any head motion using MCFLIRT (Jenkinson et al., 2002). Images were then examined visually for gross motion artifacts that cannot be corrected with simple realignment. When motion artifacts were detected, a nuisance regressor for each affected volume was included in the general linear model. In addition 1 run for one subject was excluded for excessive motion (>10% volumes exhibiting motion artifacts). Data were temporally filtered with a high-pass filter cutoff of 100 seconds and spatially smoothed with a 8mm full width half maximum Gaussian kernel in three dimensions.

Statistical Analysis

Statistical analyses were performed at the single subject level using a general linear model (GLM) with fMRI Expert Analysis Tool (FEAT, version 5.98). Separate regressors modeled the preparatory and target periods of each condition, so that activity could be examined specifically in the preparatory period. This was made possible by jittering the length of the preparatory period between 2 and 10 seconds to reduce the correlation between preparatory and target period regressors. A regressor was included for each preparatory condition, resulting in 6 preparatory regressors (PrepC, PrepI and NoPrep for biological and non-biological stimuli). These regressors modeled the entire preparatory epoch. For response period regressors, compatible and incompatible responses following NoPrep periods were also modeled separately because the compatibility for these trials becomes evident once the

mapping cue appears at the onset of the target video. As a result, there were 8 regressors modeling response period epochs, four per stimulus type (PrepC Response; PrepI Response; NoPrepC Response and NoPrepI Response). In addition to these 14 regressors modeling the mean for each trial period and condition, we included another set of preparatory regressors modeling reaction time. The RT regressors again modeled the entire preparatory period but the height of the regressor was equal to the demeaned reaction time of the subsequent response. This allowed us to examine regions in which preparatory period activity is related to subsequent performance. Error trials were modeled separately with 2 regressors, one for the preparatory period and one for the target periods. Task regressors were convolved with a canonical double-gamma hemodynamic response function.

Contrasts specified were based on predictions formulated according to the dual route theory and direct route suppression models and are discussed in detail in the Results section. First level contrast estimates were computed for each run and then registered to standard space (Montreal Neurological Institute, MNI) in three stages. The middle volume of each run of individual EPI data was registered first to the co-planar matched-bandwidth high-resolution T2-weighted image and subsequently, the co-planar volume was registered to the T1-weighted MPRAGE. Both of these steps were carried out using FLIRT (affine transformations: EPI to co-planar, 6 degrees of freedom; co-planar to MPRAGE, 6 degrees of freedom; Jenkinson and Smith, 2001; Jenkinson et al., 2002). Finally registration of the MPRAGE to MNI space (FSL's MNI Avg152, T1 2x2x2mm) was carried out with FLIRT (affine transformation, 12 degrees of freedom) and refined using FNIRT (non-linear transformation). Contrast estimates for each subject were then computed treating each run as a fixed effect. Finally, a group level analysis was performed to calculate a group mean for each contrast treating each subject as a random effect using FSL's FLAME (FMRIB's local analysis of mixed effects) stage 1 and stage 2 (Beckmann et al., 2003; Woolrich, 2008; Woolrich et al., 2004). Except where noted, all images were thresholded at $z > 2.3$ ($p<0.01$), corrected for multiple comparisons using cluster-based

Gaussian random field theory controlling family-wise error across the whole-brain at $p < 0.05$. Discussion of preparatory activity is limited to regions in which preparatory activity is greater than baseline ($p<0.05$ uncorrected) for at least one preparatory condition. This was accomplished by inclusively masking group maps after whole-brain statistical inference by each preparatory condition vs. baseline.

4.1.3 Results

Behavioral Data

Mean accuracy and mean reaction time of correct responses were calculated in each condition for each subject. Trials with RT greater than 3 standard deviations from the mean were considered outliers and excluded from analysis (0-2.8% of trials per subject). Separate 3-way repeated measures ANOVA (Stimulus Type: Biological/Nonbiological x Compatibility: Compatible/Incompatible x Preparation: Prep/NoPrep) were carried out for reaction time and accuracy using R statistical software.

Analysis of reaction times revealed significant main effects of preparation ($F_{(1,31)}=174.4$, $p<0.001$) and compatibility ($F_{(1,31)}= 205$, $p<0.001$) due to faster responses when preparatory information was available and for compatible trials, respectively (Figure 4.2). In addition, consistent with previous reports and the direct route suppression hypothesis (Stoffels 1996; Ehrenstein and Proctor, 1998; de Jong, 1995; Vu and Proctor, 2004; Shaffer, 1965; Heister and Schroeder-Heister, 1994), the 2-way interaction between preparation and compatibility was significant ($F_{(1,31)}=82.2$, $p<0.001$). This is due to greater compatibility effects for trials in which the mapping was known in advance (Prep trials). The 3-way interaction was not significant, indicating that behavior was similar for the two cue types (see Table 4.1).

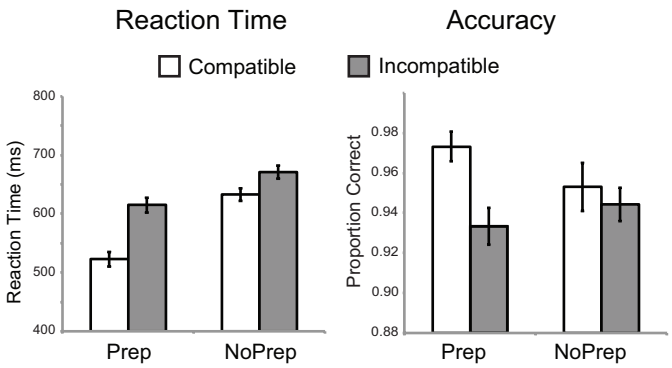

Figure 4.2: Behavioral Results. Mean reaction time and accuracy for each preparatory condition collapsed across stimulus type. Error bars represent standard error of the mean.

Table 4.1. Mean reaction time and percent error (in parentheses) for each condition

		Compatibility Condition		
Stimulus	Preparatory Condition	C	I	Compatibility effect (I-C)
Biological	Prep	521 (2.9%)	611 (7.4%)	90 (4.5%)
	NoPrep	631 (4.9%)	673 (6.6%)	42 (1.8%)
Non-biological	Prep	524 (2.5%)	619 (6.0%)	95 (3.5%)
	NoPrep	635 (4.5%)	669 (4.5%)	34 (0.0%)

For accuracy, there was a main effect of compatibility ($F_{(1,31)}$=16.9, p<0.001), reflecting better performance for compatible than incompatible trials. In addition, there was a significant preparation x compatibility interaction ($F_{(1,31)}$= 7.2, p=0.01). Accuracy was similar for compatible and incompatible trials when no preparatory information was available ($t_{(31)}$=0.92, p=0.36), consistent with the direct route suppression model in which the two conditions use the same mechanism. In contrast, accuracy was better for compatible compared to incompatible trials ($t_{(31)}$=5.9, p<0.001) when preparatory information was available, consistent with the reliance on direct or indirect routes depending on the compatibility mapping.

Preparatory Compatibility Effect: Direct route suppression and Indirect route preparation

As outlined in the Introduction, dual route models propose that responding on incompatible trials involves suppression of the incorrect automatic response (direct route) and

implementation of the rule-based stimulus-response mapping (indirect route). The fact that compatibility effects are reduced when preparatory information is absent suggests suppression occurs during the preparatory period. In addition, since an arbitrary stimulus-response mapping is required for incompatible trials, it is also possible that the indirect route (rule-based stimulus-response pairs) is prepared in advance. In contrast, compatible trials can benefit from the automatic response so preparatory suppression is absent and preparation of the rule-based stimulus-response route may be less important. Following this framework, differences between PrepI and PrepC (PrepI > PrepC) should reflect neural correlates of preparatory suppression of the automatic response and/or preparation of the indirect route. Figure 4.3 illustrates reliable differences in BOLD signal located in multiple neural systems including bilateral dorsal premotor cortex, posterior parietal cortex, anterior insula and the frontal pole for PrepI > PrepC (coordinates reported in Table 4.2). In addition, visual areas, small clusters in supplementary motor cortex, and the bilateral caudate and hippocampus are more active during PrepI than PrepC.

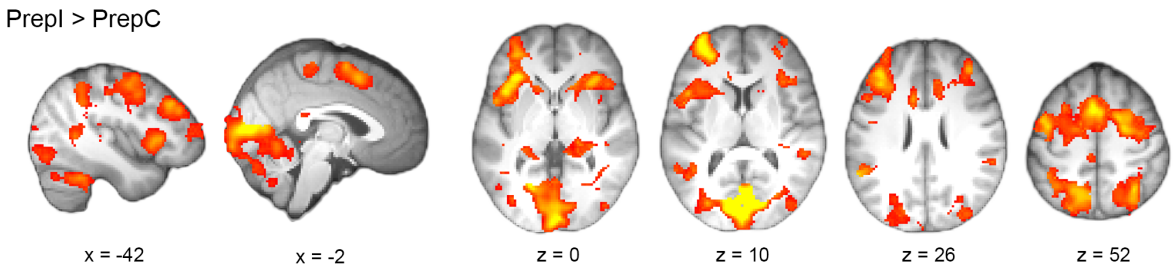

Figure 4.3: FMRI Compatibility Effect. Regions showing greater activity during preparation for incompatible compared to compatible trials, collapsed across cue types.

The interaction between cue type and preparation [(ImPrepI-PrepC)-(SpPrepI-PrepC)] was not significant, and similar neural systems were observed when the compatibility effect was examined separately for each cue type (albeit, less robustly for spatial cues; Figure 4.4). Thus, we find no evidence of cue type specificity for these processes.

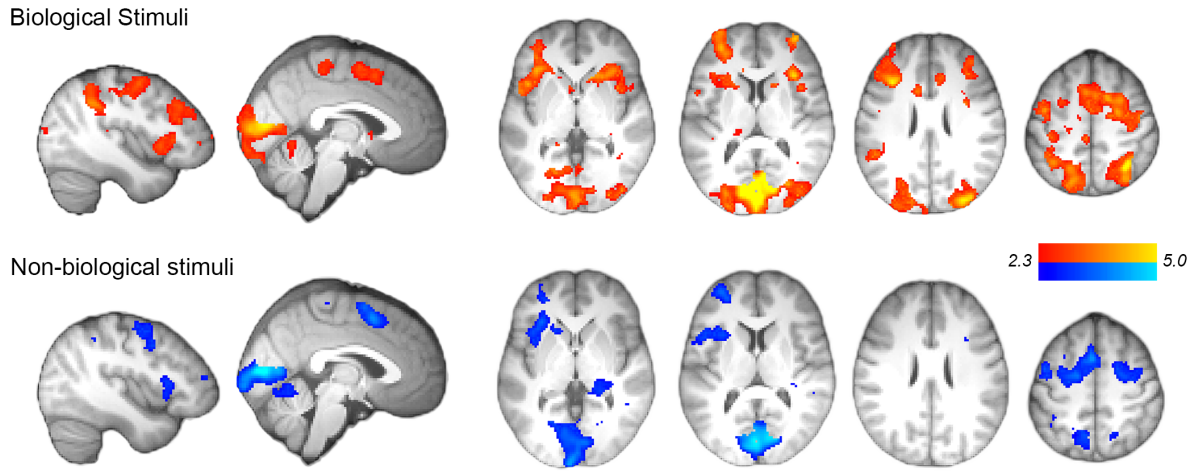

Figure 4.4: FMRI compatibility effects (PrepI > PrepC) separated by stimulus type. Compatibility effects of biological stimuli (top) and non-biological stimuli (bottom) activate similar neural systems.

To disentangle preparatory suppression from preparation of stimulus-response pairs, we introduced the NoPrep condition into the analysis. Suppression occurs not just during preparation for incompatible trials, but also when the mapping is unknown (NoPrep), since the automatic response would be incorrect half the time. Therefore, those regions related to direct route suppression in the PrepI>PrepC contrast should also be more active during NoPrep compared to PrepC trials. To identify these regions, we performed a conjunction (Nichols et al., 2005) of the PrepI > PrepC and NoPrep > PrepC contrasts. As shown in Figure 4.5 (blue), activity following this pattern was observed in left dorsolateral prefrontal cortex (DLPFC), left frontal pole, bilateral posterior parietal lobe and visual cortex. In addition, small clusters are evident bilaterally in primary motor and caudate regions, as well as in the hippocampus.

In contrast to preparatory suppression of the automatic response tendency, regions involved in preparation of particular stimulus-response pairs (preparation of the indirect route) are likely to be active during PrepI but not during NoPrep trials, because the potential stimulus-response pairs are unknown on NoPrep trials. The alternative possibility—that all 4 potential mappings are prepared during NoPrep trials (Bunge et al., 2002)—seems unlikely in this task given that the mappings are mutually exclusive (the same stimulus requires 2 different

responses depending on the rule). Consistent with this view the overlap of the contrasts PrepI > NoPrep and PrepI > PrepC identified dorsal premotor cortex and supplementary motor area (Figure 4.5, green), regions previously implicated in stimulus-response associations in the conditional motor learning literature (Grafton et al., 1998; Wise et al., 1996; Kurata et al., 2000; Passingham, 1993; Picard and Strick, 2001). Since stimulus-response pairs could be prepared during preparation for compatible trials as well, the PrepC > NoPrep contrast was also performed, but yielded no significant effects. This is in line with the dual route model, which suggests that PrepC relies more heavily on the automatic route rather than the indirect stimulus-response mapping route. There were no significant effects for the reverse compatibility effects—PrepC > PrepI, consistent with previous compatibility studies.

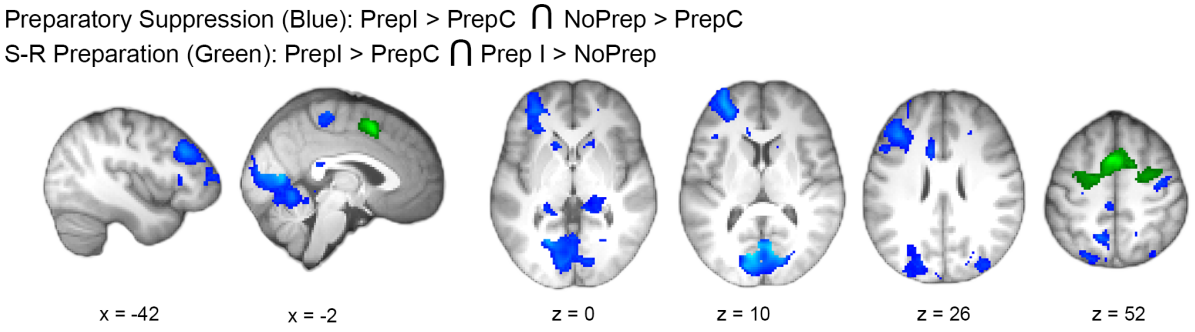

Figure 4.5 Disentangling Compatibility Effects. Neural correlates of preparatory suppression, which occurs during PrepI and NoPrep trials, is illustrated in blue as the conjunction between PrepI>PrepC and NoPrep>PrepC contrasts. Neural correlates of indirect route preparation, which occurs particularly during PrepI trials, are illustrated in green as the conjunction between PrepI>PrepC and PrepI>NoPrep contrasts.

Direct route activity

To identify regions associated with automatic response activation (via the direct route) we used reaction time to locate regions in which greater preparatory activity is associated with faster subsequent reaction time on compatible trials. This method follows from the fact that reaction time benefit for PrepC is thought to result from automatic response activation via the direct route. As shown in Figure 4.6, patterns appear to be quite different for the two cue types. For biological cues, greater activity during preparation for the compatible response in the ventral

premotor cortex is related to faster responses. In contrast, for non-biological cues, preparatory activity in the dorsal premotor cortex is related to faster subsequent compatible responses. The examination of the parameter estimates (Figure 4.6, bar graphs) suggests some level of stimulus-specificity. While the parietal and dorsal premotor regions contribute similarly regardless of cue type, when cues are biological an additional fronto-parietal loop involving ventral premotor cortex also contributes to behavior. The involvement of ventral premotor cortex for biological cues is particularly striking in light of the fact that this region has been repeatedly associated with imitative behavior (Caspers et al., 2010; Iacoboni et al., 1999; Iacoboni, 2005).

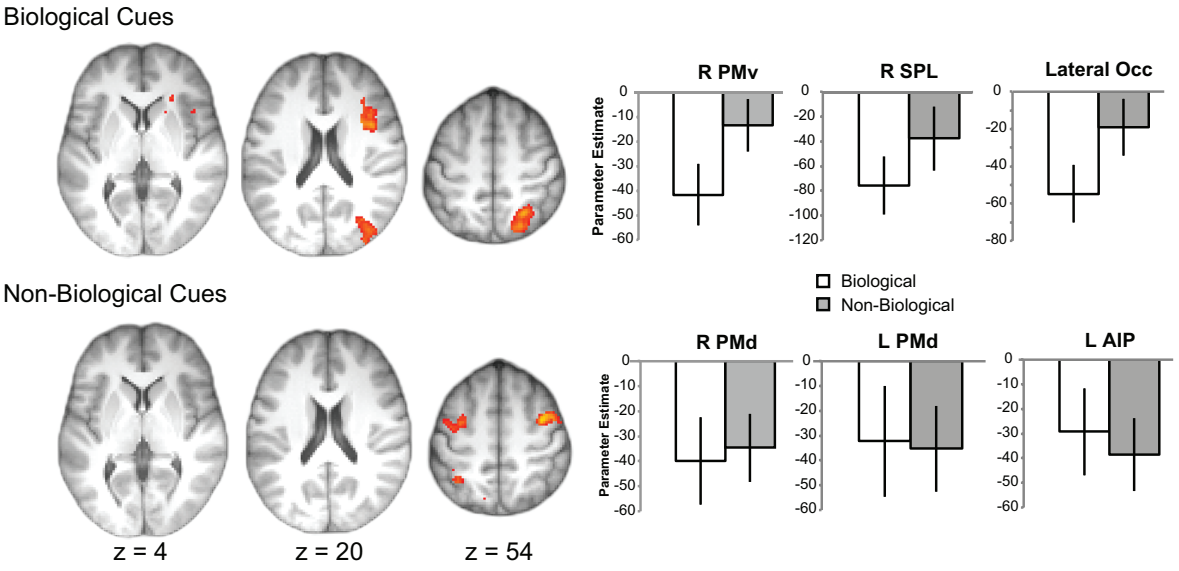

Figure 4.6: Direct Route Activity. Neural correlates of the direct route were identified as regions in which compatible preparatory activity is related to subsequent reaction time. Maps are shown for each cue type. Bar graphs depict parameter estimates of compatible preparatory reaction time regressor (negative relationship indicates higher activity related to faster responses). Error bars reflect standard error of the mean.

Table 4.2 Local maxima for significant clusters preparatory period contrasts.

		Coorinates (MNI)			
Contrast/Region	L/R	x	y	z	Z-value
Direct route suppression (PrepI>PrepC ∩ NoPrep>PrepC)					
Frontal pole	L	-32	50	6	4.81
Middle frontal gyrus	L	-40	28	30	3.95
Anterior cingulate cortex	L	-12	28	20	3.64
Dorsal premotor cortex	R	16	-6	66	2.95
	L	-24	-20	62	3.25

Contrast/Region	L/R	Coorinates (MNI) x	y	z	Z-value
Primary motor cortex	R	42	-8	48	3.17
	L	-2	-28	64	3.38
Superior parietal lobule	L	-12	-58	56	3.83
	R	28	-68	46	3.34
Lingual gyrus	L	-10	-50	-8	3.74
Primary visual cortex	R	12	-74	8	4.69
	L	-12	-70	6	5.24
Lateral occipital cortex	L	-20	-80	36	3.96
	R	28	-86	36	3.66
Caudate	R	14	20	4	3.08
	L	-16	22	-6	3.42
Hippocampus	R	20	-28	-6	3.29
	L	-22	-28	-4	3.14
Cerebellum	R	12	-56	-14	3.80
	L	-22	-62	-22	2.91
Indirect route (S-R rule) preparation (PrepI>PrepC ∩ PrepI>NoPrep)					
Supplementary motor area	L	-4	10	50	4.25
	R	8	0	64	2.98
Dorsal premotor cortex	L	-30	-4	68	4.16
	L	-16	-8	54	3.08
	R	26	-6	48	3.31
	R	48	0	42	3.21
Direct route activation (PrepC activation correlated with RT)					
Biological Cues					
Ventral premotor cortex/inferior frontal gyrus, pars opercularis	R	40	10	20	3.41
	R	34	8	28	3.19
Superior parietal lobule/anterior intraparietal sulcus	R	26	-58	52	3.61
	R	32	-58	56	3.13
	R	24	-68	52	3.42
	R	32	-70	20	3.05
Lateral occipital cortex/inferior parietal lobe	R	34	-70	26	3.18
	R	36	-78	16	3.60
Non-biological cues					
Dorsal premotor cortex	R	40	0	52	3.85
	R	40	-2	60	3.84
	L	-32	-4	54	3.0
	L	-38	-10	64	3.91
Anterior intraparietal sulcus	L	-44	-38	36	3.22

4.1.4 Discussion

We investigated the neural correlates of automatic imitative response activation and preparatory suppression of imitation within a dual route framework. Using preparatory cueing, we were able to separate processes related to automatic response suppression from the preparation and implementation of stimulus-response rules. These processes are inseparable in commonly employed blocked compatibility studies. In addition to elucidating neural correlates of preparatory control of imitation, we aimed to determine whether automatic response activation and preparatory suppression are stimulus-specific by comparing biological and non-biological cues. Results suggest that the neural systems associated with preparatory suppression are similar for biological and non-biological stimuli, whereas the neural systems for implementing the direct route show some level of dissociation for imitative and non-imitative behavior.

Preparatory suppression of automatic response activation was identified according to the dual route framework of stimulus-response compatibility. Consistent with previous literature, for both biological and non-biological cues participants were slower to respond with the incompatible compared to the compatible response, due to the need to suppress the automatic response tendency and respond instead according to the slower stimulus-response rule. Importantly, this compatibility effect was substantially reduced when the mapping was not known before the stimulus (Shaffer, 1965; Vu and Proctor, 2004; Heister and Schroeder-Heister, 1994; De Jong, 1995; Stoffels, 1996; Ehrenstein and Proctor, 1998), likely due to preparatory suppression of the automatic response when it will be detrimental to performance (Shaffer, 1965; Vu and Proctor, 2004; De Jong, 1995).

The neural correlates of preparatory suppression included left dorsolateral prefrontal cortex (DLPFC), frontal pole and early visual regions. The pattern was similar regardless of whether cues depicted biological or non-biological stimuli, suggesting that preparatory suppression mechanisms are not stimulus-specific: Whether participants have to suppress the tendency to imitate or suppress the tendency to respond with the spatially compatible response,

similar neural systems are involved. These findings contrast with previous studies of imitation control in several important ways. First, the neural systems involved in preparatory suppression of imitation are different from those observed in previous studies examining reactive inhibition of imitative tendencies. When imitative conflict (and therefore, the need for control) cannot be predicted in advance, control is associated with activity in medial prefrontal cortex (mPFC), the temporo-parietal junction, anterior insula and ventral premotor cortex (Wang et al., 2011; Brass et al., 2001b, 2005; Chapter 3.1). In contrast, when the need for control is predictable and the imitative response tendency can be strategically suppressed in advance of action observation, we observe activity in the left DLPFC, left frontal pole and visual cortex. Furthermore, there is a difference in the specificity of the preparatory control mechanisms examined here and previously studied reactive control mechanisms. Neural correlates of reactive imitation control have been shown to be distinct from those involved in other conflict tasks, including both spatial compatibility (Chapter 2.1) and Stroop tasks (Brass et al., 2003, 2005). Thus, while reactive imitative control relies on at least partly distinct mechanisms from other reactive control processes, the similar correlates for both biological and non-biological cues observed here suggests that preparatory control mechanisms are similar regardless of the stimulus that evokes the automatic response tendency.

While the precise contribution of the various regions identified cannot be determined on the basis of the current results, previous work can provide some insight into potential preparatory suppression mechanisms. We propose that preparatory suppression involves prefrontally-mediated attentional biasing of early visual cortex. The DLPFC is activated during preparation across a range of conflict paradigms, including Stroop (MacDonald et al., 2000; Egner and Hirsch, 2005; Banich et al., 2000), flanker (Luks et al., 2007) and cross-modal (Weissman et al., 2004) tasks. It has been proposed that the DLPFC is involved in biasing attention to facilitate processing of the task-relevant stimulus feature. While the emphasis tends to be on increasing attention to the relevant feature based on greater activity in visual regions

involved in processing that feature (Egner and Hirsch, 2005; Erickson et al., 2009; Weissman et al., 2004), there may also be role for DLPFC in suppressing influence of the task-irrelevant feature. Here, we propose that activity observed in early visual cortex may be related to top-down suppression of visual input in a situation where the visually-driven response is likely to be incorrect (PrepI and NoPrep trials). This may seem counterintuitive since activity is increased during PrepI and NoPrep trials, when suppression occurs. However, it can be difficult to predict the direction of BOLD signal change in a situation of top-down inhibition. The BOLD signal is correlated better with synaptic input than spiking activity (Logothetis, 2003), so when regional synaptic input is dissociated from neuronal spiking (as with inhibition) the BOLD signal may paradoxically increase (Mathiesen et al., 1998). Activity in line with this proposal was recently observed in a color-word Stroop task (Erickson et al., 2009), where participants responded to the ink color of a written word that either matched the ink color (the word “RED” in red ink) or conflicted with the ink color (the word “BLUE” in red ink). On conflict trials, where the two visual features lead to different responses, greater activity was observed not only in a functionally localized region responsible for processing the task-relevant feature—color—but also in the visual word form area, a region involved in processing the irrelevant visual feature. More importantly, activity in the word form area was negatively correlated with reaction time, exactly as would be predicted if increased activity was related to more successful suppression of irrelevant feature processing.

In the context of the current compatibility study, suppression of early visual cortex is consistent with the lack of stimulus-specificity observed. Visual suppression would lead to a general reduction in the ability of visual stimuli to affect the motor system, reducing the experience of conflict. The idea that preparatory suppression in compatibility tasks occurs through biasing of visual processing is consistent with previous behavioral data as well. Compatibility effects are observed not only due to visual or spatial similarities between stimulus and response sets, but also when there are only conceptual similarities. For example, vocal

responses (“left”/”right”) to arrow stimuli are faster when the direction is compatible. However, the elimination of compatibility effects in the absence of advance knowledge of stimulus-response mappings seems to occur only if there is perceptual similarity between the stimuli and response (Vu and Proctor, 2004), consistent with a perceptual account of preparatory suppression mechanisms.

In contrast to preparatory suppression mechanisms, which were similar for both stimulus types, we found evidence that the neural underpinnings of automatic response activation may be unique for biological stimuli. We used a novel strategy for identifying neural correlates of direct route activity using trial-by-trial variability, whereby the degree of activity in the direct route during preparation for compatible responses should predict the subsequent reaction time. Results suggest that preparatory activity in the ventral premotor cortex is correlated with compatible reaction time primarily when stimuli represent biological actions, whereas activity in dorsal premotor cortex is related to faster responding regardless of the stimulus type. This distinction in premotor cortex occurs even though the responses to the two stimulus types are identical, indicating premotor sensitivity to stimulus content when motor factors are equivalent.

To our knowledge only one other study has investigated the neural correlates of the direct route (Cieslik et al., 2010). In a spatial compatibility study in which participants responded to lateralized light flashes, stimulus-driven activity was observed in the right dorsal premotor and parietal cortices for left-lateralized stimuli and left dorsal premotor and parietal cortices for right-lateralized stimuli. Although the strategy used to identify these “bottom-up” effects was very different from the one employed here, the neural correlates parallel those observed for non-biological stimuli in the current study. Thus, the two studies provide converging evidence for direct route activation of dorsal premotor and superior parietal regions by non-biological stimuli. Building on this, we show that the direct route for biological stimuli involves ventral premotor cortex as well, a finding that fits well with premotor neurophysiology. In macaques, the ventral

premotor cortex contains neurons with motor properties that also discharge during perception of others' action (Rizzolatti and Arbib, 1998), in line with our findings.

Thus, our results suggest the existence of both imitation-specific and general purpose mechanisms. The selective activation of the ventral premotor cortex correlates with imitative performance. Yet a singular preparatory suppression mechanism can reduce unwanted motor activation by non-specifically reducing the visual input to the various routes connecting visual and motor systems.

4.1.5 References

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4.2 Preparatory suppression of imitation modulates motor resonance

4.2.1 Introduction

Automatic imitation describes a special case of stimulus-response compatibility (SRC) in which observing an action improves reaction times for imitative (compatible) responses and slows reaction times for non-imitative (incompatible) responses (see Heyes, 2011 for a review). Like many other forms of SRC (De Jong et al., 1994; Eimer et al., 1995; Stürmer et al., 2000), this compatibility effect is attributed to automatic activation of the stimulus-compatible motor representation. In the case of imitation, the mirror neuron system (MNS) has been hypothesized to underlie automatic response activation during action observation (Heyes, 2011; Ferrari et al., 2009), since it responds during the observation and execution of similar actions and provides input to the motor system (Di Pellegrino et al., 1992; Iacoboni et al., 1999; Rizzolatti and Craighero, 2004).

Some cognitive models of SRC suggest that automatic activation of the stimulus-compatible response can be suppressed when this response is likely to interfere with task goals

(Shaffer, 1965; De Jong, 1995; Vu and Proctor, 2004). In particular, inhibition occurs in preparation for incompatible responses and when the required stimulus-response mapping is unknown in advance of the stimulus (because the incompatible response is required half the time). This preparatory suppression manifests as reduced behavioral compatibility effects when the required stimulus-response mapping is unknown, because the compatible response no longer benefits from automatic response activation (Shaffer, 1965; Heister and Schroeder-Heister, 1994; De Jong, 1995; Vu and Proctor, 2004).

When extended to imitation, this model of SRC suggests that the MNS may be suppressed when automatic imitation is likely to interfere with motor responses. Although previous studies examining control of imitative tendencies have proposed mechanisms involving MNS modulation (Spengler et al., 2009; Wang et al., 2011), to date there is no neurophysiological evidence supporting this hypothesis. To test this hypothesis, we used transcranial magnetic stimulation (TMS) to measure corticospinal excitability during action observation in the setting of an imitative compatibility task. Facilitation of excitability specifically in the muscles that would be involved in performing the observed action (motor resonance) is a putative measure of MNS activity (Fadiga et al., 1995; Avenanti et al., 2007; Catmur et al., 2011). Therefore, we measured motor resonance to examine MNS-mediated imitative response activation while participants prepared to imitate or counterimitate an observed action. In line with preparatory supression models, we predicted lower motor resonance during preparation to counterimitate and during preparation for an unknown response, as compared to preparation to imitate. In addition, since this pattern could be explained by facilitation of motor resonance during preparation to imitate rather than suppression for incompatible and unknown conditions, we obtained a baseline measure of motor resonance during a control task in which participants prepared to perform an arbitrary stimulus-response mapping.

4.2.2 Methods

Experiment 1: Behavioral

Since twitches from supra-threshold TMS are likely to interfere with reaction time measures, we first ran an experiment without TMS to ensure that our novel paradigm reproduced behavioral effects associated with preparatory suppression. Specifically, we were looking for a reduction in the RT benefit for compatible compared to incompatible trials when the stimulus-response mapping is not known before the imperative stimulus.

Participants

10 participants (2/8 M/F, 18-24 years old) were recruited from an undergraduate subject pool and received course credit for participating. Participants were right-handed, neurologically healthy and were not taking psychoactive medications. The study was approved by the UCLA Institutional Review Board and written informed consent was obtained from all participants.

Imitation Task

Participants performed imitative or counter-imitative actions (flexion or extension of the right index finger) in response to video stimuli. The index finger rested on the bottom right key of a keyboard (number pad “Enter”) so that the finger was completely relaxed between responses, and flexion and extension involved pressing the key and lifting the finger off the key, respectively.

In the first frame of each video, a left hand rested palm-down with fingers facing the subject and the index finger in a half-raised position (i.e. a mirror image of the starting position of the participant’s response hand). This static frame was presented for 2.4 or 3.2 seconds and represented the preparatory period. Then, the target video (1.25 s) depicted the index finger either extending further (lifting upward) or flexing (tapping downward) from the starting position. The color of a thick border surrounding the video indicated whether subjects should imitate (green border; half of trials) or counter-imitate (red border; half of trials) the target video. On 2/3

of trials (Prep trials) the border color was presented during the preparatory period, so that subjects could prepare to imitate or counter-imitate before the target video. On the remaining 1/3 of trials (NoPrep trials), the border of the preparatory period was black and changed to green or red at the onset of the target video. Therefore, on these trials it was not possible to prepare the appropriate stimulus-response mapping before the target video. The result is 3 different preparatory states (prepare to imitate, PrepIm, prepare to counterimitate, PrepCI and prepare for unknown mapping, NoPrep) and four different target conditions (PrepCI, PrepIm, NoPrepCI, NoPrepIm; Figure 4.7A, top).

In order to measure motor resonance during the 3 different preparatory states, half of preparatory periods were interrupted by an action video during which TMS was applied in Experiment 2 (Figure 4.7B, top). These action observation (AO) videos depicted a right hand either squeezing or releasing a ball held between the index finger and thumb. AO videos were included on only half of trials to discourage participants from waiting until after the AO video to begin preparation. They were constructed of 20 frames presented at 60 Hz, with the last frame remaining on the screen for 834ms (total video length=1.15s). To maximize the likelihood that participants were preparing during the video, it was presented 2.4 or 3.2s after preparatory period onset--the same time as target videos appeared in trials without an AO video. After the AO video the preparatory period continued for 0.4 or 1.2 s before the target video was presented. There were 32 different AO videos (16 squeeze, 16 release), which varied in hand orientation and ball color (blue, orange, yellow, white) to reduce habituation.

A total of 192 trials (3.65-6.8 seconds long, depending on Prep-Target, Prep-AO video and AO video-Target intervals; 1.5s intertrial interval) comprising each of the 8 trial types (Prep/NoPrep x Imitate/Counterimitate x AO video/No AO video) occurred in a constrained random order. There were 64 PrepIm, 64 PrepCI and 64 NoPrep trials. Half of NoPrep trials were followed by imitate targets and half by counterimitate targets. Half of each preparatory condition (32 trials) included an AO video (16 squeeze, 16 release; each AO video presented

once in each preparatory condition). Each of the three preparatory conditions followed each other condition with equal probability, as did the imitate and counterimitate trials, and AO and no AO trials. There were an equal number of flexion and extension responses for each condition, with squeeze and release AO videos split evenly between responses. Following these constraints, a new order was generated for each participant. Participants were familiarized with the task first with no AO trials for 5 minutes. AO trials were then added for an additional minute of practice. The task was separated into three runs lasting about 7 minutes each, with a short break between runs. Participants were instructed to “prepare as much as possible while waiting for the finger movement so you can respond quickly and accurately.”

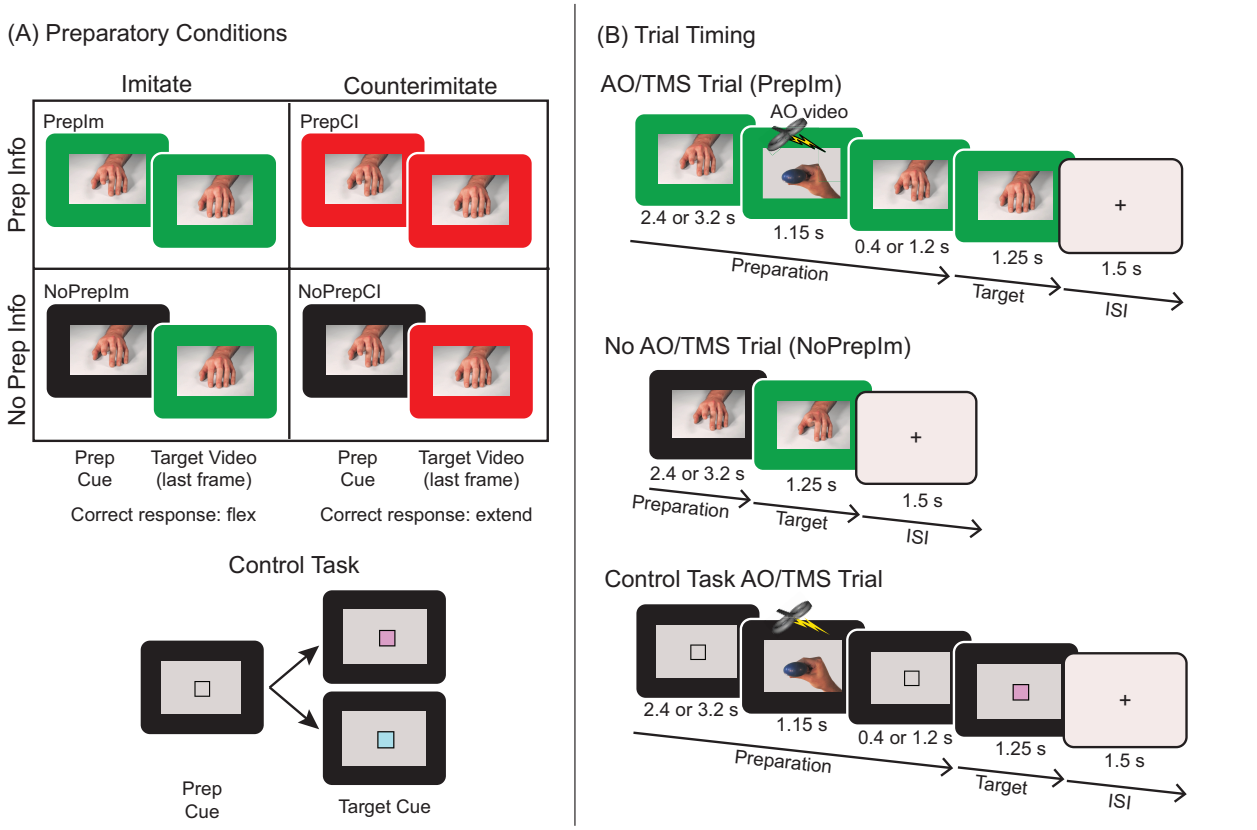

Figure 4.7 Behavioral Paradigm. (A) Imitation task and control task stimuli. For each condition the left image shows the static preparatory period image and the right image shows the last frame of the target video (Imitation task) or the target image (Control task). (B) Trial timing is shown for example PrepIm trials (Imitation Task) with (top) and without (middle) action observation (AO) videos. The image for the AO video depicts the final frame of a squeeze video. Identical timing for an example AO trial from the control task is shown at bottom.

Control Task Design.

A second control task was included as a baseline condition in which similar two-forced choice motor preparation was required, but in the absence of any stimulus-response compatibility. Participants performed the same flexion/extension responses depending on the color (cyan or magenta) of a square patch (Figure 4.7A, bottom). Trials began with an open black square (preparatory period) which was then filled in with either cyan or magenta (target). The color-response mapping was counterbalanced across participants; half of subjects performed finger flexion for cyan squares and extension for magenta squares and the other half performed the opposite mapping. An AO video interrupted the preparatory period in half of trials and timing was identical to the imitation task (Figure 4.7B, bottom). Participants performed 64 trials in a single 7-minute run. The order of imitation and control tasks was counterbalanced across subjects.

EMG Recording and Analysis

EMG activity was recorded from surface electrodes placed over the first dorsal interosseus (FDI) and extensor digitorum communis (EDC) muscles of the right hand and forearm. Data was recorded for 4.8 seconds for each trial starting 2 seconds after the onset of the preparatory period so that recordings included 0.4 or 1.2 seconds of preparation, the AO (when present) and target videos, and at least 1.2 seconds after the target video onset (response window). EMG signals were amplified (x1000), bandpass filtered online (50-450 Hz; Delsys, Inc., Boston, MA) and digitized at 5000 Hz for offline analysis.

The time of movement onset was determined for flexion (FDI) and extension (EDC) responses using custom MATLAB software implementing a double threshold procedure (Lidierth, 1986) and verified visually for each trial while blind to condition. Although the FDI was often active during finger extension as well as during flexion, activity in the EDC was selective for extension, making it possible to distinguish flexion and extension responses on EMG (see

Figure 4.8). When EMG onset or response action could not be determined due to excessive background activity or other noise, the trial was discarded (only 1.5% of trials).

Reaction time (RT) for each trial was calculated as the time of movement onset relative to the target video onset. Mean percent error and reaction times (errors and outliers greater than 3SD from the mean excluded) for each condition and subject were calculated and analyzed with 3-way repeated measures ANOVAs [2 (Prep, NoPrep) x 2 (Imitate/Counterimitate) x 2 (AO video/No AO video)]. Because we had clear directional predictions from previous compatibility studies, the interaction was explored with planned paired t-tests to determine whether the compatibility effects (difference between counterimitation and imitation) were reduced in NoPrep compared to Prep trials as proposed by the suppression hypothesis. The control task was used for comparison of motor resonance in Experiment 2, and was included in Experiment 1 only to ensure that behavioral data was collected under identical procedures as Experiment 2 (aside from the absence of TMS). Therefore, behavioral data was not analyzed for the control task.

Experiment 2: TMS

Participants

21 participants recruited through a campus newspaper and posted fliers completed Experiment 2 (8/13 M/F, 18-34 years old). Participants were right-handed, neurologically healthy, not taking psychoactive medications and had no seizure risk factors. The study was approved by the UCLA Institutional Review Board and written informed consent was obtained from all participants. Data from 1 subject were lost due to data collection error. In addition, 4 participants were unable to relax the FDI muscle consistently despite repeated reminders and were therefore excluded (11-43% of trials with >50μV root mean squared EMG activity during 100ms pre-TMS window vs. 0-5% in relaxed subjects). Data from the remaining 16 participants (4/12 M/F) were analyzed.

Tasks

Participants performed the same tasks as in Experiment 1 with the addition of TMS to measure motor resonance. Behavioral and EMG procedures were identical to Experiment 1, except the imitation task was divided into 4 runs instead of 3. In addition, at the end of the session participants performed 7-10 trials in which they squeezed and released a ball as done in the AO videos to measure FDI activity during execution of the same actions.

Transcranial Magnetic Stimulation

TMS was applied through a figure-of-eight coil (70mm diameter) connected to a Magstim 200^2 magnetic stimulator (Magstim, Whitland, Dyfed, UK). The coil was placed tangential to the scalp over left M1 with the handle pointing backward and angled 45° from the midsagittal line. At the beginning of the session, the optimal site to evoke an MEP from the FDI ("hotspot") was located. Brainsight frameless stereotaxy system (RogueResearch, Montreal, Canada) was used to record the location of the hotspot and then to monitor coil placement throughout the experiment. After locating the hotspot, the resting motor threshold (MT) was determined as the lowest intensity required to evoke an MEP of at least 50μV peak-to-peak amplitude in at least 5 out of 10 trials while the participant was relaxed. The intensity was then raised to 120% of MT for the duration of the task.

During task performance, single TMS pulses were administered over left primary motor cortex (M1) during each AO video to evoke an MEP in the right FDI. Stimulation occurred at the onset of the last AO video frame (317ms after video onset) when the hand was in the fully squeezed or fully released position. This very short period between AO video onset and stimulation was chosen to increase the likelihood that participants were in the appropriate preparatory state during stimulation, since the presence of the AO video signals that a response is not required immediately and therefore may reduce preparation. Although short periods of action observation have only rarely been used in the motor resonance literature (Barchiesi and

Cattaneo, 2012; Catmur et al., 2007; Catmur et al., 2011), a pilot study confirmed that the stimuli and timing did in fact evoke motor resonance.

EMG/MEP Recording and Analysis

EMG acquisition was the same as Experiment 1. MEPs recorded from the FDI were analyzed offline. Since even very small muscle contractions increase MEP size (Rösler et al., 2002), MEPs were excluded when activity was identified in the 100ms prior to TMS stimulation upon visual inspection (only 2.7% of trials). MEPs from error trials were also excluded from analysis. As a result of these procedures, an average of 14.3 ± 0.4 MEPs per condition were analyzed for each subject (total possible = 16). The size of each MEP (peak-to-peak amplitude) was used as a measure of corticospinal excitability of the FDI muscle. Peak-to-peak amplitude was determined in a 40ms window starting 10 ms after stimulation (Figure 4.8, inset). MEP amplitudes were then normalized to reduce the impact of between-subject and between-run variability (Catmur et al., 2011). This was accomplished by dividing each MEP measurement by the mean of all MEPs from the same run. Therefore, normalized MEP amplitudes represent proportion of the run mean amplitude.

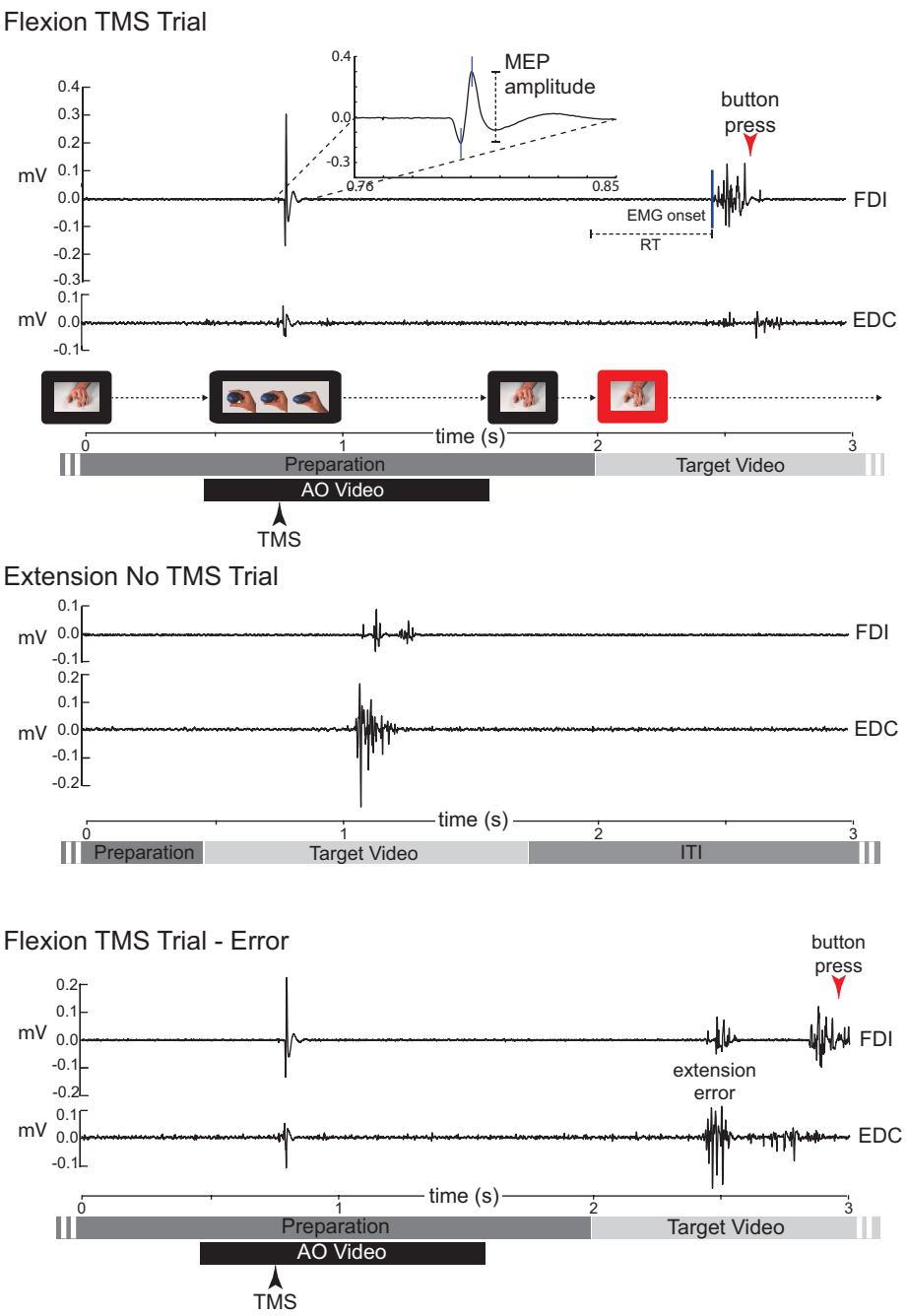

Figure 4.8 EMG (Exp. 1 & 2) and MEP (Exp. 2) analysis. The first 3 seconds of representative FDI and EDC EMG traces are shown for 3 trials from Experiment 2, Subject 4 (2.4s Prep-AO or Prep-Target interval). Top trial depicts activity in FDI indicative of a flexion response in a TMS trial. Inset illustrates MEP amplitude measurement and blue line indicates automated EMG onset identification for RT calculation. The middle trace shows activity indicative of an extension response for comparison (primarily in EDC). The bottom trace shows an error trial, which was excluded from analysis. Bars below each trace indicate the preparatory period and onset and offset of the action observation (AO) and target videos. Time of button responses as recorded by stimulus presentation software are indicated with red arrows. Black arrows indicate time of TMS pulse.

Means of the normalized MEPs were calculated for each condition (Imitation task 6 conditions: PrepIm/PrepCI/NoPrep x Squeeze/Release; Control task 2 conditions: Squeeze/Release) and analyzed with repeated measures ANOVA and planned t-tests in several stages. First, a 3 (Preparatory condition: PrepCI, PrepIm, NoPrep) x 2 (Action observed: Squeeze, Release) repeated measures ANOVA was performed to determine whether there was a preparatory effect on motor resonance in the imitation task. We explored the interaction with one-tailed t-tests based on clear a-priori directional predictions. We identified (1) which preparatory periods showed significant motor resonance (greater MEP amplitude during observation of an action involving the FDI, squeeze, compared to an action not involving the FDI, release; see Figure 4.9) and (2) whether the magnitude of motor resonance (the difference between squeeze and release MEPs) was greater for PrepIm than NoPrep and PrepCI.

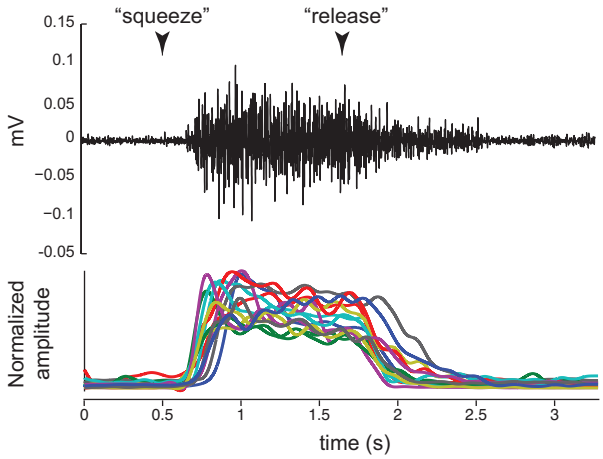

Figure 4.9: **EMG during action execution.** EMG activity from FDI measured while subjects squeezed and released a ball between the index finger and thumb (as in AO videos) in response to visual cue (cue onset indicated with arrows). Raw EMG activity averaged across subjects (top); and processed EMG for each subject averaged across 7-10 trials (bottom) indicates the FDI is active during squeeze and not during release.

Next we introduced the control task to determine whether the observed preparatory modulation of motor resonance resulted from facilitation during PrepIm or suppression during PrepCI and NoPrep trials. This was tested by comparing the magnitude of motor resonance in each imitation task preparatory condition to the magnitude of motor resonance during

preparation of an arbitrary stimulus-response mapping (the control task). All results are reported as group mean ± standard error of the mean.

For visualization, EMG obtained during execution of the squeeze and release actions was rectified, divided by the subject maximum to normalize across subjects, and lowpass filtered with a 4th order butterworth filter at 5Hz.

4.2.3 Results

Experiment 1

The 3-way ANOVA (Prep/NoPrep x Imitate/Counterimitate x AO/NoAO) on reaction times showed significant effects of preparation ($F_{(1,9)}$=102.6, p<0.0001; Prep=428±18; NoPrep=501±14), response mapping (F(1,9)=55.6, p<0.0001; Imitate=437±17; Counterimitate=492±16) and AO ($F_{(1,9)}$=70.0, p<0.0001; AO=434±17; No AO=495±16). The main effect of AO is likely due to the increased preparatory time available for AO trials. Most importantly, there was an interaction between preparatory condition and response mapping ($F_{(1,9)}$=4.57, p=0.036). Although imitation was faster than counterimitation for both Prep ($t_{(9)}$=6.06, p=0.0001) and NoPrep trials ($t_{(9)}$=3.43, p=0.004), the difference between imitation and counterimitation was greater when preparatory information was provided than when it was not ($t_{(9)}$=2.09, p=0.033) as proposed by the suppression hypothesis (Figure 4.10).

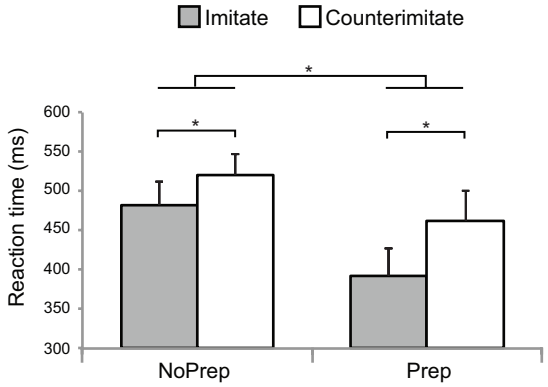

Figure 4.10: Experiment 1 results. Mean reaction time for each condition. Error bars reflect standard error of the mean.

For accuracy, only the main effect of response mapping was significant ($F_{(1,9)}$=5.1, p=0.027) with greater accuracy for imitation (95.8%±0.5%) compared to counterimitation trials (93.3%±0.1%), precluding a speed-accuracy tradeoff for the compatibility effects.

Experiment 2

The 2x3 ANOVA (PrepCI/PrepIm/NoPrep x Squeeze/Release) on normalized MEPs revealed main effects of preparatory condition ($F_{(2,15)}$=5.49, p=0.006) and an interaction between preparatory condition and observed action ($F_{(2,15)}$=3.27, p=0.044), indicating that motor resonance in the imitation task was modulated depending on the preparatory state (Figure 4.11A). Planned t-tests demonstrate that motor resonance (greater excitability in the FDI during observation of squeeze actions than release actions) occurred only during preparation to imitate (PrepIm; $t_{(15)}$=2.02, p=0.031). In contrast, and as predicted by the direct route suppression hypothesis, there was no difference between MEPs for observation of squeeze and release actions when subjects prepared to counterimitate (PrepCI; $t_{(15)}$=-0.59, p=0.719) or when the required response mapping was unknown (NoPrep; $t_{(15)}$=0.39, p=0.351). Post-hoc t-tests to explore the main effect of preparation indicate that overall excitability was greater for NoPrep trials than for both PrepIm ($t_{(15)}$=3.79, p=0.002) and PrepCI ($t_{(15)}$=3.17, p=0.006), but there was no difference between PrepIm and PrepCI corticospinal excitability ($t_{(15)}$=0.72, p=0.48).

To determine whether the difference in motor resonance for the 3 preparatory states was due to suppression on PrepCI and NoPrep trials or facilitation on PrepIm trials, we performed comparisons with the control task (Figure 4.11B). Significant motor resonance (greater MEPs for squeeze vs. release observation) occurred in the control task ($t_{(15)}$=2.27, p=0.019), when general motor preparation demands were similar to the imitation task but the stimulus-response mappings were arbitrary. The magnitude of motor resonance (difference between squeeze and release MEPs) during the PrepIm condition was similar to that observed for the control task ($t_{(15)}$=0.23, p=0.409). In contrast, motor resonance was significantly decreased compared to the

control task during PrepCI trials ($t_{(15)}$=2.35, p=0.017) and showed a similar trend for NoPrep trials ($t_{(15)}$=1.67, 0.058).

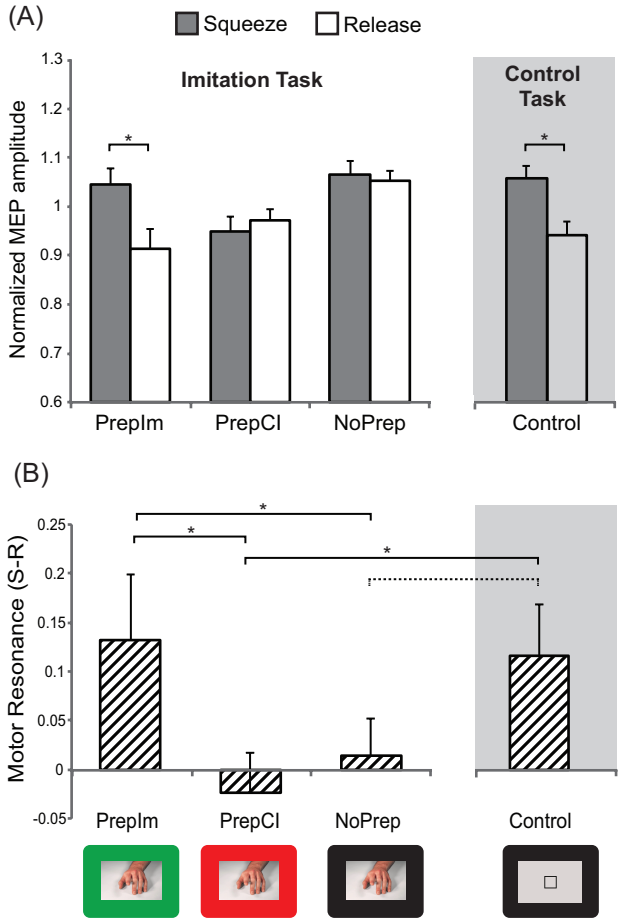

Figure 4.11: Experiment 2 Results. (A) Normalized MEP amplitudes for each condition are shown for the imitation and control tasks. Stars indicate significant (p<0.05) motor resonance. (B) Comparison of magnitude of motor resonance across conditions. Stars indicate significant difference (p<0.05) between motor resonance. The dotted line indicates a trend (p=0.06).

4.2.4 Discussion

Cognitive models of stimulus-response compatibility propose that although stimuli often activate a compatible response, this automatic response activation can be suppressed when it is likely to interfere with task goals. In Experiment 1 we extend behavioral effects typically attributed to preparatory suppression of automatic response activation to imitation, which represents a special form of stimulus-response compatibility especially relevant for human behavior (Heyes, 2011). In line with previous studies using non-imitative stimuli (Stoffels, 1996;

Ehrenstein and Proctor, 1998; De Jong, 1995; Vu and Proctor, 2004), the compatibility effect (faster imitative than counterimitative responses) was reduced when stimulus-response mapping information was not provided in advance of the imperative stimulus.

Data from Experiment 2 provide novel neurophysiologic evidence that these behavioral effects are related to preparatory suppression of specific stimulus-response links, and also suggest that the MNS can be strategically modulated when it is likely to disrupt motor responses. Motor resonance—the activation of an imitative response during action observation—was evident during preparation to imitate but not during preparation to counterimitate, or when the required response was unknown. Thus, motor resonance occured only when this imitative response activation would be helpful, and not during preparation for the two conditions in which the imitative response would interfere with behavior.

These differences in motor resonance during the imitation task could be attributed to suppression of motor resonance when it would interfere with responding (as proposed by cognitive models), facilitation of motor resonance when it would aide responding (in the case of imitation), or both. The baseline measure of motor resonance, obtained in a task with similar two-forced choice task demands but without any influence of stimulus-response compatibility, supports the suppression account. Motor resonance was similar to baseline during preparation to imitate, and lower than baseline during the counterimitation and unknown mapping conditions.

What are the implications of this motor resonance modulation? Since its discovery, motor resonance has been attributed to MNS activity and recent work has bolstered this claim. Ventral premotor and parietal regions that are homologous to macaque regions containing mirror neurons have been shown to be causally involved in motor resonance (Avenanti et al., 2007; Catmur et al., 2011; Koch et al., 2010). Thus, the present data indicate that preparatory processes inhibit the influence of MNS activity on the motor system when it is likely to activate responses that conflict with task goals. This is consistent with theories proposing MNS

modulation as a way to control unwanted imitation (Spengler et al., 2009; Wang et al., 2011). An automatic (unintended or unconscious) tendency to imitate observed actions has been demonstrated in both laboratory and naturalistic settings (Chartrand and Bargh, 1999; Brass et al., 2000), and the existence of patients who imitate uncontrollably after brain damage (Lhermitte et al., 1986; De Renzi et al., 1996) suggests that some active inhibitory mechanism is required to control automatic imitation. Consistent with this view, we show that MNS activity is present at baseline (during the control task) and when imitation is desired, but suppressed when imitation would interfere with behavior. Thus, our data add to accumulating evidence that automatic imitative tendencies are suppressed through modulation of MNS activity, and indicate that this MNS suppression can occur in a preparatory manner.

Future studies will be required to determine more specifically the locus of this preparatory modulation of MNS activity; since TMS gives access only to the primary motor cortex readout of MNS activity, it is impossible to say whether the preparatory suppression observed here occurs through inhibition of input to the MNS, the MNS itself, or output from the MNS to M1. The language of cognitive models tends to favor a mechanism that inhibits specific stimulus-response links (De Jong, 1995; Vu and Proctor, 2004). However, the behavioral data forming the basis for this hypothesis do not rule out the alternative possibilities that non-specific preparatory suppression mechanisms inhibit either visual input or motor output. For example, rather than inhibiting the ability for a particular type of stimulus to activate the corresponding response, early erroneous motor activation could instead be avoided by inhibiting the motor system generally, thus reducing the impact of any stimulus on responding.

Our data do rule out a general motor suppression account. Conditions proposed to involve preparatory suppression (PrepCI and NoPrep) showed decreased excitability in the FDI during observation of squeeze but not release actions, indicating decreased excitability of the imitative response in particular, rather than decreased motor excitability overall. In fact, the NoPrep condition had the highest excitability overall (perhaps due to greater vigilance

associated with this most difficult condition), and excitability did not differ between preparation to imitate and counterimitate. In contrast, we cannot rule out the possibility of a preparatory suppression mechanism that occurs through general inhibition of visual input, because it is possible that the preparatory modulation of motor resonance observed here is not specific to the imitation task. That is, preparation for compatible and incompatible responses to non-imitative stimuli could, in principle, also modulate motor resonance. Such a result would suggest that a general preparatory suppression mechanism inhibits visual input to the motor system, so that both the stimulus-response link relevant to the task, but also all other automatic stimulus-response links, would have reduced influence on motor responses. Further work to address the task-specificity of motor resonance modulation is warranted.

Overall, the present study provides novel evidence that relatively automatic stimulus-response links can be inhibited in a preparatory manner when they are likely to interfere with behavior, either through suppression of visual input to the system or suppression of the stimulus-response link itself. In the case of imitation, this preparatory suppression provides a mechanism by which the automatic tendency to imitate—presumably via the MNS—can be reduced when it would interfere with current goals.

4.2.5 References

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Chapter 5

Conclusions

5.1 Integration of results

Converging evidence suggests that the automatic tendency to imitate is due to imitative response activation mediated by the mirror neuron system. Recent interest in how automatic imitative tendencies are modulated has focused on relationships between imitation control and social cognitive functions. To build on these models of imitation control, I used fMRI and TMS to measure and disrupt neural activity during imitation interference and compatibility tasks. In particular, my work provides some of the first direct comparisons of brain activity associated with overcoming imitative and spatially compatible response tendencies, which allowed us to examine the relevance of the mirror neuron system in imitation control. In addition, these studies include the first investigations of preparatory control processes that may be able to minimize the influence of imitative tendencies in advance of any action observation.

With regard to reactive imitation control, results demonstrated a dissociation between imitation and spatial compatibility indicating at least partially distinct control mechanisms depending on stimulus content. In contrast, there was no evidence of stimulus-specificity for preparatory control processes. Nonetheless, TMS results indicate that preparatory control processes do affect mirror neuron system activity as evidenced by reduced motor resonance when the imitative response is likely to be incorrect.

Aside from the specific control mechanisms discussed in previous chapters, several broader conclusions can be drawn from the work presented in this dissertation. First, data from the fMRI studies described in all three chapters indicate that automatic imitation cannot be considered simply an example of spatial compatibility where the stimuli happen to represent human actions (Stürmer et al., 2000). While this is perhaps the most parsimonious view, previous behavioral studies suggest that congruency effects observed in imitation interference tasks is not fully explained by spatial compatibility (Jiménez et al., 2012; Catmur and Heyes, 2011; Bertenthal et al., 2006; Heyes et al., 2005; Brass et al., 2001a). However, some authors have raised doubt as to whether these differences are attributable to imitation specifically or instead to basic visual differences between stimuli such as salience (Aicken et al., 2007; Jansson et al., 2007). Since congruency effects are sensitive to basic visual features, the attribution of reaction time dissociations to stimulus content (i.e. biological vs. non-biological) is problematic because other visual features also differ between stimuli. However the neuroimaging studies described here provide strong support for the dissociation between imitation and spatial compatibility. Neural correlates for imitative and spatial tasks were dissociable even when reaction time effects were equated. Furthermore, the dissociations are evident through a variety of different comparisons between imitation and spatial compatibility. In Chapter 2, premotor and parietal regions were more active for finger than dot stimuli, regardless of the compatibility mapping; in Chapter 3 again different networks were activated by finger and dot stimuli regardless of the congruency, and there were also regions activated specifically by the imitative congruency effect; and in Chapter 4 preparatory activity in several regions predicted better performance for imitation but not for spatially compatible responses. Importantly, the clusters specific to imitation across these three studies overlap in the posterior part of the inferior frontal gyrus and in the anterior intraparietal sulcus, which correspond well to the regions in macaque where mirror neurons are found. Thus, these results provide strong

support for the claim that automatic imitation and spatial compatibility are supported by distinct systems, with imitation relying on the MNS in particular.

The fact that imitation is not equivalent to spatial compatibility provides an important basis for the argument that imitative control may be subserved by a dedicated mechanism and distinct neural systems. Nonetheless, it does not preclude the application of a general control mechanism. Overall, results from the studies presented here suggest that control of imitation may lie somewhere in between these extremes, involving interactions between general cognitive control and specific mirror neuron systems. In reactive control the anterior insula/frontal operculum and anterior cingulate, regions observed in many studies of response conflict, interact with the regions that are related more specifically to the biological content of the stimuli—the inferior frontal gyrus, pars opercularis and the medial prefrontal cortex. In preparatory control, dorsolateral and anterior prefrontal regions, which are involved in establishing task sets and biasing attention across a variety of stimuli and tasks, were active for preparatory control of imitation and spatial compatibility suggesting a relatively general mechanism. Yet, single pulse TMS indicated that mirror neuron activity is modulated when imitative responses are likely to interfere indicating that either the MNS is also directly modulated (and fMRI was insensitive to this modulation) or that the general control mechanism minimizes the influence of action observation on behavior by reducing visual input to the mirror neuron system. In either case, imitation control seems to be accompanied by modulation of activity in the mirror neuron system, whether it be through direct modulation of the MNS or through modulation of visual input to the MNS.

Finally, differences between neural correlates of reactive and preparatory control mechanisms highlight the importance of carefully defining control processes being examined in studies of conflict resolution. Many paradigms have been developed in the vast literature examining conflict resolution processes. This literature often focuses on disentangling resolution of conflict arising at different stages (i.e. stimulus vs. response) or examining differences

between different domains (i.e. emotional conflict vs. motor conflict). Yet, as outlined previously (Section 2.3) the tasks used also frequently differ in the time at which control can be implemented relative to the experience of conflict. Only few studies have begun to address these differences when control tasks and mechanisms are compared. Those that have, highlight dissociable mechanisms (Alpay et al., 2009; Correa et al., 2009; Boy et al., 2010; Funes et al., 2010). The present data add to this emerging view, indicating that preparatory control of imitation based on explicit cues and reactive control in response to imitative conflict recruit quite different neural systems. While preparatory control may exert control by modulating the influence of visual input to the motor system, reactive control must rely instead on modulation of the output from sensorimotor integrations systems.

5.2 Future directions

These studies represent just a first step in understanding how automatic imitative tendencies are modulated, leaving open a number of questions for future investigation. First, several follow-up studies to further test the models I propose based on the present results are desirable. In the case of reactive control, we used dynamic causal modeling to examine functional interactions between imitation control regions. Because this method is entirely dependent on the set of models tested, the winning model should be taken not as definitive evidence but instead as a starting point for additional empirical work. We aimed to get some insight into the contributions of particular regions using TMS, but unfortunately were not able to modulate behavior by targeting these regions. Further insight could be obtained instead with tasks aimed at separating the processes proposed for various regions. For example, it may be possible to explore the distinct roles of the anterior insula and medial prefrontal regions by examining inhibition of imitation in the absence of response conflict, using a stopping task rather than an interference task.

In addition, an obvious next step to understanding the mirror neuron system modulation observed in the final TMS experiment is to determine whether that modulation is specific to an imitative compatibility task. As previously mentioned (Section 4.2), this would provide valuable insight into the specificity of this preparatory control mechanism. In particular, if motor resonance is decreased in an identical task with non-imitative stimuli, it would suggest non-specific suppression of visual input to visuomotor circuits regardless of the particular sensorimotor link that needs to be inhibited. On the other hand, if suppression is specific to the imitative compatibility task, this would suggest an imitation-specific effect on the mirror neuron system, suggesting suppression specifically of visual processing of biological actions or suppression of the mirror neuron system itself.

Another important question for further study is how well the controlled laboratory paradigms required for fMRI and TMS map onto the social mimicry observed in the real world. Early data suggests the two types of automatic imitation may be supported by the same neural systems, as similar contextual factors modulate both types of mimicry (van Baaren et al., 2003; Leighton et al., 2010). However, more direct evidence for a relationship could be obtained through studies that compare measures of social mimicry and behavioral and neurophysiological measures of automatic imitation from interference paradigms in the same subjects. Similarly, manipulating contextual factors and measuring *both* social mimicry and automatic imitation could also provide further support.

More broadly, this work may be relevant for the future study of imitative and social deficits in neuropsychiatric disorders. Deficits in imitation that are not explained by simple motor deficits have been noted in autism since the first description of the disorder (for review see Williams et al., 2004). Since imitation plays an important role in the acquisition of social and language skills (Rogers and Pennington, 1991; Williams et al., 2001), early deficits in imitation have been proposed to cause the subsequent poor development of social functions. Furthermore, accumulating evidence from fMRI (Dapretto et al., 2006), TMS (Theoret et al.,

2005), MEG (Nishitani et al., 2004) and EEG (Bernier et al., 2007) studies suggest abnormal mirror neuron function during action observation and imitation, which led to the “broken mirror” hypothesis of autism. Yet, not all functions thought to be subserved by the mirror neuron system are disrupted in autism. For example, EEG markers of MNS function revealed abnormalities only for the observation of actions performed by strangers (Oberman et al., 2005) and at least some types of imitation are intact (McIntosh et al., 2006; Hamilton et al., 2007).

These seemingly conflicting results—evidence of MNS dysfunction but disruption of only a subset of functions subserved by the MNS—can be reconciled by the alternative account that previously observed dysfunctional activity in mirror neuron areas stems not from intrinsic mirror neuron dysfunction, but instead from inappropriate modulation of the mirror neuron system (Spengler et al., 2010; Hamilton, 2008). The studies described here suggest that automatic imitation involves mirror neuron modulation, indicating that these paradigms could provide a way to test this theory. For example, it would be interesting to see whether individuals with autism are able to modulate motor resonance in response to explicit cues or whether hyperimitation in interference tasks (Spengler et al., 2010) is associated with abnormal activity in prefrontal control regions involved in reactive imitation control.

In conclusion, the present work suggests that preparatory and reactive imitation control involves modulation of the mirror neuron system with contributions of more general cognitive control mechanisms. It provides a starting point for the further study of imitative deficits in neuropsychiatric disorders including autism.

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