

# Chapter 2

## Interactions Between Premotor and Motor Cortices in Non-Human Primates

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**Abstract** This review is concerned with a detailed examination of the neurophysiological mechanisms that allow fast interactions between two key components of the ‘visuomotor grasping network’ in the primate brain: ventral premotor cortex (PMv) and primary motor cortex (M1). It first reviews the anatomical linkages between them and then surveys a number of studies which have together shown that PMv can modulate activity of grasp-related activity in M1 in a grasp-specific fashion, and in particular can either facilitate or suppress M1 outputs controlling intrinsic hand muscles. The mechanisms subserving the interactions between PMv and M1, which are reciprocal, could allow for fast selection of M1 outputs that would be appropriate for the grasp of visible objects.

### 2.1 Introduction

In 1995 an important review paper by Marc Jeannerod<sup>1</sup> et al. (1995) first suggested the concept of a ‘visuomotor grasping circuit’. Grasp of objects is of course fundamental to our daily interaction with the environment, and the visual guidance

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<sup>1</sup> Marc Jeannerod RIP 2011.

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of skilled prehension and manipulation of objects is characteristic of the human motor system and its engagement in creative activities such as art, sculpture and music making as well as in technological development, tool use and manufacture. The highly-cited review by Jeannerod and his colleagues (549 citations in mid-2011) opened up a new approach to the study of cortical processing, no longer based on the properties of particular cortical areas, but focused on the transmission of information between areas: They suggested that “the transformation of an object’s intrinsic properties into specific grips takes place in a circuit that is formed by the inferior parietal lobule and the inferior premotor area (area F5). Neurons in both these areas code size, shape and orientation of objects, and specific types of grip that are necessary to grasp them.”

Interestingly research in the years since has especially highlighted the position of area F5, the rostral subdivision of the ventral premotor cortex (PMv), as a node within this circuit. Work led particularly by Giacomo Rizzolatti and the Parma group revealed why this area should be the focus of so much interest (Rizzolatti and Luppino 2001; Davare et al. 2011). First, the existence of visuomotor “canonical neurons” that discharge during selection, preparation and execution of the particular types of grasping action, and which appear to be activated by visual information about graspable objects represented in the posterior parietal cortex (area AIP). Second, the presence of connections with prefrontal cortex, which opened up possible pathways transmitting information about how the grasp should reflect the manner in which the object was to be used (the object’s ‘affordance’). Third, the existence of mirror neurons, activated not only during self-executed grasp but also during action observation of grasp. Finally, the demonstration that reversible inactivation of area F5 induces a deficit whereby the monkey shows no obvious paresis but can no longer preshape the hand appropriately for grasp of a particular object.

Pandya and Kuypers (1969) had first analysed the likely routes through which visual information could be accessed by the motor cortex. They showed that primary motor cortex (M1) did not receive any inputs from the visual associative areas in the posterior parietal cortex, but that these inputs terminated further forward in a number of premotor areas, including the ventral (PMv) and dorsal (PMd) premotor areas and the SMA. This early paper suggested that projections from these areas back into M1 might then allow vision to guide the selection and execution of fine hand movements. This was confirmed by elegant lesions studies (Haaxma and Kuypers 1974; Halsband and Passingham 1982).

Although there is evidenced that all of the major premotor areas interact with M1 during preparation and execution of movement, this review will very much focus on the interactions between PMv and M1 in the non-human primate, as a model of these wider network activities. Again, although we will focus mainly on cortico-cortical interactions, this is not to forget the importance of subcortical (pallidal and particularly cerebellar) interactions. For example, both AIP and PMv are the source of inputs to the pontine nuclei (Glickstein et al. 1985) and the cortico-cerebellar loop is also critical to visuomotor control (Stein and Glickstein 1992).

## 2.2 How Does PMv Influence the Motor Apparatus of the Hand? Descending Projections to the Brainstem and Spinal Cord

Whilst PMv has a low-threshold motor representation of the hand and digits (e.g. Godschalk et al. 1995), it does not give rise to many corticospinal projections (only 4 % of the total frontal lobe corticospinal projection (Dum and Strick 1991) and these terminate mostly in the upper cervical segments of the spinal cord (He et al. 1993). This established view has recently been re-examined by Borra et al. (2010) which investigated in detail both brainstem and spinal targets of specific regions of PMv.

Borra et al. (2010) confirmed by double injection that the subdivision of F5 (area F5p) that projects to the hand area of M1 (see Sect. 2.3 below), also projects to cervical spinal cord. The cytoarchitectonic division F5p (posterior) is located in the dorsal and posterior part of the inferior bank of the arcuate sulcus (Belmalij et al. 2009). Injection of anterograde tracers in this subdivision revealed descending projections to brainstem structures that are themselves origins of descending pathways to the spinal cord (including the superior colliculus, reticular formation and peri-aqueductal grey), and to structures involved in cerebellar motor circuits, including the red nucleus and pontine nuclei. Although Borra et al. (2010) found some sparse projections from area F5p to the lower cervical cord (segments C6-T1, which contain the motor nuclei controlling the muscles acting on the hand and digits; Jenny and Inukai 1983), the corticospinal projections seem to be mainly focused on the upper cervical segments (cf. He et al. 1993). There were no projections beyond T6. It is puzzling that despite the very high incidence of neurons in F5 with activity related to the ipsilateral hand, there are few projections to the ipsilateral grey matter.

It has been hypothesised that the F5 output maybe particularly concerned with projections to the C3-C4 propriospinal system, which originate from the spinal intermediate zone in these segments. This system was originally proposed to support accurate reaching in the cat, but is thought to be more important for grasping in the primate (Isa et al. 2007). It is also thought to mediate the recovery of grasp after spinal lesions at the mid-cervical (C5) level which interrupt the corticospinal input to the lower cervical segments, including the direct corticomotoneuronal (CM) component. Importantly, such lesions result in an immediate and severe impairment of precision grip (Sasaki et al. 2004); the process of recovery may well involve a number of different brainstem and propriospinal mechanisms (Zaaimi et al. 2012; Alstermark et al. 2011).

Despite the interesting possibilities raised by the distinctive pattern of F5 corticospinal projections, the overall conclusion must be that (a) this represents a comparatively minor component of the total frontal lobe corticospinal output and that (b) connections to the lower cervical cord are relatively weak, and do not include CM projections (Lemon 2008). Although Borra et al. (2010) concluded that the “F5 hand field can control hand muscle motoneurons through C3-C4

propriospinal neurons”, it is clear that with stimulation of F5 with single pulses and intensities that do not result in concomitant activation of M1 (see [Sect. 2.5.3](#) below), responses in hand muscle motoneurons are rarely observed (Shimazu et al. 2004; Prabhu et al. 2009). When multiple pulses and higher intensities are used to evoke motor responses from F5, these responses are lost when M1 is acutely and reversibly inactivated (Shimazu et al. 2004; Schmidlin et al. 2008). Importantly Schmidlin et al. (2008) showed that this effect was not due to any loss of tonic facilitatory output from M1 that might be needed to reveal a F5-C3-C4 proprio-spinal linkage (see their Fig. 2.6).

Recent physiological studies comparing antidromic activation of pyramidal tract neurons (PTNs) in F5 and M1 (Kraskov et al. 2009; Vigneswaran et al. 2011) have shown that F5 does not contain many PTNs with very short antidromic latencies that are commonly found in M1, and which presumably have fast-conducting axons and large somata (Sakai and Woody 1988). So the F5 corticospinal output (like that of other secondary motor areas; Maier et al. 2002) is rather different to that from M1.

### **2.3 How Does PMv Influence the Motor Apparatus of the Hand? Anatomy of PMv-M1 Connections**

The cortico-cortical network highlighted by Jeannerod et al. (1995) represents an important route through which PMv can access the many corticofugal outputs from M1 to the brainstem and spinal cord that are concerned with hand control. These include the CM component of the corticospinal output, but it is important to stress that this system operates in parallel with other descending systems that target hand motoneurons indirectly (see Lemon 2008).

Gerbella et al. (2011) have recently discussed the different pattern of cortico-cortical connections established by the three sub-divisions of area F5. Of these, the subdivision of most relevance to this review is the posterior region (area F5p), which is a hand-related field in which ‘canonical’ visuomotor neurons responsive to observation and grasp of 3D objects are particularly prominent (Raos et al. 2006; Umiltà et al. 2007). F5p has strong reciprocal connections to AIP in the posterior parietal cortex (Pandya and Kuypers 1969; Gharbawie et al. 2011). Sub-division F5p also provides the main connections with the M1 hand area (Muakkassa and Strick 1979; Godschalk et al. 1984), which are also reciprocal. Unlike the more anterior region of F5 (F5a), it has only weak connections to prefrontal areas. In terms of functional analysis, it is important to stress that all three subdivisions (including F5c in which mirror neurons are primarily located) are densely interconnected (Gerbella et al. 2011).

The PMv is also strongly interconnected with homotopical areas in the contralateral hemisphere (Dancause et al. 2007; Boussaoud et al. 2005; Rouiller et al. 1994), which contrasts with the sparser callosal interconnections found for the M1 hand area (Rouiller et al. 1994).

## 2.4 Neurophysiology of Premotor-Motor Connections

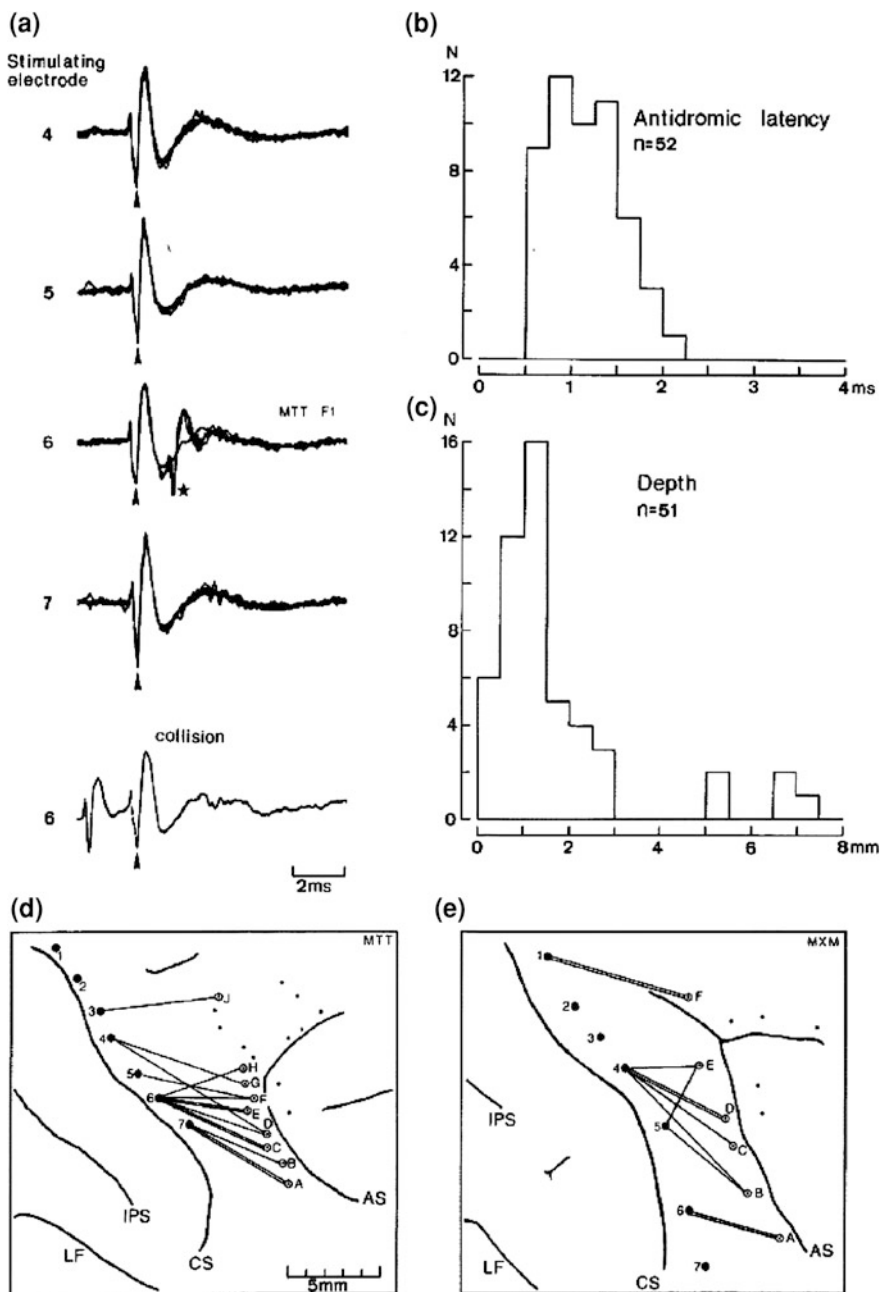
### 2.4.1 *Antidromic Responses in Cortico-Cortical Neurons*

The early anatomical descriptions of the PMv-M1 projections encouraged Godschalk et al. (1984) to investigate their physiological characteristics. In anaesthetised macaque monkeys they placed a row of seven stimulating electrodes positioned a few mm rostral to the central sulcus and spanning the arm/hand/face representations in M1 (Fig. 2.1d, e). They then recorded from the PMv ('post-arcuate region') searching for neurons with latency-invariant antidromic responses (Fig. 2.1a). These cortico-cortical neurons were found mostly at rather superficial locations (0.3–1.5 mm deep to the cortical surface; Fig. 2.1c) suggesting that they were in layers II or III (which are one important source of cortico-cortical projections; Jones and Wise 1977; Douglas and Martin 2004), rather than in lamina V. Each M1 stimulation site was separated by around 2 mm; even with a maximum stimulation intensity of 500  $\mu$ A, most of the PMv neurons could be activated only from a single site, which suggests a rather specific set of projections. These projections generally ran in a postero-medial direction (Fig. 2.1d, e). Antidromic latencies ranged from 0.6 to 2.1 ms (mean 1.2 ms; Fig. 2.1b); since the distances between sites in PMv yielding antidromic responses to stimulation sites in M1 were around 8–10 mm, this would put an upper limit on the conduction velocity of cortico-cortical axons of around 17 m/s, with most <10 m/s.

### 2.4.2 *Signs of Synaptic Interactions Between PMv and M1 at the Single Neuron Level*

Many years after the publication of Godschalk et al. (1984), we developed a means of simultaneous recording of multiple neurons from both PMv and M1 hand regions in the awake, behaving monkey (Umiltà et al. 2007). This approach was used to allow us examine the time course of activity in these two interconnected areas during performance of visually-guided reach-to-grasp task, in which monkeys were first shown a pseudo-randomly ordered set of graspable objects (examples in Fig. 2.2a), and then cued to grasp and displace them by a controlled amount. This study showed that both F5 and M1 neurons showed patterns of activity that were specific to the grasp needed for a particular object. However at the population level, the onset of this grasp-specific activity was clearly earlier in F5 than in M1, in keeping with the original hypothesis advanced by Jeannerod et al. (1995). The result is probably explained by the projection from regions of the posterior parietal cortex (and especially area AIP) to F5 (but not to M1) of information related to the visual properties of graspable objects.

An obvious question is whether the visuomotor neurons that are activated at short-latency by the presence of graspable objects can be shown to be connected to



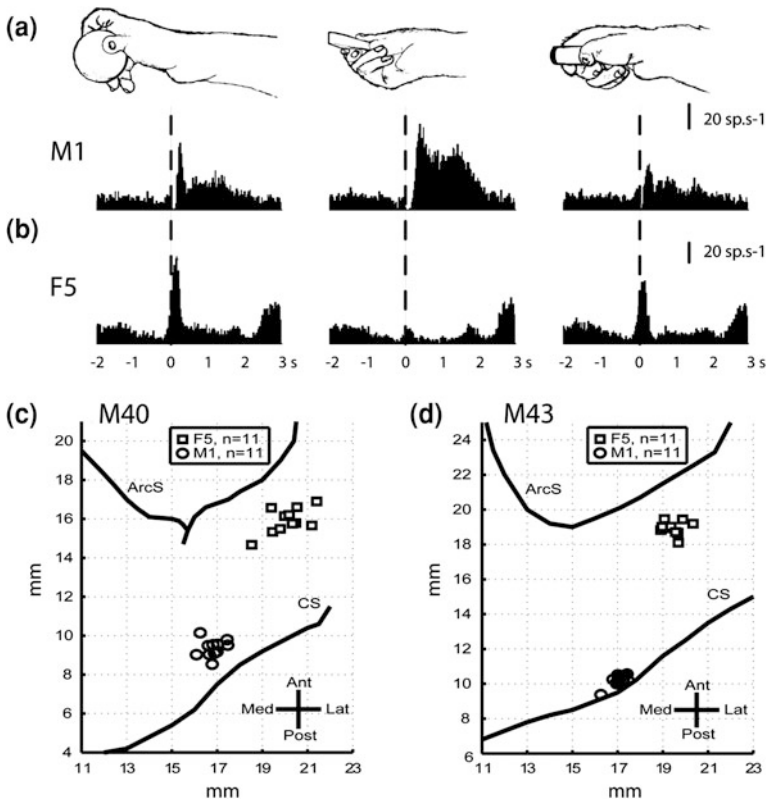
M1 neurons involved in the grasping action. We have used cross-correlation methods (see Baker et al. 2001) to examine this possibility, but analysis of many pairs of simultaneously recorded F5 and M1 neurons did not yield any signs of

◀ **Fig. 2.1** Identifying cortico-cortical projections from PMv to M1. Topographic distribution of projections from PMv to M1, as identified by antidromic identification of cortico-cortical neurons in PMv responding to electrical stimulation of the M1 hand area. **a** Recording from single PMv neuron (located in penetration F in **d**) activated antidromically by single-pulse intracortical stimulation within M1 (electrode 6). Antidromic spike indicated by *asterisk*. Four sweeps at a current strength (150  $\mu$ A) threshold for this response have been superimposed, together with one sweep at sub-threshold (no antidromic spike). The antidromic nature of the response is confirmed by collision with a spontaneous spike (*bottom trace* in **a**). Stimulation at adjacent sites (4, 5 and 7) did not activate the neuron. **b** Distribution of antidromic latencies of PMv neurons responding to M1 stimulation. Most responded within 0.5–2.0 ms. **c** Depth distribution of antidromically activated PMv neurons; most were recorded superficially (<1.5 mm from cortical surface). **d, e** Location of penetrations made in periarculate cortex in two monkeys. Those that contained neurons antidromically activated from M1 are indicated by  $\Theta$  and joined by a *solid line* to the site in M1 from which the response was obtained. *Dots* indicate penetrations in which no antidromic responses were obtained. Note consistent direction of projections. No neuron was antidromically activated from more than one M1 site. CS central sulcus, AS arcuate sulcus, IPS intraparietal sulcus, LF lateral fissure (Gosdchalk et al. 1984, Fig. 2.4, with permission)

correlation peaks indicative of synaptic connectivity (T. Brochier, personal communication). There are two possible reasons for this negative result: first, it is likely that both samples were heavily biased towards large pyramidal neurons in lamina V, whereas many of the neurons giving rise to cortico-cortical projections are in the upper laminae (see above), and second, there is accumulating evidence that the premotor-motor cortex connections are relatively indirect (see below), and may be too weak to show positive features in cross-correlograms of spike trains.

### 2.4.3 Responses of Single M1 Neurons to Stimulation of Area F5

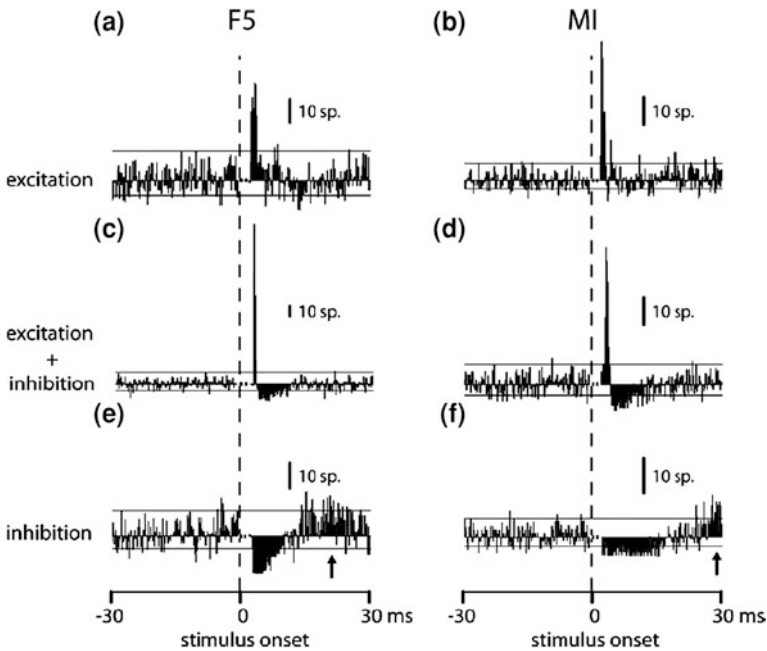
An alternative approach was to stimulate in one area, while recording from single neurons in the other; by activating many cortico-cortical projections, some of which might converge at the single neuron level, it was anticipated that signs of F5-M1 synaptic connections might be easier to detect. Therefore, we adapted the technique used by Umiltà et al. (2007) to allow us to look for responses in M1 to single-pulse intracortical stimulation within the F5 subdivision of the PMv, and vice versa (Kraskov et al. 2011). In this study all the sites (recording and stimulation) were first characterised as having neurons with clear grasp-related activity (Fig. 2.2a, b); their locations are shown in Fig. 2.2c, d. These recordings were biased towards location in deeper laminae and used much weaker stimuli (maximum 40  $\mu$ A), so it was unsurprising that we did not encounter any antidromic responses. On the other hand, synaptic responses were quite common: for M1 neurons, around 34 % showed responses to F5 stimulation, with an identical proportion of F5 neurons (34 %) responding to M1 stimuli.



**Fig. 2.2** Grasp-related activity and location of paired stimulation and recording sites in M1 and F5. **a** Hand postures used for grasping of three different objects. **b** Typical grasp-related activity of a single neuron recorded in M1 (*top*) and another in F5 (*bottom*) hand areas. Histograms of spike activity are referenced to the moment at which the monkey released a homepad to reach out, grasp and displace the object (time zero, *vertical dashed line*). **c, d** Chamber maps from two monkeys (M42, M43) based on MRI and direct stereotactic measurements of the arcuate (ArcS) and central (CS) sulci at surgery. Symbols mark surface location of pairs of electrode penetrations made in area F5 (*squares*) and M1 (*circles*) in the two monkeys

The responses observed were dominated by excitatory effects (Fig. 2.3). Pure excitatory peaks (Fig. 2.3a, b) were most commonly observed (53 % of responses). These occurred at short-latency (1.8–3.0 ms) and were of brief duration ( $\sim 1$  ms). Purely inhibitory responses (Fig. 2.3e, f) had slightly longer latencies (2–5 ms) and were of small amplitude and longer duration (5–7 ms). They accounted for only 13 % of responses, whereas mixed excitation then inhibition (Fig. 2.3c, d) was seen in 34 % of responses. Many excitatory responses exhibited double peak responses, with a second excitatory peak following the first by around 6 ms (see Kraskov et al. 2011). These authors also examined the effect of stimulus intensity, by comparing responses in neurons at a low (20  $\mu$ A) and at a higher





**Fig. 2.3** Types of synaptic response in F5 neurons to stimulation of M1 hand area. On the left are shown responses of single F5 neurons to single-pulse ICMS ( $40 \mu\text{A}$ ). Peristimulus time histograms (PSTH) are synchronised to stimulus delivery (dashed vertical line at time zero). The data shown are after correction for any changes in the average instantaneous firing rate over the course of the pre-stimulus period. Confidence limits shown are  $+2$  and  $-1$  SD above and below this value, respectively. The break in the PSTH just after zero reflects the dead-time of the discriminator (time for discriminator to be able to accurately detect spikes after recovery from large stimulus artefact). **a, b** Pure excitatory responses, which had short-latency and were very brief (**a**,  $n = 2138$  stimuli; **b**,  $n = 1939$ ). **c, d** Combined early excitatory plus later and longer lasting inhibitory responses (**c**  $n = 4158$ ; **d**  $n = 1881$ ). **e, f** Pure inhibitory responses: note the rebound in activity at the end of the inhibitory period (arrows) (**e**,  $n = 3355$ ; **d**,  $n = 4246$ ). Note that similar types of response were obtained in M1 neurons to stimulation of F5 (right hand column). From Kraskov et al. 2011 (with permission)

intensity ( $40 \mu\text{A}$ ). They found that inhibitory effects were more pronounced with the stronger shocks.

Careful examination of the responses suggested the following: First, although the excitatory responses were of short-latency (Fig. 2.3a), they showed significant latency jitter to successive shocks, indicating that they were mediated by an oligosynaptic, rather than a monosynaptic pathway (see Fig. 2.5e). One possibility is that intracortical stimuli within F5, for example, activate the axons of cortico-cortical neurons which converge and terminate in a rather specific manner in M1 on local excitatory interneurons, which in turn synapse on pyramidal neurons. This is based on the fact that responses were found for only about a third of the paired sites tested, and that a given neuron showed rather different effects (e.g. single or double excitatory peak, or inhibition or no response) when tested from different sites.

Second, M1 pyramidal cells can also be inhibited by cortico-cortical inputs, through the action of local excitatory inputs to inhibitory interneurons (Fig. 2.3e). It is speculated that the convergence of these inhibitory inputs is greater than for excitatory inputs on pyramidal neurons, as this might explain the predominant inhibition at higher stimulus strengths. Interestingly, an earlier report by Tokuno and Nambu (2000), who used relatively strong stimuli (100–150  $\mu$ A), found that responses of PTNs in M1 to PMv stimulation were dominated by long-lasting (90 ms) inhibition; 23 of 27 PTNs showed pure inhibitory responses, 11 showed excitation–inhibition, and none showed pure excitation. This is clearly a very different set of results to the predominantly facilitatory effects reported by Kraskov et al. (2011). Similarly, the strong currents induced by TMS in humans might explain why in general inhibitory effects have dominated reports using TMS [but see Davare et al. (2008) for an important exception].

## 2.5 Effects of Stimulating PMv on Corticospinal Outputs from M1

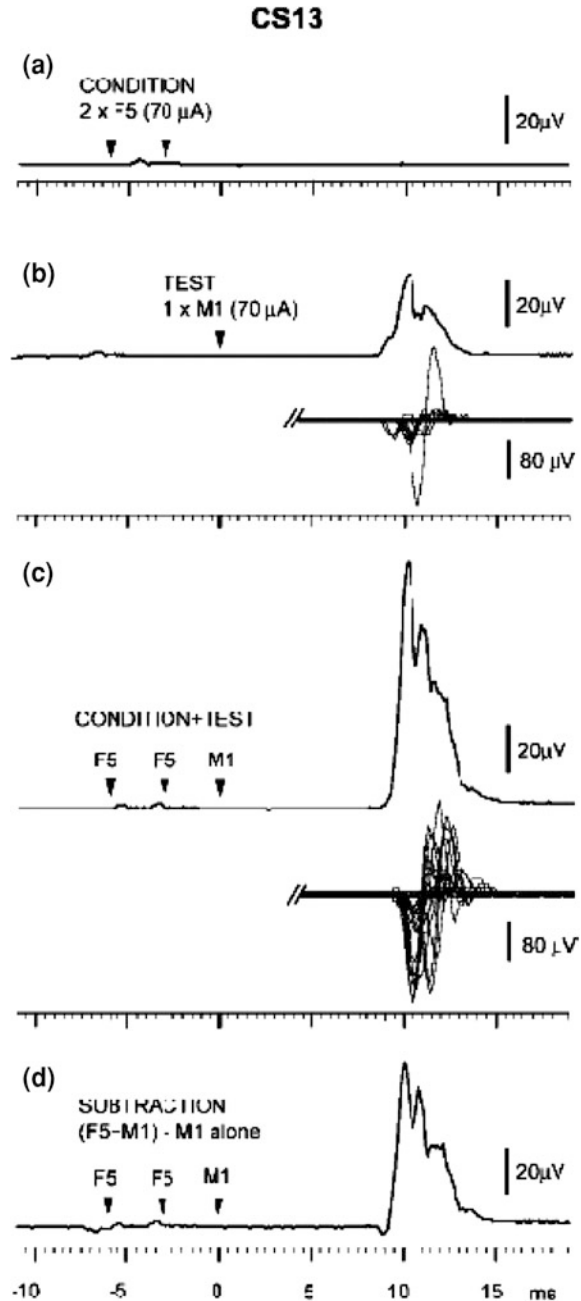
### 2.5.1 EMG Responses to Cortical Stimulation in Sedated Monkeys

A complementary approach was introduced to demonstrate that PMv–M1 interactions directly influence the corticospinal output from M1 (Cerri et al. 2003). Here the idea was to use a single intracortical stimulus to generate descending activity from M1 that discharged motoneurons supplying the hand muscles, as detected by a short-latency EMG response (similar to the MEP in human TMS studies). One could then examine the effects on the EMG response of conditioning stimuli delivered to PMv. Cerri et al. (2003) found that single or double stimuli delivered to F5, which given alone produced no EMG response, could produce robust facilitation of EMG responses evoked from the M1 hand area (Fig. 2.4). The monkeys used in this study were chronically implanted with small arrays of intracortical microwires, located in F5 and M1 regions that yielded digit movements in response to repetitive intracortical stimulation (rICMS); the most effective F5 electrodes were located in the region we now recognise as F5p.

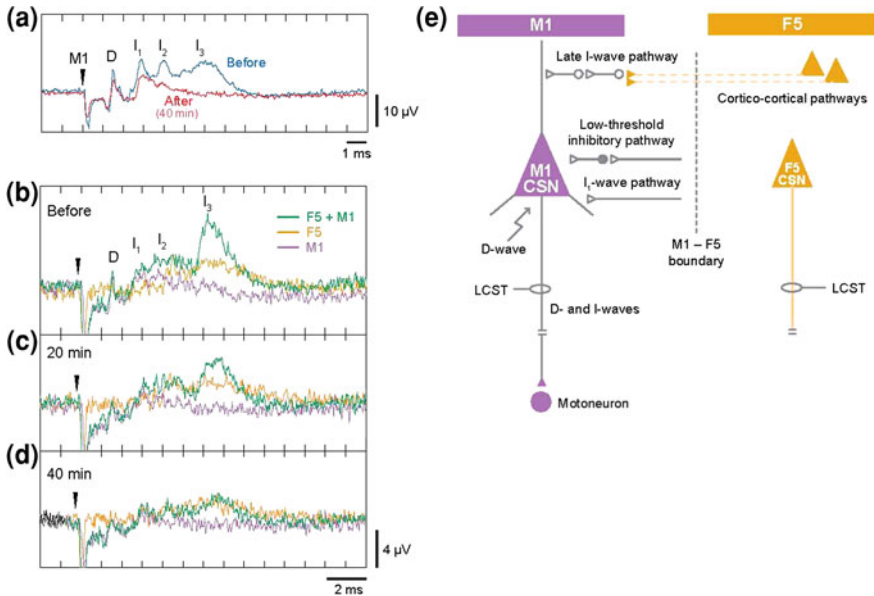
The significance of these findings was the demonstration of a fast and effective route through which F5 could modulate the M1 output controlling hand muscles, which is of obvious potential importance for visuomotor coordination.

Condition-test experiments were carried out using pairs of intracortical microwires, one as cathode and the other as anode. Separate controls established that the direct effects of the stimuli used did not spread much more than 1–2 mm from the stimulation site i.e. there was no direct spread of current from F5 to M1. The studies were carried out with monkeys lightly sedated with ketamine/medetomidine HCl, such that there was still some background tone in the hand muscles.

**Fig. 2.4** Facilitation of responses evoked from M1 by conditioning stimulation of area F5. Typical set of results from a monkey under light ketamine sedation. Averages of rectified electromyographic (EMG; 50 sweeps) recorded from thenar muscles contralateral to stimulated cortex. **a** Double F5 conditioning shocks ( $2 \times 70 \mu\text{A}$ , 3 ms separation) did not evoke an EMG response. **b** Single test shocks applied to M1 ( $1 \times 70 \mu\text{A}$ ) yielded a clear short-latency EMG effect with an onset latency of about 8 ms; 23 superimposed sweeps are shown below the average at the same time scale to indicate variation in amplitude and latency of the test responses. **c** double F5 conditioning shocks delivered before the M1 test shock (condition-test interval: 3 ms) greatly facilitated the response; 23 superimposed unrectified sweeps are shown below the average at the same time scale to indicate variation in amplitude and latency of the conditioned responses. **d** Subtraction (average in **c** minus average in **b**) shows the additional effect of the conditioning shocks. (from Cerri et al. 2003, with permission)



Under these conditions, the facilitation of the EMG responses from F5 was large (Fig. 2.4d): around 4-fold with single F5 pulses, and up to 12-fold with double pulses, given 3 ms apart. These values are considerably larger than obtained



**Fig. 2.5** Facilitation of corticospinal outputs from M1 by ventral premotor cortex (F5) stimulation. **a** Intracortical stimulation with a single pulse in the hand area of M1 evokes a series of descending corticospinal volleys: the D (direct) wave and a number of indirect (I) waves (*blue trace*). Forty minutes after microinjection of the GABAa agonist, muscimol, close to the M1 stimulation site, the late I waves ( $I_2$ ,  $I_3$ ) are mostly abolished (*red trace*); there is a small reduction in the  $I_1$  wave and no obvious effect on the D wave. Averages of 150 sweeps, volleys recorded from the C3 spinal level. **b–d** Effects of muscimol injection in M1 on F5-M1 interaction. A single test (T) M1 shock was conditioned (C) by a single shock to the F5 division of PMv (*green*). Responses to the F5 shock alone are *orange* and to the M1 shock alone are *purple*. With a C–T interval of 0 ms, there was a marked facilitation of the  $I_3$  wave. Twenty minutes after muscimol injection (**c**), this facilitation was considerably reduced, and it was abolished after 40 min (**d**). Averages of 100 sweeps. **e** Possible mechanisms explaining facilitation of late I waves (elements in *grey*). On the left of the diagram, represent the three classes of excitatory inputs to corticospinal neurons (CSNs): the D wave, the  $I_1$  wave, and the later ( $I_2$  and  $I_3$ ) waves. A low-threshold inhibitory input pathway is also shown. These four inputs are all excited by stimulation within M1. The model proposes that the main excitatory input from F5 to M1 converges on the late interneuronal pathways in M1 giving rise to the  $I_2$  and  $I_3$  waves, thereby allowing F5 to influence I wave generation in M1 corticospinal neurons. Note that although these neurons project directly to hand motoneurons, this is probably not the case for those located in F5 (from Lemon 2008, with permission)

during twin-coil TMS studies in humans and show that the interactions between well-focused sites can be very large indeed, possibly because there is less concomitant inhibition (see Sect. 2.4.3).

Examination of the EMG response latency gave some clues as to its origin. We compared it with that evoked by direct stimulation of the pyramidal tract (PT) at the medullary level. The earliest EMG responses to PT stimulation will be those mediated by direct, CM connections (Olivier et al. 2001). We found that the EMG

responses evoked by *test* shocks to M1 (Fig. 2.4b) were typically around 3 ms longer than those from the PT.

What is the explanation? Stimulation of the motor cortex, even with single TMS or electrical shocks, results in high-frequency repetitive discharge of corticospinal neurons, which is highly synchronised into successive waves of descending activity in the corticospinal tract (Fig. 2.5a, e; see Di Lazzero et al. 2008). Intracortical stimuli act by discharging intracortical axons. The direct (D) wave results from direct activation of the axons of corticospinal neurons. Other axons that are excited feed into local interneuronal networks that lie upstream of the corticospinal neurons, and which lead to trans-synaptic excitation of them, generating a number of indirect waves ( $I_1$ ,  $I_2$ ,  $I_3$  etc.; Fig. 2.5e) (Amassian et al. 1987; Ziemann and Rothwell 2000; Di Lazzaro et al. 2008). Each wave of activity is separated from the next by around 1–1.6 ms. Thus Cerri et al. (2003) speculated that the EMG responses to M1 stimulation are due to the accumulating depolarisation in spinal motoneurons, synchronised with the D and I wave inputs. However, the motoneurons are not actually discharged until the EPSPs generated by the  $I_2$  or  $I_3$  waves have arrived at the motoneurons.

As might be expected from this rather complex generation of the EMG response, the latency of the *conditioned* responses showed some considerable variation (Fig. 2.4c). The facilitation, by the conditioning PMv shock, of the different waves of activity generated by the test M1 shock could be expected to produce EMG responses ranging from those with latencies shorter than the test response (due to facilitation of the D or  $I_1$  waves) to those with rather similar latencies (facilitation of the  $I_2$  and  $I_3$  waves): and this is what was found, but with a clear preference for responses reflecting discharge of motoneurons by the  $I_1$  and especially by the  $I_2$  waves (Cerri et al. 2003).

Examination of the EMG responses at different condition-test intervals confirmed the short time course of the PMv-M1 interaction. The first significant effects were observed at a condition-test (C-T) interval of 1 ms, and intervals up to 15 ms continued to show facilitation; at a C-T interval of 30 ms the conditioned response had returned to baseline (Cerri et al. 2003).

### ***2.5.2 Corticospinal and Motoneuron Responses in Anaesthetised Monkeys***

The significance of this short-latency interaction was clarified by a subsequent study, carried out in deeply anaesthetised macaques, in which the interaction between F5 and M1 was assessed by means of direct recording from the corticospinal tract and intracellularly from responding spinal motoneurons (Shimazu et al. 2004). These experiments showed that stimulation of macaque F5, which by itself evoked little or no detectable corticospinal output, could produce a robust modulation of motor outputs from M1. Thus, whereas single stimuli delivered to

M1 electrodes evoked the characteristic pattern of D and I waves (Fig. 2.5b, purple trace; see Sect. 2.5.1), single shocks delivered to F5 were ineffective (see orange trace in Fig. 2.5b) and even double shocks, with a 3 ms separation, evoked small I waves but no D wave, and only with high intensities.

However, when the test (T) M1 shock was conditioned (C) by single or double F5 shocks, there was strong facilitation of  $I_2$  and  $I_3$  waves from M1, but the D wave and  $I_1$  waves remained unaffected (Fig. 2.5b, green trace). The facilitation of the late I waves was again observed with short C-T intervals, as in the EMG study. Although the conduction time from F5 to M1 is short (1–2 ms; Godschalk et al. 1984, Sect. 2.4.1 above), this would still allow ample time for activity generated by a shock to F5 to facilitate interneuronal circuits generating the later  $I_2$  and  $I_3$  waves.

Further evidence that it was these late waves that were important for the motor response was deduced by recording intracellularly from motoneurons innervating hand and forearm muscles. These recordings revealed no postsynaptic effects from single F5 shocks, but in contrast, the same stimuli produced a robust facilitation of EPSPs evoked from M1, whose onset closely followed the arrival of  $I_2$  and  $I_3$  waves at the spinal segment in which the recordings were made. The facilitation was particularly marked in hand muscle motoneurons, of which 92 % showed this facilitatory effect.

The key question posed by Shimazu et al. (2004) was: where was the site of interaction between F5 and M1? Three pieces of evidence were advanced to suggest that the interaction was within M1 itself. The first was that the short-latency of the interaction indicated a site close to F5, the second was that the time course of the interaction, which showed a characteristic waxing and waning of the facilitatory effect that fitted exactly with the timing of I waves originating from M1. The final piece of evidence was that after microinjection of the GABA-agonist muscimol in M1, the F5-induced facilitation of late I waves from M1 was completely abolished (green traces in Fig. 2.5b–d).

### ***2.5.3 Cortico-Cortical Circuit Activated During F5-M1 Interactions***

Shimazu et al. (2004) suggested that “the corticocortical pathways excited by F5 stimulation terminate preferentially on the cortical interneurons involved in generation of the late I waves, explaining why the D and  $I_1$  waves were not facilitated to the same extent as the later I waves. The late I wave pathway is probably oligosynaptic, with conduction delays in the order of 2–4 ms. It is more susceptible to GABA<sub>A</sub> agonists such as diazepam and muscimol than the  $I_1$  pathway, ... (Ilic et al. 2002); this would explain why muscimol depressed the  $I_2$  and  $I_3$  components (Fig. 2.5a) and abolished their facilitation from F5” (see Fig. 2.5 b–d). Their proposed circuit is shown in Fig. 2.5e.

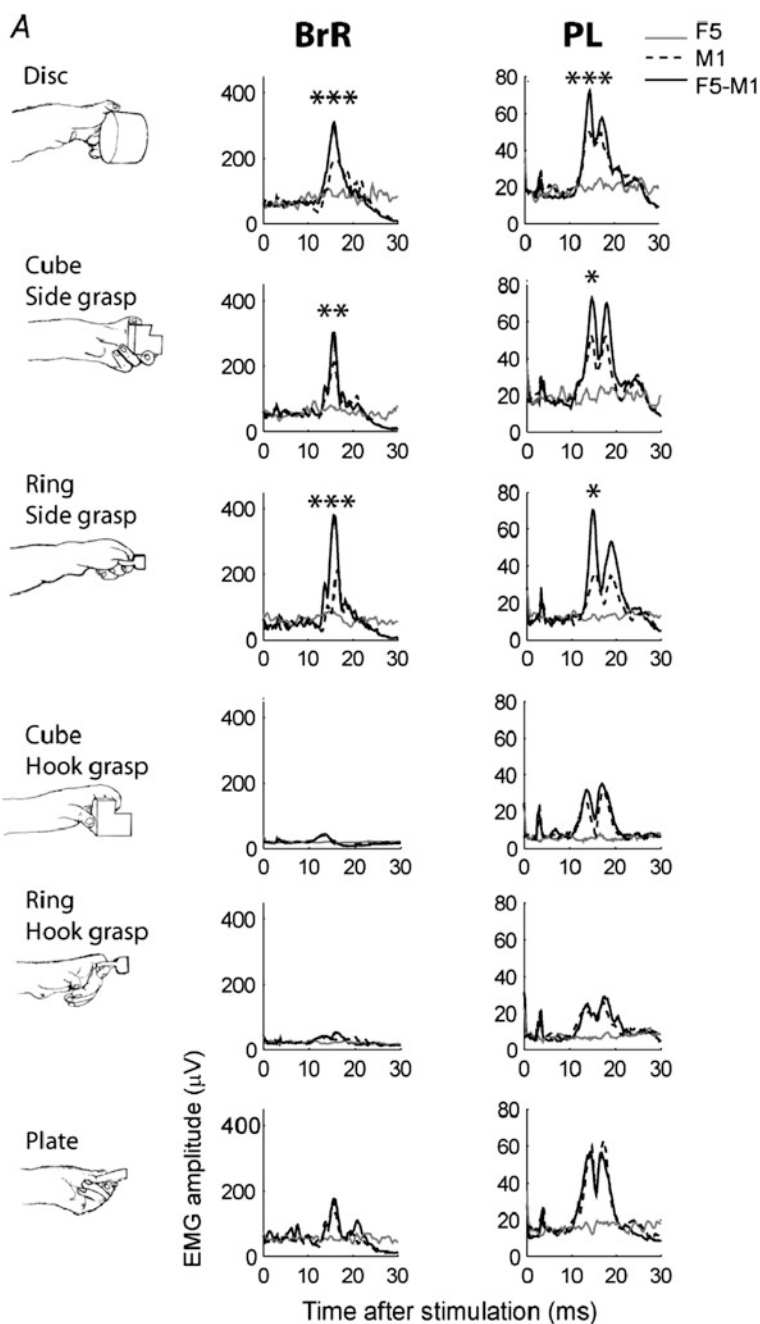
One potentially puzzling result of these studies was that if the number of shocks or stimulus intensity to F5 was increased, descending volleys and resulting motor responses could be observed. A clue to the answer was that the I waves evoked by these strong stimuli had fast conduction velocities ( $\sim 80$  m/s), that were identical to those for I waves evoked by M1 stimulation. Since we know that the corticospinal fibres derived from F5 itself are relatively slowly conducting (see [Sect. 2.1](#) above), these I waves cannot have originated from F5, but probably resulted from intense excitation of the networks in M1 by cortico-cortical inputs activated by strong F5 stimulation. In other words, the later I waves resulting from F5 stimulation were actually conveyed in corticospinal neurons whose cell bodies were in M1. This has subsequently been shown by direct recording from single corticospinal neurons (Maier et al. in preparation). Further evidence for this mechanism comes from the finding that muscimol inactivation of the M1 hand area greatly reduces the I waves evoked by strong F5 stimulation (Shimazu et al. [2004](#)).

## 2.6 Stimulus Evoked F5-M1 Interactions in the Awake, Behaving Monkey

Although the studies described above provided some useful insights into the potential circuitry underlying PMv-M1 interactions, they do not tell us how these structures interact during behaviourally relevant conditions. To address this issue, we applied the same F5-M1 stimulation protocols in awake monkeys trained to carry out a visuomotor reach-to-grasp task (Brochier et al. [2004](#); Prabhu et al. [2009](#)). Once again, the electrode locations were chosen on the basis of previous rCMS mapping of the M1 and F5 hand areas. The EMG responses evoked by M1 test (T) stimulation were recorded from contralateral hand, digit and arm muscles during reach-to-grasp of visually presented objects, which were presented in a pseudo-random order at the beginning of each trial. Stimuli were delivered just as monkeys began to move, a few hundred ms before they first contacted the object.

Conditioning (C) stimulation of F5, at intensities that were subthreshold for any motor effects, caused considerable modulation (over twofold) of the test (T) EMG responses. The pattern of facilitation was specific. First, it was particularly evident at short C-T intervals. Second, this facilitation was only present in some, but not all muscles, and during reach-to-grasp of some, but not all objects. Modulation of responses was common in extrinsic and intrinsic muscles acting on the thumb and index finger. Finally, facilitation was found only for particular combinations of F5 electrodes.

Examples of the interaction effects produced by F5-M1 stimulation during the reach-to-grasp of six different objects are shown in [Fig. 2.6](#). The responses shown are from two forearm muscles, brachioradialis (BrR) and palmaris longus (PL). F5 stimulation produced significant (\* in [Fig. 2.6](#)) facilitation of both muscles during





◀**Fig. 2.6** Grasp specificity of F5 conditioning of M1 stimulation and EMG activity during reach-to-grasp **a** averaged evoked EMG responses from brachioradialis (BrR) and Palmaris longus (PL) to F5 conditioning (C) (*grey* traces), M1 test (T) stimuli (*dashed* traces) and combined F5-M1 stimulation at C-T = 3.5 ms (*black* traces) during grasp of six different objects. Stimuli were delivered 50 ms just as the monkey reached to grasp to the objects. Wilcoxon's signed-rank test: \*  $P < 0.05$ , \*\*  $P < 0.001$ , \*\*\* $P < 0.0001$ . All figures are with 10 % outliers removed. Averages are of 23–67 trials per condition. Note that strong C-T (F5-M1) interactions were only obtained for grasp of some objects (*disc, cube or ring*), with side grasp, but not the others (from Prabhu et al. 2009, with permission)

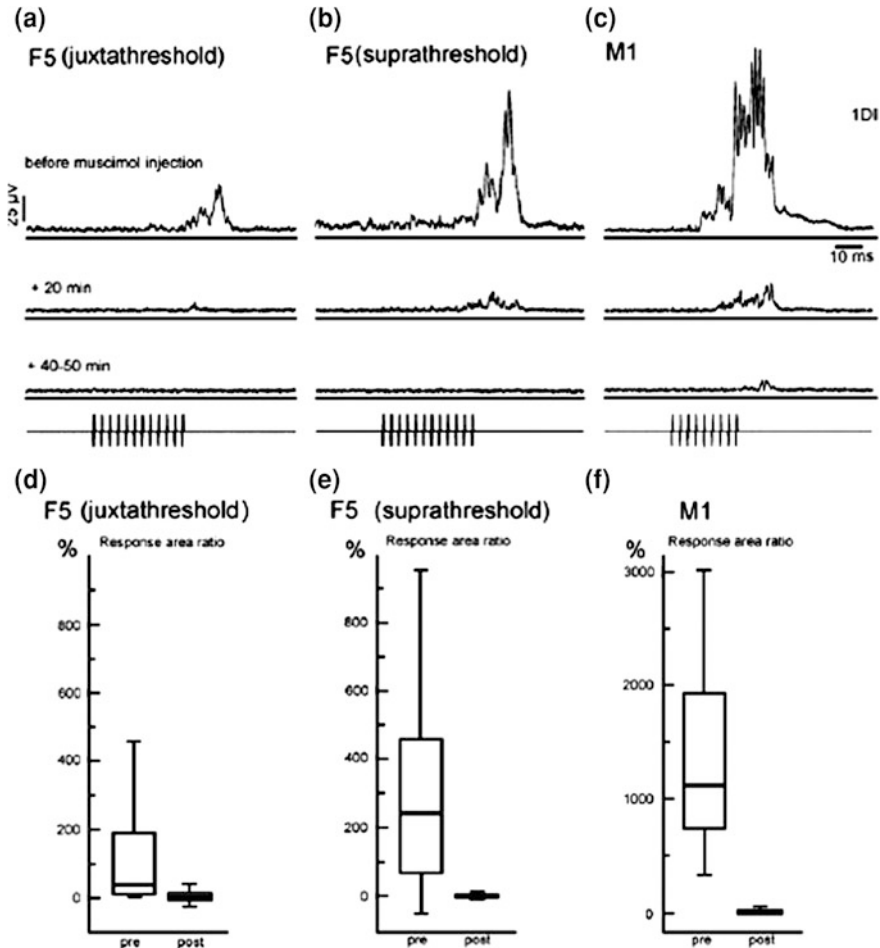
reach-to-grasp of the disc, and of both a cube and a ring, when a side grip (object grasped between thumb and side of the index finger) was used. However, when a hook grip (involving only the index finger) was used to grasp either the ring or the cube, no facilitation was found. Finally, there was no facilitation of either muscle for grasp of the plate.

Unfortunately, the basis of this differential facilitation was unclear: there was no obvious relationship between either the level of EMG activity at the time the C-T stimuli were delivered, nor to the pattern of activity associated with the particular grasps tested. Clearly more work is needed here; the analysis might well be more straightforward if C-T stimuli were delivered during the 'observation period', when the monkey can see the object, but is still waiting for the cue to grasp it. In TMS studies of human volunteers, grasp-specific F5-M1 interactions are already clearly present in this period (Prabhu et al. 2007; Davare et al. 2008).

Interestingly, Prabhu et al. (2009) also reported signs of suppression: at later C-T intervals (1–6 ms), F5 stimulation caused significant suppression of the test M1 response. This raises the possibility that suppression of M1 outputs can be used to sculpt M1 outputs that ultimately help to shape the hand to grasp an object. In general, the results are in keeping with the concept that during visually guided grasp, F5 modulates corticospinal outputs from M1 in a muscle- and grasp-specific manner.

## 2.7 Are the Motor Responses Evoked by Stimulation of PMv also Mediated Through M1?

The lateral premotor subdivision of Brodmann area 6, was one of the earliest regions properly identified as giving rise to well-defined motor responses in the hand and digits when stimulated electrically (Leyton and Sherrington 1917), and this has been confirmed many times since (Kurata and Tanji 1986; Rizzolatti et al. 1988; Weinrich and Wise 1992; Godschalk et al. 1995). Using trains of intra-cortical stimuli (rICMS), the thresholds for exciting digit movements from PMv tend to be higher than in M1, but the responses are certainly very robust. Given the findings described above, it is of course interesting to question whether these



**Fig. 2.7** Abolition of motor responses evoked by stimulation in F5 by muscimol injection in M1. **a–c** Average rectified EMG responses from an intrinsic hand muscle (IDI) evoked by rICMS (pulse train shown in *bottom* trace) before and after a microinjection of muscimol into the M1 hand area. **a** Averaged EMG response evoked by repetitive intracortical microstimulation (rICMS) in the F5 hand area at an intensity close to threshold (juxtathreshold) for evoking a response (12 pulses, 80  $\mu$ A). **b** Responses evoked by rICMS in F5 at an intensity 25 % above threshold (suprathreshold; 12 pulses, 100  $\mu$ A). **c** Responses evoked by rICMS in the M1 hand area (9 pulses, 45  $\mu$ A). Control responses evoked before muscimol (**a–c**, *top* traces) were greatly reduced 20 min after the muscimol inactivation (*middle* traces). After 40–50 min (*bottom* traces), responses to F5 stimulation were completely abolished whereas those to M1 stimulation were very small. All averages are of 50 sweeps. **d–f** Quantitative analysis of decrease of EMG responses after muscimol injection in M1. Stimulation details are as in **a–c** Box plots show a decrease in the area ratio of the EMG responses evoked by rICMS before (pre) and after (post) (50 min after last injection of muscimol in the M1 hand area) injection in one monkey. The plots show the median (thick horizontal bar) data between the 25 and 75 % quartiles (box) and between 10 and 90 % (error bars) of the area of the EMG response normalised to the background level of EMG activity ('response area ratio'). Note the difference in the relative sizes of the EMG responses evoked from F5 and M1 (from Schmidlin et al. 2008, with permission)

motor responses might also depend upon the integrity of M1. We tested this by recording, from digit muscles, responses that were evoked by rICMS delivered to area F5, before, during and after temporary inactivation of the M1 hand area with microinjections of muscimol (Schmidlin et al. 2008). The study was carried out in lightly sedated macaques.

As Fig. 2.7 shows, muscimol injection in the M1 hand area not only greatly reduced EMG responses evoked from M1 with rICMS, but also reduced or abolished responses from F5, over a similar time course (20–50 min). Muscimol in M1 also reduced the level of background EMG activity in the contralateral hand (compare background EMG levels in Fig. 2.7b for example), and the hands was paretic for several hours after the injection. However, because EMG responses to direct activation of the corticospinal tract (using PT stimulation) were significantly less affected than the responses to F5 stimulation, it is unlikely that reduced motoneuronal excitability explained the loss of the evoked responses from F5. Finally, as in the Shimazu et al. (2004) study, muscimol injections in M1 greatly reduced the corticospinal volleys evoked by rICMS in F5. The results suggest that the motor effects evoked from F5 depend, at least in part, on cortico-cortical interactions with M1, leading to activation of M1 corticospinal outputs to hand muscles.

These findings are important first for the specific case of understanding the interactions between F5 and M1, but more generally, because they demonstrate that a characteristic property of one cortical area (ICMS in F5 producing digit movements at low-threshold) is actually dependent upon the integrity of another area (the hand representation of M1).

## 2.8 What About Reciprocal Projections from M1 to Area F5?

The function of the ‘forward’ projection from area F5 to M1 is at the heart of the concept of the ‘visuomotor grasping circuit’. However, all of the anatomical studies of PMv-M1 connectivity have stressed the reciprocal nature of the connections between these structures. Indeed, Dum and Strick (2005) showed that the normalised strength and density of the interconnections between the M1 and PMv digit zones were rather similar, and originated in equal measure from deep and superficial laminae. On the basis of the anatomical origin, Dum and Strick (2005) considered that the two projections operated at an equivalent hierarchical level. Kraskov et al. (2011) found that responses in single M1 neurons to stimulation within F5 were equally common as F5 neurons responding to M1 stimulation.

The functions of the ‘return’ connections from M1 to F5 are still unknown, but they could be involved in updating both frontal and parietal areas as to the current state of the active motor network, and such a signal might be important in identifying the ‘agency’ of actions, allowing higher order structures to tag movement-related activity as self-generated or due to the actions of another. Also, these return connections would be required to update internal models about an object’s physical

properties. Internal models will then allow prediction of the forces required in the subsequent manipulation of the same object (Loh et al. 2010).

## 2.9 Functional Considerations and Summary

The experimental studies reviewed here give some clues as to how PMv, from its nodal position in the visuomotor grasping circuit, might influence skilled grasp. The studies have stressed the importance of the cortico-cortical connections between PMv and M1, and have shown that these connections possess all the key characteristics to allow PMv to modulate grasp-related outputs from M1.

- First, the connections allow fast interactions. This is important because we know that the grasping circuit is activated very rapidly by vision of grasping objects. Both monkey and human experiments indicate that grasp-related changes are already present around 100–150 ms after object presentation (Umiltà et al. 2007; Prabhu et al. 2007).
- Second, the connections, at least when tested with electrical stimulation, are very powerful and allow M1 outputs to be deeply modulated.
- Third, in the awake monkey, F5 inputs can either facilitate or suppress M1 corticospinal outputs.
- Finally, the connections allow grasp-specific changes in M1 outputs, which is obvious importance in matching the grasp to the physical properties of the object.

There may be some interesting parallels between the PMv-M1 interactions described here and those reported for gain control of smooth pursuit eye movements (Tanaka and Lisberger 2001). The facilitation exerted by F5 on motor outputs from M1 may also act as a gain control system on these outputs; this could be part of a wider control system that helps to shape the pattern of activity across different hand muscles appropriate for grasp of specific objects.

This review has highlighted the point that the integrity of the M1 hand area is essential for the function of F5. However, all of these studies were done in intact, healthy monkeys. There is considerable evidence from the human and animal stroke literature (Chollet et al. 1991; Liu and Rouiller 1999; Nudo 1999; Frost et al. 2003; Dancause et al. 2005; Ward 2006; Ward and Frackowiak 2006) that after damage to M1, PMv can play a role in the longer term recovery of hand motor function. This is very different to the effects of acute inactivation of M1, as described by Schmidlin et al. (2008). Clearly long-term compensatory changes cannot involve the same interactions with M1, and must depend to some extent on plastic changes in the connections of PMv to other surviving motor areas (including PMd and the SMA) and subcortical and spinal changes, possibly including recruitment of reticulospinal (Zaaimi et al. 2012) and/or propriospinal systems (Borra et al. 2010).

The studies described in this review were all done in the macaque monkey model. However, the results obtained have constantly informed and prompted

parallel experiments in the human (Prabhu et al. 2007), especially those led by Davare and colleagues (Davare et al. 2008, 2009, 2010, 2011), which have also demonstrated a powerful interaction between PMv and M1 in the human brain that is strongly influenced by preparation to grasp visible objects. It is arguable whether we would be able to properly interpret the results of these non-invasive studies without the knowledge gained from the monkey research.

**Acknowledgments** I want to particularly thank Thomas Brochier and Alexander Kraskov who helped me with this review. Many other colleagues participated in the research summarised here, including Gita Prabhu, Eric Schmidlin, Peter Kirkwood, Marc Maier, Gabriella Cerri, Hideki Shimazu, Sam Shepherd, Chris Seers, Alessandra Umiltà and Rachel Spinks, and I thank them all.

Funded by: Wellcome Trust, BBSRC, NC3Rs and MRC

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Cortical Connectivity

Brain Stimulation for Assessing and Modulating Cortical  
Connectivity and Function

Chen, R.; rothwell, j. (Eds.)

2012, VIII, 368 p., Hardcover

ISBN: 978-3-642-32766-7