The SMA was defined on the basis of cortical stimulations as the medial part of Brodmann area 6 in front of the primary motor representation of the leg. The “syndrome” of “SMA epilepsy” represents in the neurologist’s mind seizures arising from the medial frontal lobe, characterized by an arrest of activity with asymmetrical tonic posturing of the upper more often than the lower limbs, conjugated adversion of the head and eyes, SA, and sometimes vocalization. Most of the typical symptoms of the so-called SMA seizures have been reproduced by ESs of the medial frontal cortex during intraoperative and extraoperative long-term intracranial EEG monitoring. Also, the role of the SMA in motor planning has long been recognized by using movement-related potentials and by studying the effects of lesions.

Despite the recognition of a distinct architectonic anterior subdivision of Brodmann area 6 and a functional

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Somatosensory, motor, and reaching/grasping responses to direct electrical stimulation of the human cingulate motor areas

Clinical article

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Object. Surgery for frontal lobe drug-resistant epilepsies is often limited by the apparent widespread distribution of the epileptogenic zone. Recent advances in the parcellation of the medial premotor cortex give the opportunity to reconsider “seizures of the supplementary motor area” (SMA), and to assess the contribution of cingulate motor areas (CMAs), SMA proper (SMAp), and pre-SMA to the symptomatology of premotor seizures.

Methods. The authors reviewed the results of extraoperative electrical stimulation (ES) applied in 52 candidates for epilepsy surgery who underwent stereotactic intracerebral electroencephalographic recordings, focusing on ES of the different medial premotor fields; that is, the anterior and posterior CMA, the SMAp, and the pre-SMA. The ES sites were localized by superposition of the postoperative lateral skull x-ray and the preoperative sagittal MR imaging studies.

Results. Among 94 electrodes reaching the medial premotor wall, 57 responses were obtained from the anterior CMA (13 cases), the posterior CMA (11), the pre-SMA (18), and the SMAp (15). The ES of the pre-SMA and SMAp gave rise most often to a combination of motor (31 cases), speech-related (22), or somatosensory (3) elementary symptoms. The ES of the CMA yielded simple (17 of 24) more often than complex responses (7 of 24), among which sensory symptoms (7) were overrepresented. Irresistible exploratory reaching/grasping movements were elicited at the vicinity of the cingulate sulcus, from the anterior CMA (3 cases) or the pre-SMA (1). Clinical responses to ES were not predictive of the postoperative neurological outcome.

Conclusions. These findings might be helpful in epilepsy surgery candidates, to better target investigation of the CMA, pre-SMA, and SMAp, and therefore to provide a better understanding of premotor seizures.

(Key Words • anterior cingulate cortex • electrical stimulation • intracranial recording • supplementary motor area)
heterogeneity within the SMA, the real identification of a pre-SMA and motor areas buried in the CS (CMA)s was not achieved until recently, both in humans and animals. Subsequently, a considerable number of studies was published to clarify the specific contribution to motor control of the different medial premotor areas, showing that rostral CMA and pre-SMA were involved in the early stage of motor learning, the selection of motor responses, and complex movements.

In the setting of presurgical investigations of frontal lobe epilepsies, these data remain underexploited because of the small size and limited accessibility of these cortical areas, and due to the current concept of a very rapid spread of frontal ictal discharges over broad areas both ipsilaterally and bilaterally, making it difficult to constrain focal frontal lobe seizures. However, isolated case reports and short series have highlighted the possibility that frontal lobe seizures can originate from a discrete epileptogenic focus belonging to the SMAp, pre-SMA, or CMA, and can be cured by surgery that has been tailored based on intracranial recordings.

Despite well-known limitations, cortical ES provides the opportunity to perform functional mapping of the cerebral cortex and a unique way to mimic symptoms of epileptic seizures and to clarify their topographic origin. We therefore reviewed the clinical effects of ES applied over the medial premotor cortex, as routinely performed in patients with medically intractable epilepsy who were evaluated at our institution between 1993 and 2003. The main aim was to clarify the pre-SMA, SMA, and CMA responses to ES in humans and their potential contribution to the symptomatology of frontal lobe seizures.

**Methods**

**Patient Selection**

Among 261 patients with partial epilepsy who underwent prolonged video-SEEG monitoring as part of presurgical evaluation at Grenoble Hospital between January 1993 and December 2003, we selected those in whom at least 1 of the depth electrodes was implanted in the SMA region and/or surrounding cortex of the mesial frontal cortex; that is, in an ROI that included all mesial premotor areas (Fig. 1, see also Localization of Stimulation Sites). Patients with large space-occupying lesions were excluded from the study. Findings on MR imaging were unremarkable in 17 cases, and have demonstrated nontumoral lesions in others that never involved the ROI.

**Patient Population**

We found 52 patients (35 male and 17 female patients) who met the selection criteria. One patient underwent exploratory procedures twice, so that 53 SEEG studies were analyzed. Age at the time of SEEG ranged from 6 to 49 years (mean age 23.5 years), age at epilepsy onset ranged from 4 months to 22 years (mean 6.7 years), with a mean epilepsy duration of 16.7 years (range 3–40 years). On the basis of the video-SEEG monitoring, the theoretical epileptogenic zone proved to be exclusively frontal (31 patients), central (1), insulofrontal (1), frontotemporal (5), temporal (4), temporoparietal (1), parietal (3), temporoccipital (1), or multifocal (2). In the 3 remaining patients, depth recordings were inconclusive (nonlocalizing findings, no seizure recorded).

Forty-four patients underwent a resective surgery, 1 had a frontal disconnection, and 5 underwent palliative surgery (for a summary of postoperative neurological outcome see Table 1). The 2-year follow-up showed that 24 of the 50 patients were seizure free, 4 of 50 had rare relapsing seizures, and the remaining 22 had a bad outcome (3 in Engel Class III and 19 in Engel Class IV). Postoperative de novo deficits were observed in 12 cases, among which 5 were related to resections including the premotor cortex of the medial wall; deficits included a decrease in spontaneous movements with slight transient hemiparesis (4 patients), which was associated with dynamic aphasia (surgery of the dominant hemisphere) in all but 1 (non-dominant hemisphere). Taking into account the severity of epilepsy, 1 patient underwent a large resection including the primary motor strip, resulting postoperatively in a permanent hemiparesis. When available, the pathological analysis revealed focal cortical dysplasias (13 cases), nonspecific scars (5), dysembryoplastic neuroepithelial tumors (3), cortical tubers (2), hippocampal sclerosis (2),

**Fig. 1.** A: Standardized proportional grid system, lateral view, showing the primary ROI (gray shaded area). B: Graph with numbered shaded areas showing parcellation of the ROI. 1, SMAp; 2, pre-SMA; 3, CMAp; 4, CMAa.
ganglioglioma (1), hamartoma (1), and arachnoid cyst (1). One patient had a frontal disconnection (without pathological analysis) and the remaining 13 patients showed no pathological abnormalities. Curative epilepsy surgery was not possible in the 5 remaining patients, in whom SEEG recordings demonstrated seizures involving both anterior frontal and primary motor areas without previous motor deficit (2 patients), seizures involving the insula (1), or were inconclusive (no seizure recorded in 2). All 5 of these patients underwent palliative surgery, including a vagus nerve stimulation (2), subthalamic stimulation (2), and radiosurgery (1).

### Implantation of Intracerebral Electrodes

Depth electrodes were implanted unilaterally in 35 cases (23 on the right, 12 on the left side) and bilaterally in 18 cases. Ictal symptoms that justified the implantation of electrode(s) within the region of the SMA were tonic axial or asymmetrical posturing of ≥ 1 limbs, vocalizations or SA, and versive movements of the eyes and/or head at the beginning or in the course of the seizure. Anatomical targets were assessed using both preoperative MR imaging studies and stereotactic teleradiography matched with Talairach's stereotactic atlas. Implantation of the electrodes was performed under the same stereotactic conditions, with the help of a computer-driven robot, by using a lateral orthogonal trajectory in a majority of the cases, or an oblique route when necessary. Each electrode had a diameter of 0.9 mm and comprised 10 or 15 leads of 2-mm length positioned 1.5 mm apart (DIXI Microtechniques).

### Intracerebral Recordings and Stimulations

Intracerebral recordings were conducted extraoperatively in patients with chronic conditions, after cautious lowering of antiepileptic medication, by using an audio-video-EEG monitoring system (Biomedical Monitoring System, Campbell; since 1996, Micromed), which allowed us to record up to 96 depth EEG channels. All patients underwent recording of interictal and ictal discharges before and/or after ES studies.

The ESs were delivered on several days before or after SEEG recordings under continuous video-EEG control, during sessions that lasted 1–2 hours. Bipolar stimulations were performed at 50 Hz (pulse width 1 msec, maximum duration 5 seconds) and applied between contiguous contacts at different levels along the axis of each electrode. Bipolar electrical stimuli were delivered using a constant current rectangular pulse generator, at intensities ranging from 0.2 to 3 mA depending on the stimulated site (World Precision Instruments; and since 1996, Micromed). Each stimulation was performed after checking that the depth EEG exhibited its usual baseline activity. During stimulations, patients were asked to count or list series of words loudly to check the speech function, and subsequently to

### TABLE 1

**Summary of postoperative neurological deficits and unexpected complications without neurological deficit, with respect to the site of resection**

<table>
<thead>
<tr>
<th>Resection</th>
<th>No. w/ Preexisting Deficit</th>
<th>De Novo Postop Deficit</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>frontal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>extended frontal premotor &amp; prefrontal</td>
<td>6</td>
<td>0</td>
<td>1 trans facial paresis</td>
</tr>
<tr>
<td>med premotor</td>
<td>5</td>
<td>0</td>
<td>2 trans aphasia &amp; hemiparesis</td>
</tr>
<tr>
<td>orbitoventromedial</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>med &amp; lat prefrontal</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>med &amp; lat premotor</td>
<td>3</td>
<td>1 hemiparesis</td>
<td>2 trans akinesia (1 w/ aphasia)</td>
</tr>
<tr>
<td>lat prefrontal</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>orbitofrontal-lat</td>
<td>1</td>
<td>1 hemiparesis</td>
<td>0</td>
</tr>
<tr>
<td>orbitofrontopolar</td>
<td>1</td>
<td>0</td>
<td>1 trans hemiparesis</td>
</tr>
<tr>
<td>med prefrontal</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>primary motor &amp; premotor</td>
<td>2</td>
<td>1 hemiparesis</td>
<td>1 hemiparesis</td>
</tr>
<tr>
<td>focal premotor electrocoagulation</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>temporal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>standard lobectomy</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>temporal posterior</td>
<td>1</td>
<td>0</td>
<td>1 trans aphasia</td>
</tr>
<tr>
<td>parietal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>med</td>
<td>3</td>
<td>0</td>
<td>2 trans ataxia; 1 trans hypes-thesia</td>
</tr>
<tr>
<td>lat</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>multilobar</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>anteromesial temporal &amp; anterior frontal</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>temporoccipital</td>
<td>1</td>
<td>0</td>
<td>1 contralat hemianopia</td>
</tr>
<tr>
<td>temporoparietal</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>others</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gamma Knife (hypothalamic hamartoma)</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>subthalamic stimulation</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>vagus nerve stimulation</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>total</td>
<td>49</td>
<td>3</td>
<td>11</td>
</tr>
</tbody>
</table>

*DVT = deep venous thrombosis; med = medial; trans = transient.*
stand with the arms outstretched in the supination position, sometimes followed by a sustained posture with the legs flexed at hip and knee. Negative motor responses were tested during alternate movements of supination and pronation of the forearm or rapid tapping of the thumb against each fingertip. All overt symptoms (posturing, E/HD, inhibition of motor activity, and slowing or arrest of speech) were described in the online database by the examiner (neurologist).

**Analysis of Electrically Induced Clinical Responses**

The effects of ES delivered over the electrodes located in the ROI were retrospectively reviewed from the raw data sheets and videotapes, focusing on the stimulations of sites located in the medial frontal premotor cortex. We considered only stimulations performed < 10 mm from the midsagittal plane in the mediolateral dimension, to avoid as far as possible the stimulation of corticopyramidal fibers. Depth EEG data were analyzed to ensure the absence of elicited afterdischarge at or beyond the stimulating electrode. Only symptoms elicited at the lowest intensity for a given ES site were taken into account.

Clinical responses were assessed taking into account motor phenomena of the limbs, conjugate movements of the eyes and/or head version, somatosensory symptoms, speech disturbances, and psychological effects (Table 2). Motor and somatosensory responses were detailed according to their lateralization (contra-, ipsi-, or bilateral) and localization (≥ body segments, proximal or distal, upper and/or lower limb). Motor symptoms were divided into tonic contraction, axial or localized postural disturbance, and numbness of ≥ 1 limbs. Slowing or total inhibition of sequential movements of the fingers or the hands were classified as NMRs, as previously described by Lüders and colleagues. Sensory experiences were defined as tingling sensations, sensation of warmth, numbness, paresthesias, and pain. Speech disturbances were defined as a slowing or arrest of speech when the patient was counting or listing the days of the week or the months of the year. Palilalia was defined as persevera-

| TABLE 2 |

**Clinical responses to ES of the frontal medial cortical wall**

<table>
<thead>
<tr>
<th>Premotor Field</th>
<th>Pre-SMA</th>
<th>SMAp</th>
<th>CMAa</th>
<th>CMAa2</th>
<th>CMAp</th>
<th>CMAp3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of electrodes reaching each premotor field</td>
<td>34</td>
<td>26</td>
<td>9</td>
<td>13</td>
<td>5</td>
<td>7</td>
<td>94</td>
</tr>
<tr>
<td>no. of sites where ESs were effective</td>
<td>18</td>
<td>15</td>
<td>4</td>
<td>9</td>
<td>5</td>
<td>6</td>
<td>57</td>
</tr>
<tr>
<td>no. of sites where ESs were negative</td>
<td>15</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>ES not done</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>seizure or after discharge</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

**TP**

1. 2. 2. 1. 1. 7.

**TLPI**

1. 3. 1.

**Illusion of movement**

1. 1.

**NMR**

1. 1.

**SA**

3. 1. 1. 2. 1. 8.

**Palilalia**

1. 1.

**Sensory**

1. 1. 1. 3. 1. 7.

**Overt R/G**

1. 1.

**Urge to laugh**

1. 1.

**Total**

6. 7. 4. 5. 4. 4. 30.

**Complex responses**

1. 2. 2. 1. 1. 4.

**TP & SA**

1. 1.

**TP & Sensory**

1. 1. 1.

**Sketched-out R/G & SA**

2. 2. 2.

**TLPI & SA**

4. 2. 6.

**NMR & SA**

1. 1. 2.

**NMR & SA & E/HD**

2. 2.

**TLPI & E/HD**

1. 1.

**SA & E/HD**

2. 1. 3.

**SA & Sensory**

1. 1.

**E/HD & SA & TLPI**

1. 1. 2.

**E/HD & Palilalia & TLPI**

1. 1.

**E/HD & SA & Sensory**

1. 1.

**Total**

12. 8. 0. 4. 1. 2. 27.

* Simple and complex denote elementary (that is, simple) and complex (a combination of motor, sensory, and speech symptoms and/or E/HD) responses to ES; E/HD describes contralateral oculocephalic deviation; illusion of movement means a transient illusion of elevation of the contralateral arm; NMR is a negative motor response such as slowing or inhibition of sequential movements of the hands or tapping of the fingers; overt R/G denotes an irresistible urge to grasp objects; SA includes speech arrest or slowing; sketched-out R/G describes a slight gesture of groping and reaching/grasping movements; TLPI describes transient limb postural instability observed when the arm(s) and/or leg(s) were held in a sustained position.
Functional mapping of the human cingulate motor areas

tions on a syllable or a song when speaking. Eyes and/or head deviation was categorized into contralateral or ipsilateral deviation with respect to the side of ES.

All other unexpected subjective symptoms or behaviors were taken into account and detailed as far as possible from the videotapes. Neurological postoperative deficits were retrospectively identified and correlated with the effects of ESs.

Localization of Stimulation Sites

In a first step, the 3D coordinates of each contact of the sites of stimulation belonging to the ROI were determined according to the stereotactic normalized system of Talairach and Tournoux, on the basis of a postoperative lateral and frontal skull x-ray study superimposed on the preoperative MR images. In a limited number of cases, the position of the electrode was also directly visualized on a postoperative MR imaging study. In a second step, each site of ES was assigned to a cortical subfield of the medial premotor cortex. For that purpose and for each patient, we traced the anatomical landmarks of Talairach and Tournoux (AC, PC, AC–PC line, VAC line, and VPC line) as well as the main sulci of the medial wall on the medial sagittal slice of the high-resolution MR image, and measurements of the anteroposterior dimension of the brain were done. The pre-SMA, SMAp, CMAa, and CMAp were then individually delineated in relation to the CS and according to cytoarchitectonic studies and neurophysiological studies. Because there are no visible anterior and posterior landmarks for the SMA, we selected as boundaries of the 4 medial premotor fields those previously proposed by Picard and Strick based on the meta-analysis of PET studies summarizing activations of the medial wall during motor paradigms. Thus, the pre-SMA was defined as the region located above the CS, anterior to the VAC, extending anteriorly to the VAC up to 17% of the total anteroposterior length of the brain, whereas the SMAp corresponded to the area between the VAC and the VPC and above the CS. For the definition of the CMA, we considered separately sites located in the ventral and dorsal banks around the CS. We defined the CMAp as the ventral bank of the CS, the CMApv as the dorsal bank of the CS with the same anterior and posterior limits as for the SMAp. The CMAa, was defined as the region lying on the ventral bank of the CS and the CMAav as the dorsal bank of the CS, located ahead of the VAC line and extending 28.6% of the anteroposterior length of the brain anteriorly to the VAC line.

Results

Anatomical Location of the Sites of Stimulation

Of the 649 electrodes implanted during the 53 SEEG investigations (an average of 12.2 electrodes per patient), 117 reached the ROI (Fig. 2). Among these 117 sites of the ROI initially thought to belong to 1 of the medial premotor areas, the careful anatomical study of individual ES sites demonstrated that the tips of 23 electrodes reached the medial wall below the inferior bank of the CS, from which they were separated by a bundle of white matter, thus lying in the dorsal part of the cingulate gyrus proper.

These 23 sites were not included in the analysis. Therefore, among the 94 relevant ES sites, 34 were lying in the pre-SMA, 26 in the SMAp, 22 in the CMAa (9 in the CMAav and 13 in the CMAaav), and 12 in the CMAp (5 in the CMAP, and 7 in the CMAPv) (Table 2).

Electrically Induced Responses: Global Findings

Clinical responses to ES (mean intensity 1.65 mA, range 0.5–3 mA) were obtained in 43 patients from stimulation of 57 of the 94 sites, among which 18 sites were lying in the pre-SMA, 15 in the SMAp, 13 in the CMAa (4 in the CMAav and 9 in the CMAaav), and 11 in the CMAp (5 in the CMAP, and 6 in the CMAPv) (Table 2). The ESs were not done in 3 cases, and the results were excluded from the analysis in 7 additional cases because of the occurrence of a provoked seizure or electrical afterdischarge once the ES was stopped. No responses occurred for the remaining 27 ES sites (mean intensity 2.74 mA, range 2–3 mA). We checked that the rate of clinical responses without afterdischarge was the same whether or not the ES sites belonged to the epileptogenic zone.

Among the 57 elicited clinical responses, motor positive (including TP, TLPI, and E/HD) or motor negative signs were observed at 41 ES sites, speech disturbances at 33 (SA in 31 and pallialia in 2), somatosensory symptoms at 10, and psychological signs (urge to laugh) at 1.

Motor symptoms involved the superior limb (25 cases), the head and eyes (conjugated contralateral deviation, 8), the inferior limb (3), the eyes only (contralateral deviation without conjugated deviation of the head, 2), and the head alone (cervical extension, 1). The type of motor sign most commonly found consisted of a TLPI of 1 limb (13 cases), TP (13), and contralateral E/HDs (11). The TLPI corresponded to an inability to hold the arm(s) or leg(s) in a sustained position, time-locked with the stimulation, without evidence of increased tone. In all but 1 case, TP
involved at least the shoulder, and often the elbow, so as to
give the arm a transient posture combining abduction and
raising, with protrusion of the shoulder and sometimes a
rotational component. The other types of motor responses
comprised R/G movements in 4 cases, NMR in 5 cases,
and an illusion of movement in 1 case. The first case of R/G
movement, which has been previously published in detail,26
started with an irresistible urge to grasp accessible objects
in the visual field, followed by reaching behavior with the
arm contralateral to the stimulation side (overt R/G). In
the 3 remaining cases, R/G consisted of a slight gesture of
groping and R/G movements with the hand contralateral
to stimulation, as if the patient was groping around and
trying to pick up a small object (sketched-out R/G). The
E/HD never occurred alone but was always part of com-
plex responses, including either TP of the upper limbs or
speech-related responses.

Speech-related responses (SA in 31 cases and palil-
lia in 2) were common and were most often associated
with other symptoms (in 24 of 33 cases). Somatosensory
responses were infrequently associated with other elicited
symptoms and consisted of paresthesias (4 cases), num-
Bnness (3), electric sensation (2), or a sensation of warmth in
1 limb (1). They involved the inferior limb, the superior
limb, the back (3 cases each), or all 4 limbs (1 case).

All E/HDs (10 cases) and all but 2 motor and soma-
tosensory responses were lateralized on the side of the
body contralateral to the ES site (1 motor response was ax-
ial and 1 sensory response was characterized with bilateral
paresthesias).

Simple responses (motor, sensory, speech, or psycho-
logical symptoms) were observed at 30 of 57 ES sites, at a
mean intensity of 1.51 mA (range 0.5–3 mA). They con-
sisted most frequently of TP of the contralateral arm and/or
leg (7 cases), speech disturbances (9), and somatosensory
symptoms (7). Complex responses were observed at 27 of
57 sites, at a mean intensity of 1.87 mA (range 0.5–3 mA).
They consisted of multiple combinations of ≥ 2 elementary
symptoms, the most frequent of which consisted of the as-
association of TLPI of 1 limb with SA (6 cases).

Anatomoclinical Correlations

With respect to the hemispheric dominance for lan-
guage, 28 of 57 responses were obtained from the non-
dominant hemisphere. All types of symptoms were elic-
ited from both hemispheres, with the exception of the 2
cases of palilalia, which were observed after stimulation of
the dominant hemisphere.

Among the 57 ES sites where stimulations were ef-
fective, motor responses were observed at 12 of 18 pre-
SMA sites, 14 of 15 SMAp sites, 7 of 13 CMAa sites,
and 6 of 11 CMAP sites. Transient limb postural insta-
bility was observed mainly when stimulating pre-SMA
or SMAp regions (11 of 13). Eyes and/or head deviation
also demonstrated a predominance for pre-SMA/SMAp
regions (8 of 11). Tonic posturing, by comparison, was
observed equally in pre-SMA/SMAp (6 of 13) and CMA
(7 of 13) regions. Three of the 4 R/G behaviors occurred
when stimulating the CMA region, and 1 when stimulat-
ing the pre-SMA at the vicinity of the CS. All 5 NMRs,
during which the patients were unable to carry on with
sequential movements, were elicited by pre-SMA and
SMAp ES, and more precisely at a transitional region be-
tween pre-SMA and SMA centered on the VAC line (see
Fig. 3). Finally, 1 patient reported an illusion of move-
ment of the upper limb contralateral to the stimulation of
the SMAp at 0.6 mA (higher intensity was not applied).

Somatosensory symptoms were more common with
ES of the nondominant hemisphere (7 of 10 cases) and
occurred more frequently when stimulating the CMA re-
gion (7 of 10), especially its posterior aspect (5 of 7).

Speech-related responses were evoked more frequent-

![Fig. 3](image-url)
Functional mapping of the human cingulate motor areas

ly with ES of the dominant hemisphere (24 of 33 cases). Speech arrest was observed most often when stimulating the pre-SMA or the SMAp region (22 of 31), whereas the 2 cases of palilalia were elicited from the pre-SMA region of the dominant hemisphere. An urge to laugh was induced by low-intensity stimulation of the CMAa (Talairach coordinates x = 4, y = 16, z = 37), that is, at the same region where we elicited an urge to grasp in another patient (see above).

Overall, all types of responses were elicited in overlapping areas (Fig. 3). However, motor responses, including TLPI and NMR, were obtained more anteriorly and dorsally than those including TP; responses with E/HD were elicited more anteriorly than those without; and sensory responses were elicited more ventrally than the motor responses. Additionally, most of the pre-SMA and SMAp responses involving the cephalic extremity, including the mouth and eyes, were obtained ahead of the VAC line, whereas lower-limb sensorimotor responses were elicited more posteriorly behind the VPC, with the representation of the arm lying below and overlapping the VAC (Fig. 4). Last but not least, involuntary R/G movement, sensory responses, and pressure to laugh were overrepresented in the CMA region, whereas NMR and E/HD were underrepresented (Fig. 5).

Correlations Between Responses to ESs and Neurological Postoperative Outcome

Overall, 12 patients had postoperative de novo neurological deficits, with complete recovery in all but 2 cases (hemiparesis and hemianopia in 1 each). Only 1 case was related to an unexpected complication (transient paresthesias, caused by a vascular spasm). Among 5 patients who had a postoperative motor deficit, 4 occurred in cases of surgery involving the medial premotor cortex but sparing the primary motor cortex (results summarized in Table 3). These deficits involved a slowing of spontaneous movements with akinesia and slight hemiparesis, which were associated in 3 cases with a dynamic aphasia (reduction of spontaneous speech). All deficits recovered to wholeness in 3–4 weeks. Only 1 patient had a persistent hemiparesis, which was related to a resection involving both premotor and primary motor cortex.

Discussion

In the setting of the preoperative workup for drug-resistant epilepsies, ES appears to be the best method to
define the symptomatogenic zone, that is, “the area of cortex which, when activated by an epileptic discharge, produces the ictal symptoms.” In that respect, we retrospectively studied the effects of intracerebral ES of the medial premotor cortex in epileptic patients, taking advantage of recent advances coming from the breaking up of the SMA region and surrounding cortex into several functional subdivisions.

We observed that ES at low intensities in the pre-SMA, SMAp, and CMA gave rise to a wide range of motor, sensory, behavioral, and speech responses that could occur either separately (simple responses) or in various combinations (complex responses). The low level of stimulation we used, ranging from 0.2 to 3 mA, probably explains why we also collected a relatively high frequency of “negative” ES results (that is, ES that did not elicit any clinical signs). Although both clinical responses were elicited in overlapping areas of the mesial premotor wall, we found that there existed some differences that might help to differentiate the pre-SMA and SMA regions from the CMA region on clinical grounds. Notably, motor responses including TLPI and NMR were obtained more anteriorly and dorsally within the medial premotor cortex (pre-SMA and SMAp), whereas those including TP were elicited more posteriorly and ventrally, also involving the CMA region. Sensory responses were elicited more ventrally than motor responses, and more especially from the CMA region. Clinical responses to ES were not predictive of the neurological postoperative outcome. Before we discuss the original contribution of our study about the responses of the CMA to ES, we will first compare our results with ES of the SMA and pre-SMA to those in previous studies.

Stimulations of the Pre-SMA and SMA

**Methodological Concerns.** It is possible that the effects of pre-SMA ES have been underestimated in our study, as well as in previous ones, due to insufficient intensities of stimulation, or because motor inhibition and/or speech fluency were not systematically studied. Lupin et al. reported higher motor thresholds in response to ES in F6 (pre-SMA) than in F3 (SMAp) in monkeys. Compared with previous studies, we used low-intensity stimula-

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<th>Stimulation of the Pre-SMA and SMA</th>
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<td><strong>TABLE 3</strong> Postoperative neurological outcome and effects of stimulations in medial premotor areas after surgery involving the premotor medial wall*</td>
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<td>Stimulation Status</td>
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<td>ES+</td>
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<td>* ES+ = ES elicited a clinical response; ES− = ES elicited no response. † Two patients (1 in whom results of ES were positive and 1 in whom results were negative) had a preexisting motor deficit with no worsening after surgery.</td>
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As a matter of fact, the motor symptoms we observed were more discrete than those reported in the aforementioned studies and were confined to 1 limb, and they never involved both upper and lower limbs, nor were they bilateral. However, these findings should mainly concern positive motor symptoms rather than negative ones, because Chauvel et al. showed that speech or movement arrest alone did not depend on the stimulus strength when stimulating with intensities ranging from 2 to 8 mA.

Despite the lack of a macroscopic anatomical landmark between the SMA and pre-SMA, one can expect distinctive responses to ES related to the different connections of the 2 areas. The pre-SMA is mostly connected with the prefrontal cortex and dorsal aspect of the ACG, whereas the SMAp establishes bilateral connections with the primary motor cortex, lateral premotor cortex, primary somatosensory cortex, superior parietal cortex, parietal operculum, and insular cortex. Overall, we did not find major differences between the SMA and pre-SMA responses. Two main hypotheses can be suggested to explain the lack of discrimination between SMA and pre-SMA responses in our study: 1) interindividual variations in microscopic anatomy (an ES located in projection of the VAC line can belong either to the SMA or pre-SMA); or 2) in this retrospective study, the SMA has been previously targeted with reference to the work of Talairach and Bancaud, who observed that the higher density of positive motor responses was located just in front of the VAC line; thus, the anterior part of the pre-SMA and the posterior part of the SMAp were underinvestigated.

We did not describe the clinical symptoms of spontaneous seizures of the affected patients because our main objective was to clarify the localization of elementary signs and symptoms rather than the epileptic symptomatology. We systematically excluded from analysis elicited responses that resembled a patient’s usual seizures, symptoms associated with an afterdischarge, and stimulations applied inside or at the vicinity of an epileptogenic lesion. However, we cannot rule out the possibility that abnormal connections and plastic changes related to the repetition of seizures can modify responses to ES.

**Functional Heterogeneity.** Overall, we observed a functional heterogeneity not only in the SMAp, but also in the pre-SMA, that was not previously reported. The functional heterogeneity of the SMA was first mentioned during intraoperative and short-term extraoperative functional mapping of the SMA, and detailed later during long-term extraoperative stimulations. However, these authors pooled together sites located in the SMAp and pre-SMA. More recently, blood oxygenation level–dependent activations were observed in the SMA during various motor, sensory, verb generation, listening comprehension, and working memory tasks. In broad outline, the SMAp seems to support most of the functions that were attributed to the SMA, whereas the pre-SMA is involved upstream in the process of motor planning. Studies examining single-cell activity in monkeys showed that pre-SMA neurons are more active than SMA neurons when the animals have to move from a motor plan to a new one, and for the processing of visual cues to plan
forthcoming actions, whereas SMAp neurons are more active when selecting and executing the appropriate motor program.25

Phenomenology and Anatomoclinical Correlations. We did not observe the classic triad of SMA stimulation (TP plus SA plus E/HD), possibly due to the low level of ES intensity we used. Such complex responses, indeed, are usually observed at higher intensities (up to 10 V)23 and/or at ES located more laterally,30 so that they were not taken into account in our analysis. Chauvel et al.14 reported that motor effects are likely to occur in combination, according to stereotyped sequences, beginning with speech and motor arrest, associated or not with vocalization, and followed by raising and abduction of the upper limb with head and eye movements, as if the patients were looking at the arm movement. In a very few cases of pre-SMA and SMAp stimulations (1 case each), we observed a minor form of the triad, in the shape of the combination of an SA, E/HD, and TLPI. For example, we observed in Case 29 a slowing and arrest of the tapping of the left hand during the ES of the right SMA (x = 0, y = 4, z = 47) at 0.6 mA (50 Hz), whereas the ES of the same site at 0.8 mA elicited the beginning of a contralateral E/HD and elevation, plus abduction of the left arm. Still, this observation emphasized how the elicited symptoms may vary according to the ES intensity.

The results in Case 29 illustrate also a crucial issue relative to anatomical-functional correlations. The ES at coordinates x = 0, y = 4, and z = 47 was arbitrarily allocated to the SMAp according to the definition of our sub-regions of interest, but only a microscopic examination of the cortical organization could demonstrate that it did not belong to the pre-SMA.53 Speech-related responses were the most frequent type of responses we observed, and were elicited from 15 of 18 of the pre-SMA ES sites and 9 of 15 of the SMA ES sites. It remains unclear if SA should be classified as an NMR or not, as proposed by Lim et al.,30 with respect to the inhibition of the movement of the tongue at the time of the SA. This issue remains puzzling because the association of SA with positive motor symptoms, which was observed in 3 cases in our study, has also been reported repeatedly by others, thus pointing in these cases to a positive rather than a negative underlying process. With respect to surgical series, the transient early postoperative speech reduction after surgery of the medial frontal lobe including the SMA seems to result from both the transient deactivation of language areas and default of initiation of the motor speech program. The pathophysiological basis of palilalia, which has been reported repeated after stimulation of the dominant hemisphere in earlier studies, is still unclear because this symptom was also reported in the setting of parkinsonism, and was mainly characterized by a motor inhibition.

Transient limb postural instability was the most frequent form of motor symptom that we observed after pre-SMA or SMAp stimulation, whereas it was very uncommon when stimulating the CMA. Such a postural instability cannot be easily classified with certainty as a motor-positive response, because we did not use a polygraphic control during most of the ESs. Therefore, TLPI might result from a tonic contraction, a motor inhibition, or a transient ataxia. However, TLPI demonstrated a clear proximal predominance of movements that involved simultaneously the shoulder and the elbow in all but 1 case. Thus, it might be related to what has been described in animals54 and in humans under the term “proximo-axial and anticipatory postural adjustments” when stimulating the SMA.39,47

Overt TP was elicited in only 3 cases, from sites located more laterally, near the boundary between the SMAp and pre-SMA. In the study by Fried et al.,23 a “subjective experience of movement in the absence of overt motor activity” was also reported for 6 ES sites in 3 patients, but the exact localization was not specified.

Regarding responses including contralateral E/HD, they were also obtained in the pre-SMA or the anterior part of the SMAp (coordinate y between −3 and +12 mm), but there was 1 response that was elicited more caudally (y = −20). The pathophysiological basis of eyes/head movement in humans is still unclear. The more caudal responses can be allocated to the supplementary eye field around the paracentral sulcus (Grosbras et al.,25), whereas those obtained more anteriorly could be supported by a more rostral frontal eye field.31

The NMRs were elicited in the pre-SMA and in the more anterior part of the SMAp, in the vicinity of the VAC line. These findings are consistent with those of Lüders et al.,33 who placed the “medial negative area” ahead of the region from which they evoked positive motor responses, and anteriorly to the VAC line, thus in the pre-SMA. Their physiopathological hypothesis was that NMRs can result from the transient disruption of corticospinal pathways involved in the fine-tuning of distal movement, rather than of corticoreticulospinal pathways responsible for postural adjustments and locomotion.52 The NMRs we observed, including slowing and clumsiness for fine sequential movements, shared what Lüders et al. called an “apraxia of fine movement,” without postural tone disturbance.

Somatotopic Organization. The ES sites from which we elicited motor or sensory responses involving the face (mouth and throat, related to speech responses) and eyes (E/HDs) were located more anteriorly than the leg, whereas the representation of the arm stretched out more ventrally on both sides of the VAC line (Fig. 4). A somatotopic organization was previously described in the SMAp in animals34,35 and humans,12,25,41 with representations of the eyes and face, hand, and leg located along a rostrocaudal axis. In the setting of surgery for gliomas of the frontal lobe, Fontaine et al.22 observed a correlation between the topography on the motor deficit and the location and extent of the resection within the SMA. However, studies in both animals44 and humans41 showed overlapping representation of the face and arms rather than a well-defined somatotopic
organization. In 2 cases, we observed motor responses involving the lower limb in isolation (TF and TLPI, 1 each) when stimulating the mid-dorsal part of the SMAp. Contralateral or bilateral tonic posturing of lower limbs was previously reported using grids but not in large series of ES with depth electrodes.

Stimulations of the CMA

To our knowledge, surgical series of extraoperative stimulations of the CMA have not been previously reported, although isolated case reports referred to ES of the CMA (Diehl et al. and Kremer et al.). Moreover, only a few case reports focused on the clinical deficits related to focal lesions of the CMA. Turken and Swick made a comprehensive neuropsychological study of a patient with a low-grade tumor overlapping the anterior CS and including both CMAa and CMAP. They demonstrated an impairment of performance for divided attention and Stroop-like tasks depending only on manual, but not vocal, responses. Some rare cases of “alien hand syndrome” related to lesions, seizures, and/or stimulations of the medial frontal cortex were also reported. Diehl et al. reported a TP of the left forearm and wrist from stimulations of both ventral and dorsal banks of the CMAP at high intensities (11 and 10 mA), and a tonic extension of the left leg from the ventral bank of the CMAa at an intensity of 6 mA. Kremer et al. observed an irresistible urge to grasp with low-intensity ES of the ventral bank of the CMAa. Moreover, we assume that some of the ES sites from which Bancaud et al. elicited “complex coordinated movements adapted to environmental constraints” were lying in the more dorsal part of Brodmann area 24, at the vicinity of the CMAa.

One of the first publications supporting the role of the cingulate cortex in motor control was the observation in monkeys reported by Penfield and Welch that a motor representation of the lower limb was buried in the CS (probably in the caudal CMA, based on recent anatomical studies). Connections and functions of the CMA were later detailed by Dum and Strick, and others, and were summarized in a review by Picard and Strick. The CMA is interconnected with the SMA and the primary motor cortex, although the anterior, posterior, ventral, and dorsal subfields of the CMA share distinct connections. The CMAa is involved together within a widely distributed network for the planning of complex movements according to internal stimuli and motivational state, whereas the CMAP is involved downstream in the process of movement execution. Moreover, some of the functions attributed to the dorsal aspect of the ACG could involve also the CMA; that is, complex cognitive and motor processes involving detection of novelty, monitoring of conflict, motor selection, planning, and execution.

With stimulations of the CMA, we elicited various sensorimotor symptoms and elaborate R/G behaviors. These responses were obtained at low intensities ranging from 0.6 to 3 mA (mean 1.9 mA), although Luppino et al. reported a need for stronger currents to activate the CMA than were needed for the SMA in monkeys, and the stimulation only occasionally evoked movements in the anterior CMA, although relatively low-intensity currents were able to trigger movements of both the fore- and hindlimbs in the posterior CMA. We elicited positive motor responses in CMAa, CMAP (both ventral and dorsal), but not in the CMAa. The paucity of motor responses evoked from the CMAa correlates with the low density of corticospinal neurons found in this area.

However, we elicited distal movements of the contralateral hand and fingers at 3 sites in the CMAa, as if the patients were groping around and handling a small object in the dark. With regard to experimental studies and to our own case report of overt R/G behavior under ES of the anterior CMA, we assumed that these symptoms, which we named “sketched-out reaching/grasping movements,” were the minor expression of more complex R/G behavior. This type of response was not clearly detailed in previous ES studies, although Chauvel et al. mentioned “slight tonic movement of the wrist or rapid tremor of the hand” and “gestural automatisms” when stimulating the medial premotor cortex. In the rostral part of F6 in monkeys, Rizzolatti et al. identified neurons related to R/G arm movements. In humans and using functional MR imaging, the pre-SMA and CMA were recently shown to belong, together with lateral premotor, prefrontal, and parietal cortex, to the distributed cortical network involved in visually triggered reaching movements.

Most of the sensory responses we observed (7 of 10) were elicited in the CMA (2 in the CMAa and 5 in the CMAP), rather than in the SMA (1) and pre-SMA (2). This seems in line with the study of Lim and colleagues, in which most of the sensory responses elicited by SMA stimulation were in fact located in the vicinity of the CS and could be related to the CMA rather than to the SMA. Cadoret and Smith showed, using single-unit recordings in monkeys, that hand-related neurons in the ventral bank of the CS have well-defined proprioceptive or cutaneous receptive fields and that motor responses could be elicited by intracortical microstimulation from some of these locations.

The urge to laugh was induced by ES of the ventral bank of the CS (x = 4, y = 16, z = 37), in the CMAa, at low-intensity (1 mA) stimulation, and was repeatable with higher intensities. Large-scale cortical and subcortical networks are responsible for laughter and associated emotional components. Our patient’s urge to laugh was not accompanied by an emotional context of mirth, in accordance with previous results of ES of the SMA or ACG (see Sperli et al. for review). Conversely, Krolak-Salmon et al. were able both to trigger a laugh from stimulation of the left pre-SMA and to record on the same contact a specific potential related to the expression of happiness.

Most of the responses elicited in the CMA could also be evoked with stimulations of the other surrounding areas; that is, the SMAp and pre-SMA. Nevertheless, 2 specific aspects need to be kept in mind: 1) sensory responses elicited from ES of the medial wall, involving either the limb or the head and trunk, were likely to arise from the banks of the CS; and 2) complex behaviors related to overt or “sketched-out” R/G movement were mainly evoked by stimulation of the CMA, supporting the role of these regions in the control of “intention to action.”
Conclusions

The aim of this study was to bridge the gap between neurophysiological and epileptological findings about the medial premotor cortex. The results of ES of the frontal medial wall confirm that the pre-SMA and CMA support some of the clinical responses previously allocated to the SMA in humans. We suggest that recent advances in the anatomical and functional parcellation of the medial premotor cortex should lead to tailored targeting of the SMA, pre-SMA, and CMA at the time of depth recordings for drug-resistant frontal lobe epilepsies.

The next step should focus on the assessment of the contribution of each medial premotor field to the symptomatology of frontal lobe seizures, to improve the probability of circumscribing a discrete focus from an apparent widespread symptomatic zone, and to propose more tailored surgery for drug-resistant cases.

Disclaimer

The authors do not report any conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

References