

CHAPTER 30

Motor cognition: TMS studies of action generation

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Introduction

The discovery and earliest applications of TMS both involved the motor system (Barker *et al.* 1985). Since then, TMS has been used in three quite different ways to study motor cognition. First, TMS can be used to provide a controllable and physiologically-specified input to the skeleto-motor system. Several sensory studies, for example, have used TMS to generate muscle contractions in the absence of volition and movement preparation. This allows controlled psychophysical studies of the perception of bodily movement (Haggard *et al.* 2002; Ellaway *et al.* 2004; Haggard and Whitford 2004). In other studies, TMS-evoked movements are used as perturbations of the motor apparatus. Here the focus is on preparatory and reactive adjustment for the perturbation (Bonnard *et al.* 2003 2004). In this method, TMS is generally delivered over the primary motor cortex, but effects on the brain are less important than the effects on the body. Although this use of TMS has great value as a peripheral stimulus for studying kinesthesia, it is logically quite different from the use of TMS to study specific brain areas and processes, and so is not considered further here.

A second, very important use of TMS has been as an online probe of cortical motor excitability. This is reviewed in detail elsewhere

(e.g. Chapter 9, this volume). A TMS test pulse can provide a known, if artificial, input to the motor cortex. This will cause a twitch in target muscles (motor-evoked potential, MEP) whose amplitude can be precisely measured. It may also cause an inhibition of ongoing electromyogram (EMG) (silent period, SP). In cognitive-motor studies, the size of these excitatory or inhibitory effects is measured as a function of cognitive factors like task, expectancy and so forth. Changes in the motor output for a constant TMS input are interpreted in terms of differences between conditions, or across time, in motor system excitability. Importantly, this method can provide a completely implicit and on-line measure of the state of the cortical action system. Often a test pulse is preceded by a conditioning stimulus such as a sensory input or a conditioning TMS pulse to the same or another brain area.

Third, TMS can be used to interfere with cognitive-motor processes involved in action control, and widely described throughout this volume. Because the brain processes involved in generating a simple action are essentially serial, a single TMS pulse delivered at an appropriate time over an actively involved brain area may disrupt action control. Such single-pulse effects tend to be highly informative, because of their temporal and spatial specificity. On the other

hand, their interpretation rests on a serial model of action control, which may not be sufficient for all situations. Other studies have used off-line TMS effects, as a short-term virtual lesion. This approach may be more powerful than single-pulse approaches, since it does not depend on precisely timing a single pulse with respect to the underlying brain processes. However, by the same token, it cannot clarify *at what stage* of the action control process a particular brain area makes its contribution.

TMS allows the experimenter to selectively interfere with a specific brain process. It is therefore particularly adapted to testing serial models of cognitive processing (Donders 1868; Sternberg 1969). In these models, processing is assumed to occur in a serial sequence of independent modules, which implement distinct and independent operations. The successful completion of each operation allows the next module to begin its operation. The value of these models is widely debated. Recent studies view the visual system as a parallel rather than serial architecture, involving multiple interconnected processing streams (Milner and Goodale 1993).

In contrast, the brain's action system can be viewed in two distinct ways. Voluntary actions involve a clearly serial process (cf. Figure 30.1). Volition or intention can be seen as the input to the process. These are followed by action selection or specification. At this stage, a specific set

of motor commands generating an appropriate movement pattern must be retrieved from the many alternatives, thus achieving the desired goal. This stage corresponds to the inverse model or planner of computational models (Ghahramani *et al.* 1996). Preparation for action then follows. This may involve further elaboration of the motor command itself, but also more general anticipatory modulation of reflex pathways and sensory areas likely to receive afferent feedback as a result of the impending action (Voss *et al.* 2006). A key moment in the serial control of action is the release of the motor command from the motor cortex, down the corticospinal tract (CT). The corticospinal volley drives the actual contraction of the muscles, and is the proximate cause of the movement itself. This point therefore marks the transition between action preparation and action execution. For some very simple 'ballistic' actions, the model may be considered to stop here. In most cases, however, afferent feedback from the moving effectors, and also internal feedback from predictions based on efference copy, are used to monitor the progress of the movement. Monitoring allows the motor command to be adjusted if it is incorrect, thus reiterating the model. It also allows the successful completion of one movement to serve as the trigger for the next movement in a sequence. Finally, action monitoring may be used for



Fig. 30.1 A simple serial, hierarchical model of action control suitable for interpreting TMS studies. Note the increasing quantity and specificity of information as the action is elaborated.

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perceptual processes beyond the immediate motor control system, such as self-recognition and agency (Haggard 2005).

Not all action research fits well with this serial model. Several neurophysiological, neuroimaging and behavioral studies have focused on the sensory guidance and internal representation of action by a network of parietal and premotor regions (for a review see Freund *et al.* 2005). These studies focus on the transformation of sensory representations into motor codes, and the commonality between visual and motor representations of action. However, the results do not always support a simple serial flow from sensation to action. Neurophysiological and neuroimaging results often reveal visual responses in 'motor' areas, while responses in early sensory areas can show dramatic top-down modulation according to current motor task (Ruff *et al.* 2006). A recurrent feedback model may therefore be more appropriate than a strictly serial model for those sensorimotor actions that involve relatively direct responses to environmental stimuli. In the following we first review studies which can be situated within a simple serial model of action generation. These studies have in common that they largely focus on the control of voluntary or internally generated actions. Here TMS has predominantly been used as a technique to temporally disrupt specific cognitive processes at particular times. Second, we will discuss the use of TMS in research focusing on perception–action linkage, such as reaction and interaction with the environment, including the social environment. In that tradition, parallel and interactive models dominate over serial models, but TMS has still proved an important research tool, notably in measuring cortical excitability.

Intentional actions and the serial model of action generation

Context and motivation for action

Human action is generally goal-directed. Our actions therefore occur in the context of our internal environment (e.g. needs and desires) and the opportunities afforded by the current external environment. The agent's emotional

and motivational states therefore constitute a reason for action. Neurophysiological evidence supports the existence of anatomical–functional links from the limbic system to premotor areas, mediated by connections to the cingulate and prefrontal cortical regions. These earliest contextual antecedents of action have proved difficult to study with TMS for two reasons. First, many motivational and limbic structures lie deep within the brain and cannot be stimulated externally. Second, antecedent states such as motivations and drives provide a tonic background to action rather than a single neural event. They are not therefore amenable to investigation using phasic interventions such as TMS.

In one of the few TMS studies to investigate action antecedents, Oliveri *et al.* (2003) used TMS to investigate the role of the supplementary motor area (SMA) as a mediator between emotion and action. They accordingly measured cortical excitability of primary motor cortex (M1) during processing of emotional versus nonemotional visual stimuli. Subjects were required to perform arbitrary movements in response to unpleasant or neutral pictures of people, animals or landscapes. The subjects received a single TMS pulse over the left M1, which was randomly preceded by paired TMS over the ipsilateral left SMA, left premotor cortex (PM) or right M1. The amplitudes of motor-evoked potentials (MEPs) recorded from subject's right first dorsal interosseus (FDI) after conditioning TMS were compared against those obtained after single TMS of the left M1. The authors showed that conditioning TMS to SMA selectively enhanced MEP amplitudes when subjects responded to emotionally unpleasant pictures, and not when neutral visual cues were presented. However, conditioning TMS of PM or of the contralateral primary motor area did not show this effect. This finding confirms a specific functional link between SMA and primary motor areas in the control of movements that are triggered by emotional processing of certain visual cues. SMA seems to serve as a key area for transforming motivations, such as emotional states, into motor responses.

Intention and planning of action

Once a contextual reason for action exists, and a particular action goal is identified, the brain

faces a series of computational problems before the action itself can be initiated. In particular, most goals can be achieved by a number of different means. The brain must identify just one of the possible movements consistent with an action goal before a detailed motor command can be assembled. In computational motor control this is known as the inverse or planning problem (Wolpert 1997). The premotor areas immediately in front of the primary motor strip play a particular role in selecting the specific movement that will be made given a general action goal.

The dorsal premotor cortex (PMd) seems to be particularly concerned with the selection of movements according to learned associations. Schluter *et al.* (1998) showed that stimulation of the left PMd disrupts the selection of movements that will be made with either hand. In their study subjects were asked to perform a choice reaction with either their index or middle finger of one hand in response to a shape presented on-screen. Reaction times were measured while subjects received a TMS pulse over the contralateral cortex. TMS over premotor areas, when applied at intervals close to movement onset, significantly delayed response time. This effect was present both in a group of subjects who used their left hand to respond while being stimulated over the right hemisphere, and in a second group who used the right hand while being stimulated over the left hemisphere. In contrast, TMS over the primary motor cortex delayed responses only at longer cue-stimulus intervals (>300 ms). Moreover, a second experiment stimulating either left or right PMd suggested that the neural system for action selection was lateralized to the left hemisphere. Stimulation of the left hemisphere replicated the delay found when subjects used two digits of the right hand to respond. It also delayed responses in a separate block using the left hand. Right hemisphere stimulation affected only contralateral and not ipsilateral responses. These findings show that premotor cortex is functionally relevant in an early stage of movement selection whereas the motor cortex comes into play at a later stage. In particular, they fit well with the serial model of action: disruption of action selection was found at an earlier time and an anatomically upstream location compared

disruption of final motor output. This study indicates the high scientific potential of combining single-pulse TMS and precisely timed task in order to investigate classic serial models of cognitive psychology. Once an action is selected, it may be initiated immediately, or maintained in a state of preparation to be finally triggered at a later time. The phrase 'motor attention' has been used for this state of preparedness occurring between selection and execution of action. In the primate, cells active in the delay period between a selection cue and a go-stimulus are widely found in both premotor (Boussaoud and Wise 1993) and parietal (Goldberg *et al.* 1990; Li *et al.* 1999) regions. Human studies suggest that premotor and parietal regions may act in concert to prepare a selected action. For instance, Rushworth *et al.* (2001) have shown that redirecting of covert orienting is impaired when the parietal cortex is temporarily disrupted by TMS. In their experiment a visual precue preceded the presentation of an imperative stimulus indicating which of two manual responses to execute. On infrequent trials, the precue provided invalid information so that the subject had to shift from one intended movement to making a quite different movement. A brief train of rTMS was applied over the left anterior parietal region after target presentation but prior to response execution. Reaction times were impaired but only in invalid trials. This result suggests that the parietal cortex contributes either to the processes of reselection of a novel motor response or to preparation to perform this response. This motor attentional effect was distinct from a spatial orienting effect tested by the same authors using a conventional orienting paradigm, and found to be localized more posteriorly within the parietal cortex.

Selection and specification of intentional action

TMS can also be used to influence movement selection externally and even independently from a person's conscious movement intention. For instance, Brasil-Neto *et al.* (1992) studied the influence of TMS on forced-choice response times. Subjects were required to extend their index finger in response to the click of a

TMS pulse. Moreover, they were instructed to freely choose either their right or left finger for making the response but this decision was only to be made after hearing the TMS click. Subthreshold TMS was delivered over the prefrontal or motor area. In a control situation subjects were stimulated peripherally. Hand preference was only then affected when TMS was delivered over the motor cortex: when being stimulated over this area, subjects more often chose the hand contralateral to the stimulated site. The effect of hand preference was most pronounced in responses with very short latency (<200 ms). This bias replicated Ammon and Gandevia (1990) but suggested that the effect was focal and restricted to motor, not frontal, areas of the brain. Another important observation is that in both studies subjects were unaware of the preference in their responses. They felt that their decisions were entirely made in a neutral way. This finding could also be interpreted as evidence suggesting that motor selection can precede the conscious intention to select a given response. Selection could even generate conscious intentions (Haggard and Eimer 1999).

Movement execution

Once a movement is selected, the motor command must be sending down the CT for its execution. Day *et al.* (1989) showed that a single magnetic stimulus can interfere with processes controlling the initiation of simple reaction movements. Subjects were trained to flex or extend their wrist following an auditory signal. In one-third of the trials, subjects received a single magnetic stimulus to the contralateral motor cortex of varying intensity but sufficiently strong to produce a flexor muscle response. The pulse was delivered at a predefined onset time after the tone and just before the expected onset of the wrist movement. When TMS was delivered, the execution of the movement was delayed up to 150 ms. Furthermore, the amount of delay turned out to be a function of both stimulus intensity and the onset time prior to the movement: the delay increased with increasing stimulus intensity and the closer the stimulus was to the expected onset of the voluntary action. However, the brain stimulus did not

show any effect on the organization of the pattern of the agonist (flexor)/antagonist (extensor) muscle activities. Thus the form of the response still remained intact. In contrast, stimulation of peripheral nerves did not lead to similar effects of delaying movement onset. Interestingly and in line with a serial model of action control, TMS led only to a delay, not to an abolition, of a voluntary action. Thus, it seems that only the selective part of the central motor program, probably the release of the motor command, was transiently disrupted or rather temporarily inhibited.

In a similar vein, Pascual-Leone *et al.* (1992a) compared simple reaction times (RTs) to go-signals of different modalities and investigated the effects of TMS on RTs. In their study, subjects were asked to flex their right elbow as rapidly as possible in order to touch the shoulder with their right hand in response to a go-signal. Shortest RTs occurred for auditory go-signals followed by somatosensory, and then visual. In all cases RTs were shorter with increasing intensity of the signal. This effect is probably due to different recognition time for the different go-signal modalities. However, in line with Day *et al.* (1989), longest RTs (i.e. longer than the RTs to any other go-signal) were found to TMS over the contralateral motor cortex at above threshold intensity, i.e. at an intensity to induce an MEP in the responding arm. In contrast, shortest RTs, even shorter than reactions to auditory signals, occurred to either TMS at subthreshold intensity over the contralateral hemisphere or to TMS over the ipsilateral motor cortex. TMS over parietal and frontal areas did not have an effect on RTs. The effect of shortening of RTs by TMS over the contralateral motor cortex at subthreshold intensity was also replicated in a further study by Pascual-Leone *et al.* (1992b).

Goal-directed movements require frequent updating of the movement trajectory via feedback loops throughout its execution. A key brain area mediating these processes seems to be the posterior parietal cortex (PPC). Desmurget *et al.* (1999) tested the hypothesis that the PPC supports on-line motor adjustment by computing the instantaneous differences between hand and target locations.

Subjects pointed to visual targets in the peripheral visual field which either remained

stationary or changed position during saccadic eye movements. Subjects could not visually monitor their pointing movement. Just after movement onset, TMS was applied over the left PPC. This intervention abolished on-line trajectory adjustments. Moreover, this effect occurred only when the visual target jumped to different positions but not when it remained stationary. This finding supports PPC involvement in on-line movement corrections. PPC might serve as a 'neural comparator' which computes a current motor error. Johnson and Haggard (2005) were unable to replicate these effects, though their TMS intensities were lower than those that appear to have been used by Desmurget *et al.* (1999).

Motor awareness

Neuroscientists have recently shown a developing interest in the conscious experience of action. Several studies have used TMS to investigate what processes within the motor system are associated with consciousness and which are not. These studies have typically used TMS paradigms developed for investigating motor execution, and assessed how they influence motor awareness.

For example, Haggard and Magno (1999) used Day *et al.*'s (1989, see above) method to delay simple RT movements to auditory stimuli. They also asked subjects to judge the time at which they felt they reacted, by indicating the position that a clock hand had occupied at the time of their response. Single-pulse TMS was delivered over contralateral motor cortex 75 ms before the expected reaction. This intervention delayed voluntary reactions by >200 ms. However, subjects' reports of *when* they reacted suggested that less than half of this delay entered into awareness. Stimulation over a more anterior location (electrode site FCz) produced shorter delays in actual RT, of which a relatively *larger* proportion entered into awareness. The authors concluded that intervening on the voluntary motor system at the MI level had only minor effects on awareness, because an important component of motor awareness is generated upstream of MI, in the premotor areas.

Voss *et al.* (2006) used the same method of TMS-induced delay, but focused on awareness

of sensory events during movement. They measured the well-known sensory suppression effect: sensitivity to electrocutaneous stimuli on a moving body part is reduced relative to sensitivity when the same body part is at rest (Angel and Malenka 1982). Voss *et al.* found that this sensory suppression was also present during an RT task in the time window when a voluntary action was expected, but had been artificially delayed by TMS over contralateral MI (Day *et al.* 1989). Controls showed that the suppression during the TMS-induced delay period could not be attributed to direct masking of the electrocutaneous stimulus by TMS effects on SI. Instead, the finding of sensory suppression during TMS-induced delays was used to localize the signals involved in sensory suppression. The signals that produce sensory suppression must originate upstream of the primary motor cortex.

A more precise localization was proposed by Haggard and Whitford (2004). They asked subjects to judge whether the first or second of two involuntary movements (MEPs produced by MI TMS) was larger. When the first, test MEP occurred during a self-generated voluntary movement, it was less likely to be judged larger than the second, reference MEP, compared with test MEPs delivered at rest. This effectively replicates previous sensory suppression results. However, a conditioning TMS pulse delivered over the SMA 10 ms before the test stimulus abolished the sensory suppression effect. The authors concluded that the SMA is actively involved in generating the efferent signals that modulate afferent input through sensorimotor gating.

Motor sequencing

In order to perform a goal-directed behaviour, we have to organize actions in a specific spatiotemporal order. A couple of studies confirmed that the medial frontal cortex and, in particular, the human pre-supplementary motor area (pre-SMA), plays an important role in the sequencing of actions. More precisely, SMA seems to be particularly involved in both the encoding of movement sequences and in the planning of forthcoming movements in a motor sequence retrieved from memory.

Müri *et al.* (1995) investigated the role of SMA in the cortical control of sequences of memory-guided saccades. Subjects were asked to fixate a central point while four different targets appeared laterally on either one or both sides of a screen. The task was to remember the order of target appearance without looking directly at them. Then the fixation point disappeared and subjects were required to make saccades successively to the targets in the same order in which they appeared. While subjects performed the task, TMS was delivered over SMA or as a control over the occipital cortex at random time intervals during three different phases: the target presentation phase, the memorization phase or the phase in which the saccades were executed. Stimulation over SMA and not over the occipital cortex induced an increase in error rates but only when TMS was delivered during the phase of target presentation. This indicates that the learning phase was selectively disturbed and that SMA appears to be functionally relevant in memory encoding. The finding that performance was not affected when SMA was stimulated during the execution phase indicates – in line with a serial model of motor control – that once the motor program is initiated it is no longer under control of the SMA region.

Gerloff *et al.* (1997) asked subjects to learn playing three finger-sequences of different complexities for ~8 s periods with their right hand following a metronome beat of 2 Hz. Task complexity was varied as follows. In a 'simple' sequence they repetitively (16 times) pressed one key using their index finger. In a 'scale' sequence they used four fingers and pressed consecutively four different notes but always in the same order (i.e. 5–4–3–2–5–4–3–2 etc.). Finally, in a 'complex' sequence subjects played a nonrepetitive and nonconsecutive order by using four fingers. Subjects practised the sequence until they could play it from memory 10 times consecutively without making any errors. During the actual experiment subjects were asked to play a certain sequence (complexity varied randomly). Two seconds after the first key press, high-frequency (15–20 Hz) rTMS was delivered over the fronto-central midline including SMA. When subjects performed complex movement sequences, TMS led to interference with the organization of the future components

in this sequence. In contrast, stimulation over MI induced accuracy errors in both the complex and scale sequences, whereas stimulation over other control regions (F3, F4, FCz, P3, P4) did not cause interference at all. Moreover, rTMS over SMA and MI, respectively, led to different timing patterns of error induction: error induction following stimulation over SMA occurred ~1 s later than with stimulation over MI. The result of this study suggests that SMA is of critical importance for the time-dependent organization of *future* elements in complex sequential actions retrieved from memory. Thus, before sending movement commands to primary motor areas for execution, SMA seems to be a key area for organizing upcoming movements in a complex motor sequence.

Kennerly *et al.* (2004) investigated the role of pre-SMA in the internal organization of motor elements within a sequence organization and initiation (cf. Sternberg 1969). In their first experiment the authors asked subjects to learn a bimanual sequence of 12 alternating movements so that they could perform the sequence from memory. In line with several behavioral studies on sequence learning, subjects showed a spontaneous organization of the long sequences of finger key-press movements into smaller component units or 'chunks'. With practice, subjects typically executed short phrases within the overall motor sequence as a single 'chunk', characterized by a low interval between successive movements. In contrast, the interval between some successive elements consistently showed a higher RT, suggesting a chunk boundary (cf. Sternberg 1969). The authors used 0.5 s trains of 10 Hz repetitive TMS to transiently disrupt pre-SMA activity at three different stimulation times: just prior to the first movement, at the chunk point, i.e. the movement with the highest RT within the sequence, and finally at nonchunk points, i.e. a low RT movement in the middle of a pre-organized chunk. Repetitive TMS over pre-SMA disrupted performance, i.e. caused significantly longer RTs, when it was applied at the initiation of a new sequence chunk but not during the course of an ongoing chunk. This effect was specific to pre-SMA since no disruptive effect of TMS was seen when it was applied over PMd. One elegant feature of this study was the clear separation between the

cognitive and motor components of the task. The motor execution for a key press that marked a chunk point was similar to that for one that did not. However, the movements clearly differed with regard to the cognitive organization of the sequence as a whole. Within the serial model of action (cf. Figure 30.1), the chunk point was more strongly associated than nonchunk points with a number of cognitive processes. These included stopping the previous chunk, retrieval of the next chunk from motor memory, and preparation of the motor programs required for the next chunk.

In a study by Müri *et al.* (1996) subjects were asked to fixate a central point on-screen. Two seconds later, a target appeared laterally for 50 ms with unpredictable position and randomized amplitude. A go-signal indicated to perform a saccade to the remembered position of the flash. After 2 s the target reappeared and subjects made a corrective saccade, if necessary. A single TMS pulse was delivered over the right PPC or the dorsolateral prefrontal cortex (DLPFC) randomly at different time intervals in relation to the target's appearance: between 160 and 360 ms after target presentation; during the encoding phase, i.e. between 700 and 1500 ms; and finally at 2100 ms, i.e. 100 ms after the fixation point disappeared. TMS showed both temporal and topographic specific effects. Stimulation over PPC and not over DLPFC significantly affected contralateral saccade accuracy and bilateral saccade latency. This effect was present when TMS was delivered 260 ms after target presentation indicating that PPC is functionally relevant especially during early phases of encoding and sensorimotor integration processes (cf. Goldberg *et al.* 1990). Additionally, the latency of saccades increased when TMS over PPC was delivered 2100 ms after target presentation. This later effect was attributed to a second function of PPC in triggering saccade execution. In contrast, stimulation over DLPFC selectively affected contralateral saccade accuracy, but only when the pulse was applied during later periods of encoding, i.e. between 700 and 1500 ms after target presentation. This study therefore is evidence that the prefrontal cortex plays a crucial role in the preparation of memory-guided movements. Moreover, it does so later than the PPC. Whereas the PPC seems

to be more relevant in early sensorimotor integration processes, the DLPFC seems to control memory processes relevant to the subsequent action. Taken together these studies indicate that the DLPFC seems to control memory retrieval, whereas composing the retrieved items in memory into an appropriate composite action sequence might be a main function of the SMA.

TMS studies of intentional action: concluding remarks and future prospects

TMS can be used to clarify the relationship between cognition and action in the human brain. TMS works well for testing serial models of cognitive processing because it can selectively and temporarily disrupt identified brain functions. In this way one can prove whether a certain brain area carries out the cognitive operation that is essential for a certain task at a given time point. Here, we have approached voluntary, goal-directed action as a computational problem, involving a sequence of several separate modular processing stages or components. Voluntary action starts with an abstract description of the goal. This abstract task description has then to be translated into a detailed movement pattern. Only when an appropriate movement has been selected from many alternatives can the motor plan be sent to the output areas of the motor cortex for final execution. Feedback from execution allows monitoring and correction of ongoing actions, and may also contribute to chaining successive movements into an overall action sequence. Neuropsychological studies of the cognitive-motor functions of the frontal lobe (for an overview see Stuss and Knight 2002) confirm that inhibition of action is at least as important as generation of action in these brain regions. The nature of inhibitory components within the action control system as a whole is not yet well understood, and remains an important area for future research. TMS has the potential to measure effects of inhibition directly within the cortex using paired-pulse (Chapter 11, this volume) and double-pulse (Haggard and Whitford 2004) techniques. This avoids the key problem of psychological studies of inhibition, namely that inhibition cannot be

easily quantified because it does not produce overt behavior.

TMS studies of perception–action linkage

Not all research on motor cognition is in line with this serial model. A large body of evidence suggests a strong linkage or even communality between sensory, notably visual, and motor representations of action. Direct reactions to environmental stimuli, and reciprocal interactions with the environment, may be better explained by parallel models of cognitive processing. The traditional view of perception and action in terms of two independent processing systems has been challenged by research showing that the properties of a visual stimulus constrain the motor process of generating a response to that stimulus, and vice versa. An area of special interest has been the brain's 'mirror systems', that respond to both self-generated actions and also to observing actions of others. TMS has proved a valuable tool for testing parallel models of perception–action linkage, because it can be used to measure cortical excitability and, thus, the involvement of the motor system in a temporally precise way during action observation. Here we review a series of TMS studies that provide convincing evidence for the tight coupling between perception and action. Taken as a group, these studies suggest that the actions of others are covertly resonated or re-enacted online, with high temporal fidelity. The effects on the observer's motor system revealed by TMS are even somatotopically specific.

Action representation

The view on the motor system that dominated during the last century has been challenged in the last 20 years. The classical view was based on the existence of two complete representations of body movements located in the posterior part of the frontal lobe (Woolsey *et al.* 1952). The first representation was located on the lateral cortical convexity, and included Brodmann's area 4 and part of area 6. This representation was called 'primary motor cortex' or M1. The second representation, smaller and less precise than M1,

was located on the mesial cortical surface, and was named supplementary motor area (SMA; Woolsey *et al.* 1952). A series of anatomic and functional studies have shown, first in nonhuman primates and more recently in humans, that this picture of the motor cortex is too simplistic. First, area 4 is functionally distinct from area 6. Second, area 6 is not homogeneous but is formed by a multiplicity of distinct anatomical areas. Third, these various motor areas are characterized by peculiar afferent and efferent connections and seem to play different functional roles in motor control (see above). The organization of the motor system in the frontal cortex is mirrored in the posterior parietal lobe. Again, several independent areas are involved in different aspects of the sensorimotor transformation processes. Frontal and parietal lobes are reciprocally connected according to the following rule. Each frontal motor area receives its main afferents from one single parietal area, which is also the main target for its efferent projections. In this way, the reciprocally connected motor and parietal areas constitute series of specialized circuits working in parallel. These circuits transform sensory information into a specific action and form the basic elements of the motor system. It is important to note that neural activity associated with action execution has also been observed in many posterior parietal areas and that somatosensory, visual and acoustic stimulations evoke responses in many frontal regions.

Linkage between visual and motor representations of actions: mirror neurons

This neural organization of the motor system could hardly have been represented by a model describing a simple serial flow from sensation to action. Indeed, one of most fascinating discoveries of recent decades is that some premotor neurons, in addition to their motor discharge, respond also to the presentation of purely visual stimuli. This functional property led to substantial change in views of motor system organization. Neurons with this property belong to different parieto-frontal circuits, such as the LIPFEF circuit (Bruce and Golberg 1985), which is essentially involved in the control of eye movements, the VIP–F4 circuit that plays a role

in encoding the peripersonal space and in transforming object locations into appropriate reaching movements, and also the AIPF5 circuit, in which hand and mouth goal-directed actions are represented. The discovery of the AIP-F5 circuit and the functional properties of its neurons stimulated the idea that the motor system is also involved in high-level cognitive functions such as the understanding of others' actions and social communication.

From a motor point of view, neurons in F5 seem to code especially the *goal* of the actions. This evidence comes from electrophysiological studies indicating that neurons fire during object-directed actions such as grasping, holding and manipulating, whereas they do not fire during actions that involve a similar muscular pattern but do not aim at manipulating a certain object (e.g. scratching or grooming). Moreover, some F5 neurons discharge independently from the acting effector: they fire when the monkey grasps an object with its right or left hand or with its mouth.

From a sensory point of view, area F5 contains two different categories of visuo-motor neurons. Neurons of the first category discharge when the monkey observes graspable objects, and they have been called 'canonical neurons' (Rizzolatti and Fadiga 1998). These neurons discharge at the mere presentation of objects whose shape and size are congruent with the type of grip motorically coded by the same neurons: neurons that are active during observation of small objects are also active during precision grip (Murata *et al.* 1997). These functional properties indicate a close link between graspable objects and the respective actions that they afford: whenever a graspable object is perceived, the most suitable grasping action is automatically evoked. Neurons of the second category discharge when the monkey observes hand actions performed by other individuals and have been called 'mirror neurons'. These neurons discharge when the monkey manipulates objects, as well as when it observes another individual making similar goal-directed actions (di Pellegrino *et al.* 1992). In contrast to canonical neurons, mirror neurons do not discharge by the mere visual presentation of objects. An interaction between a biological effector and an object is a necessary condition for mirror

neuron activity. The mirror neuron response is not affected according to whether the actions are executed by a human or by another monkey, nor whether the action occurs near or far from the observing monkey (implying that the size of the observed hand is unimportant). Typically, mirror neurons show congruence between the observed and executed action. That is, the neuron's visual response occurs selectively when viewing the same kind of action which selectively evokes motor responses in the neuron when the monkey performs it. That is, the effective motor action coincides with the action that, when seen, triggers the neurons. The most likely interpretation for visual discharge in mirror neurons is that the observed action automatically evokes an internal motoric representation of the same action. In other words, the properties of mirror neurons seem to suggest that an observed action is covertly re-enacted by the observer's motor system.

The human mirror system as investigated by TMS

In recent years, a series of brain-imaging studies has investigated whether a mirror neuron system is also present in the human brain. Indeed, it has been demonstrated that when an individual observes an action a network of cortical areas is activated, including the ventral premotor cortex, the inferior frontal gyrus, the inferior parietal lobule and the superior temporal cortex (see for review Rizzolatti and Craighero 2004). This network is also involved when an individual executes the action. However, given the limited temporal resolution of brain-imaging studies, it is still unclear whether the internal replication of an observed action reflects an *on-line* or *off-line* process. TMS can provide an alternative technique to tackle this question. Single- or paired-pulse TMS allows measurement of cortical excitability during different phases of an observed action. Moreover, this technique is able to verify a specific involvement of the motor system by discriminating those muscles that are involved in the motor replica. The first attempt to study corticospinal (CS) excitability during action observation was made by Fadiga *et al.* (1995). Single-pulse TMS was applied over the hand motor representation in

M1 and MEPs were recorded from four intrinsic hand muscles. Participants were tested under four experimental conditions: observation of an experimenter grasping different objects; observation of an experimenter drawing geometric shapes in the air; observation of different objects; a dimming detection task. The study showed three main results. First, CS excitability is modulated by action observation, indicating that the human motor system is concretely involved during the perception of others' action. Second, modulation of CS excitability is present also during observation of intransitive actions (arm movements). This finding may reflect a main difference between the human mirror neuron system and that of monkeys. In the latter, mirror neurons only respond during the observation of transitive actions (see above). Third, motor excitability is limited only to those muscles that are specifically involved in the observed action. In fact, MEPs recorded from the opponens pollicis (OP) muscle were modulated only during observation of grasping movements and not during arm movements, whereas MEPs recorded from the other three muscles [extensor digitorum communis (EDG), flexor digitorum superficialis (FDS), and FDI] were modulated during both action observation conditions. The latter finding might be due to the fact that during the actual execution of arm movements, the OP muscle is not contracted.

Recently, Montagna *et al.* (2005) elegantly showed that, during the observation of action, those specific muscles are activated in the observer which he/she would also recruit for overtly executing the observed movement. MEPs were recorded from three forearm muscles [FDI, flexor carpi radialis (FCR), and FDS] while subjects were watching a human hand performing a reaching and grasping movement on a screen. The excitability time-course during the observed action was explored at four different phases of the movement: at mid-hand opening; at the end of hand opening; at the mid-hand closing on the object; and when fingers contacted the object. In a separate block of experimental trials, subjects overtly imitated the reaching and grasping movement in synchrony with the observed action, in order to show the temporal pattern of activation of the same muscles that had been investigated during

action viewing. In this condition, EMG signals were selectively recorded from the same forearm muscles recorded during the observation condition. The results showed a remarkable correlation between the temporal pattern of EMG recruitment in the imitation condition and the time course of MEP modulation in the observation condition. In other words, each subject's MEP facilitation resembled the idiosyncratic EMG patterns that they produced when asked to make overt imitative movements. This indicates that during the observation of a specific action, the same muscles are activated as the observer would use in their own execution of that action. Most importantly, the modulation followed the same temporal order as when they would have been recruited for overtly executing the observed movement. This suggests that 'motor resonance' really means that an observed action is re-enacted in terms of the observer's own motor control strategy adapted to the same task.

Several TMS studies have been carried out which aimed at investigating the nature of the 'human mirror system'. One major aim was to explore whether muscle facilitation has a cortical origin or not. A series of experiments (Strafella and Paus 2000; Baldissera *et al.* 2001; Patuzzo *et al.* 2003) have demonstrated that the facilitation of MEPs induced by action observation is due to the enhancement of M1 excitability produced through excitatory cortico-cortical connections. The double-stimulus TMS technique has mainly been used to determine the origin of CS facilitation. This technique consists of a subthreshold conditioning TMS pulse followed by a suprathreshold TMS test pulse at various delays. By considering different delays between the two pulses it is possible to investigate changes in the excitability of excitatory or inhibitory interneurons within M1 itself. In fact, intracortical inhibition is usually observed for short (1–5 ms) or long (50–200 ms) intervals between conditioning and test TMS pulses, whereas intracortical facilitation is usually observed for 8–20 ms intervals. Strafella and Paus (2000) used this technique and stimulated left M1 during action observation. Results showed a decreased intracortical inhibition at the 3 ms interstimulus interval, indicating that CS facilitation is attributable to cortico-cortical facilitating connections.

Another field of investigation was devoted to understand whether the specific activation of the observer's muscles is temporally coupled to the dynamics of the observed action. Gangitano *et al.* (2001) used TMS to stimulate the left hemisphere and evoke MEPs in the contralateral FDI muscle, while subjects were watching a video clip of a hand approaching and grasping a ball. TMS pulse was delivered at five different times, covering all different movement phases. Results showed that response facilitation was differently tuned depending on the different phases of the grasping action. MEP amplitude became larger with increasing finger aperture and became smaller during the closure phase, indicating that the mirror system compares the observed action with the internal correspondent also in terms of a temporal coding. In a more recent study Gangitano *et al.* (2004) investigated whether this pattern of modulation was the consequence of a 'resonant plan' evoked at the beginning of the observation phase or whether the plan was fractioned in different phases sequentially recruited during the course of the ongoing action. The authors therefore used the same procedure as in Gangitano *et al.* (2001) with the following exception: subjects were shown video clips representing an unnatural movement, in which the temporal coupling between reaching and grasping components was disrupted, either by changing the time of appearance of maximal finger aperture, or by substituting it with an unpredictable closure. In the first case, the observation of the uncommon movements did not exert any modulation in motor excitability. In the second case, the modulation was limited to the first time-point. Modulation of motor excitability was clearly suppressed by the appearance of the sudden finger closure and was not substituted by any other pattern of modulation. This finding suggests that a motor plan, which includes the temporal features of the natural movement, is activated immediately after the observed movement onset and is discarded when these features cease to match the visual properties of the observed movement. Thus, the human mirror system seems to be able to infer the goal and the probability of an action during the development of its ongoing features.

In a very accurate and precise experiment Borroni *et al.* (2005) aimed at verifying the degree of correspondence, especially with respect to a fine temporal resolution, between the observation of prolonged movements and its modulatory effects in the observer. For this purpose the authors asked subjects to watch a cyclic flexion–extension movement of the wrist. The same sinusoidal function was used to fit both observed wrist oscillation and motor resonance effects on the observer's wrist motor circuits. In this way the authors could describe a continuous time course of the two events and precisely determine their phase relation. MEPs were elicited in the right forearm muscle (FCR) of subjects who were observing a 1 Hz cyclic oscillation of the right prone hand executed by another person. The results indicated that movement observation elicited a parallel cyclic excitability modulation of the observer's MEP responses following the same period as the observed movement. Interestingly, the MEP modulation preceded the muscle activation of the observed movement, indicating that the mirror system anticipates the movement trajectory, rather than simply reacting to visual events in the movement. The same results were obtained when the observed hand oscillation was executed with different frequency (1.6 Hz) and when the hands of the actor and observer were supine. In a control condition subjects were confronted with an oscillatory movement of the metal platform itself, without the actor's hand resting on it. The platform was oscillated by a human actor hidden behind a screen, so that the movement profile was identical to the flexion–extension movement of the visible actor's hand. However, this condition did not evoke any resonant response in the observer. These findings suggest that during observation, motor pathways are modulated so that the motor command which is needed to execute the observed movement is reproduced with high temporal fidelity. Romani *et al.* (2005) demonstrated that motor excitability can be modulated also by the observation of biomechanically impossible movements. Participants observed sequences of abduction/adduction movements of a right index finger, a right little finger, and of extension/flexion movements of a right

index finger. Based on the angular displacements of the fingers, movements were defined as biomechanically possible or impossible. The results showed a selective motor facilitation of the muscle that would be involved in actual execution of the observed movement for possible movements and, most interestingly, also for movements well beyond the normal range of joint mobility. This finding seems to suggest that the human mirror system does not differentiate biologically possible and impossible movements. It rather seems that even impossible movements are coded in the frontal mirror system, suggesting that observation-related motor facilitation is not due to coding muscles *per se* but to coding the role a specific muscle plays in a given overall action. The fact that the action is achieved by impossible means does not concern the mirror system.

TMS study of frames of reference for mirror systems

A different field of research on this topic addresses the question of whether postural congruency between the observer and the model modulates CS facilitation. For instance, Maeda *et al.* (2002) investigated the role of visual perspective on movement observation-induced motor excitability. Subjects viewed a model's right hand abducting either the thumb or index finger, or vertically moving the index finger. Critically, subjects saw the model's hand either from a first-person or a third-person perspective. The results first of all confirmed that action observation enhances motor output to the muscles involved in the observed movement regardless of its orientation. However, the degree of modulation depended on the hand orientation. Greater modulation of motor excitability was observed for movements in first-person than in third-person perspective. In contrast to this study, Urgesi *et al.* (2006) recently obtained different results by slightly modifying the same paradigm. They recorded MEPs from the FDI and abductor digiti minimi muscles during observation of right index and little finger abduction/adduction movements of models keeping their hands in a palm-down or palm-up position. In different conditions also observers

were asked to keep their right-hand palm down or up so that the observer's posture was congruent or not congruent to the observer's posture. The authors found that mirror motor activation is more influenced by the topographic matching of the model's movement on the observer's motor system than by the spatial and postural congruency between the model and observer's hand. The authors attributed the discrepancy to the fact that in Maeda *et al.*'s (2002) paper the inversion of the hand orientation not only changed the side of space where the finger movements were directed, but also the perspective from which the hand stimuli were viewed. In a similar vein, Patuzzo *et al.* (2003) investigated whether the observation of one's own or another's action influences CS excitability differently. The authors confronted subjects with videos of their own or another's hand performing the same movements. No significant differences between the self and other condition were found. It is interesting to note that high-functioning individuals with autism spectrum disorder, when tested with a paradigm very similar to that used by Maeda *et al.* (2002), lack muscle-specific facilitation only during observation of moving hands presented from a first-person perspective (Theoret *et al.* 2005).

Action representation beyond the visual modality

Finally, several studies investigated motor excitability to TMS during acoustic, rather than visual action perception. In fact, action-generated sounds and noises are also very common in our daily environment. Monkey studies show that a proportion of mirror neurons indeed not only respond to visual stimuli, but also become active when the monkey is listening to an action-related sound (Kohler 2002). Aziz-Zadeh *et al.* (2004) used TMS to explore whether an equivalent effect is present also in humans. The authors stimulated the left and right hemisphere and recorded MEPs from the contralateral FDI muscle while subjects were listening to bimanual hand action sounds (e.g. typing or tearing a paper), or to control sounds (e.g. walking, thunder). The results showed that sounds associated with hand actions produced greater CS

excitability than the control sounds. Moreover, this facilitation was exclusively lateralized to the left hemisphere. Fadiga *et al.* (2002) investigated whether speech listening is also able to increase MEPs recorded from the listeners' tongue muscles. Subjects were instructed to listen carefully to a sequence of acoustically presented verbal and nonverbal stimuli, while their left motor cortex was magnetically stimulated in correspondence with tongue movement representations. The embedded consonants in the middle of the verbal stimuli determined whether the pronunciation required either slight tongue tip movement (e.g. double 'f') or strong tip movement (e.g. double 'r'). The results showed that listening to words containing, for instance, a double 'r' consonant led to an increase of tongue MEPs relative to all the other experimental stimuli. This finding seems to suggest that listening to speech leads to specific activation of speech-related motor areas in the listener.

Summary and conclusion

To conclude, TMS has been a key methodological tool for studying motor cognition. In studies of the serial processes of action generation, TMS has been used to identify and describe the individual processes that extend along the motor processing chain from motivation and volition to muscle contraction. Here, TMS has been used both as an excitability measure, and also as a transient inactivation. In studies of the parallel loops linking perception to action, TMS has been used primarily, though not exclusively, as a probe to measure excitability. In the future, double-pulse approaches may offer the interesting possibility of disrupting one arm of such loops in order to modulate effects of TMS, including excitability effects, elsewhere in the loop. In both cases, the high temporal resolution of TMS has been important in giving precise information about the time course of neural information underlying action. Finally, TMS offers a conceptual as well as a methodological advance. Scientific knowledge of action systems has lagged behind knowledge of perceptual systems because it is easy to deliver a controlled input to perceptual systems, but harder to deliver a controlled input to the action system. TMS has allowed neuroscientists to activate or inactivate

the brain's action systems artificially. This has provided key insights into normal motor function.

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