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Cortical mechanism for the visual guidance of hand grasping movements in the monkey
A reversible inactivation study

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Summary
Picking up an object requires two basic motor operations: reaching and grasping. Neurophysiological studies in monkeys have suggested that the visuomotor transformations necessary for these two operations are carried out by separate parietofrontal circuits and that, for grasping, a key role is played by a specific sector of the ventral premotor cortex: area F5. The aim of the present study was to test the validity of this hypothesis by reversibly inactivating area F5 in monkeys trained to grasp objects of different shape, size and orientation. In separate sessions, the hand field of the primary motor cortex (area F1 or area 4) was also reversibly inactivated. The results showed that after inactivation of area F5 buried in the bank of the arcuate sulcus (the F5 sector where visuomotor neurones responding to object presentation are located), the hand shaping preceding grasping was markedly impaired and the hand posture was not appropriate for the object size and shape. The monkeys were eventually able to grasp the objects, but only after a series of corrections made under tactile control. With small inactivations the deficits concerned the contralesional hand, with larger inactivations the ipsilateral hand as well. In addition, there were signs of peripersonal neglect in the hemispace contralateral to the inactivation site. Following inactivation of area F5 lying on the cortical convexity (the F5 sector where visuomotor neurones responding to action observation, 'mirror neurones', are found) only a motor slowing was observed, the hand shaping being preserved. The inactivation of the hand field of area F1 produced a severe paralysis of contralateral finger movements with hypotonia. The results of this study indicate the crucial role of the ventral premotor cortex in visuomotor transformations for grasping movements. More generally, they provide strong support for the notion that distal and proximal movement organization relies upon distinct cortical circuits. Clinical data on distal movement deficits in humans are re-examined in the light of the present findings.

Keywords: premotor cortex; area F5; muscimol; hand grasping; monkey

Abbreviation: AIP = anterior intraparietal area

Introduction
Primates, humans in particular, possess an extraordinary ability to interact manually with objects, to reach for them and grasp them. Analysis of grasping movements has shown that the configuration formed by the hand in contact with the object is the end-result of a motor sequence that begins well ahead of the action of grasping itself. The fingers begin to shape during the transport of the hand. This process of visuomotor transformation involves a progressive opening of the hand with straightening of the fingers, followed by a closure of the grip until it matches the size of the object (Jeannerod, 1984; Gentilucci *et al.*, 1991; Jakobson and Goodale, 1991; Paulignan *et al.*, 1991; see also Jeannerod 1988). The amplitude of maximum grip aperture covaries linearly with the object size (Marteniuk *et al.*, 1990).

The execution of grasping movements requires the integrity of the primary motor cortex (F1 or area 4). Following lesions in this area, grasping movements, especially those demanding a subtle control of the fingers, are strongly impaired (Fulton, 1943; see also Hepp-Reymond, 1988; Porter and Lemon, 1993). Because lesions of F1 cause a profound impairment of individual finger force and movement control, the grasping

deficits following F1 lesioning are most likely accounted for by these basic motor deficits. They are not due to a specific damage to the mechanisms underlying the visuomotor transformation for grasping movements. Single neurone studies agree with this deficit interpretation, showing that in the monkey very little visual information reaches F1 (see Wannier *et al.*, 1989).

The hand field of monkey F1 receives a rich input from a specific sector of the ventral premotor cortex, area F5 (Matsumura and Kubota, 1979; Muakkassa and Strick, 1979; Matelli *et al.*, 1986). Recording studies have shown that many neurones of area F5 discharge in association with hand movements (Kurata and Tanji, 1986; Rizzolatti *et al.*, 1988; Hepp-Reymond *et al.*, 1994). Among them the most common are those related to grasping movements. Some of the 'grasping' neurones are nonspecific, discharging with all types of grips. Others discharge in association with particular types of grip such as precision grip, finger prehension and whole hand prehension (Rizzolatti *et al.*, 1988; Murata *et al.*, 1997; see also Rizzolatti *et al.*, 2000).

More recently it has been shown that area F5 is formed by two main cytoarchitectonic sectors (see Rizzolatti *et al.*, 1998). One roughly coincides with the part of F5 that is located on the cortical convexity (F5 convexity), the other with the part that is buried in the arcuate sulcus (F5 bank). In both sectors there are neurones that, in addition to firing in association with a motor action, respond to visual stimuli. Visual neurones of F5 bank respond to the presentation of three-dimensional objects of different size and shape (Rizzolatti *et al.*, 1988; Murata *et al.*, 1997). Typically, they show a strict congruence between the type of grip they code and the size and shape of the object effective in triggering their visual response. These neurones have been named 'canonical neurones' (Rizzolatti and Fadiga, 1998). In contrast, visual neurones recorded from F5 convexity become active only when the monkey observes an individual performing an action directed toward an object. These neurones have been called 'mirror neurones' (Gallese *et al.*, 1996; Rizzolatti *et al.*, 1996).

The F5 bank (the sector where canonical neurones are located) is richly connected with the anterior intraparietal area (AIP) (Luppino *et al.*, 1999). This area is characterized by the presence of a large number of neurones that are active in association with grasping/manipulation movements (motor dominant neurones), presentation of visual stimuli (visual dominant neurones) and both hand actions and object presentations (visuomotor neurones) (Taira *et al.*, 1990; Murata *et al.*, 1996, 2000; Sakata *et al.*, 1995).

On the basis of the functional properties of the AIP and F5, it has been proposed that the visuomotor transformations necessary for organizing grasping movements are mediated by the AIP–F5 circuit. The activity of F5 neurones represents the step that transforms the object representations coded in the AIP into a format suitable to activate area F1 motor neurones plus a series of subcortical centres among which are the basal ganglia and cerebellum (Jeannerod *et al.*, 1995; Sakata *et al.*, 1995; Gallese *et al.*, 1997; Fagg and Arbib, 1998).

The main aim of the present study was to test the validity of this hypothesis by inactivating area F5 in the monkey. If the hypothesis is correct, inactivation of F5 should produce a specific deficit of object grasping that could not be explained by paralysis or somatosensory deficit.

A further aim of the study was to assess the validity of the distinction between F5 bank and F5 convexity. If this distinction is correct, only the inactivation of the F5 bank should produce an impairment of object-to-movement transformations. Inactivation of F5 convexity should produce some motor deficit because mirror neurones have motor properties, but the capacity to shape the hand according to the object to be grasped should remain basically unaffected.

Finally, to differentiate the symptoms due to visuomotor deficit from those due to paralysis, an inactivation of F1 hand field was carried out in a separate set of experiments with the same monkeys in which F5 was inactivated. A preliminary account of some of the results was published elsewhere (Gallese *et al.*, 1997).

Methods

Subjects

The experiments were carried out on two monkeys (*Macaca nemestrina*). All experimental and surgical procedures were approved by the Veterinarian Animal Care and Use Committee of the University of Parma and complied with the European law on the humane care and use of laboratory animals.

Clinical testing

Before the experiments, the monkeys were seated quietly on a primate chair, to receive food from the hand of the experimenters and to be touched by them. When this was achieved their motor abilities were tested as follows.

Reaching and grasping

Objects of different size and shape (usually food) were introduced in the four quadrants of the visual space at different distances from the monkeys, which were trained to reach for and grasp them. Testing was repeated several times and the accuracy of the monkey in reaching the targets was observed and videotaped for further analysis. Reaching was also studied by employing Travis's test (Travis and Woolsey, 1956). A board with six small holes (diameter of each hole = 2.0 cm) arranged in two horizontal rows was placed in front of the monkey. The holes were equidistant from one another (distance between holes = 8.5 cm). A raisin was placed inside each hole and the monkey had to use, in separate sessions, either its right or left hand in order to grasp it. The

testing was repeated four times for each hand. The hole location, at which the monkey started grasping, the spatial sequence it used to pick up raisins, and the way in which food was retrieved were noted and filmed.

Grasping was examined first informally by presenting and giving the monkey small pieces of food held by the experimenter between his fingers. Orientation was changed in different trials. After this preliminary testing, grasping was examined using an apparatus similar to that described by Kuypers (Haaxma and Kuypers, 1975). It consisted of a round movable plastic block with a slit in its centre inserted into a plastic ring. By rotating the block the slit could be presented in different orientations. Four orientations were typically used: horizontal, vertical, 45° clockwise and 45° anticlockwise.

Head/mouth movements were studied by presenting food (held by forceps) in the space around the mouth. The hands were blocked. The monkey's normal response consisted of head movements toward the food accompanied by contraction of the facial musculature on the side where the food is presented, opening of the mouth and protrusion of the tongue. The monkey then grasped food in its mouth.

Testing for neglect signs

Tests for neglect were the same as described in a previous study (see Rizzolatti *et al.*, 1983). Briefly, they consisted of the presentation of a variety of objects inside and outside the monkey's peripersonal space. Single objects and pairs of objects in competition were also used. Extrapersonal, distal peripersonal space and peribuccal space were tested.

Formal testing

In order to standardize reaching and grasping movements, the monkeys were tested before and after inactivation in a specially devised apparatus. The apparatus consisted of a box containing a computer-driven rotating turntable on which geometric solids of different size and shape could be placed. The front door of the box was made of liquid crystal material. It could be automatically lowered during the trials. In front of the box, there was a short plane with a switch. Two metal plates formed the switch. A trial began when the monkey pressed the switch using its thumb and index finger. After 200 ms the liquid crystal door became transparent allowing the monkey to see the object located inside the box. After a variable period of time (1.2–1.8 s), the front door was lowered and the monkey was allowed to reach for and grasp the object. Once the monkey grasped the object, it had to pull it in order to receive a liquid reward. The reward was delivered through a tube placed near the monkey's mouth. If the monkey released the switch before the front door was lowered, the trial was aborted.

Five different objects requiring five different types of grip were used. They were (i) a thin plate (width = 30 mm; height = 10 mm; thickness = 4 mm); (ii) a small sphere (diameter = 5 mm); (iii) a large sphere (diameter = 40 mm); (iv and v) two cylinders (length = 60 mm; diameter = 17 mm) horizontally and vertically oriented, respectively. All the objects were attached to a support which was tilted at ~45° toward the monkey. The objects were presented one at a time, always in the same central position (distance from the monkey's hand starting position = 145 mm). The two small objects (thin plate and small sphere) evoked a grip made by the opposition of the pulpar surface of the index finger and the thumb (precision grip) and a grip performed using the thumb and the radial surface of the second phalanx of the index finger (side grip), respectively. The large sphere and the two cylinders evoked a 'whole hand' prehension. The sphere was grasped by all fingers and the cylinders by all fingers but the thumb. The two cylinders required two different wrist orientations congruent with the objects' longitudinal axes.

The behaviour of the monkeys during testing was videotaped. In addition, the kinematics of arm movements were recorded using a computerized movement recording system (Elite System; BTS, Milan, Italy; see Ferrigno and Pedotti, 1985) consisting of two infrared TV cameras (sampling rate =100 Hz) and a processor that elaborated the video images in real time and reconstructed the three-dimensional position of infrared reflecting markers.

Our initial intention was also to record the kinematics of finger movements. However, after cortical inactivation, alterations in the hand starting position and subsequent movements were such as to frequently render the kinematic reconstruction of finger movement impossible. Thus, the data on finger posturing before and during grasping are based exclusively on the analysis performed on videotape recordings. Data on the reaching (transport) phase of reaching/grasping movement were, however, recorded and analysed. The data were collected using a marker placed on the styloid apophysis of the radius. The studied parameters were arm trajectory and arm velocity components along the three major axes (x = sagittal axis, y = vertical axis, z = horizontal axis). In addition, we measured the vector representing the time course of the wrist position during the movement and calculated the velocity of its module change. The statistical analysis was carried out on the peak velocity of the module change. In humans it is well established that there is a relationship between the velocity of the transport component and the object size (Gentilucci *et al.*, 1991; Jakobson and Goodale, 1991; Corradini *et al.*, 1992; Chieffi *et al.*, 1992; Chieffi and Gentilucci, 1993). Thus, although we have no direct data on grasping kinematics after cortical inactivation, inference on visuomotor transformation for grasping could be deduced from the characteristics of the transport component.

A *t*-test for independent samples was employed in order to compare the kinematic values of arm movements before and after inactivation. The test was applied to the total movement time and peak velocity.

Recording and electrical microstimulation procedures

The surgical procedures for single neurone recordings and intracortical microstimulation were the same as described in previous studies (see Gentilucci *et al.*, 1988; Rizzolatti *et al.*, 1990). The surgery was performed under ketamine anaesthesia (12 mg/kg i.m., repeated every 20 min). After surgery, the monkeys were monitored until full wakefulness. They were given ketorolac (0.5 mg/kg, i.m. twice) for analgesia and returned to their home cage.

After surgery the ventral part of the agranular frontal cortex was functionally explored (single neurone recordings and intracortical microstimulation) in order to assess the location of areas F1 (primary motor cortex), F4 and F5 (the two areas constituting the ventral premotor cortex), to delimit the location of the hand field within F1 and to find out the sector of F5 where canonical neurones are located and in which mirror neurones are mostly located. The techniques used for recording single neurones and for intracortical microstimulation have been described previously and will not be repeated here (Gentilucci *et al.*, 1988; Luppino *et al.*, 1991).

The criteria used to functionally characterize the different areas were the following. *Area F1*: low threshold of excitability to microstimulation (typically a few microamps when stimulating deep layers), vigorous discharge during active movements, response to passive somatosensory stimuli from virtually all recorded sites. *Area F4*: moving the electrode rostrally from F1 hand field, appearance of proximal and axial movements to electrical stimulation, increase in stimulation threshold, appearance of visual responses, presence of large tactile receptive fields located on the face and body and of visual peripersonal receptive fields around the tactile ones. *Area F5*: going further rostrally, re-appearance of distal movements though requiring higher stimulation currents than F1, disappearance of spatially organized receptive field typical of F4, visual responses to the presentation of 3D objects or complex actions, presence of a large number of neurones discharging in association with goal-directed hand movements.

The distinction between F5 bank and F5 convexity was made using the depth at which F5 neural activity was recorded in each penetration as a criterion. Neurones recorded at a depth of <3 mm were considered F5 convexity neurones. Neurones recorded at a depth of >3 mm were considered F5 bank neurones. In the penetrations made in the F5 bank, the border between cortex and white matter was, in general, at a depth of 5.5–6 mm from the cortical surface. Functionally, visually driven F5 bank neurones responded to the presentation of 3D objects, while visually driven F5 convexity neurones were mostly mirror neurones.

Inactivation procedures

Muscimol injection

Once the location of areas F1, F4 and F5 was assessed and the sectors of interest within F1 and F5 sufficiently characterized, the inactivation experiments were started. They were carried out as follows. The monkey was seated on a primate chair with its head in a fixed position. A microelectrode penetration (inclination 30° lateral to the vertical axis) was made in the site chosen for the injection in order to confirm the site's functional properties. The microelectrode was then withdrawn and replaced by a stainless steel microinjection cannula connected to a 10 µl Hamilton microsyringe. The cannula was mounted on the same micromanipulator used for recording, such that its needle passed through the same track as the microelectrode. The cannula was lowered 500 µm below the depth of the site chosen for the injection and subsequently raised again to the correct depth. Muscimol, a GABA agonist, was slowly injected by pressure over a period of 30 min at a rate of 0.5 µl/5 min (Hikosaka and Wurtz, 1985; Hikosaka *et al.*, 1985; Martin, 1991; Martin and Ghez, 1993; see also Martin and Ghez, 1999). Thirty minutes after the microinjection was completed, the cannula was withdrawn. The depth chosen for muscimol injection was 1.5 mm for F5 convexity and 4.5 mm for F5 bank (posterior bank of the arcuate sulcus) and F1 bank (anterior bank of the central sulcus).

Muscimol dose and volume

Three microlitres (3 µl) of a muscimol solution (concentration 5 µg/µl) were injected in all experimental sessions, except in the last three of Monkey 2, in which the muscimol concentration was trebled (15 µg/µl) and the volume used was also 3 µl. Table 1 shows the injection locations and their characteristics. In Monkey 2 the multiple injections were spaced at 2 mm distances from each other. In Monkey 1, the multiple injections were made as follows: distance from the most medial injection to the central one = 2 mm; from the central one to the most lateral = 3 mm. The distances were in stereotaxic parameters.

The injected volume and the muscimol dosage of the present experiments were the same as those successfully used by Gallese and colleagues for inactivating area AIP (Gallese *et al.*, 1994). A dosage of muscimol of concentration 5 µg/µl has also been employed in many recent inactivation experiments (Kubota, 1996; Schieber and Poliakov, 1998; Brochier *et al.*, 1999; Kurata and Hoshi, 1999; Schieber, 2000). The volume used, however, was higher than that most commonly injected (1 µl) (see Kurata and Hoffman, 1994; Kermadi *et al.*, 1997; Schieber and Poliakov, 1998; Brochier *et al.*, 1999; Martin *et al.*, 2000; Schieber, 2000). Injecting a higher volume may have two consequences: (i) to produce tissue damage; (ii) to induce a large drug diffusion, thus inactivating cortical fields or areas adjacent to the chosen one.

There are two functional findings which demonstrate that following a 3 µl injection the tissue damage, if present, is minimal. First, in control experiments we injected a volume (3 µl) of saline solution equal to that of the muscimol injection into F5 bank. No deficit in the monkey's behaviour was observed. Secondly, Demer and Robinson reported no

Table 1 Inactivation sites, number of injections, muscimol doses and injection depth for each experimental session

Monkey	Injected region	Muscimol concentration (μg/μl)	Muscimol volume per injection (μl)	Number of injections	Total volume injected (μl)	Total muscimol injected (μg)	Injection depth (mm)
1	F5 bank—left	5	3	1	3	15	4.5
1	F5 bank—left	5	3	3	9	45	4.5
1	F5 convexity—left	5	3	1	3	15	1.5
1	F5 convexity—left	5	3	3	9	45	1.5
1	F1—left (hand field)	5	3	1	3	15	4.5
1	F1—left (shoulder field)	5	3	1	3	15	4.5
2	F5 bank—left	5	3	1	3	15	4.5
2	F5 bank—left	15	3	3	9	135	4.5
2	F5 convexity—left	5	3	1	3	15	1.5
2	F5 convexity—left	15	3	3	9	135	1.5
2	F1—left (hand field)	5	3	1	3	15	4.5
2	F1—left (hand field)	15	3	2	6	90	4.5

functional deficit after infusion of ~10 μl of saline and glucose in the sites in which an injection of an equal volume of lidocaine was found to be effective (Demer and Robinson, 1982). Finally, in our experiments the probability of damage was minimized by injecting the muscimol solution at a rate much slower than that commonly used.

The second issue that the use of a large volume of muscimol (3 μl) may raise is that of the injection spread. In the rat it is known that a muscimol injection of 1 μl causes a spread to a 1.5–2 mm radius (Martin, 1991). It is likely that, with the same injected volume, the spreading is similar in monkeys. However, if one considers that, in comparison with the rat, the cell packing of the monkey cortex is less dense per volume unit (Rockel *et al.*, 1980; see also Jones, 1999) and the size of the monkey cortex much larger, volumes such as those used in the present experiments should not be much different functionally from the classical 1 μl injected in cortices smaller than that of a monkey. These considerations are particularly true for F5 where hand movements are represented for several millimetres inside the postarcuate bank of the arcuate sulcus. Finally, the dissociation observed between deficits following muscimol injection in the bank and in the convexity of F5 (see Results) indicates that the spread from the target area to other areas was not such, at least in the present experiments, as to invade areas with different functions.

Testing after muscimol injection

All testing (see above) was repeated after inactivation. The testing started 1 h after the last injection. Typically, clear neurological deficits began to appear at this time. The full-fledged picture of the deficits was present 2–3 h later. The deficits then remained stable for several hours. The testing lasted ~6 h, and was repeated the next day. Because the recovery was complete after 24 h, further testing sessions were not carried out. The neurological deficits were similar in the two monkeys. The severity of deficits, however, was always greater in Monkey 1.

Histology

Histological data are available for Monkey 1. They are not for Monkey 2, which is still alive. However, the functional characterization of the various agranular frontal areas described above and the consistency of the neuronal data with those of our previous experiments (see Rizzolatti *et al.*, 1981*a*, *b*; Gentilucci *et al.*, 1988; Fogassi *et al.*, 1996; Gallese *et al.*, 1996; Murata *et al.*, 1997) leave little doubt about the areas that were inactivated in the latter monkey.

Before sacrificing Monkey 1, a series of small electrolytic lesions (10 μA cathodal current for 10 s) was made in its cortex at the border of the studied region. The monkey was then anaesthetized with ketamine (15 mg/kg i.m.) and, after an additional dose of thiopental sodium (30–40 mg i.v.), perfused through the left ventricle with warm buffered saline followed by fixative (for details, see Matelli *et al.*, 1985). The animal was then placed in the stereotaxic apparatus, the dura was removed and the stereotaxic coordinates of the arcuate and the central sulci assessed. The head was blocked on a stereotaxic frame, the brain removed from the skull, photographed and then frozen and cut coronally (section thickness 60 μm). The sections were stained using the Nissl method. The location of penetrations and of the sites where muscimol was injected was reconstructed and related to the cytoarchitectonic areas of the frontal agranular cortex.

Results

Inactivation of area F5 bank

Small inactivations

Clinical picture. Following inactivation of F5 bank (single injection) both monkeys showed a clear preference for using the arm ipsilateral to the inactivation site. However, the contralateral arm was used when the ipsilateral arm was blocked. This arm preference was present for the whole duration of the testing. There was no misreaching. The monkeys also had difficulties in correctly rotating the wrist of the contralesional arm to grasp an obliquely presented

object. The deficit was especially marked when radial wrist rotation was required. This deficit was also evident in the Kuypers' test. Grip force was diminished. The ipsilateral hand appeared to be normal.

In addition to impairments in hand movements, the monkeys also showed a moderate deficit in mouth movements. When food was presented near the mouth contralateral to the inactivation side, grasping movements were executed in a stereotyped way without the richness of facial movements observed on the other side.

Formal testing. Figure 1 shows the reaching-to-grasp movements performed prior to (upper part of the figure) and after inactivation (lower part of the figure) in the testing apparatus. Single frame images redrawn from video records are presented. The grasped object was the thin plate.

A comparison of the movement patterns before and after inactivation shows a clear hand-shaping deficit after inactivation. When the hand reached the object, the posture of the fingers was not appropriate for object grasping. The object was eventually grasped, but only after a series of corrections made under tactile control. The total movement time was lengthened. Note that after the inactivation the monkey showed difficulty in pressing and holding the switch of the testing box.

Not all grips were equally affected. The deficit was severe for small objects such as the thin plate and the small sphere (see Methods). Unlike before inactivation, the monkeys tried to grasp these objects using all of their fingers and succeeded only after object tactile exploration. Grasping of large objects (large sphere, vertical and horizontal cylinders) was basically normal.

Figure 2, upper row, shows the trajectories and the velocity profiles of the transport component of the hand contralateral to the inactivated side prior to (left) and after (right) inactivation. The mean values of peak velocity prior to inactivation were the following: thin plate 80.96 cm/s (SD = 5.28); large sphere 90.33 cm/s (SD = 4.47); horizontal cylinder 93.96 cm/s (SD = 7.66). The mean values of peak velocity after inactivations were the following: thin plate 69.21 cm/s (SD = 5.09); large sphere 73.94 cm/s (SD = 3.25); horizontal cylinder 69.99 cm/s (SD = 4.37). Statistical analysis showed that following inactivation the peak velocities significantly decreased with respect to the control for all objects [thin plate $t(19) = 5.18$, $P < 0.001$; large sphere $t(16) = 8.66$, $P < 0.001$; horizontal cylinder $t(17) = 8.24$, $P < 0.001$]. Furthermore the difference in peak velocity between the thin plate and the horizontal cylinder was no longer present.

Large inactivations

Clinical picture. Following a triple injection in the bank of F5, both monkeys showed a neurological symptomatology more severe and complex than following a single injection. The major differences were a greater severity of the movement deficits of the contralateral hand, grasping deficits of the ipsilateral hand and signs of contralateral peripersonal neglect.

Formal testing. The use of the hand contralateral to the injection site was dramatically impaired in Monkey 1. The monkey often refused to make the reaching-to-grasp movements toward small objects and, when it made them, grasping was clumsy and performed by shaping the hand in a way inappropriate to object size, shape and orientation. Errors in hand shaping also characterized the prehension of the vertical cylinder in the reaching/grasping task. This object was frequently grasped by its top instead of, as prior to inactivation, by its oblong part (main cylinder axis). The large sphere and the horizontal cylinder were grasped almost normally. Note that the orientation of these stimuli is such that they can be reached by a simple hand transport without an accurate hand shaping and wrist rotation.

The deficits observed in Monkey 2 were qualitatively similar but much milder than those in Monkey 1. The movement kinematics were studied in this last monkey. The data are presented in Fig. 2 (middle row, left**).** The mean values of the peak velocity after inactivation were the following: thin plate 65.22 cm/s (SD = 3.41); large sphere 65.71 cm/s (SD = 6.34); horizontal cylinder 63.80 cm/s (SD = 5.27). The peak velocity of the contralesional hand was significantly reduced with respect to control [thin plate $t(19) = 8.0$, $P < 0.001$; large sphere $t(22) = 10.52$, $P < 0.001$; horizontal cylinder $t(18) = 10.25$, $P < 0.001$] and not affected anymore by the object size (middle row left, bottom part).

In addition to deficits of the contralateral hand, large inactivation of F5 bank also determined a deficit in hand shaping of the hand *ipsilateral* to the inactivation side. The deficit was not accompanied by any other motor deficits. Figure 3 illustrates the reaching-to-grasp movements of the ipsilateral hand of Monkey 1 after large inactivation. In addition to the lack of an appropriate hand shaping, the hand aperture was exaggerated and prolonged in time. As a consequence, movement time was about twice that of the same hand before injection. The object was eventually grasped, but only after tactile exploration (Fig. 3, last frames).

The grasping behaviour was less impaired with large objects. However, errors were also observed with these objects. The vertically oriented cylinder, for example, was occasionally grasped with the hand placed on its top rather than on its oblong surface as prior to the inactivation. The wrong hand shaping was always corrected after contact with the object and no deficit in finger movement dexterity was detected.

Neglect symptoms. Both monkeys showed a clear tendency to react less to stimuli presented in the peripersonal space contralateral to the inactivation site. This neglect symptomatology was present when stimuli were presented around the mouth, arm and body. When food was presented bilaterally, the monkeys always preferred that presented ipsilaterally. When a threatening stimulus was presented near the animal, the arm and face motor responses as well as

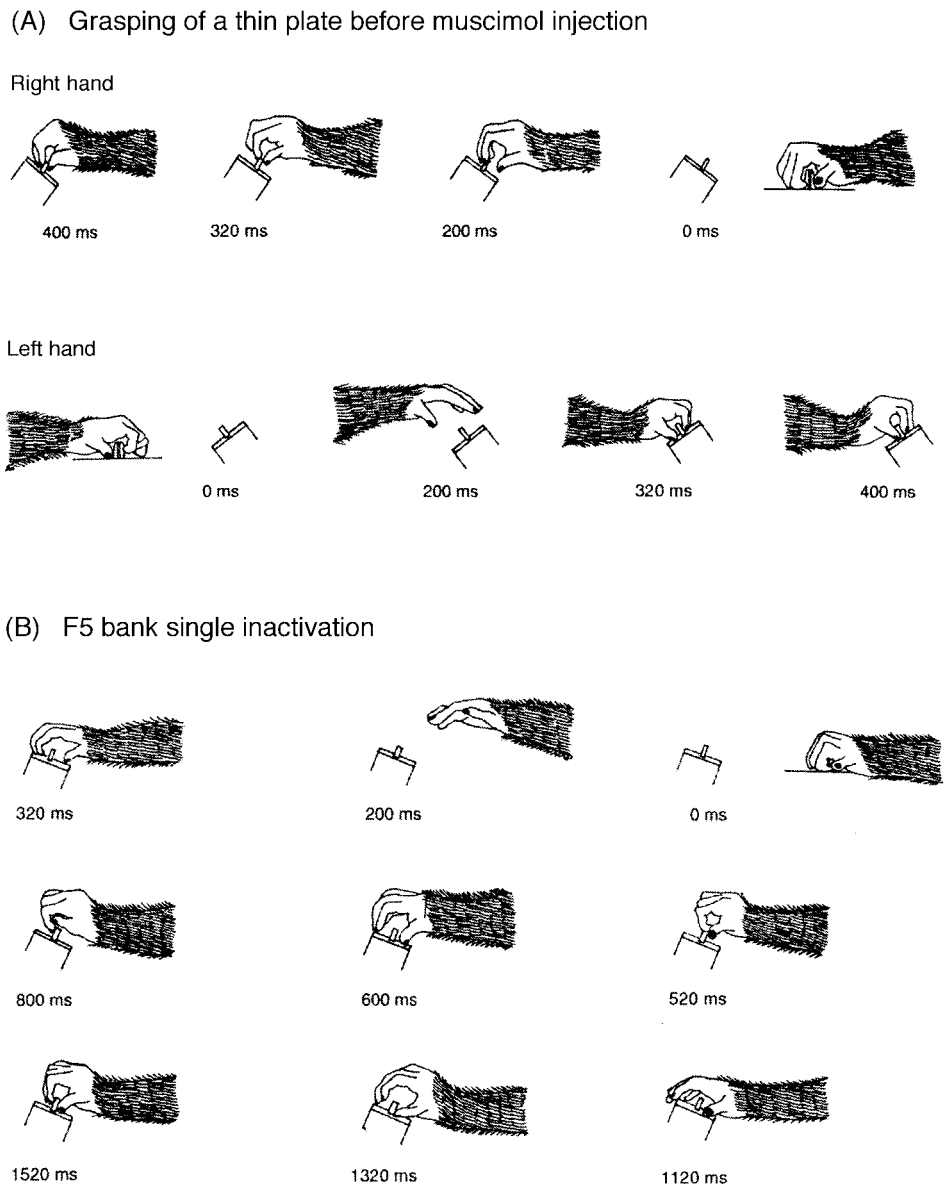

Fig. 1 Preshaping and actual grasping of a small object (thin plate). (**A**) Single frame images redrawn from video of a typical control trial executed with the right hand and the left hand, prior to inactivation. The first frame (0 ms) shows the location of the hand at the beginning of the trial. Note in the following frame (200 ms) that the hand opened before contact with the object (hand shaping). The movement was accomplished in 400 ms. (**B**) Single frame images redrawn from video of a typical test trial executed with the hand contralateral to the injection site after a single muscimol injection in the bank sector of area F5. Note that the monkey succeeded in grasping the object only after many attempts. The time given below each frame image was calculated from the onset of hand movement.

emotional reactions were less evident if the stimulus was presented contralateral to the inactivation site. Orienting responses and emotional reactions were fairly normal when stimuli were presented in the far space.

Both monkeys showed a peculiar behaviour in the Travis's box task following inactivation. Before inactivation they preferred to pick up food beginning from the holes on the extreme right when using the right hand and from the holes on the extreme left when using the left hand. Following inactivation, regardless of the hand used, the food located in the holes ipsilateral to the injection site was consistently taken first.

Inactivation of area F5 convexity

Small inactivations

Clinical picture. Following a single injection in F5 convexity, no clear clinical deficits were evident. Similarly, no obvious deficits were evident from video-tape analysis.

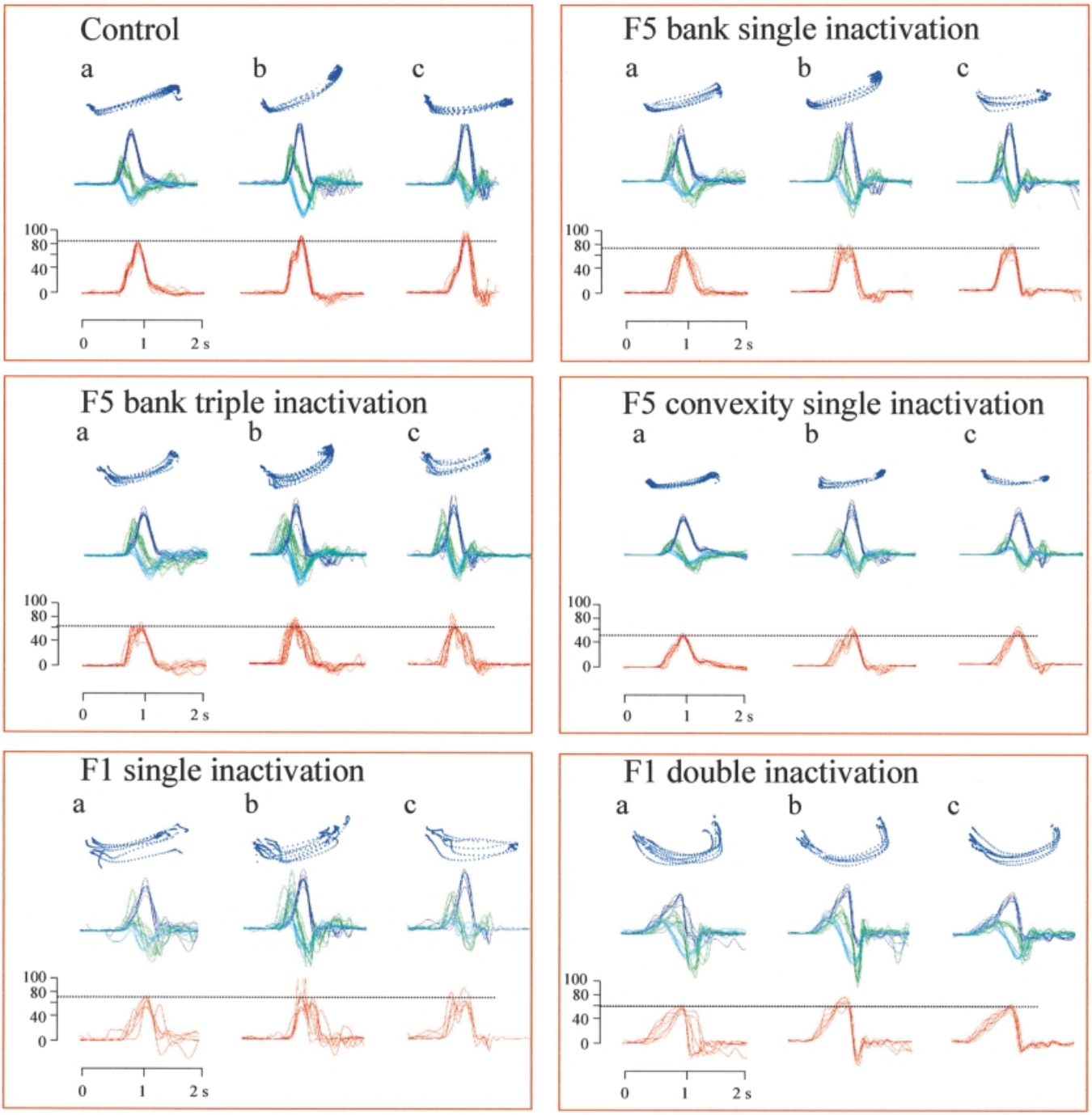

Fig. 2 Trajectories and velocity profiles of the transport component of the reaching-to-grasp movements of the contralesional hand of Monkey 2 recorded prior to and after inactivations. Each panel shows from top to bottom: (i) arm trajectories (hand starting point on the left); (ii) profiles of velocities of *x* (dark blue), *y* (green) and *z* (light blue) components of the hand movement (*x*, positive values indicate movements toward the target; *y*, positive values indicate movements directed upward; *z*, positive values indicate movements directed toward left and negative values toward right); (iii) profiles of the change of the velocity module of the arm movement vector. Peak velocity is the maximal value of arm velocity at the end of acceleration phase. In all panels the letters a, b and c indicate grasping of thin plate, large sphere, and horizontal cylinder, respectively. The dotted line in the lowest part of each panel corresponds to the value of the peak velocity recorded during grasping of the small object. Abscissae: time expressed in seconds; ordinates: velocity expressed in cm/s.

Formal testing. Figure 2, middle row right, shows the trajectories and the velocity profiles of the transport component of the hand contralateral to inactivated side. The mean values of peak velocity were the following: thin plate 51.73 cm/s (SD = 2.04); large sphere 56.08 cm/s (SD = 5.0); horizontal cylinder 53.72 cm/s (SD = 4.31). The

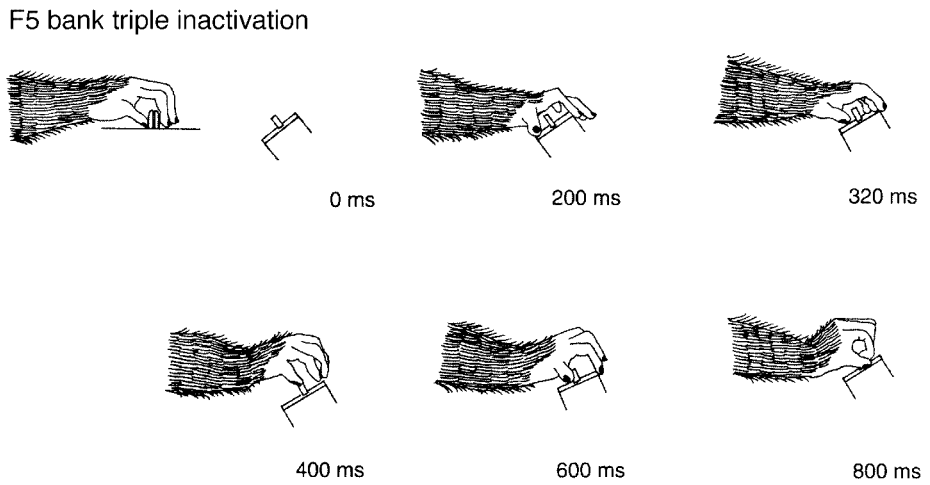

Fig. 3 Preshaping and actual grasping of a small object (thin plate). Single frame images redrawn from video of a typical test trial executed with the hand ipsilateral to the injection sites after triple muscimol injection in the bank sector of area F5. Note that shaping of the hand is incorrect, with prolonged and exaggerated finger opening phase. Other conventions as in Fig. 1.

statistical analysis showed that peak velocity of the contralateral hand was markedly reduced [thin plate $t(19) = 16.38$, $P < 0.001$; large sphere $t(16) = 15.32$, $P < 0.001$; horizontal cylinder $t(16) = 13.23$, $P < 0.001$] with respect to the pre-inactivation values. In spite of this reduction, contrary to F5 bank inactivation, the object size still influenced movement kinematics, thus showing that the object size was still processed after F5 convexity inactivation. A comparison between thin plate and large sphere peak velocities showed that peak velocity for small objects was significantly lower [$t(16) = 2.51$, $P < 0.05$] than that for large objects.

Large inactivations

The deficits following large inactivation were basically the same as those after small inactivation. In addition, in both monkeys, a mild motor deficit of the mouth appeared. When food was presented near the mouth contralateral to the inactivation side, the mouth grasping movement was less prompt and executed with a lesser opening of the mouth. Furthermore, in Monkey 1 grasping movements made with the contralateral hand were slower than before inactivation, with a difficulty in orienting the wrist appropriately to retrieve food through a horizontally oriented slit. Hand shaping and grip were executed correctly.

Inactivations of area F1

Small inactivations, hand field

Clinical picture. Inactivation of F1 hand field produced a marked paresis of the fingers of the hand contralateral to the injected side, accompanied by a severe reduction of grip force and hypotonia. In accordance with the functional properties of the neurones recorded from the site where muscimol was subsequently injected, movements of the thumb and the index finger were the movements most affected.

The capacity to grasp objects was strongly impaired. Both monkeys reached for the tray on which objects were located using a stereotyped, 'flat' hand posture that enabled them to 'retrieve' food rather than to grasp it (for similar results see Matsumura *et al.*, 1991; Schieber and Poliakov, 1998*a*; Brochier *et al.*, 1999). Precision grip could not be executed. Radial wrist rotation was impaired in Monkey 1.

Formal testing. Grasping of large and small objects was strongly impaired in Monkey 1 with the hand contralateral to the injection site. The ipsilateral hand was normal.

An example of the contralateral hand deficit is shown in Fig. 4. The figure illustrates how the monkey attempted to grasp a small object (thin plate) after inactivation. The monkey reached for the object using a 'flat' hand configuration. The fingers were kept in a semiflexed posture both during reaching and after object contact. While, as shown in Fig. 4, precision grip was completely disrupted, grasping of large objects was still possible, although the monkey achieved it by flexing the phalanxes of the fingers, but not the metacarpophalangeal joints.

Figure 2, lower row, left, shows the trajectories and velocity profiles of the transport component for the contralateral hand of Monkey 2 after inactivation. The mean values of peak velocity were the following: thin plate 65.02 cm/s (SD = 8.1); large sphere 71.33 cm/s (SD = 21.0); horizontal cylinder 70.85 cm/s (SD = 9.33). The peak velocity was significantly reduced with all objects [thin plate $t(15) = 4.93$, $P < 0.001$; large sphere $t(16) = 2.80$, $P < 0.05$; horizontal cylinder $t(13) = 5.14$, $P < 0.001$]. Note the high variability of the trajectories in different trials, due to the difficulty in executing the task because of hand paresis. In spite of this, the difference

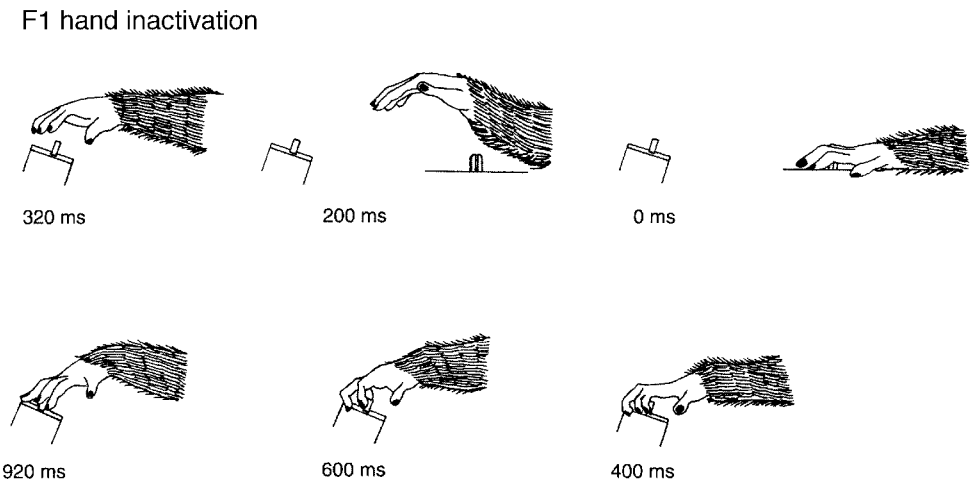

Fig. 4 Example of a test trial after the single inactivation of the F1 hand field. Single frame images redrawn from video during a failed attempt to grasp a small object (thin plate) with the hand contralateral to the injection site. Note that the monkey could not press the switch at the trial onset. During the reaching movement fingers were constantly kept in a semi-flexed posture. Movement time was almost double with respect to the control situation. Other conventions as in Fig. 1.

of peak velocity between large and small objects was still present, although it did not reach significance.

Small inactivations, shoulder field

Clinical picture. Inactivation of the F1 shoulder field produced a severe reduction of force in the contralateral arm. When threatening stimuli were presented near the monkey, the monkey did not push them away, as it typically did prior to inactivation. Similarly, when food was presented, the monkey did not reach for it. In those rare cases, in which it tried to do so, the arm movement was executed slowly and in a step-like fashion. There was a mild deficit of the ipsilateral arm, the movement velocity of this arm being slightly reduced. Grasping movements of both hands were normal. No deficits in wrist rotation were detected.

Formal testing. The kinematic analysis of arm transport of Monkey 1 showed a clear-cut decrease in peak velocity of both contralateral and ipsilateral arm with all tested objects. The mean values of peak velocity for the contralateral hand prior to inactivation were the following: thin plate 59.92 cm/s (SD = 6.50); large sphere 67.98 cm/s (SD = 4.53); horizontal cylinder 74.35 cm/s (SD = 3.8). After inactivation the values were the following: thin plate 53.67 cm/s (SD = 8.03); large sphere 47.34 cm/s (SD = 13.6); horizontal cylinder 50.28 cm/s (SD = 3.91).

The mean values of peak velocity for the ipsilateral hand prior to inactivation were the following: thin plate 72.45 cm/s (SD = 2.62); large sphere 78.26 cm/s (SD = 3.68); horizontal cylinder 76.64 cm/s (SD = 5.83). After inactivation they were: thin plate 43.50 cm/s (SD = 5.91); large sphere 47.30 cm/s (SD = 4.36); horizontal cylinder 50.89 cm/s (SD = 3.19). It is clear that, following inactivation, both arms were impaired. Particularly affected were movements directed towards large objects when performed by the contralateral arm, while the deficit was virtually equal for all objects when movements were performed by the ipsilateral arm. Note that while the scaling according to object size was no longer evident during movement made with the contralateral arm, it was still present with the ipsilateral arm, the difference between the small object and the horizontal cylinder being significant [$t(9) = 2.65$, $P < 0.05$].

Large inactivations

Clinical picture. Following a double muscimol injection in the hand field of area F1, the neurological deficits were the same as those after a single injection, but more severe. In Monkey 1 the paresis of the contralateral hand was such as to produce a complete incapacity to grasp small objects, especially when they were placed on a flat surface. In Monkey 2, the distal deficits were less strong and accompanied by some impairment of proximal movements.

Formal testing. The testing of Monkey 1 in the formal reaching/grasping task showed a deficit more severe than in clinical testing. Grasping was completely disrupted. As after a single injection, the monkey tried to reach for the objects, but used an awkward hand configuration that did not allow a correct grasping and pulling of the objects.

Figure 2, lower row right, shows the trajectories and the velocity profiles of the transport component of the contralateral hand recorded after injection in the bank of area F1 in Monkey 2. The peak velocity mean values were the following: thin plate 57.37 cm/s (SD = 4.19); large sphere 66.16 cm/s (SD = 5.6); horizontal cylinder 56.21 cm/s (SD = 4.6). Peak velocity was significantly reduced for all objects [thin plate $t(16) = 9.95$, $P < 0.001$; large sphere $t(14) = 9.5$, $P < 0.001$; horizontal cylinder $t(15) = 11.59$,

$P < 0.001$]. The trajectories of the contralateral hand deviated toward the right side with all objects, but the monkey always reached the end point. The deviation of trajectories is likely to be due to an extension of the inactivation to the shoulder field. An alternative possibility is that this deficit was due to the presence in the hand field of neurones controlling proximal hand movements intermingled with those controlling distal hand movements. The trajectory deviation particularly impaired the grasping of the horizontal cylinder. A significant difference in peak velocity was present between the small object (thin plate) and one of the large objects (sphere) [$t(11) = 3.24$, $P < 0.01$]. It was absent between the small object and the horizontal cylinder, possibly due to the large increase of reaching time for this latter object (pre-inactivation time = 281 ms, post-inactivation time = 675 ms).

Anatomical locations of the injection sites

As described in Methods, histological correlation is only available for Monkey 1. The left hemisphere of this monkey is shown in Fig. 5 (upper left). The outlined rectangle shows the cortex that was functionally explored (see Methods) plus some adjacent frontal and parietal areas. All injection sites, as defined by stereotaxic coordinates, were reconstructed**.** The lower part of Fig. 5 shows two injection sites, one in F5 convexity (section 1), one in F5 bank (section 2). The location of the inactivation sites was in accordance with the presumed site locations based on the functional properties of the recorded neurones.

Discussion

Deficits after inactivation of area F1 (area 4)

The inactivation of the hand field of area F1 caused severe deficits in the execution of contralateral hand and finger movements. They consisted of force reduction, hypotonia and a strong impairment in the capacity to perform individual finger movements. The presence of hand paresis probably also explains the fact that the scaling of arm peak velocity was difficult to detect following F1 inactivation. However, in Monkey 2, which had a weaker paresis, this scaling was still present in part. The spared correlation between arm velocity and object size, typical of normal monkeys (Fogassi *et al.*, 1991) and humans (Gentilucci *et al.*, 1991; Paulignan *et al.*, 1991; Corradini *et al.*, 1992), supports the executive nature of the observed deficits. Had monkeys lost the capacity to perform the visuomotor transformations, the reaching movements would have been executed at a fixed, stereotyped velocity.

The symptomatology observed following F1 inactivation is in full accord with classical data reporting force deficit, flaccidity, and severe impairment in individual finger movements after lesioning of the primary motor cortex (Trendelenburg, 1911; Jacobsen, 1934; Fulton, 1943; for recent reviews see Hepp-Reymond, 1988; Porter and Lemon, 1993). They also confirm the recent inactivation data showing that muscular weakness is one of the main consequences of F1 inactivation (Brochier *et al.*, 1999; see also Matsumura *et al.*, 1991; Schieber and Poliakov, 1998*a*).

Hand movements are represented, in addition to F1, in several other motor areas (Mitz and Wise, 1987; Luppino *et al.*, 1991; He *et al.*, 1993; see also Rizzolatti *et al.*, 1998), some of which, like F2 and F3, have direct connections with the spinal cord (Murray and Coulter, 1981; Dum and Strick, 1991; He *et al.*, 1993; Porter and Lemon, 1993). The present data show that, in spite of this, the activity of F1 cannot be compensated by other motor areas even in the case of limited damage to F1.

The reversible inactivation of the F1 shoulder field produced hypotonia and a pronounced decrease in the forelimb force, especially on the side contralateral to the inactivation. The deficits caused a strong reduction in the velocity of reaching movements, but did not affect the ability to grasp objects. These findings confirm the selectivity of the performed inactivations and, in addition, stress the specificity of F1 functional fields.

Deficits after inactivation of F5 (bank sector)

The major deficit following inactivation of the bank sector of area F5 was the loss of monkey capacity to shape the hand according to the visual characteristics of the object during grasping movements. The deficit was particularly evident for small objects, for which it was also present following small inactivations. After large inactivations the grasping of large objects was also affected.

A striking difference between motor behaviour following inactivation of F1 and F5 was that, following F5 inactivation, monkeys were still able to grasp and manipulate objects after touching them. The execution of individual finger movements was preserved. It was the visuomotor transformation leading to action that was impaired. The visuomotor nature of the deficits was confirmed by the study of transport kinematics. The influence of object size on peak velocity of the transport component was lost after F5 inactivation. This was true even for the large objects that, judging from hand configuration, were grasped in a correct fashion.

A second important difference between F1 and F5 lesions was that, following F5 inactivation, both hands and not only that contralateral to the lesion were affected. It is important to note that while some motor weakness and clumsiness could be observed in the hand contralateral to the lesion after F5 inactivations, especially in the case of large inactivations, the deficit of the ipsilesional hand was exclusively visuomotor. The presence of ipsilateral hand deficit is consistent with the presence in area F5 of a high percentage of neurones that discharge in association with movements of the ipsilateral, as well as of the contralateral hand (Rizzolatti *et al.*, 1988).

It is important to note that the symptomatology following inactivation of F5 (bank) is very similar to that obtained after inactivation of area AIP, that is, of the parietal area of which

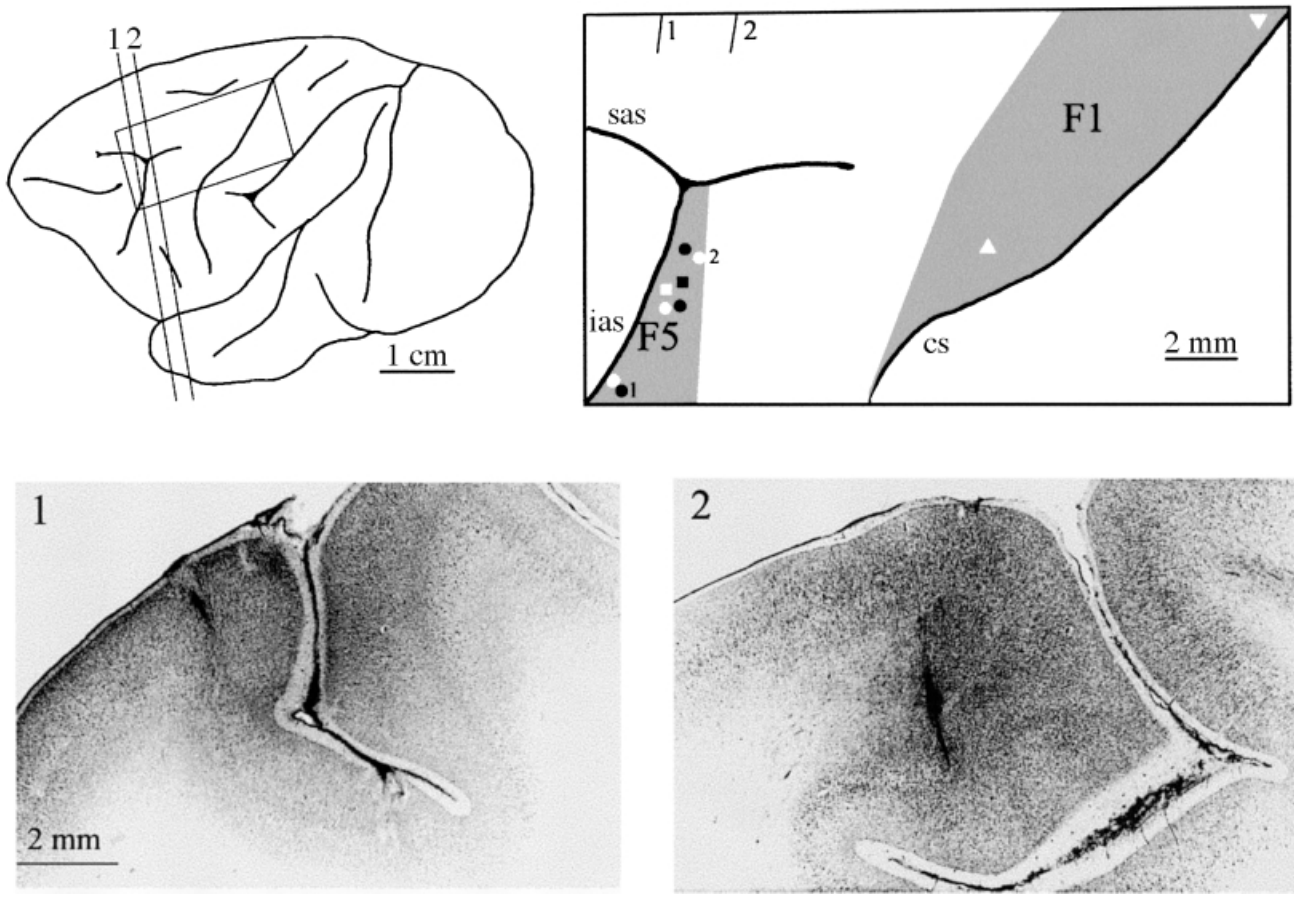

Fig. 5 Anatomical location of the injection sites. The upper left panel shows a lateral view of the left hemisphere of Monkey 1. The rectangle highlights the cortical region which was functionally characterized by means of single neurone recordings and intracortical electrical microstimulation, plus some adjacent frontal and parietal areas. The upper right panel shows an enlarged view of the same region. Shaded areas indicate the sectors of areas F5 and F1 which were mapped in detail in the present study. Symbols indicate the entry points of the different muscimol injections. Empty square = single injection in F5 bank; empty circles = triple injection in F5 bank; filled square = single injection in F5 convexity; filled circles = triple injection in F5 convexity. Note that the entry points of injections in F5 convexity are not necessarily caudal to those of injections in F5 bank, the crucial localizing factor being the injection depth (see text). Upright and inverted triangles indicate the entry points of two single injections in F1 hand and shoulder sectors, respectively. The small numbers (1 and 2) near the filled and the empty circles correspond to the two injection tracks shown in the lower panels **1** and **2**, respectively. The lower panels illustrate two photomicrographs of the two coronal sections indicated with vertical lines in the upper panels. The sections, stained with the Nissl method, show the location of two injection sites in F5 convexity (section 1), and F5 bank (section 2). Cs = central sulcus; ias = inferior arcuate sulcus; sas = superior arcuate sulcus.

F5 is the major target (see Introduction). In both cases the deficit consists of a deficit of hand shaping for grasping objects, particularly small objects, with a lengthening of movement time. In both cases the affected grip can be corrected with tactile exploration of the target objects (Gallese *et al.*, 1994, 1997).

The visuomotor deficits observed after inactivation of areas AIP and F5 are in accordance with the neuronal properties of these areas. On the basis of their common characteristics, it has been proposed that F5 and AIP constitute a circuit for the visual guidance of hand movements (Jeannerod *et al.*, 1995; Murata *et al.*, 1997; Gallese *et al.*, 1997; Rizzolatti *et al.*, 1998; see also Fagg and Arbib, 1998 for a computational model of the circuit). This proposal is fully supported by the results reported here.

Neglect deficits after reversible inactivation of F5 (bank sector)

Some years ago Rizzolatti and colleagues described that, following lesion of the ventral part of the postarcuate cortex (the cortex lying caudal to the inferior limb of the arcuate sulcus), monkeys showed neglect of somatosensory and visual stimuli presented in the contralesional personal and peripersonal space (Rizzolatti *et al*., 1983). A similar deficit was recently reported by Schieber and Poliakov and, later, Schieber after reversible inactivation of the same cortical region (Schieber and Poliakov, 1998*b*; Schieber, 2000).

The neglect following postarcuate cortex lesion has been interpreted as being due to damage of the caudal sector of the postarcuate cortex, namely of area F4, rather than to damage of F5 (Rizzolatti and Berti, 1990; Rizzolatti *et al.*,

1994). This is because the receptive field properties of F4 neurones indicate their involvement in coding of space (Gentilucci *et al.*, 1983, 1988; Fogassi *et al.*, 1992, 1996; Graziano *et al.*, 1994, 1997) and because the neglect deficit following postarcuate lesions appeared as a negative image of F4 receptive field organization.

However, the results reported in the present study, while confirming the presence of neglect symptomatology after postarcuate lesion, also show that a lesion of F5 alone (without involvement of F4) may determine neglect symptoms. How can this finding be reconciled with F5 neurone properties? A possibility is that the spatial neglect after an F5 lesion is not due to damage of typical F5 neurones (see Introduction), but to a population of neurones, located in F5, which are endowed with a receptive field organization similar to those of F4 neurones.

Two independent lines of evidence appear to support this view. First, besides containing neurones responding to object presentation and mediating visuomotor transformations for grasping, F5 contains a small percentage of neurones with spatial properties similar to those of F4 neurones (our unpublished observations). Secondly, Savaki and Dalezios in a [^{14}C]deoxyglucose mapping study of the monkey brain during reaching for visual targets, showed a strong metabolic activation in a strip located within the posterior bank of the inferior limb of the arcuate sulcus (Savaki and Dalezios, 1998). Since solving a reaching task requires spatial information, this finding suggests that a sector within F5 is functionally different from the rest of this area and elaborates spatial information.

In conclusion, these results suggest that area F5, in addition to its role in transforming the 3D features of an object into motor representation enabling distal movements, also plays a role in coding space. It is possible that the close anatomical proximity of neurones involved in the two tasks may give some time advantage for coordinating proximal and distal movements.

Motor deficits after inactivation of F5 (convexity)

Functionally, F5 convexity is different from F5 bank. The major difference is that visuomotor canonical neurones—those responding to object presentation—are rare in that location, whereas mirror neurones—those active during action observation—are common. If the hypothesis that the visuomotor transformations necessary for grasping objects are carried out by canonical neurones is true, inactivations of F5 convexity should have a minor, if any, effect on hand shaping preceding object grasping.

The results confirmed this hypothesis. After inactivation of F5 convexity, the hand shaping during reaching-to-grasp movements was normal. Similarly, unlike after F5 bank inactivation, the scaling of arm peak velocity with respect to the object size remained normal. The only evident deficit was the decrease in peak velocity of the contralateral hand. The majority of motor neurones located in F5 convexity discharge in association with distal and not proximal movements. Thus, movement slowness, observed following F5 convexity inactivation, most likely reflects a reduction in grasping skill and the assurance that, with normal hand transport velocity, the object will be efficiently grasped, rather than a primary deficit in the arm transport.

Clinical implications

The inactivation data of the present study and those concerning the inactivation of area AIP (Gallese *et al.*, 1994) clearly show that in the monkey there is a cortical circuit for visuomotor transformations necessary for visually guided hand movements. This circuit, previously suggested on the basis of single neurone studies, is formed by parietal area AIP, premotor area F5, and the primary motor cortex F1 (see Jeannerod *et al.*, 1995; Rizzolatti *et al.*, 2000). Recent data strongly suggest that a similar circuit also exists in humans. Using functional MRI, Binkofski and colleagues showed that the manipulation of multifaceted objects, requiring continuous changes of finger configurations, produced a selective activation of a sector of the intraparietal sulcus and of the ventral premotor cortex (Brodmann area 44) (Binkofski *et al*., 1999). On the basis of their anatomical location and cytoarchitectonic characteristics, these areas are likely to be the human homologues of monkey areas AIP and F5, respectively. Thus, it is plausible that the visuomotor transformations described by monkey single neurone studies also occur in humans.

Traditionally, the organization of distal movements in humans has been considered to depend basically on the integrity of the primary motor cortex. However, impairments in distal movements have also been described following premotor cortex lesions. A well-known syndrome related to a lesion restricted to the premotor cortex is myelokinetic apraxia (Kleist, 1934). In this syndrome, patients are unable to manipulate objects correctly in the absence of any obvious deficit of force. As described by Kleist, they behave as if they have never used the common objects before they were asked to manipulate them (Kleist, 1934).

Parietal patients with optic ataxia also have difficulties in shaping the hand according to the physical properties of objects to be reached and grasped (see De Renzi 1982). In some of these patients, some time after the lesion has occurred, the reaching deficits may recover leaving the capacity to correctly orient and shape the hand impaired (see Jeannerod *et al.*, 1994). Recently, evidence has been provided that in humans there is a representation of distal movements in the anterior part of the lateral bank of the intraparietal sulcus. Binkofski and co-workers described that, after a lesion centred to this region, patients show selective deficits in the coordination of finger movements required for grasping objects, their reaching movements being only mildly disturbed (Binkofski *et al.*, 1998).

Taken together, all these data indicate that, in both humans and monkeys, distal and proximal movements are organized in parallel circuits, each of which perform specific computational operations. The implication of this finding is that in humans, a cortical lesion may affect both proximal and distal movements, independently or simultaneously. The prevalence in parietal lesions of symptomatology affecting proximal movements is probably due to there being a greater probability of the proximal system being affected by pathological noxa.

Finally, it is interesting to note that the inactivation of area AIP and F5 gave very similar deficits. This finding strongly suggests that with small lesions not invading adjacent structures, the deficits following parietal and premotor lesions could also be virtually indistinguishable in humans.

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