Human eye fields in the frontal lobe as studied by epicortical recording of movement-related cortical potentials

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Summary
We studied the generator location of premovement subcomponents of movement-related cortical potentials (MRCPs) [Bereitschaftspotential (BP), negative slope (NS′) and motor potential (MP)] associated with voluntary, self-paced horizontal saccade in the human frontal lobe. Self-paced horizontal saccade, wrist (or middle finger) extension and foot dorsiflexion were employed in 10 patients (lateral surface of the frontal lobe in seven and mesial in three) as part of the presurgical evaluation, and data of five patients (lateral in four and mesial in three) were used in the final analysis. On the lateral frontal lobe, the maximum BP, NS′ or MP with horizontal saccade was seen at or 1–2 cm rostral to the hand, arm or face area of the primary motor cortex (MI) in all four subjects investigated. This area exactly corresponded to the frontal eye field (FEF) identified by electrical stimulation. The amplitude of MRCPs with saccade was smaller than that with hand movements. On the mesial surface, within the supplementary motor area (SMA) proper, BP and/or NS′ for horizontal saccade was located 1–2 cm rostral to that for hand and foot movements. BP and/or NS′ delineated the supplementary eye field (SEF) at the rostral part of the SMA proper, and SEF partly overlapped with the hand and foot areas of the SMA proper. At the area just rostral to the vertical anterior commissure line and/or the pre-SMA defined by electrical stimulation, BP and/or NS′ was seen invariably, regardless of the sites of movements, and in contrast with the SMA proper, there was no somatotopic representation. No clear MPs were elicited by eye movements on the mesial surface. In one of the two subjects whose MRCPs with horizontal saccade were recorded simultaneously from the lateral and mesial surfaces of the frontal lobe, BP from the SEF and pre-SMA preceded that from the FEF. It is concluded that MRCPs with horizontal saccade are useful for defining the FEF, SEF and pre-SMA, and that the SEF and pre-SMA become active in preparation for horizontal saccade earlier than the FEF.

Keywords: human eye field; frontal lobe; movement-related cortical potential (MRCP); horizontal saccade; epicortical recording

Abbreviations: AD = afterdischarge; BP = Bereitschaftspotential; ECoG = electrocorticogram; NS′ = negative slope; MP = motor potential; MRCP = movement-related cortical potential; MI = primary motor area; SI = primary sensory area; SMA = supplementary motor area; FEF = frontal eye field; SEF = supplementary eye field; VAC = vertical anterior commissure

Introduction

Since the first description of Bereitschaftspotential (BP) by Kornhuber and Deecke in 1965, movement-related cortical potentials (MRCPs) preceding self-paced, repetitive voluntary movements have been recognized to reflect a central motor control process (Kornhuber and Deecke, 1965; Shibasaki et al., 1980; Barrett et al., 1986). Through extensive studies by means of subdural electrodes in epilepsy patients, MRCPs have been shown to be generated from the primary sensorimotor area (MI-SI), supplementary motor area (SMA) proper and pre-SMA (Neshige et al., 1988; Sakamoto et al., 1991; Ikeda and Shibasaki, 1992; Ikeda et al., 1992, 1995a, b; Yazawa et al., 1997, 1998, 2000). By combined studies with electrical stimulation, somatotopic localization of MRCPs along the central sulcus and in the SMA proper has been demonstrated (Neshige et al., 1988; Ikeda and Shibasaki, 1992; Ikeda et al., 1992, 1995a, b; Ikeda and Shibasaki 2003).

Two distinct cortical eye fields have been identified by electrical stimulation and neuroimaging studies in the human frontal lobe. One is the frontal eye field (FEF) located on the lateral convexity (Foerster, 1931, 1936; Penfield et al., 1950, 1954; Woolsey et al., 1979; Godoy et al., 1990; Paus 1996; Luna et al., 1998; Lobel et al., 2001), and the other is referred to as the supplementary eye field (SEF) on the mesial aspect (Penfield et al., 1950, 1954; Woolsey et al., 1979; Lim et al., 1994; Petit et al., 1996; Grosbras et al., 1999). Previous studies with electrical cortical stimulation have shown that the FEF is located just rostral to the MI between the face and arm areas (Godoy et al., 1990; Blanke et al., 2000). The SEF in humans is closely associated with the head region of the SMA proper (Lim et al., 1994). It has been suggested that the FEF is involved in preparation for and the triggering of purposive saccades, whereas the SEF is important in integrating oculomotor and skeletomotor behaviour (Pierrot-Deseilligny et al., 1995; Gaymard et al., 1998; Tehovnik et al., 2000).

So far in functional neurosurgery, little attention has been paid to the cortical areas in the frontal lobe responsible for oculomotor movements, possibly because a restricted unilateral cortical lesion produces only minor and transient clinical oculomotor deficits (Pierrot-Deseilligny et al., 1995). Moreover, the somatotopic mapping of eye fields by means of MRCPs recorded from subdural electrodes has not been thoroughly investigated, because the majority of intracranial studies of MRCPs have employed hand or finger movements (Sakamoto et al., 1991). To our knowledge, there has been only one study in which MRCPs with voluntary horizontal saccade were recorded simultaneously from FEF and SEF, but it was based on a single subject (Sakamoto et al., 1991).

Electrical cortical stimulation by subdurally placed electrodes is an established technique for mapping functional areas adjacent to the lesions in surgical candidates (Lüders et al., 1987; Lesser et al., 1992). However, the brain mapping it provides is fragmented, mainly due to the relatively long inter-electrode distance of the implanted electrodes. In addition, since epilepsy patients tend to have a low threshold for afterdischarges (ADs) in response to electrical stimulation, it is often impossible to increase the stimulus intensity so as to elicit a response. For these reasons, electrical stimulation may not always detect functionally critical brain areas.

In this study, in order to clarify where, on the lateral and mesial surface of the frontal lobe, each subcomponent of MRCPs with eye movements is generated, we recorded MRCPs associated with horizontal saccade in patients with a focal frontal lobe lesion manifesting partial epilepsy. We also investigated the functional difference between the FEF and SEF in two patients in whom MRCPs with saccade were recorded simultaneously from both areas. The results of the present study have appeared previously in abstract form (Yamamoto et al., 2002).

Methods

Subjects

MRCPs were recorded in 10 patients with brain tumour and/or intractable partial seizure. The subdural electrodes were placed on the lateral surface of the frontal lobe in all patients and on the mesial surface in seven of them. The data recorded at or adjacent to the brain lesions (lateral in six and mesial in two patients) were excluded from analysis in order to avoid the possible effect on the data. We also excluded the mesial frontal data of two patients whose subdural electrodes did not cover the SMA proper or pre-SMA as defined by electrical cortical stimulation. Furthermore, the mesial frontal data of one patient with medically intractable complex partial seizure was excluded from the final analysis because of frequent occurrence of habitual seizures during the recording. As the result, we finally analysed data recorded from four lateral and three mesial surfaces in five patients (Table 1). In two patients (Patients 3 and 4), we recorded MRCPs from the lateral and mesial surface simultaneously.

Each subdural electrode was made of platinum (AD-Tech, Racine, WI, USA) and arranged as a grid or strip. Each electrode, 3 mm in diameter, was placed with its centre 1 cm from that of the neighbouring ones. Informed consent was obtained from all patients before the investigation after the purpose and possible consequences of the studies had been explained according to Clinical Research Protocol No. 79, approved by the Committee of Medical Ethics, Kyoto University Graduate School of Medicine, Clinical Research Protocol No. 98-1, approved by the Ethics Committee of the Shizuoka Medical Institute of Neurological Disorders, and Clinical Research Protocol No. 25-1 of the Tokyo Women’s Medical University.

Data acquisition

Task movements consisted of self-paced, voluntary horizontal saccade, wrist or middle finger extension, and foot dorsiflexion, all contralateral to the implanted electrode.

For eye movements, the subjects were comfortably seated on a reclining bed. They were asked to fixate on a central fixation point on a white screen placed 110 cm in front of them, to move their eyes as quickly as possible to the visual target point, which was placed 25° contralateral to the implanted side, and to return immediately to the...
central position. The task was repeated every 5–10 s in a self-paced manner. An electro-oculogram (EOG) for horizontal eye movements was recorded by electrodes placed over the bilateral outer canthi. To identify and exclude the blink artefacts, an EOG for vertical eye movements was also recorded by the electrodes placed above and below the right eye.

For recording MRCPs associated with wrist or middle finger extension and foot dorsiflexion, the subjects lay comfortably on a bed in the supine position. Each individual task was performed in a self-paced manner once every 5–10 s, as done previously in the same laboratory (Ikeda et al., 1992, 1995a, b; Yazawa et al., 1997, 1998, 2000; Kunieda et al., 2000). An electromyogram (EMG) was recorded by a pair of cup electrodes placed over the skin overlying the extensor carpi radialis muscle in the forearm for wrist or finger extension, and the anterior tibialis muscle on the shin for foot dorsiflexion.

Before data acquisition, the subjects were trained so that they could perform each task briskly and correctly. Verbal instruction was given to the subjects as necessary whenever their performance was found to be poor. Electroocardiograms (ECoGs) were recorded continuously from 10–64 subdural electrodes with a bandpass filter setting of 0.015–120 Hz. All subdural electrodes were referenced to a scalp Ag–AgCl electrode placed on the skin over the mastoid process contralateral to the side of implantation.

**Data analysis**

All input signals were digitized at the sampling rate of 500 Hz and stored on magneto-optical disks with a digital EEG equipment (EEG 2100 and 1100; Nihon Kohden, Tokyo, Japan). After identifying the EOG or EMG onset of each task carefully by off-line visual analysis, we averaged artefact-free ECoG segments time-locked to the EOG or EMG onset. A total of more than 60 trials was selected for each subject, two ensemble-averaged waveforms were obtained for the time window from 3 s before to 2 s after the EOG or EMG onset. The baseline of the waveform obtained was determined by visual inspection of the individual average waveforms from the segment 3±2 s prior to movement onset. Peaks were determined by visual inspection of the individual average waveforms and measured with a cursor. The time to movement onset was measured relative to the EOG or EMG onset.

MRCPs preceding voluntary movements can be divided into three phases: the Bereitschaftspotential (BP), the negative slope (NS') and the motor potential (MP) (Kornhuber et al., 1965; Shibasaki et al., 1980; Barrett et al., 1986; Neshige et al., 1988). In this study, BP and NS' were defined as a negative or positive potential starting 1000–1500 ms and 100–400 ms, respectively, before the EOG or EMG onset. The MP was defined as a negativity beginning 50–100 ms before and peaking just after the movement onset. If NS' was followed by an MP with ill-defined onset, the NS' and the following premovement activity were described together as NS'/MP. The amplitude of BP was measured relative to the baseline (baseline to peak), and that of NS' and MP was measured from the peak of the preceding activity to its peak.

In order to characterize the time course of the slow potentials, the average responses were digitally low-pass filtered at 10 Hz. The mean ± 2 SD of the activity during the first 10% of the analysis window was defined as the level of resting activity. The onset of the slow response was determined with the aid of a linear regression line, as shown in Fig. 1. The regression line for BP was calculated from the time when the 10 Hz low-pass filtered signal exceeded the range of the resting activity to the peak of the slow shift. However, if the signal amplitudes returned to the resting activity range within 500 ms after the onset, a new onset time was sought. The intersection of the regression line (1 in Fig. 1) with the baseline was used as the calculated onset for BP (4 in Fig.1). The regression lines for NS' and MP were determined from the peak of BP (for NS') and NS' (for MP), respectively, to the peak of each activity (2 and 3 in Fig. 1, respectively). The intersection of the regression line of BP with that of NS' (2 in Fig. 1) was used as the calculated onset for NS' (5 in Fig. 1). The intersection of the regression line of MP (3 in Fig. 1) with the baseline was used as the calculated onset for MP (6 in

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**Table 1 Clinical profile of five subjects whose data were analysed**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age, sex</th>
<th>Aetiology</th>
<th>MRI findings</th>
<th>Seizure onset zone</th>
<th>History of seizure</th>
<th>Data analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30, male</td>
<td>Malignant astrocytoma</td>
<td>Cystic mass at the right paracentral lobule</td>
<td>Not defined</td>
<td>7 months</td>
<td>L</td>
</tr>
<tr>
<td>2</td>
<td>32, female</td>
<td>Cortical dysplasia</td>
<td>No visible lesion</td>
<td>Left SFG</td>
<td>14 years</td>
<td>L</td>
</tr>
<tr>
<td>3</td>
<td>15, female</td>
<td>Cortical dysplasia</td>
<td>No visible lesion</td>
<td>Right SFG and MFG</td>
<td>4 years</td>
<td>L &amp; M</td>
</tr>
<tr>
<td>4</td>
<td>20, male</td>
<td>Cortical dysplasia</td>
<td>No visible lesion</td>
<td>Left paracentral lobule</td>
<td>6 years</td>
<td>L &amp; M</td>
</tr>
<tr>
<td>5</td>
<td>18, female</td>
<td>Cortical dysplasia</td>
<td>Small high-intensity area on FLAIR in superior frontal sulcus</td>
<td>Left SFG</td>
<td>15 years</td>
<td>M</td>
</tr>
</tbody>
</table>

SFG = superior frontal gyrus; MFG = middle superior frontal gyrus; L = lateral surface of frontal lobe; M = mesial surface of frontal lobe.
Fig. 1. When the linear regression line did not fit well with the actual waveform, the final determination of the onset was done visually (Nagamine et al., 1996). Only potentials exceeding 10 μV from the baseline or the preceding peak were accepted in this study.

In the present study, ECoGs were continuously recorded from subdural electrodes, referenced to an electrode placed on the skin over the mastoid process contralateral to the side of electrode implantation. This reference electrode served to pick up the EOG associated with horizontal saccade during the actual recording. For the data analysis, however, we employed one of the intracranial electrodes or an electrode placed on the falx cerebri as the reference, which did not elicit any symptoms or signs on electrical stimulation even with the maximum stimulus intensity and duration, and which was not contaminated with any movement-related activities. By using an intracranial electrode chosen in this manner, any eye movement-induced artefact was eliminated from the data on averaging.

The generator source of MRCPs with horizontal saccades was determined in relation to the hand area of the MI and the SMA proper and/or pre-SMA, both defined by electrical stimulation. In addition, we compared the distribution of MRCPs between horizontal saccades and hand movements on the lateral surface, and among eye, hand and foot movements on the mesial surface. In the two patients (Patients 3 and 4) in whom MRCPs for horizontal saccade were recorded simultaneously from the mesial and lateral surfaces of the frontal lobe, the functional difference between the lateral and mesial surfaces was investigated.

Cortical functional mapping by electrical stimulation

High-frequency cortical electrical stimulation was carried out by applying electric current to each electrode in monopolar fashion by using as a reference an intracranial electrode that did not produce any clinical symptoms on stimulation. For this purpose, repetitive square-wave electric currents of alternating polarity with pulse width 0.3 ms and frequency 50 Hz were delivered to each subdural electrode for 1–5 s (SEN-7203 and ss-102J; Nihon Kohden). During the stimulation study, ECoGs were monitored continuously to detect any induced ADs or EEG seizure patterns. The stimulus current was increased gradually until (i) the maximum of 15 mA was reached or (ii) ADs were elicited with intensity <15 mA. Details of the stimulation method have been described elsewhere (Lüders et al., 1987; Lesser et al., 1992).

Cortical sites where the stimulation elicited muscle contraction were defined as positive motor areas, and the areas where stimulation interfered with tonic muscle contraction or rapid alternating movements were defined as negative motor areas (Lüders et al., 1987, 1995). Identification of the SI and MI was based on subjective sensation and positive motor responses, respectively, elicited by stimulation of each electrode. As the electrodes were located on the crown of the gyrus, M1 in the present study might include both Brodmann’s areas 4 and 6 (Zilles et al., 1995; White et al., 1997).

The eye fields were identified on the basis of the observation of contralateral or ipsilateral eye deviation with or without head version elicited by cortical stimulation, and regarded as the FEF and SEF on the lateral and mesial surface, respectively, of the frontal lobe (Godoy et al., 1990; Lim et al., 1994; Blanke et al., 2000). During the stimulation study for eye fields, the subjects were asked to look straight ahead with the head kept in the neutral position. In the present stimulation study, however, FEF was identified only in one subject (Patient 2, Fig. 2) and SEF was defined in none of the subjects.

In the mesial frontal cortex, the SMA proper was identified by its unique response to stimulation, consisting of a predominantly tonic motor response of the upper as well as the lower limbs, either unilaterally or bilaterally, and of the trunk, neck and face (Fried et al., 1991; Lim et al., 1994). When areas on the mesial hemisphere wall showed a negative motor response, they were termed the supplementary negative motor area (SNMA) and regarded as part of the pre-SMA. When neither positive nor negative motor responses were elicited, those electrodes located rostral to the vertical anterior commissural (VAC) line on the mesial surface of the superior frontal gyrus were judged to be on the pre-SMA (Picard and Strick, 1996; Wise et al., 1996; Zilles et al., 1996).

To identify the locations of implanted electrodes on the mesial surface of the frontal lobe, a T1-weighted MRI obtained with the electrodes placed in the subdural space was used in Patient 3–5. The anterior commissure–posterior commissure (AC–PC) line and VAC lines were drawn on a midline sagittal MRI according to the atlas of Talairach and Tournoux (Talairach and Tournoux, 1988).

The cingulate sulcus defined by MRI is shown as a dotted line in Figs 6A, 7A and 8A. The central sulcus was defined on the basis of the phase reversal of the N20–P20 peak of somatosensory evoked potentials (SEPs) following median nerve stimulation at the wrist, intra-operative observation and/or MRI, and is shown in panel A of Figs 2–5.

Results

Electrode location and functional mapping defined by electrical stimulation in each patient are shown schematically (Figs 2–9). Onset times and waveforms of MRCPs for eye and hand movements are also indicated for each individual subject (Figs 2–9).

MRCPs for saccadic eye movements on the lateral surface of the frontal lobe (n = 4)

We analysed the generator location of MRCPs with horizontal saccade on the lateral surface of the frontal lobes in four subjects (Patients 1–4) (Figs 2–5, Table 1). Electrical cortical stimulation defined the hand MI in all four subjects and FEF in one of them (Patient 2) (Fig. 3). Horizontal saccade produced BP, NS’ and MP in all of the four subjects studied (Figs 2–5). BP, NS’ or MP with saccade was located at or 1–3 cm rostral to the hand, arm or face areas of MI, and was seen at two or three electrodes. In Patient 2, whose FEF was identified by electrical stimulation, the generator location of BP, NS’ and MP with horizontal saccade was found to be just on the FEF (Fig. 3). The generator location of MRCPs with eye movements overlapped that for hand movements in two out of three subjects (Patients 3 and 4) (Figs 4 and 5), but the maximum electrode for saccade was located rostral to that for hand. In three subjects (Patients 2 and 4) (Figs 3–5), we compared the maximum amplitude of MRCPs for saccade with that for hand movements. The maximum amplitude for eye movements (24.8–41.3 μV) was smaller than that for hand movements (54.6–107 μV).
MRCPs for saccadic eye movements on the mesial surface of the frontal lobe (n = 3)

We analysed MRCPs with self-paced, horizontal saccade from the mesial surface of the frontal lobes in three subjects (Patients 3–5) (Figs 6–8, Table 1). Electrical cortical stimulation defined the SMA proper in two subjects (Patients 3 and 4) (Figs 6 and 7) and the pre-SMA also in two (Patients 4 and 5) (Figs 7 and 8), but SEF was identified in none of the subjects.

At least two different generator locations for BP and/or NP were identified: one was located at the rostral part of the SMA proper, defined by electrical stimulation (Figs 6 and 7), and the other was the pre-SMA (Figs 7 and 8). However, clear MPs were seen in none of these areas. At the SMA proper, MRCPs with horizontal saccade were located rostral to those for hand and foot movements, whereas MRCPs at the pre-SMA showed no somatotopic distribution (Fig. 8).

MRCPs with eye movements on the mesial versus lateral frontal lobe (n = 2)

MRCPs with horizontal saccade were simultaneously recorded from the lateral and mesial surfaces of the frontal lobe in two subjects (Patients 3 and 4). In Patient 4, BPs from the SMA proper (b5) and pre-SMA (a5 and b7) started 1980–2200 ms before the EOG onset, and BP on the lateral surface (B4) started 1080 ms before the EOG onset (Fig. 9).

Discussion

MRCPs with horizontal saccade from the lateral surface of the frontal lobe

On the lateral surface of the frontal lobes, BP, NS' and MP with saccade were located at or 1–3 cm rostral to the hand, arm or face areas of MI, and were restricted to two or three electrodes in all four subjects investigated (Figs 2–5 and 10).
With regard to the subcomponents of MRCPs, BP, NS’ and MP were recognized in four, three and four subjects, respectively. The most prominent NS’/MP was seen 1–2 cm rostral to the hand MI (Figs 2–5 and 10). On the lateral surface of the human frontal lobe, eye movements are elicited by electrical stimulation between the hand and face MIs, with a variable degree of rostral extension (Penfield et al., 1954; Godoy et al., 1990). A recent study showed that the posterior part of the middle frontal gyrus was the main region where eye movements were elicited by electrical stimulation (Blanke et al., 2000). Contralateral gaze deviation is elicited when stimulating one to four electrodes (two on average) (Godoy et al., 1990) or two to eight electrodes (Blanke et al., 2000) placed at an inter-electrode distance of 1 cm on the lateral surface of the frontal lobe in humans. In one subject in the present study (Patient 2), whose FEF was identified by electrical cortical stimulation, the maximum NS’/MP was seen just at the FEF (Fig. 3). Therefore it is suggested that at least NS’/MP represents the location of the FEF most reliably while the subjects perform self-paced horizontal saccade, and it could be clinically useful for functional mapping of the human FEF. The present study shows for the first time that eye movements produce not only BPs but also NS’s and MPs in the human FEF (Figs 2–5 and 10).

We studied MRCPs with eye and hand movements on the lateral surface in three subjects in order to clarify the difference in waveform pattern and subcomponents between the two different movements (Patients 2–4) (Figs 3–5). Waveform patterns of MRCPs for saccade were different from those for hand movements, even though they were seen at or adjacent to the hand MI with some degree of overlap (Figs 3–5). In all three subjects in whom MRCPs with eye and hand movements were recorded on the lateral surface (Patients 2–4), the maximum amplitude of the premovement potentials with saccade was always smaller than that with hand movements (Figs 3–5). Recent imaging studies have suggested that the human FEF is located in the depth of the precentral sulcus (Paus, 1996; Courtney et al., 1998; Luna...
et al., 1998; Rosano et al., 2002), which might be consistent with experimental observations in primates, whose FEF is defined in the arcuate sulcus (Bruce and Goldberg, 1985; Bruce et al., 1985). If the FEF is buried in the precentral sulcus also in humans, it might explain the difference in amplitude of MRCPs between saccade and hand movements. As the subdural electrodes are usually placed on the gyral convexity, it is impossible to stimulate the sulcal walls. This is one of the major limitations of this technique, and is the major reason why the FEF defined by this method is located on the crown of the gyrus and not in the sulcus. If the electrodes were implanted within the sulcus, the FEF might be delineated also within the sulcus, as neuroimaging studies have shown (Paus, 1996; Courtney et al., 1998; Luna et al., 1998; Rosano et al., 2002). Furthermore, while most imaging studies have been done in healthy subjects, electrical stimulation studies have been available only in patients with some cerebral lesions or epileptic disorders. Thus, we must always consider the effect of the brain lesions or cortical reorganization induced by the lesions on the eye fields.

**MRCPs with horizontal saccade from the mesial surface of the frontal lobe**

On the mesial surface of the frontal lobe, Talairach and Bancaud (1966) showed, by means of electrical stimulation using depth electrodes, that eye deviation was produced when stimulating a cortical area rostral to the region where the upper limb movements were evoked. Lim and colleagues (Lim et al., 1994) also showed that the eye field in human mesial frontal lobe was closely associated with the head region of the SMA proper, and thus the human SEF has been defined as the rostral part of the SMA proper. However, its anatomical location is still not well defined, probably because there is considerable inter-individual variability even among normal subjects (Grosbras et al., 1999).

Ikeda et al. (1992) showed that the premovement slow potentials for movements of different parts of the body (tongue, finger, foot, etc.) follow a somatotopic representation within the SMA proper that is consistent with the results of electrical stimulation. In order to study the location and extent of the SEF on the mesial surface of the frontal lobe, we...
compared the generator location of MRCPs with horizontal saccade, and contralateral hand and foot movements within the SMA proper as defined by electrical stimulation \((n = 2, \text{Patients 3 and 4})\). Even though the area that generated MRCPs with horizontal saccade and contralateral hand movements were observed are encircled by small and large dotted lines, respectively. \(\text{Fig. 5}\) Onset time of each subcomponent. Waveforms of MRCPs with horizontal saccade \((\text{C})\) and contralateral hand movements \((\text{D})\). In \(\text{C}\) and \(\text{D}\), large, medium and small arrows show the onset of BP, NS’ and MP, respectively. Arrowheads indicate the peak of MP. An electrode placed over the falx cerebri was used as the reference. Seizure onset zone was found on the mesial surface of the frontal lobe.

Besides the SEF, BPs or NS’s were invariably seen in a relatively small area on the mesial surface of the frontal lobe regardless of the body part of the voluntary movements (eye, hand and foot), and there was no somatotopic representation \((\text{Yazawa et al.}, 2000)\). It was located just rostral to the VAC line and/or the negative motor area defined by electrical stimulation, and thus it is regarded as the pre-SMA. No clear MPs were observed at the pre-SMA \((\text{Figs 6–8})\). Patient 5, in whom all electrodes were located rostral to the VAC line and the negative motor area was defined by electrical stimulation, showed these characteristics \((\text{Fig. 8})\). These results are in good agreement with the functional characteristics of the pre-SMA as revealed by the recent neuroimaging studies of humans and experimental animals \((\text{Wiesendanger, 1986; Luppino et al., 1991; Matsuzaka et al., 1992; Tanji et al., 1994; Picard and Strick et al., 1996})\). Pre-SMA is significantly activated in association with higher-order functions of motor
Fig. 6 MRCPs with horizontal saccade and contralateral hand and foot movements on the mesial surface of the right frontal lobe in Patient 3. (A) Schematic representation of the locations of three 1 × 6 subdural strip electrodes. Waveforms of MRCPs recorded from 12 electrodes (a1–a6 and b1–b6) are shown for each movement. (B) Onset time of each subcomponent. (C) Horizontal saccade. (D) Contralateral middle finger extension. (E) Contralateral foot dorsiflexion. Large and small arrows show the onset of BP and NS/MP (or NS′), respectively. Arrowheads indicate the peak of MP. Horizontal dotted bars in C, D and E indicate the electrodes where MRCPs were recognized for each task. An electrode placed over the falx cerebri was used as the reference.
control, such as intrinsic movement selection, motor learning, complex movements, go/no go trials and so on, independently of the body parts involved. These results are also consistent with the observation that, from the electrodes placed at or just adjacent to SNMA, usually rostral to the VAC line, slow negative potentials were recorded consistently in association with movements of various parts of the body, showing, unlike the SMA proper, no clear somatotopic representation (Yazawa et al., 2000). Thus, the pre-SMA is also involved in preparation not only for the voluntary movements of the hand and foot but also for horizontal saccades in humans, as reported in the primate (Fujii et al., 2002).

MRCPs recorded from the pre-SMA show unique characteristics (Yazawa et al., 2000). As a matter of fact, MRCPs could even differentiate the pre-SMA from the SMA proper. According to this paper and our subsequent studies, activities from the pre-SMA tend to be smaller than those from the SMA proper, and show no apparent motor potentials MPs. In

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Fig. 8 MRCPs with horizontal saccade and contralateral hand and foot movements on the mesial surface of the left frontal lobe in Patient 5. (A) Schematic representation of the location of 10 subdural electrodes (a1–a4 and b1–b6). (B) Onset time of each subcomponent. Waveforms of MRCPs with horizontal saccade (C), contralateral middle finger extension (D) and contralateral foot dorsiflexion (E). Large and small arrows show the onset of BP and NS', respectively. Arrowhead indicates the peak of MP. An electrode placed on the lateral surface where no symptoms were elicited by electric stimulation and where no MRCPs were observed was employed as the reference.

Fig. 7 MRCPs with horizontal saccade and contralateral hand and foot movements on the mesial surface of the left frontal lobe in Patient 4. (A) Schematic representation of the location of four 1 × 6 and one 1 × 5 subdural strip electrodes. Waveforms of MRCPs recorded from 19 electrodes (a1–a6, b1–b7 and c1–c6) are shown for each movement. (B) Onset time of each subcomponent. (C) Horizontal saccade. (D) Contralateral middle finger extension. (E) Contralateral foot dorsiflexion. Large and small arrows show the onset of BP and NS'/MP, respectively. Arrowheads indicate the peak of MP. Horizontal dotted bars in C, D and E indicate the electrodes where MRCPs were recognized for each task. An electrode placed over the falx cerebri was used as the reference. TA = tibialis anterior muscle.
addition, the pre-SMA invariably produces MRCPs, regardless of the sites of movements, while the SMA proper shows relatively clear somatotopy. When these results are considered together with previous experimental data in monkeys, it can be postulated that the pre-SMA plays a different role in voluntary movements from the SMA proper.

In addition, we have to consider the possibility of the spread of activities from the SMA proper to the pre-SMA. However, since the foot area of the SMA proper is situated most caudally (farthest from the pre-SMA), the pre-SMA and the SMA proper most likely serve as independent generators of MRCPs, at least as far as foot movement is concerned. The MRCP study provides further evidence that the pre-SMA plays a different role in voluntary movements from the SMA proper.

In Patient 4 (Fig. 7), even though MRCPs suggested the locations for each of the three areas (SMA proper, SEF and pre-SMA), which were almost consistent with these areas as defined by the results of electrical cortical stimulation and the VAC line, a clear border delineating the SMA-proper, SEF and pre-SMA was not found. This might have been due to the limitation of the spatial resolution of the electrode placement used in this study. Subdural electrodes with a smaller inter-electrode distance (e.g. 5 mm) might enable us to distinguish those areas more clearly.

As shown in Figs 6D and 7D, activities related to foot movement were seen more widely over the mesial frontal lobe than those related to eye or hand movements. On the mesial surface of the frontal lobe, at least three distinct areas are active for foot movement; MI, SMA proper and pre-SMA. These three areas are located close to one another. Since MI produces the most prominent movement-related activity among these areas, it is expected that the activities related to foot movement are most conspicuous and widely seen over the entire length of the MI, SMA-proper and pre-SMA.

PET studies have shown that the cingulate cortex participates in the control of eye movements in humans (Petit et al., 1993; Paus et al., 1993). In the present study, however, since subdural electrodes were not placed on the cingulate cortex, we have no data with which to discuss the role of the cingulate cortex in saccadic eye movements based on the present MRCP study.

Fig. 9 MPCPs recorded simultaneously from the lateral and mesial surfaces of the right frontal lobe in Patient 4, each of which is partly shown in Figs 5 and 7, respectively. (A) Anatomical location of the implanted electrodes and functional maps obtained by means of electrical stimulation. (B) Onset time of each subcomponent. Representative waveforms of MRCPs for horizontal saccade on the lateral surface (C) and mesial surface (D). Large arrows show the onset of BP.
Sensitivity of MRCPs in motor mapping of eye fields in the human frontal lobe

MRCPs with horizontal saccade delineated the SEF in the present two subjects (Patients 3 and 4), whereas electrical stimulation did not identify the SEF. With regard to the FEF, MRCPs could identify it in all four subjects, whereas electrical stimulation did so in only one subject. Thus, for the mapping of eye fields in the human frontal lobe, recording of MRCPs can be a more sensitive method than conventional electrical stimulation. There are three possible reasons for the advantage of MRCP recording over electrical stimulation. First, for the presurgical investigation, once we obtain any kind of positive response on electrical stimulation of a pair of electrodes, we usually do not increase the stimulus intensity any further for that particular pair of electrodes. This is because, once a particular cortical area has been found to have a certain function, it is not necessary to know any further, at least for clinical purposes, whether that area has any other functions. In fact, the FEF is located near the hand–mouth area of M1, and the SEF is located just rostral to the SMA proper. Furthermore, greater stimulus intensity is required to produce positive responses in the FEF and SEF than in the M1 and SMA proper, respectively. Thus, the conventional electrical stimulation that we employed in this study might have failed to identify cortical functions, if any, other than the responses elicited with the lowest stimulus intensity.

Secondly, as discussed above, electrical stimulation is unable to delineate the function of the cortical sulci, whereas the epicortical recording of MRCPs with subdural electrodes can also reflect the activities generated in the cerebral sulci if the sources are not too deeply situated. For the purpose of presurgical evaluation, subdural electrodes 3 mm in diameter are used at an inter-electrode distance of 10 mm. Thus, electrical stimulation cannot be used in the study of cortical functions unless the electrode covers the area, whereas MRCP can be recorded even if the generator is not exactly situated under the electrode, as long as the solid angle of the current source is open for the recording electrodes. If smaller electrodes with a shorter inter-electrode distance were used for the cortical stimulation study and if higher stimulus intensity was applied, a more detailed motor map with regard to the eye fields might be obtained.

Thirdly, self-paced, voluntary movements may activate a larger cortical area compared with electrical stimulation.

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**Fig. 10** Characteristics of MRCPs with horizontal saccade in the lateral and mesial frontal lobes. (A) On the lateral surface of the frontal lobe, MRCPs with horizontal saccade (BP, NS' and MP) were observed at or 1–3 cm rostral to the arm, hand or face MI. (B) MRCPs with saccade on the mesial surface of the frontal lobe. Within the SMA proper, BP and NS' with eye movements were located rostral to those for hand and foot movements, showing somatotopic distribution. In the pre-SMA, BPs and/or NS's were located in the same area regardless of the body parts of the movements.
Comparison of MRCPs between the mesial and lateral surfaces of the frontal lobe

In this study, we recorded MRCPs with saccade from the mesial and lateral surfaces of the frontal lobe simultaneously in two subjects (Patients 3 and 4). At least in one of them, BPs from the SEF and pre-SMA started earlier than those from the FEF (Fig. 9). A previous study, by means of epicortically recorded MRCPs (Sakamoto et al., 1991), failed to prove that the SEF was activated earlier than the FEF. Other imaging studies by fMRI or PET cannot determine the time difference of the activation in these regions because of the limited time resolution. Our results show that the SEF and pre-SMA become active earlier than the FEF when preparing for self-paced, horizontal saccade.

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