

SHORT COMMUNICATION

Cortical reorganization after brain damage: the oculomotor model

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Abstract

Recovery from eye movement deficits after cortical lesions is amazingly rapid and almost complete, which is in sharp contrast to most other neurological deficits of cerebral lesions. The underlying mechanisms of this successful recovery remain uncertain. We had the rare opportunity to examine two patients with recovery from saccade deficits after a lesion restricted to the frontal eye field (FEF) by means of transcranial magnetic stimulation (TMS). The results provide direct evidence that recovery depended on the integrity of the oculomotor regions of the nonlesioned contralesional hemisphere, and that the compensatory network is task-specific.

Introduction

When studying mechanisms of neuroplasticity and recovery after brain lesions, the oculomotor system has two decisive advantages: (i) eye movements can be easily and precisely recorded and (ii) the subcortical and cortical organization of eye movements involving distinct regions in parietal and frontal lobes is well understood (reviewed in e.g. Pierrot-Deseilligny *et al.*, 1995; Leigh & Zee, 1999).

From monkey studies it is known that surgical ablation of the frontal eye field (FEF) has little effect on oculomotor behaviour as long as the other oculomotor structures are left intact. In contrast, the simultaneous removal of both the FEF as well as the superior colliculus (Schiller *et al.*, 1980) or the parietal eye field (PEF; Lynch, 1992) have profound effects on the oculomotor behaviour. These lesion studies suggest that the neuronal network controlling eye movements is capable of compensating for the loss of one single centre area by transferring its function to the nonlesioned oculomotor areas.

Whether similar mechanisms of recovery of eye movements after a cortical lesion are effective also in humans is not known. Apart from a transfer of function from the lesioned to an intact region of the ipsilesional or contralesional hemisphere within the oculomotor network, the taking over of function by the area adjacent to the lesion is also discussed (Werhahn *et al.*, 2003).

To test these hypotheses we stimulated different ipsilesional and contralesional cortical regions of the oculomotor network with single pulse transcranial magnetic stimulation (TMS). TMS is today an established method to study cortical plasticity and recovery mechanisms (Pascual-Leone *et al.*, 2000). This method allows the transient inactivation of a cortical region, and therefore acts as a transient 'virtual lesion'. If the hypothesis of a transfer of function within the oculomotor network is true, inactivating a region within the network that participated as a substrate in mediating functional recovery should uncover the original deficit in a patient who has recovered. However, if the hypothesis of a cortical reorganization adjacent to the lesion is true, inactivation of nonlesioned

regions within the oculomotor network should not uncover the original deficit. In two patients, whose eye movement disorder recovered after a small cortical stroke restricted to the FEF, we measured visually guided horizontal saccades using two types of saccade paradigms (i.e. overlap and gap paradigm, Fig. 2) during which TMS was applied. An acute lesion of the FEF in humans influences saccade triggering by increasing contralesional saccade latency in the overlap, but not in the gap paradigm (Rivaud *et al.*, 1994; Gaymard *et al.*, 1999; Pierrot-Deseilligny *et al.*, 2002). Three cortical regions of the oculomotor network were stimulated: the contralesional frontal cortex including the FEF and the ipsilesional and contralesional posterior parietal cortex (PPC) including the PEF. We hypothesized that contralesional latencies should be increased in the overlap, but not in the gap paradigm if the region responsible for recovery is inactivated by TMS.

Materials and methods

Subjects

The study was approved by the local ethical committee of the University of Bern and was consistent with the Declaration of Helsinki. Both patients gave written consent prior to participation.

Patient 1

A 64-year-old, right-handed man was hospitalized after sudden clumsiness of his right hand. There was no visual field defect and no sign of neglect, he had corrected to normal vision. Intentional saccades, which were hypometric to the right side recovered within three weeks. Diffusion-weighted magnetic resonance imaging showed a small hyperintense, ischemic lesion affecting the FEF (see Fig. 1). The eye movement recording and TMS session was also performed 8 weeks after the stroke.

Patient 2

A 61-year old, right-handed woman was hospitalized after sudden paresis of her left hand. Visual fields were unaffected, there was no

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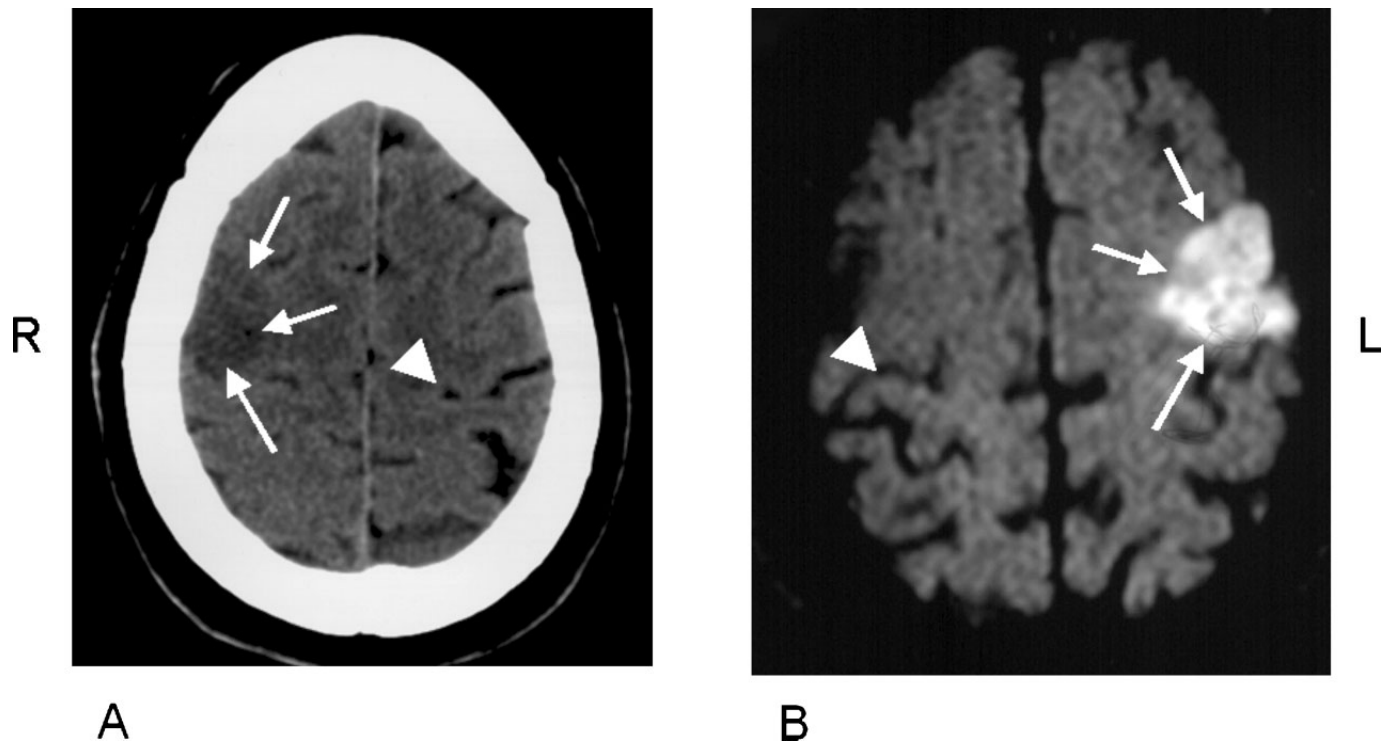


FIG. 1. (A) A representative CT scan slice of patient 2 with the right FEF lesion, marked by three arrows. (B) Diffusion-weighted MR-imaging of patient 1 with the left FEF lesion. The anatomical localization of the FEF in humans is at the superior part of the precentral sulcus, near the caudal end of the superior frontal sulcus (Rosano *et al.*, 2003). The central sulcus is marked on the other hemisphere by a white triangle.

neglect and she had normal vision. Intentional saccades, which were hypometric to the left side recovered within four weeks. Computer tomography revealed a hypodense lesion affecting the right FEF (see Fig. 1). The eye movement recording and TMS session was performed 8 weeks after the stroke.

Oculomotor paradigm

Two oculomotor paradigms were tested (Fig. 2A). In the gap paradigm, a central fixation point was presented with pseudo-randomised durations between 1500 and 2500 ms. A lateral target at 12° from the central fixation point (with unpredictable direction) appeared 200 ms after the offset of the central fixation point and was shown for 1000 ms. In the overlap paradigm, the central fixation point remained visible during the presentation of the lateral target. Subjects had to perform a saccade to the target. Subjects were seated in total darkness with the head on a chin rest to avoid head movements. Eye movements were measured bitemporally by means of electro-oculography (EOG; sampling frequency 1000 Hz, bandwidth 0–100 Hz). The digitized signal was stored on the computer for the off-line analysis.

For each condition (no stimulation, TMS over the contralesional FEF, TMS over the ipsilesional and contralesional PEF) and direction of saccades (left, right), at least 15 saccades with gap or overlap condition were acquired. The trials were presented in blocks with constant stimulation site/condition.

TMS procedure

TMS was applied over the contralesional FEF, the ipsilesional PPC and the contralesional PPC by using a MagStim high speed Stimulator (MagStim Company Limited, Wales, UK) with a round coil (diameter 120 mm) 100 ms after the appearance of the lateral visual target.

The FEF was localized according to previously described procedures (Müri *et al.*, 1991; Thickbroom *et al.*, 1996; Ro *et al.*, 1999). In brief, the individual motor threshold was determined by slight muscle twitching of the subject's relaxed small hand muscles. The stimulus intensity was set to 60–70% of the stimulator output, being 110 and 125%, respectively, of the individual motor resting threshold in all subjects. The handle was then moved anterior to the hand area, 2–3 cm on average. The handle of the coil was pointed backwards and the inducing current was from posterior to anterior. The coil was fixed in position using a holding clamp and a tripod.

The region of the PPC was stimulated (Elkington *et al.*, 1992; Müri *et al.*, 1996) by placing the posterior part of the coil tangentially 3 cm posteriorly and 3 cm laterally to the vertex, while the anterior part was lifted from the scalp, the handle pointing backwards. As the magnetic field declines very rapidly with increasing distance, this placement prevents an unsuitable spread of the stimulus, which is kept sufficiently large to achieve the desired effect. Stimulus intensity was identical to that of FEF stimulation, the coil was fixed similarly as in FEF stimulation.

Statistical analysis of the data

For the gap and overlap paradigm, the mean latency for each direction was calculated from 15 trials without stimulation. Then, and in order to compare the TMS effects between patients, we calculated the percentage increase in latency with stimulation for each patient separately. The value was calculated as a percentage for the different TMS conditions and for each direction as follows: $100 \times [(latency \text{ with stimulation} / \text{mean latency without stimulation}) - 100]$. Thus, a value of 0% means no TMS effect on saccade latency. In a next step, the data of both patients were regrouped to ipsilesional and contralesional saccades, and to ipsilesional and

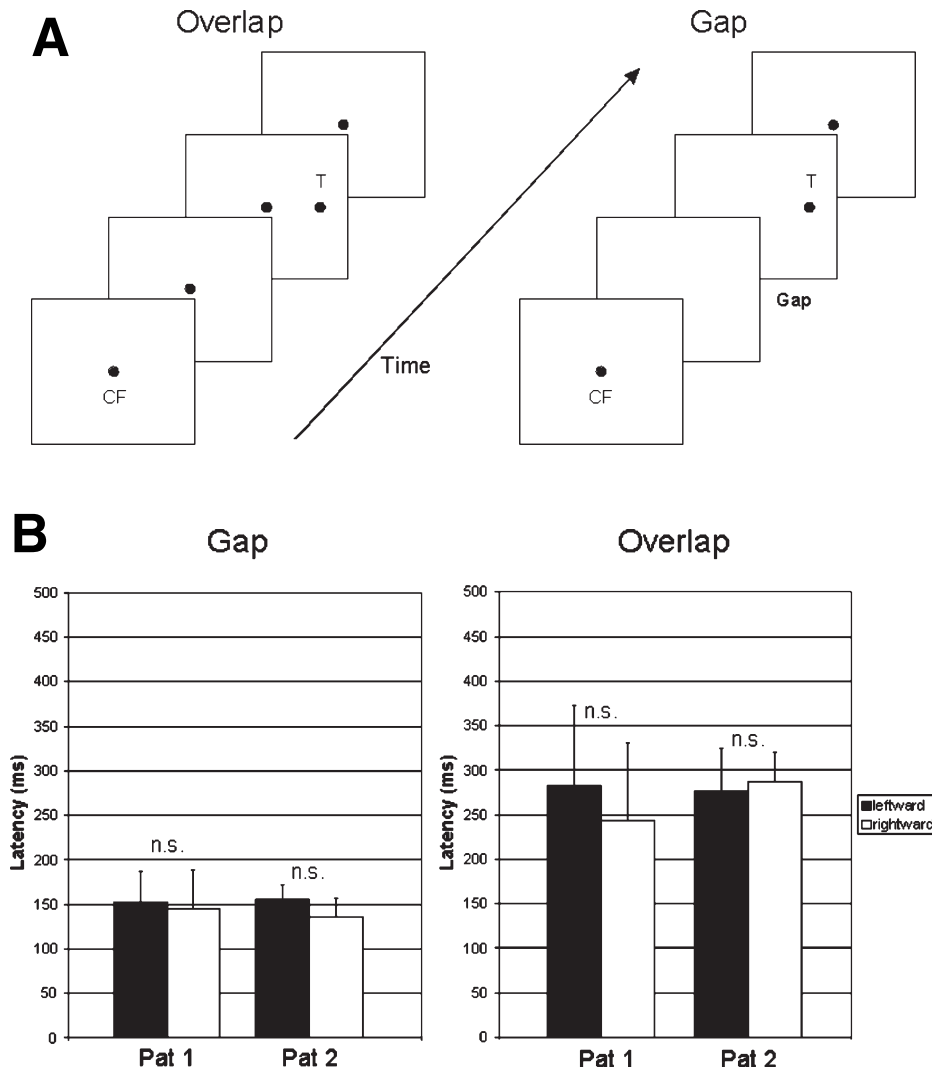


FIG. 2. (A) Two basic oculomotor paradigms were tested, both requiring patients to perform visually guided saccades to a lateral target. In the gap paradigm, a central fixation point (CF) was presented with pseudo-randomised durations between 1500 and 2500 ms. A lateral target (LT) 12° from the CF (with unpredictable direction) appeared 200 ms after the offset of the CF and was shown for 1000 ms. Patients had to perform a saccade to the target. In the overlap paradigm, the CF remained visible during the presentation of the LT. (B) Mean saccade latencies (standard deviation) without TMS are shown for the gap and overlap paradigm. In both patients there were no significant differences between leftward and rightward saccades suggesting recovery from the saccade deficit.

contralesional stimulation sites. The mean percentage of change in latency was calculated for each condition, and the statistical comparison was based on a one sample *t*-test against a hypothetical value of 0% (i.e. TMS has no effect).

Results

Mean saccade latencies of both patients without TMS are shown in Fig. 2B. In each patient, there was no significant difference in latency between leftward and rightward saccades, as revealed by *t*-test.

In the gap paradigm (Fig. 3A), stimulation of the contralesional FEF had no significant effect on percentage of increase in latency (for contralesional saccades, 3%; for ipsilesional saccades, 3%), which may be explained by the fact that the FEF is not critically involved in the control of the gap paradigm. Stimulation of the PEF resulted in a significant percentage increase in latency (contralesional stimulation, for contralesional saccades 5%, for ipsilesional saccades 17%; ipsilesional stimulation, for contralesional saccades 17%, for ipsilesional saccades 5%).

A different pattern was observed in the overlap condition (Fig. 3B). The percentage increase in latency for contralesional saccades significantly increased after contralesional FEF stimulation (for contralesional saccades 23%, for ipsilesional saccades 4%) and PEF stimulation (for contralesional saccades 14%, for ipsilesional saccades 2%), respectively. Such a TMS effect is the reverse of that found in the gap paradigm in our patients and what is generally observed in healthy subjects. We therefore performed a control experiment in three healthy subjects. The percentage of increase in latency after frontal and parietal stimulation significantly increased for contralateral saccades (Table 1), but not for ipsilateral saccades. These results indicate that transient inactivation of the contralesional oculomotor network by TMS uncovered the original saccade deficit after the FEF lesion.

Stimulation of the ipsilesional PEF resulted also in a significant increase in the contralesional percentage increase in latency (for contralesional saccades 17%, for ipsilesional saccades 8%). As the TMS effect is in the order what we expect from experiments in healthy subjects, a contribution of this region to oculomotor recovery is difficult to evaluate.

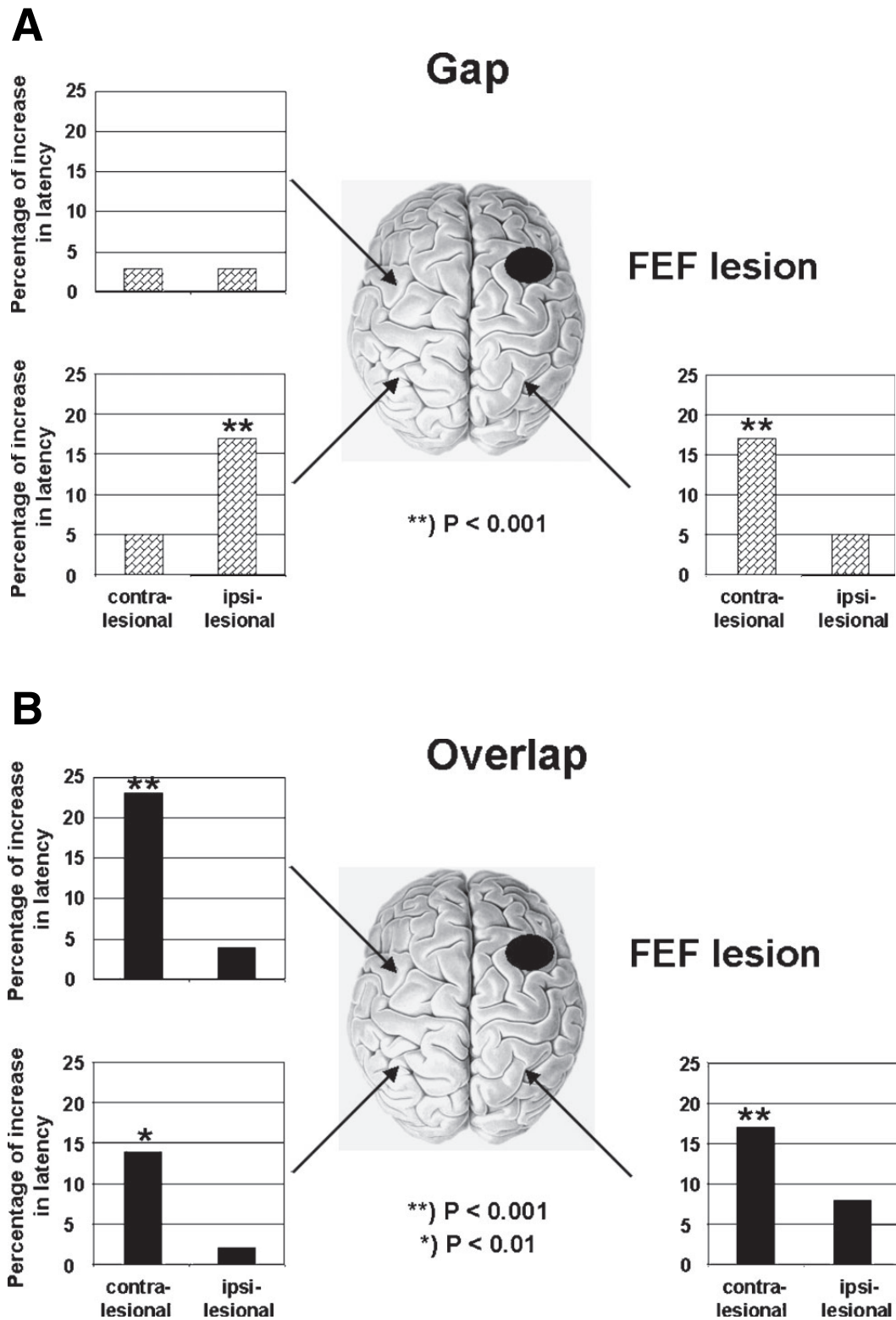


FIG. 3. (A) The results of the gap paradigm are shown. Bars show the mean percentage of change in latency. Saccade triggering in the gap paradigm, which is not under FEF control, was not influenced by FEF stimulation. Parietal stimulation affected gap saccade triggering exclusively for contralateral direction. (B) The results of the overlap paradigm are shown. Bars show the mean percentage of change in latency. In the overlap paradigm, which is under FEF control, TMS of the contralesional FEF and PPC induced significant increase in latency of contralesional (i.e. ipsilateral to the stimulation site) saccades. This effect is the 'reverse' of that observed in the gap paradigm.

Discussion

The current study provides direct evidence that the compensating oculomotor regions involved in the recovery processes are mainly

in the contralesional hemisphere. Both frontal and parietal stimulation of the contralesional hemisphere uncovered the original FEF deficit in the overlap paradigm. Therefore, the hypothesis of a

TABLE 1. Effect of TMS in healthy subjects on the percentage of increase in latency after frontal and parietal stimulation

Stimulation	Increase in latency after stimulation (%)			
	Left hemisphere		Right hemisphere	
	Ipsilateral	Contralateral	Ipsilateral	Contralateral
Frontal	7 ± 2.4	15 ± 3.7*	6 ± 2.4	11 ± 3.1*
Parietal	6 ± 3.7	17 ± 4.8*	5 ± 3.6	16 ± 3.9*

The data are presented as means ± SEM. The percentage significantly increased for contralateral saccades, but not for ipsilateral saccades. This contrasts with the TMS effect observed in our patients. * $P < 0.05$.

takeover of function by regions adjacent to the lesion seems unlikely. This is in contrast to recovery mechanisms after lesions of the motor cortex; ipsilateral areas seem to play a major part in those patients who show a fair recovery (Fridman *et al.*, 2004) while the contralesional motor cortex only come into play in poorly recovered patients (Turton *et al.*, 1996; Johansen-Berg *et al.*, 2002).

An explanation for the underlying mechanism for oculomotor recovery may be that FEF and PPC neurons have the potential to operate saccades in both directions. Single cell recordings in monkeys have shown saccade-related activity for contralateral and ipsilateral saccades (Schlag *et al.*, 1998; Barash *et al.*, 1991). Furthermore, a recent study (Seidemann *et al.*, 2002) in monkeys found, that the direction of the saccade elicited by electrical stimulation depended on the state of depolarization or hyperpolarization of the FEF. These and the current results suggest that in the intact brain, ipsilateral saccade direction is inhibited by transcallosal interactions of the homologous area of the other hemisphere. The lesion of one area may result in the loss of the transcallosal inhibition and the contralesional area may take over the control of saccade triggering in both directions. Such biological mechanisms would explain the rapid and near complete recovery of eye movements as observed in clinical practice.

In the motor cortex, recovery of motor function seems to depend on inhibitory interhemispheric interactions between homologous areas (reviewed in Ward & Cohen, 2004). Poor motor recovery correlated with an abnormally high interhemispheric inhibition between the primary motor cortices of the intact and lesioned hemisphere in patients with chronic subcortical stroke. (Murase *et al.*, 2004). An imbalance of interhemispheric inhibition may therefore play a decisive role in functional recovery of both oculomotor and motor function.

A further important result of the study is that recovery and compensation mechanisms in the oculomotor domain seem to be task-specific; in the gap task where the FEF is not involved much, contralesional FEF stimulation had no significant effect on saccade latency. Furthermore, contralesional parietal stimulation showed no 'reverse' effect on saccade triggering suggesting that the compensatory network is not used for saccade control when the patients had to perform gap saccades. This indicates a high flexibility of the brain for reorganization of the network involved in eye movement control.

In conclusion, the results demonstrate that the rapid and almost complete recovery from eye movement disturbances after a FEF lesion is due to a compensatory substitute within the cortical network involving the contralesional hemisphere. Perilesional takeover of lost function or ipsilesional compensation by the parietal areas are less probable. Finally, the compensatory mechanisms are function-specific, i.e. the contralesional network

is used only for the paradigm, which is under the control of the FEF.

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Abbreviations

FEF, frontal eye field; PEF, parietal eye field; PPC, posterior parietal cortex; TMS, transcranial magnetic stimulation.

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