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Movement-related potentials associated with bilateral simultaneous and unilateral movements recorded from human supplementary motor area

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Abstract

To clarify the differences of movement-related potentials (MRPs) among ipsilateral, contralateral and simultaneous bilateral movements, MRPs with finger, thumb or foot movements were recorded from subdural electrodes chronically implanted on the supplementary motor area (SMA) in 3 patients, and also from the primary sensorimotor area in two of them being evaluated for epilepsy surgery. As a result: (1) SMA generated clear pre-movement potentials regardless of the type of movement. Its amplitude was almost identical between contralateral and bilateral movements except for the motor potential (MP). The pre-movement potentials associated with ipsilateral movements were relatively smaller than those with contralateral or bilateral movements. (2) The primary sensorimotor area generated clear pre-movement potentials in contralateral and bilateral movements with similar amplitude. With ipsilateral hand movements, however, only a small Bereitschaftspotential (BP) and no negative slope (NS') or MP was seen, and ipsilateral foot movements were not preceded by any BP. It is, therefore, most likely that, as far as the preparation for simple voluntary self-paced movement is concerned, the SMA plays an equally important role in unilateral and bilateral movements, whereas the primary sensorimotor area is involved predominantly in the preparation of contralateral movements.

Keywords: Bereitschaftspotential; Bilateral movements; Supplementary motor area

1. Introduction

The functional role of the supplementary motor area (SMA) in relation to the primary sensorimotor area is still debated. Namely, two hypotheses, i.e., "supramotor" and "supplementary" function have been proposed (Deecke et al., 1985; Goldberg, 1985; Wiesendanger, 1986; Wiesendanger et al., 1987). The "supplementary" function hypothesis speculates that the SMA and primary sensorimotor area are active in parallel with and complementary to each other in the programming, initiation and execution of the voluntary movements. This hypothesis was suggested when it was initially named so in humans (Penfield and Welch, 1951; Woolsey et al., 1952), and subsequently it has been supported not only by clinical observations but also by experimental animal studies (Penfield and Jasper, 1954; Laplane et al., 1977; Fox et al., 1985; Schell et al., 1986; Hyland et al., 1989; Alexander and Crutchler, 1990a,b; Crutchler and Alexander, 1990; Chen et al., 1991; Schmidt et al., 1992). The "supramotor" function hypothesis, on the other hand, speculates that the SMA initiates and regulates voluntary movements contributing to the generation of a new motor program and to the control of the execution of established movements (Eccles, 1982; Goldberg, 1985). This idea was supported by cerebral blood flow studies in human (Orgogozo and Larsen, 1979; Roland et al., 1980; Rao et al., 1993) and by experimental animal studies (Tanji and Kurata, 1982, 1985a,b; Tanji et al., 1987, 1988; Matsuzaka et al., 1992).

Damage to the SMA in humans initially produces reduced spontaneous speech, akinesia and slowness of repetitive or alternating movements of the upper limb contralateral to the SMA lesion (Penfield and Jasper, 1954; Laplane et al., 1977; Schell et al., 1986; Rostomily et al., 1991),

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but those symptoms recover in several weeks. Eventually, only slowness, mainly involving the opposite extremities, and difficulties in bimanual motor performances as well as in rapid alternating movements remained. Similar observations were also made on lesion studies in monkeys. Transient neglect of the contralateral arm and impairment of smooth movements (Brinkman, 1984), severe difficulty of sequential movements (Halsband, 1983), and deficits in bimanual coordination (Brinkman, 1981,1984) were observed. Therefore, it is certain that the SMA has a significant role in preparation and/or execution of bilateral movements (Porter, 1990), although the question as to whether the SMA is upstream of or parallel to the primary motor area still remains unsolved.

In previous studies of movement-related potentials (MRPs) in which cortical potentials were directly recorded from human SMA with subdural electrodes in patients during preparation for epilepsy surgery, it was demonstrated that bilateral SMAs generated pre-movement potentials (Bereitschaftspotential: BP by Deecke et al., 1969 and negative slope: NS′ by Shibasaki et al., 1980), even preceding unilateral simple movements (Ikeda and Shibasaki, 1992; Ikeda et al., 1992). Furthermore, potentials recorded subdurally from the human SMA preceding single unilateral movements were as large as those with repetitive unilateral movements (Ikeda et al., 1993). These results led us to the hypothesis that the SMA might play an equally significant role in preparation for simple and "complex" movements, provided that the motor task was unilateral.

As has been mentioned above, it is apparent that an SMA lesion permanently affects bimanual maneuvers as well as unilateral sequential movements. However, our previous invasive MRP studies did not give any clue to the question as to whether the SMA generates pre-movement potentials more actively in bilateral movements than in unilateral ones. Comparison of MRPs of the SMA between bilateral and unilateral movements would shed light on the SMA function, especially regarding the hypothesis that the SMA plays a more significant role in bilateral than in unilateral movements. Thus the present study is aimed at complementing our previous results for understanding human SMA function.

2. Materials and methods

2.1. Subjects

The data were obtained from 3 patients with a diagnosis of medically intractable partial epilepsy. All patients were evaluated for epilepsy surgery using chronically implanted subdural electrode grids according to the Cleveland Clinic Epilepsy Surgery Protocol (Morris, 1992). Invasive recording and electrical stimulation of the cortex were done with chronically implanted subdural electrode strips or grids (Hahn and Lüders, 1987). Each electrode was made of stainless steel, 3 mm in diameter, and the center-to-center interelectrode distance was 1 cm. This technique can help to identify (1) the extent of the epileptogenic region, and (2) the function of the cortex around the epileptogenic region (Lueders et al., 1982; Lüders et al., 1987). Informed consent was obtained from all patients following the procedures approved by the Institutional Review Board at the Cleveland Clinic Foundation.

Patient 1 was a 19-year-old right-handed woman with medically intractable partial seizures of unknown etiology since the age of 11 years, consistent with supplementary motor seizures (Morris et al., 1988). Her neurological examination was unremarkable. Bimanual alternating and unilateral sequential movements of the hand or foot were also normal. An MRI of the brain was normal. PET scan demonstrated hypometabolism at the left fronto-central area. The intracarotid sodium amobarbital (Wada) test demonstrated speech and memory dominance in the right hemisphere. The Wechsler Adult Intelligence Scale (WAIS) full-scale IQ was 87. For presurgical evaluation of the seizures, the patient had initially one 1×11 and one 1×4 subdural electrode strip at the left mesial fronto-central area, one 1×11 at the right mesial fronto-central area, and two 1×11 and one 1×4 at the left lateral frontal area. Seven days afterwards, two more 1×11 subdural electrode strips were added on the right mesial to lateral fronto-central region in order to localize the seizure focus. The 3 strips placed on the mesial areas are illustrated in Fig. 1.

Patient 2 was a 48-year-old right-handed man with medically intractable partial seizures since the age of 27 years, which always started with a sudden vibration-like pain in the left third to fifth fingers. The etiology was unknown. His neurological examination demonstrated dysesthesia in the left third to fifth fingers, and absent deep tendon reflexes throughout. Postictally, the patient demonstrated a transient weakness of those 3 fingers, but not in the thumb. Bimanual alternating and unilateral sequential movements of the hand or thumb were normal. An MRI of the brain was normal. The Wada test demonstrated that the left hemisphere was dominant for speech and that memory function was represented by each hemisphere independently. For presurgical evaluation of the seizures, the patient had an 8×8 subdural electrode grid at the right lateral fronto-parietal area and two 1×11 subdural electrode strips at the right mesial fronto-central area, as shown in Fig. 1.

Patient 3 was a 33-year-old right-handed man with medically intractable partial seizures of unknown etiology since the age of 12 years. Supplementary motor seizures were suspected. His neurological examination was normal, and bimanual alternating and unilateral sequential movements of the hand or fingers were normal. An MRI of the brain was normal. A PET scan demonstrated patchy hypometabolic areas in the right hemisphere. The Wada test demonstrated speech and memory dominance in the right

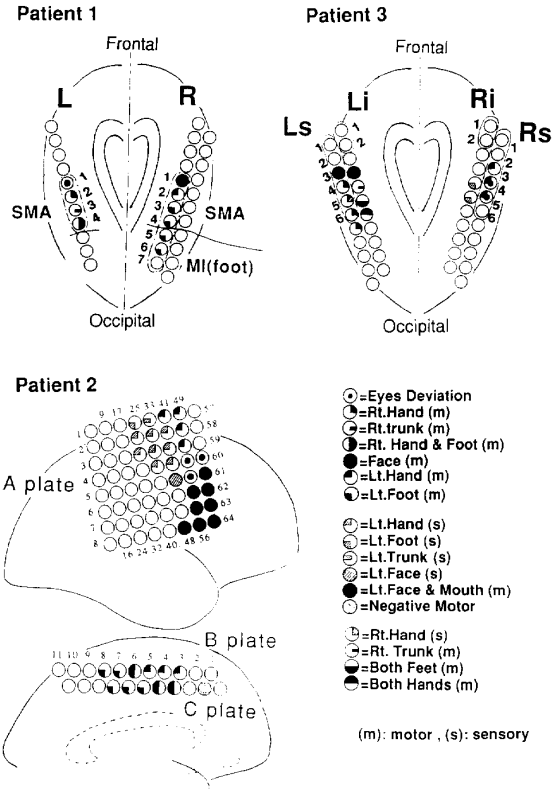


Fig. 1. Schematic representation of the placement of subdural electrode strips (patients 1, 2 and 3) and grid (patient 2). Each diagram shown was copied directly from the lateral view of an X-ray film and the sagittal views of MRI as described in Methods. The lines across the subdural electrode strips in patient 1 represent the location of the precentral sulcus. The site of the responses to electrical stimulation of each of the different implanted electrodes is indicated in the symbol in the figure. More details are given in the text.

and left hemispheres, respectively. WAIS full-scale IQ was 75. For surgical intervention of the seizures, the patient had a total of six 1 × 11 subdural electrode strips; two on each side of the bilateral mesial fronto-central areas, and one each at the left lateral frontal and parietal areas. The strips at the bilateral mesial fronto-central areas are illustrated in Fig. 1.

2.2. Cortical stimulation and anatomical localization of the electrodes

Each subdural electrode was individually stimulated to identify cortical function. Electrical currents were applied at progressively increasing intensity until (1) either movements or paresthesias were elicited, (2) after-discharges occurred, or (3) a maximum stimulus intensity of 15 mA was reached. Details of the stimulation methodology have been described elsewhere (Lüders et al., 1987; Lesser et al., 1992). It has been confirmed that the current spread to the adjacent or distant areas, which could lead to false positive findings, does not occur in this method (Lüders et al., 1987; Lesser et al., 1992; Nathan et al., 1993). Cortical regions at which stimulation elicited muscle contraction were identified as "positive motor area" (Lüders et al., 1985, 1988). The SMA was identified by its unique responses on the mesial surface as described by Penfield and Welch (1951), consisting of predominantly tonic positive motor responses of the upper as well as lower limb and of the trunk, neck and face, either unilaterally or bilaterally. Stimulation of some rostral parts of the SMA elicited negative motor responses affecting any part of the body.

The anatomical location of the subdural electrodes in the interhemispheric fissure was also assessed as follows, and it was taken into account when interpreting the functional mapping of the cortex by electrical stimulation as described above (Lim et al., 1994). A lateral view of the skull X-ray film, taken with subdural electrode grids or strips, was superimposed upon the sagittal view of the T1-weighted MRI image taken before surgery, using common landmarks (i.e., nasion and inion) by adjusting the size to each other.

2.3. Movement paradigms

Unilateral and bilateral voluntary movements of the foot were studied in patient 1, and those of the thumb and finger in patients 2 and 3. For unilateral foot movements in patient 1, the patient was laid in a supine position on a bed, and brisk extensions of an ankle joint, immediately followed by a return to the resting position by relaxing the dorsiflexed foot, were repeated at a self-paced rate of approximately once every 5 sec. This was done for the right and left foot movements separately, and for bilateral simultaneous movements.

For unilateral finger movements in patient 2, brisk voluntary abductions of the thumb at the metacarpophalangeal joint, immediately followed by a return to the resting position by relaxing the abducted thumb, were repeated at a self-paced rate of approximately once every 5 sec in a supine position. Like in the foot movements, the thumb movements as described above were executed unilaterally for each hand and bilaterally simultaneously. In patient 3, brisk voluntary extensions of the middle finger were employed for the movement and were also studied for unilateral and bilateral simultaneous movements.

The subject was told to keep quiet during each recording session and also asked to postpone the next task movement for several seconds if he accidentally moved prior to the task movement. Before recording sessions, the subject was given a training period until the examiner was satisfied that the subject consistently produced brisk movements preceded and followed by complete relaxation. One recording session typically lasted 5–6 min. The sessions of the left, right and bilateral movements were repeated in this order at least 3 times for each, with an intermission of a few minutes between sessions.

2.4. Recording of MRPs

Cortical recordings were done simultaneously from 66 to 86 subdural electrodes in each patient. All the recordings were performed in the Epilepsy Monitoring Unit concurrently with continuous video-EEG seizure monitoring (Burgess, 1992; Collura et al., 1992). For electromyogram (EMG) recording, a pair of cup electrodes were placed on the skin overlying the anterior tibial muscle for foot dorsiflexion (patient 1), abductor pollicis brevis muscle at the thenar eminence for thumb abduction (patient 2), and the extensor digitorum muscle in the forearm for middle finger extension (patient 3). All subdural electrodes were referenced to a scalp electrode over the left mastoid (TP7) in patient 1, one of the subdural electrodes over the lateral convexity in patient 2, and one subdural electrode over the mesial frontal area in patient 3. The reference subdural electrode did not elicit any symptom on stimulation and showed no ictal or interictal epileptiform discharges. All recorded potentials were led to two or three 32-channel EEG amplifiers (NEC San-ei BIOTOP) for amplification, filtering and simultaneous monitoring. Recording amplitude was set to 5 mV full-scale, 12 bits for the EEG, and 500 μV full-scale, 12 bits for the EMG. The low frequency filter (LFF) was set to 0.016 Hz for EEG recording and to 5 Hz for EMG recording. The high frequency filter (HFF) was set to 100 Hz for both EEG and EMG recordings. A 60 Hz notch filter was used in all channels. Signal monitoring with a non-fade graphic terminal at a sweep speed of 30 mm/sec was done throughout the examination. All of the above electrographic output signals were digitized by an analog-to-digital converter at a sampling rate of 200 Hz/channel, and stored on an HP9000/835 using 670 Mbyte disks for subsequent off-line analysis.

2.5. Data analysis

To average EEG signals time-locked to the onset of the movements of interest, computer programs adopting a concept originally described by Barrett et al. (1985) were developed. Visual inspection on an interactive graphics terminal permitted us to obtain essentially artifact-free epochs and allowed precise manual identification of the EMG onset of the trigger movements (Neshige et al., 1988; Ikeda et al., 1992, 1993). Movements which were not brisk enough to identify a clear EMG onset or movements associated with other recording artifacts were eliminated. Bilateral movements in which the difference of EMG onset between the two sides was more than 100 msec were also eliminated. Otherwise, a leading EMG onset of either side was taken as the fiducial point for averaging. A total of 123–163 epochs were selected for each trial. After confirming that two ensemble averaged EEGs of 61–81 epochs each were almost identical, a grand averaged EEG was finally made. All analysis epochs began 3000 msec before and ended 2000 msec after the time-locking fiducial EMG onset. Computer-assisted methods were used to measure time intervals and amplitudes, based on the calibration data obtained during data collection. The baseline was derived from the average of the segment from 3000 to 2500 msec before the trigger point for each channel. For the terminology of components of the subdurally recorded potentials in the present study, the conventional one used for the scalp-recorded MRPs was adopted except for the polarity; Bereitschaftspotential (BP) was defined as a slow, usually negative, shift which started about 1.5–2 sec before the EMG onset and gradually increased in amplitude (Kornhuber and Deecke, 1965). The steeper potential following the BP, starting about −300 msec to the EMG onset, was defined as negative shift (NS′) (Shibasaki et al., 1980; Barrett et al., 1986). The much steeper potential following the NS′, starting about −100 to −50 msec to the EMG onset, was defined as a motor potential (MP) (Deecke et al., 1969; Shibasaki et al., 1980).

3. Results

3.1. Cortical mapping (Fig. 1)

Cortical mapping of the mesial brain surface was based on the results of electrical stimulation and on the anatomical location of the electrodes. The results of electrical stimulation are illustrated in Fig. 1.

In patient 1, the nearly horizontal lines across the electrode strips indicate the location of the precentral sulcus. Stimulation at R5 elicited clonic movements at the left ankle, while stimulation at R2, R3 and R4 elicited tonic posturing with flexion of the right hip and knee and inversion of the right ankle at the same time. The precentral sulcus was located between R4 and R5. It was concluded, therefore, that the SMA was located at and anterior to R4, and the primary motor foot area was located at and posterior to R5. The anterior part of the SMA demonstrated positive motor responses in the arm and face. Antero-posterior somatotopy, as previously reported in the human SMA (Fried et al., 1991; Lim et al., 1994), was observed. In patient 2, stimulation of the right mesial fronto-central subdural electrodes elicited mainly positive motor responses as illustrated in Fig. 1. These motor responses were seen in the face, arm, trunk and bilateral feet. All these responses were typical SMA responses (Penfield and Welch, 1951) and also demonstrated somatotopy. Stimulation of the subdural grids at the right lateral convexity elicited a somatotopic representation of the primary sensorimotor cortex along the central sulcus. In patient 3, stimulation of bilateral subdural strip electrodes elicited a somatotopic representation in the SMA which was similar to that seen in the two other patients.

3.2. Movement-related potentials

Unilateral movements

Fig. 2a demonstrates MRPs associated with left foot movements recorded subdurally from the left and right mesial brain surfaces in *patient 1*. On the mesial surface contralateral to the movements (right hemisphere), a clearly defined positive BP started at about −2600 msec at both SMA foot areas (R3) and primary motor foot areas (R5). The BP at R3 gradually increased in amplitude until −60 msec (+55.5 μV), then it was followed by a slowly increasing negative deflection until +2000 msec. The positive BP at R5 was followed by a steeper negative deflection (NS′) at −400 msec, then turned into a much steeper negativity at −50 msec (MP). A clear transient negative activity started at +115 msec and peaked at +140 msec (reafferent potential: RAP by Kornhuber and Deecke, 1965). In the SMA ipsilateral to the movements (left SMA), a clearly defined positive BP started at about −2600 msec at L4 and L3, which was similar to that seen in the contralateral (right) SMA. The positive BP at L4 was stable in amplitude until the EMG onset (−28.8 μV), at which time a steeper positive deflection of 600 msec duration occurred. Otherwise no clear MP was seen, although a small negative shift was apparently seen at L3 and L2 from −400 msec to +2000 msec.

Fig. 2b demonstrates MRPs associated with the right foot movements recorded subdurally from the left and right mesial surface in *patient 1*. In the mesial surface ipsilateral to the movements (right hemisphere), a clearly defined positive BP started at about −1300 msec. It was seen at the SMA foot area (R3), but not at all at the primary motor foot area (R5). The BP at R3 gradually increased in amplitude and peaked at +65 msec (+36.1 μV), then it decreased in amplitude gradually over the following 2 sec. A clear negative transient activity started at +168 msec and peaked at +223 msec at R5. Otherwise no slow potentials were seen at R5 throughout. A smaller deflection which corresponded to the transient negative activity, as described above at R5, was also seen at R4. In the SMA contralateral to the movements (left SMA), a clearly defined positive BP started at about −2500 msec at L4 and L3. The overall distribution and wave forms of pre-and post-movement potentials at the left SMA (L4, L3 and L2) were almost identical between the left and right movements (Fig. 2a and 2b, respectively).

Fig. 3a demonstrates MRPs recorded from the right primary sensorimotor area and the right SMA in association with left thumb abduction in *patient 2*. At the primary sensorimotor area, a negative BP started at −2500 msec in the wider area along the central sulcus (A41, A45 and A49–51), and a steeper "negative" NS′ started at −500 msec in a more localized area (especially A43 and A41), at which electrical stimulation elicited either motor or sensory responses of the right hand. A positive NS′ was also seen at the hand sensory area (A35). At the right SMA, a BP started at −2200 msec at B3 and C4, and a clearly defined NS′ started at −500 msec mainly at the SMA hand area (B5, B4 and C6). MPs at the primary sensorimotor area and SMA were similar in amplitude (−51.1 μV at A43, and −57.1 μV at B5 at the EMG onset).

Fig. 3b demonstrates MRPs recorded from the right primary sensorimotor area and the right SMA in association with right thumb abduction in *patient 2*. At the primary sensorimotor area, a negative BP started at −2000 msec at a small number of electrodes (A50 and A41). No clear pre-movement potentials were seen at other electrodes (A43, A35, etc.) where the large BP, NS′ and MP were seen with the left thumb movements. Moreover, the BP was not followed by clear NS′ or MP. At the right SMA, on the contrary, a clearly defined, mostly negative BP/NS′ started at −2200 to −500 msec, mainly at the SMA hand area (B2–5, C3 and C4). The amplitude of BP and NS′ to right thumb movements was 50–60% of that elicited by left thumb movements (−24.0 μV and −40.7 μV, respectively, at B5 at −100 msec). MP elicited by right thumb movements starting at the EMG onset was ill defined as compared with left thumb movements.

In *patient 3*, in association with the right middle finger movements, a clear positive BP was seen at Rs4 (right SMA hand area). The BP started at about −1800 msec and gradually increased in amplitude until the EMG onset (+30.9 μV at Rs4). Small BP and NS′ were also seen at the adjacent electrodes (Rs3, Rs2, Rs5) as well as at the left SMA hand area (Ls4, Ls5). In association with left middle finger movements, pre-movement potentials were seen at the right and left SMA hand areas (Rs4, Ls4, Ls5). The wave form and amplitude of these potentials were similar to those elicited by right finger movements.

Bilateral movements

Fig. 2c demonstrates MRPs associated with simultaneous bilateral foot movements recorded subdurally from the left and right mesial brain surface in *patient 1*. In the right mesial area, the BPs at R3 (SMA foot area) and R5 (primary motor foot area) were almost identical to those with the left foot movements (Fig. 2a) in terms of wave form and amplitude. The post-movement potentials at R5 were also identical in bilateral and left foot movements (Fig. 2d). However, the MP at R3 (SMA foot area) started at −105 msec and became more positive with bilateral movements as compared with left foot movement. The MP peaked at +105 msec with an amplitude of +72.2 μV. Fig. 2d shows superimposed MRPs elicited by bilateral and left foot movements, demonstrating the similar BPs and significantly different MPs and post-movement potentials in the two movements.

In the left SMA, the pre-movement potentials with the bilateral foot movements were almost identical to those with either the left or right foot movements (Fig. 2c). However, the positive MP at L4, which started at the EMG

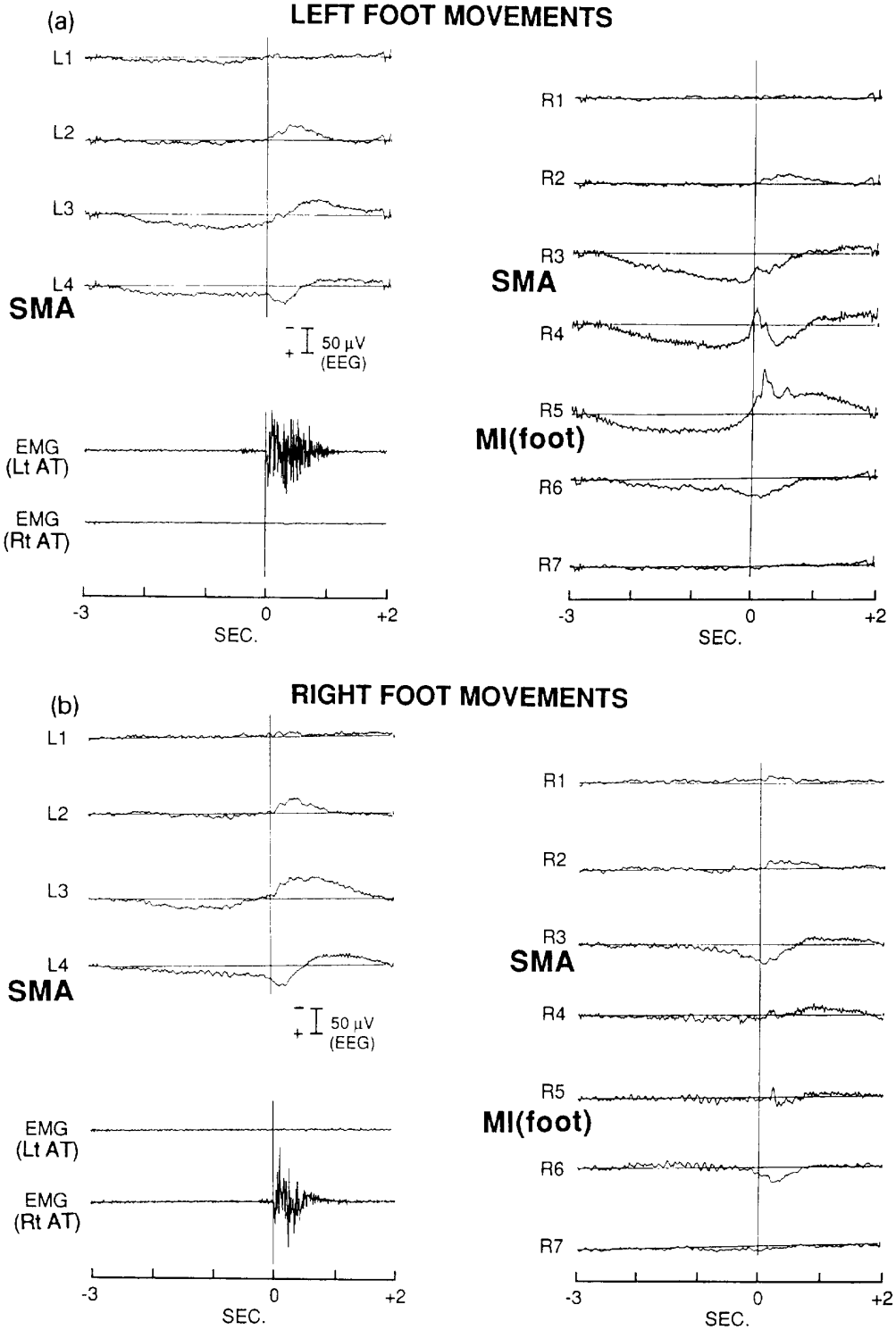
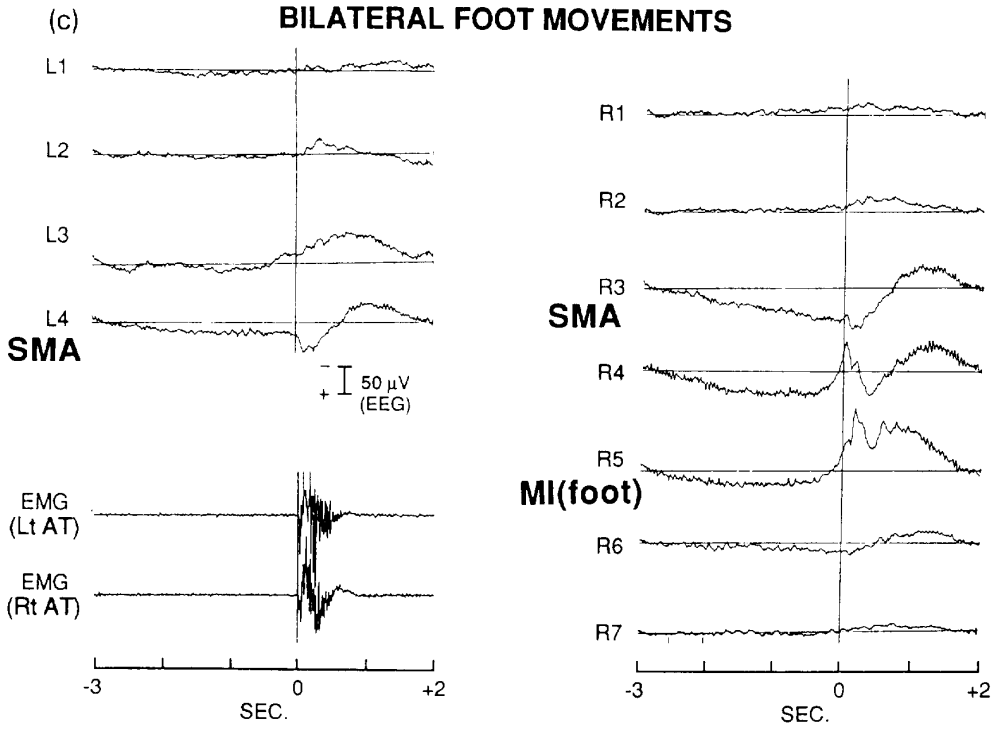


Fig. 2. Movement-related potentials (MRPs) recorded subdurally from both the left and right mesial brain surfaces in patient 1 in association with voluntary, self-paced, left (a), right (b) and bilateral simultaneous (c) foot dorsiflexions. Each electrode number corresponds to that in Fig. 1. Lt AT = left anterior tibial muscle; Rt AT = right anterior tibial muscle; SMA = supplementary motor area; MI = primary motor area.. a: average of 142 trials. b: average of 151 trials. c: average of 123 trials. d: superimposition of the averaged wave forms associated with the left foot (thin lines) and the bilateral foot (thick lines) movements.

onset, was larger (+55.5 μV at +110 msec) than that with the left (+28.8 μV at +110 msec) or the right (+38.8 μV at +110 msec) foot movements.

Fig. 3c demonstrates MRPs recorded from the right primary sensorimotor area and the right SMA in association with bilateral thumb abductions in *patient 2*. At the primary sensorimotor area, like in case of the left thumb movements (Fig. 3a), a negative BP started at −2500 msec at the primary hand sensorimotor area along the central sulcus (A41–43 and A49–51), and an NS′ started



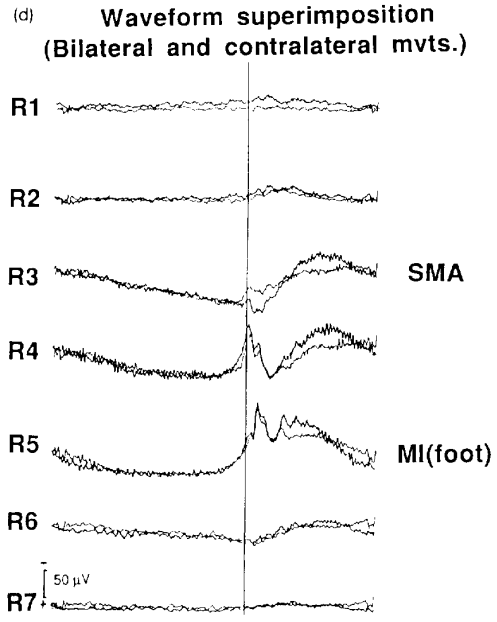


Fig. 2 (continued).

at −500 msec at a more localized area (A43 and A41). A positive NS', as elicited also with left thumb movements, was present at the hand sensory area (A35). At the right SMA, as seen also with unilateral movements, a BP started at −2200 msec mainly at B3, and a clear NS' started at −500 msec at the SMA hand area mainly at B5. The potentials at the primary sensorimotor area and at the SMA were similar in amplitude (−45.7 μV at A43, and −37.1 μV at B5 at the EMG onset). At B5, MP followed and peaked at +200 msec with an amplitude of −71.4 μV. It

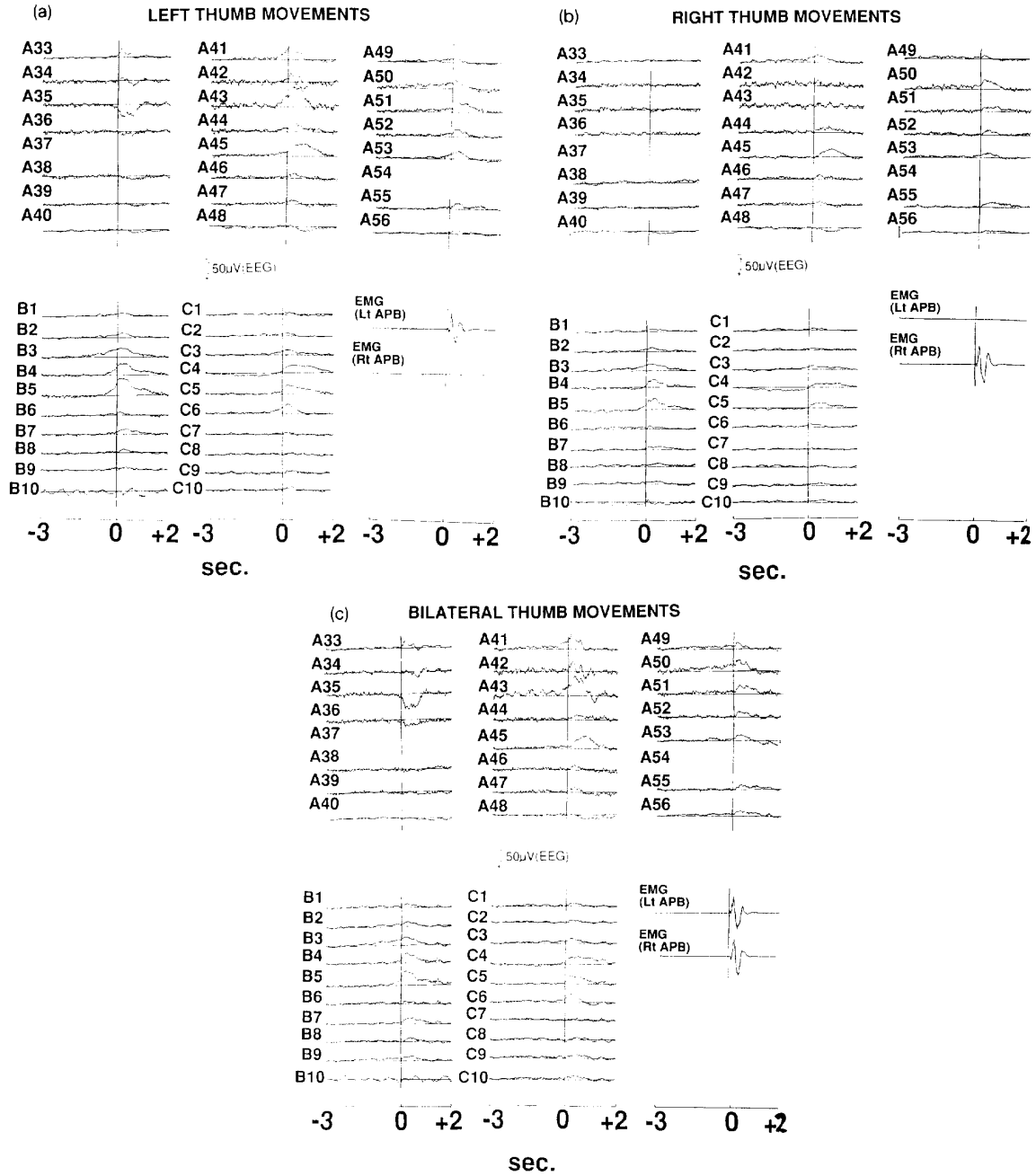


Fig. 3. MRPs subdurally recorded from the right primary hand sensorimotor area (upper panel: A33–A56) and the right SMA (lower panel: B1–10, C1–10) in patient 2 in association with voluntary, self-paced, left (a), right (b) and bilateral simultaneous (c) thumb abductions. Each electrode number corresponds to that in Fig. 1. Lt APB = left abductor pollicis brevis muscle; Rt APB = right abductor pollicis brevis muscle. a: average of 128 trials. b: average of 163 trials. c: average of 134 trials.

was larger than that elicited by the right thumb movements (−51.4 μV at B5), and similar to that elicited by left thumb movements (−80.0 μV at B5).

In *patient 3*, in association with bilateral finger movements, a clear positive BP was seen at Rs4 (right SMA hand area). The distribution, wave form and amplitude of pre- and post-movement potentials were similar in bilateral and unilateral movements (+28.1 μV and +30.9 μV with bilateral and left finger movements, respectively, at Rs4 at the EMG onset).

4. Discussion

The present study revealed mainly 2 findings about the SMA function for the initiation of voluntary movements, as compared with the primary sensorimotor area. (1) The SMA generated clear pre-movement potentials for either contralateral, ipsilateral or bilateral movements. BP and NS′ were almost identical for contralateral and bilateral movements, but MP was different between them. BP, NS′ and MP generated by ipsilateral movements were slightly smaller than those generated by contralateral or bilateral movements. (2) The primary sensorimotor cortex generated almost identical pre-movement potentials for contralateral and bilateral movements. However, it generated ill-defined pre-movement potentials for ipsilateral movements.

As regards the first finding, it is worthwhile noting that the amplitude of pre-movement potentials seen with bilateral movements was smaller than those expected from a simple summation of two potentials associated with ipsilateral and contralateral movements. In experimental studies of single unit recordings in monkeys, it was previously reported that a very small subgroup (4.3%, 5.4% and 11%) of SMA movement-related neurons was active before voluntary movements, exclusively for right, left, and bilateral movements, respectively ("exclusive neurons") (Tanji et al., 1987, 1988). This type of exclusive neuron was not seen in the primary motor area. In addition, Tanji et al. (1987) reported another population (38%) of SMA movement-related neurons which were active before all 3 types of movement (right, left and bilateral). Therefore, taking into account these experimental findings, the present results suggest that movement-related potentials, which are the expression of extracellular field potentials, are most likely to be predominantly a reflection of SMA neurons activated by all 3 types of movement with only a small contribution of the "exclusive neurons."

Regarding the components of pre-movement potentials seen in SMA, particularly in patient 1, it was shown that BP and NS′ at SMA elicited by contralateral and bilateral movements were almost identical, whereas the following MP at SMA had a larger deflection for bilateral movements. This finding is consistent with the recent scalp-recorded MRP study with unilateral and bilateral movements (Lang et al., 1991). This study demonstrated that, during actual motor execution, negative potentials at the vertex were present in bimanual complex motor sequences, but absent with simple unilateral motor sequences, whereas BP was seen in both situations. This finding suggests the possibility that SMA plays a more significant role during the actual execution of bilateral movements (represented as MP), rather than prior to the onset of the movements (represented as BP and NS′). They also reported that a significantly higher activity at the vertex during execution was seen during either unilateral or bilateral sequential movements rather than during single motor performance (Lang et al., 1988, 1989, 1990). It is also in good agreement with the result of cerebral blood flow study with complex finger movements (Shibasaki et al., 1993). It is thus suggested that the SMA may play a special role in the execution but not necessarily in the preparation of the so-called precise or skillful motor tasks.

With regard to the second finding, the pre-movement potentials with hand movements were recorded from the primary hand sensorimotor area in one patient (patient 2), and those with foot movements from the primary motor foot area in another patient (patient 1). Neshige et al. (1988), in similar recording circumstances to the present study, reported the presence of BP at the primary hand sensorimotor area with ipsilateral hand movements in 3 epilepsy patients. The ipsilateral BP was relatively small, and no NS′ and MP followed the BP in their studies. These findings are consistent with the results observed in patient 2 in the present study. Namely, with ipsilateral hand movement a small BP was seen from the primary hand sensorimotor area but no clear NS′ or MP developed. For ipsilateral foot movements, the authors previously reported the absence of any pre-movement potential at the primary motor foot area in 2 patients (Ikeda et al., 1992). Patient 1 in the present study confirmed these results. These findings suggest that the ipsilateral primary sensorimotor hand or foot area of the human brain plays an almost negligible role in the generation of pre-movement as well as post-movement potentials. Therefore, unlike the SMA, the amplitude of pre-movement potentials recorded in the primary sensorimotor area with bilateral movements was just like a simple summation of two potentials associated with ipsilateral and contralateral movements. This result is consistent with previous animal studies which showed that, contrary to SMA neurons, most movement-related neurons in the primary motor area were simply related to the activity of the contralateral muscles (Evarts, 1966; Matsunami and Hamada, 1981; Tanji et al., 1987, 1988).

Scalp-recorded MRPs with unilateral and bilateral movements were previously studied (Kristeva et al., 1979, 1990, 1991). They interpreted their results as suggesting active participation of bilateral sensorimotor areas for generating pre-movement potentials. However, with the methodology used in their studies it is still uncertain how much of the pre-movement potentials was generated in the SMA as opposed to the primary sensorimotor area.

Previously cerebral blood flow studies demonstrated that SMA was significantly more active during actual execution of unilateral motor sequences than during simple movements (Orgogozo and Larsen, 1979; Roland et al., 1980; Shibasaki et al., 1993). It certainly means that the SMA is more active in association with the so-called complex movements than the simple ones. However, it remains unclear as to whether the observed activity at the SMA is the cause or the consequence of the behavioral act, because those studies provide the information about the total changes in the cerebral blood flow or metabolism occurring from about 40 sec before the measurement (Wiesendanger, 1986). The same limitations, i.e., poor temporal resolution, are also applied to functional MRI studies which showed similar results (Rao et al., 1993). In contrast, field potential studies, like the present one, provide information with high temporal resolution, and complement blood flow studies. Therefore, we can conclude that both electrophysiological and cerebral blood flow studies suggest that during movement preparation the human SMA is similarly active in unilateral and bilateral movements, but that during the actual motor execution it becomes more active in bilateral than in unilateral movements.

In the present study, patients 1 and 3 had pre-movement potentials with positive polarity. Invasive animal studies demonstrated that the pre-movement potentials had a dipolar distribution with a negative pole at the surface and a positive pole in the deep gray matter. Therefore it most likely represents excitatory postsynaptic potentials (EPSPs) generated in the superficial parts of apical dendrites of cortical pyramidal neurons (Hashimoto et al., 1979). Previously the authors' group showed the positive pre-movement potentials recorded by subdural electrodes in some subjects, regardless of the type of movement (Ikeda et al., 1992, 1993, 1995). Therefore, as previously discussed (Ikeda et al., 1992), these positive potentials recorded by subdural electrodes could be explained by the orientation of the dipole; a dipolar generator in a sulcus would project out of the positive and negative potentials toward the opposite direction. In this case only the positive potentials could be recorded because of the limited placement of subdural electrodes.

Recent anatomical and physiological studies in monkeys demonstrated that the SMA is subdivided at least into rostral (pre-SMA or F6) and caudal parts (SMA-proper or F3) (Luppino et al., 1991, 1993; Matsuzaka et al., 1992), and that the two had independent functions. Since the SMA-proper in monkeys has a somatotopic organization, it is possible that MRPs demonstrated in the SMA in the present and previous studies (Ikeda et al., 1992, 1993) were generated from the SMA-proper also in man. However, it still remains unsolved whether human SMA could be subdivided into the SMA-proper and pre-SMA as seen in monkeys.

Finally, it is worthwhile considering several technical limitations when interpreting the results of subdural MRP studies and comparing them with other scalp-recorded MRP studies. Closely spaced subdural electrodes can only record field potentials which is a reflection of the activity of neurons covered by the subdural electrodes. No single unit activity can be detected. In addition, the subdural electrodes do not cover the whole brain surface. Therefore, only part of the SMA was explored in each patient, and the possibility that more active parts of SMA adjacent to the explored areas might have been missed, cannot be excluded. Comparative studies of cerebral blood flow with PET or functional MRI would be helpful to complement those results. In addition, the stainless steel electrodes used in these studies are not optimal to record the so-called DC brain potentials (Caspers, 1974). Although we opened the LFF down to 0.016 Hz for cortical recordings, the type of electrode used indicates that the actual LFF cut-off was most probably higher than that. Therefore, the present data may not completely be comparable to scalp-recorded DC potentials, recorded by silver-silver chloride electrodes. In spite of these limitations, subdural MRP studies have provided new insight into the generation of MRPs (Neshige et al., 1988; Sakamoto et al., 1991; Ikeda and Shibasaki, 1992; Ikeda et al., 1992, 1993, 1995), and certainly the comparison of potentials recorded from different cortical areas in the same patient should give reliable results.

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References

Alexander, G.E. and Crutchler, M.D. (1990a) Preparation for movement: neural representations of internal direction in three motor areas of the monkey. J. Neurophysiol., 64: 133–150.

Alexander, G.E. and Crutchler, M.D. (1990b) Neural representations of the target (goal) of visually guided arm movements in three motor areas of the monkey. J. Neurophysiol., 64: 164–178.

Barrett, G., Shibasaki, H. and Neshige, R. (1985) A computer-assigned method for averaging movement-related cortical potentials with respect to EMG onset. Electroenceph. clin. Neurophysiol., 60: 276–281.

Barrett, G., Shibasaki, H. and Neshige, R. (1986) Cortical potentials preceding voluntary movement: evidence for three periods of preparation in man. Electroenceph. clin. Neurophysiol., 63: 327–339.

Brinkman, C. (1981) Lesions in supplementary motor area interfere with a monkey's performance of a bimanual coordination task. Neurosci. Lett., 27: 267–270.

Brinkman, C. (1984) Supplementary motor area of the monkey's cerebral cortex: short- and long-term deficits after unilateral ablation and the effects of subsequent callosal section. J. Neurosci., 4: 918–929.

Burgess, R.C. (1992) Design and integration of computer systems. In: H.O. Lüders (Ed.), Epilepsy Surgery. Raven Press, New York, pp. 291–296.

Caspers, H. (1974) DC potentials recorded directly from the cortex. In: A. Rémond (Ed.), Handbook of Elecroencephalography and Clinical Neurophysiology, Vol. 10, Part A. Elsevier, Amsterdam, pp. 7–11.

Chen, D.F., Hyland, B., Maier, V., Palmeri, A. and Wiesendanger, M. (1991) Comparison of neuronal activity in the supplementary motor area and in the primary motor cortex in monkeys. Somatosens. Motor Res., 8: 27–44.

Collura, T.F., Jacobs, E.C. and Burgess, R.C. (1992) Operations support and users interface of computer systems. In: H.O. Lüders (Ed.), Epilepsy Surgery. Raven Press, New York, pp. 297–305.

Crutchler, M.D. and Alexander, G.E. (1990) Movement-related neuronal activity selectively coding either direction or muscle pattern in three motor areas of the monkey. J. Neurophysiol., 64: 151–163.

Deecke, L., Scheid, P. and Kornhuber, H.H. (1969) Distribution of readiness potentials, pre-motion positivity and motor potentials of the human cerebral cortex preceding voluntary movements. Exp. Brain Res., 7: 158–168.

Deecke, L., Kornhuber, H.H., Lang, W. and Schreiber, H. (1985) Timing function of the frontal cortex in sequential motor and learning task. Hum. Neurobiol., 4: 143–154.

Eccles, J.C. (1982) The initiation of voluntary movements by supplementary motor area. Arch. Psychiat. Nervenkr., 231: 423–441.

Evarts, E.V. (1966) Pyramidal tract neuron activity associated with a conditioned hand movement in the monkeys. J. Neurophysiol., 29: 1011–1027.

Fox, P.T., Fox, J.M., Raichle, M.E. and Burde, R.M. (1985) The role of cerebral cortex in the generation of voluntary saccades: a positron emission tomographic study. J. Neurophysiol., 54: 348–369.

Fried, I., Katz, A., McCarthy, G., Sass, K.J., Williamson, P., Spencer, S.S. and Spenser, D.D. (1991) Functional organization of supplementary motor cortex studied by electrical stimulation. J. Neurosci., 11: 3655–3666.

Goldberg, G. (1985) Supplementary motor area structure and function: review and hypotheses. Behav. Brain Sci., 8: 567–616.

Hahn, J. and Lüders, H. (1987) Placement of subdural grid electrodes at the Cleveland Clinic. In: J. Engel, Jr. (Ed.), Surgical Treatment of the Epilepsies. Raven Press, New York, pp. 621–627.

Halsband, U. (1983) Higher disturbances of movements in *Macaca fascicularis* following discrete neocortical ablations. Neurosci. Lett., Suppl. 14: S154.

Hashimoto, S., Gemba, H. and Sasaki, K. (1979) Analysis of slow cortical potentials preceding self-paced hand movements in the monkeys. Exp. Neurol., 65: 218–229.

Hyland, B., Chen, D.F., Maier, V., Palmeri, A. and Wiesendanger, M. (1989) What is the role of the supplementary motor area in movement initiation? Progr. Brain Res., 80: 431–436.

Ikeda, A. and Shibasaki, H. (1992) Invasive recording of movement-related cortical potentials in human. J. Clin. Neurophysiol., 9: 509–520.

Ikeda, A., Lüders, H.O., Burgess, R.C. and Shibasaki, H. (1992) Movement-related potentials recorded from supplementary motor area and primary motor area: role of supplementary motor area in voluntary movements. Brain, 115: 1017–1043.

Ikeda, A., Lüders, H.O., Burgess, R.C. and Shibasaki, H. (1993) Movement-related potentials associated with single and repetitive movements recorded from human supplementary motor area. Electroenceph. clin. Neurophysiol., 89: 269–277.

Ikeda, A., Lüders, H.O., Burgess, R.C., Sakamoto, A., Klem, G.H., Morris, H.H. and Shibasaki, H. (1995) Generator locations of movement-related potentials with tongue protrusions and vocalizations: subdural recording in human. Electroenceph. clin. Neurophysiol., 96: 310–328.

Kornhuber, H.H. and Deecke, L. (1965) Hirnpotentialänderungen bei Willkürbewegungen und passiven Bewegungen des Menschen: Bereitschaftspotential und reafferente Potentiale. Pflügers Arch., 284: 1–17.

Kristeva, R., Keller, E., Deecke, L. and Kornhuber, H.H. (1979) Cerebral potentials preceding unilateral and simultaneous bilateral finger movements. Electroenceph. clin. Neurophysiol., 47: 229–238.

Kristeva, R., Cheyne, D., Lang, W., Lindinger, G. and Deecke, L. (1990) Movement-related potentials accompanying unilateral and bilateral finger movements with different inertial loads. Electroenceph. clin. Neurophysiol., 75: 410–418.

Kristeva, R., Cheyne, D. and Deecke, L. (1991) Neuromagnetic fields accompanying unilateral and bilateral voluntary movements: topography and analysis of cortical sources. Electroenceph. clin. Neurophysiol., 81: 284–298.

Lang, W., Lang, M., Uhl, F., Koska, Ch., Kornhuber, A. and Deecke, L. (1988) Negative cortical DC shifts preceding and accompanying simultaneous and sequential finger movements. Exp. Brain Res., 71: 579–587.

Lang, W., Zilch, O., Koska, Ch., Lindinger, G. and Deecke, L. (1989) Negative cortical DC shifts preceding and accompanying simple and complex sequential movements. Exp. Brain Res., 74: 99–104.

Lang, W., Obrig, H., Lindinger, G., Cheyne, D. and Deecke, L. (1990) Supplementary motor area activation while tapping bimanually different rhythms in musicians. Exp. Brain Res., 79: 506–514.

Lang, W., Cheyne, D., Kristeva, R., Lindinger, G. and Deecke, L. (1991) Functional localization of motor processes in the human cortex. In: C.H.M. Brunia, G. Mulder and M.N. Verbaten (Eds.), Event-Related Brain Research. Electroenceph. clin. Neurophysiol., Suppl. 42. Elsevier, Amsterdam, pp. 97–115.

Laplane, D., Talairach, J., Meininger, V., Bancaud, J. and Orgogozo, J.M. (1977) Clinical consequences of corticectomies involving the supplementary motor area in man. J. Neurol. Sci., 34: 301–314.

Lesser, R.P., Gordon, B., Fisher, R., Hart, J. and Uematsu, S. (1992) Subdural grid electrodes in surgery of epilepsy. In: H.O. Lüders (Ed.), Epilepsy Surgery. Raven Press, New York, pp. 399–408.

Lim, S.H., Dinner, D.S., Pillay, P., Lüders, H., Morris, H.H., Klem, G., Wyllie, E. and Awad, I. (1994) Functional anatomy of the human supplementary sensorimotor area: results of extraoperative electrical stimulation. Electroenceph. clin. Neurophysiol., 91: 179–193.

Luedders, H., Hahn, J., Lesser, R.P., Dinner, D.S., Rothner, D. and Erenberg, G. (1982) Localization of epileptogenic spike foci: comparative study of closely spaced scalp electrodes, nasopharyngeal, sphenoidal, subdural, and depth electrodes. In: H. Akimoto, H. Kazamatsuri, M. Seino and A.A. Ward (Eds.), Advances in Epileptology. The 13th Epilepsy Int. Symp. Raven Press, New York, pp. 185–189.

Lüders, H., Lesser, R.P., Dinner, D.S., Hahn, J.F., Salanga, V. and Morris, H.H. (1985) The second sensory area in human: evoked potential and electrical stimulation studies. Ann. Neurol., 17: 177–184.

Lüders, H., Lesser, R.P., Dinner, D.S., Morris, H.H., Hahn, J.F., Friedman, L., Skipper, G., Wyllie, E. and Friedman, D. (1987) Commentary: Chronic intracranial recording and stimulation with subdural electrodes. In: J. Engel, Jr. (Ed.), Surgical Treatment of the Epilepsies. Raven Press, New York, pp. 297–321.

Lüders, H., Lesser, R.P., Dinner, D.S., Morris, H.H., Wyllie, E. and Godoy, J. (1988) Localization of cortical function: new information from extraoperative monitoring of patients with epilepsy. Epilepsia, 29 (Suppl.): S56–S65.

Luppino, G., Matteli, M., Camarda, R.M., Gallese, V. and Rizzolatti, G. (1991) Multiple representations of body movements in mesial area 6 and the adjacent cingulate cortex: an intracortical microstimulation study in the macaque monkey. J. Comp. Neurol., 311: 463–482.

Luppino, G., Matteli, M., Camarda, R. and Rizzolatti, G. (1993) Cortico-

cortical connections of area F3 (SMA-proper) and area F6 (pre-SMA) in the macaque monkey. J. Comp. Neurol., 338: 114–140.

Matsunami, K. and Hamada, I. (1981) Characteristics of the ipsilateral movement-related neuron in the motor cortex of the monkey. Brain Res., 204: 29–42.

Matsuzaka, Y., Aizawa, H. and Tanji, J. (1992) A motor area rostral to the supplementary motor area (presupplementary motor area) in the monkey: neuronal activity during a learned motor task. J. Neurophysiol., 68: 653–662.

Morris, H.H. (1992) Protocols for surgery of epilepsy in different centers. In: H.O. Lüders (Ed.), Epilepsy Surgery. Raven Press, New York, pp. 786–788.

Morris, H.H., Dinner, D.S., Lüders, H., Wyllie, E. and Kramer, R. (1988) Supplementary motor seizures: clinical and electroencephalographic findings. Neurology, 38: 1075–1082.

Nathan, S.S., Sinha, S.R., Gordon, B., Lesser, R.P. and Thakor, N.V. (1993) Determination of current density distributions generated by electrical stimulation of the human cerebral cortex. Electroenceph. clin. Neurophysiol., 86: 183–192.

Neshige, R., Lüders, H. and Shibasaki, H. (1988) Recording of movement-related potentials from scalp and cortex in man. Brain, 111: 719–736.

Orgogozo, J.M. and Larsen, B. (1979) Activation of the supplementary motor area during voluntary movements in man suggests it works as a supramotor area. Science, 206: 847–850.

Penfield, W. and Jasper, H. (1954) Functional localization in the cerebral cortex. In: Epilepsy and the Functional Anatomy of the Human Brain. Little, Brown and Co., Boston, MA, pp. 88–102.

Penfield, W. and Welch, K. (1951) The supplementary motor area of the cerebral cortex: a clinical and experimental study. Arch. Neurol. Psychiat., 66: 289–317.

Porter, R. (1990) The Kubelberg lecture. Brain mechanisms of voluntary motor commands. A review. Electroenceph. clin. Neurophysiol., 76: 282–293.

Rao, S.M., Binder, J.R., Bandettini, P.A., Hammeke, T.A., Yetkin, F.Z., Jesmanowicz, A., Lisk, L.M., Morris, G.L., Mueller, W.M., Estkowski, L.D., Wong, E.C., Haughton, V.M. and Hyde, J.S. (1993) Functional magnetic resonance imaging of complex human movements. Neurology, 43: 2311–2318.

Roland, P.E., Larsen, B., Lassen, N.A. and Skinhøj, E. (1980) Supplementary motor area and other cortical areas in organization of voluntary movements in man. J. Neurophysiol., 43: 118–136.

Rostomily, R.C., Berger, M.S., Ojemann, G.A. and Lettich, E. (1991) Postoperative deficits and functional recovery following removal of tumors involving the dominant hemisphere supplementary motor area. J. Neurosurg., 75: 62–68.

Sakamoto, A., Lüders, H. and Burgess, R. (1991) Intracranial recordings of movement-related potentials to voluntary saccades. J. Clin. Neurophysiol., 8: 223–233.

Schell, G., Hodge, C.J. and Cacayorin, E. (1986) Transient neurological deficit after therapeutic embolization of the arteries supplying the mesial wall of the hemisphere, including the supplementary motor area. Neurosurgery, 18: 353–356.

Schmidt, E.M., Porter, R. and McIntosh, J.S. (1992) The effects of cooling supplementary motor area and midline cerebral cortex on neuronal responses in area 4 of monkeys. Electroenceph. clin. Neurophysiol., 85: 61–71.

Shibasaki, H., Barrett, G., Halliday, E. and Halliday, A.M. (1980) Components of the movement-related cortical potentials and their scalp topography. Electroenceph. clin. Neurophysiol., 49: 213–226.

Shibasaki, H., Sadato, N., Lyshkow, H., Yonekura, Y., Honda, M., Nagamine, T., Suwazono, S., Magata, Y., Ikeda, A., Miyazaki, M., Fukuyama, H., Asato, R. and Konishi, J. (1993) Both primary motor cortex and supplementary motor area play an important role in complex finger movement. Brain, 116: 1387–1398.

Tanji, J. and Kurata, K. (1982) Comparison of movement-related activity in two cortical motor areas of primates. J. Neurophysiol., 48: 633–653.

Tanji, J. and Kurata, K. (1985a) Contrasting neuronal activity in supplementary and precentral motor cortex of monkeys. I. Responses to instructions determining motor responses to forthcoming signals of different modalities. J. Neurophysiol., 53: 129–141.

Tanji, J. and Kurata, K. (1985b) Contrasting neuronal activity in supplementary and precentral motor cortex of monkeys. II. Responses to movements triggering vs. nontriggering sensory signals. J. Neurophysiol., 53: 142–152.

Tanji, J., Okano, K. and Sato, K.C. (1987) Relation of neurons in the nonprimary motor cortex to bilateral hand movement. Nature, 327: 618–620.

Tanji, J., Okano, K. and Sato, K.C., (1988) Neuronal activity in cortical motor areas related to ipsilateral, contralataral, and bilateral digit movements of the monkeys. J. Neurophysiol., 60: 325–343.

Wiesendanger, M. (1986) Recent developments in studies of the supplementary motor area of primates. Rev. Physiol. Biochem. Pharmacol., 103: 1–59.

Wiesendanger, M., Hummelsheim, H., Bianchetti, M., Chen, D.F., Hyland, B., Maier, V. and Wiesendanger, R. (1987) Input and output organization of the supplementary motor area. In: R. Porter (Ed.), Motor Area of the Cerebral Cortex. Ciba Foundation Symposium 132. John Wiley and Sons, Chichester, pp. 40–53.

Woolsey, C.N., Settlage, P.H., Meyer, D.R., Spencer, W., Pinto-Hamuy, T.P. and Travis, A.M. (1952) Patterns of localization in precentral and "supplementary" motor areas and their relation to the concept of a premotor area. Res. Publ. Ass. Res. Nerv. Ment. Dis., 30: 238–264.