Negative myoclonus induced by cortical electrical stimulation in epileptic patients

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Negative myoclonus (NM) is a motor disorder characterized by a sudden and abrupt interruption of muscular activity. The EMG correlate of NM is a brief (<500 ms) silent period (SP) not preceded by any enhancement of EMG activity (i.e. myoclonus). This study investigated the role of premotor cortex (PMC), primary motor cortex (MI), primary somatosensory area (SI) and supplementary motor area (SMA) in the pathophysiology of cortical NM by means of intracerebral low frequency (1 Hz) electrical stimulation. In three drug-resistant epileptic patients undergoing presurgical evaluation, we delivered single electric pulses (stimulus duration: 3 ms; stimulus intensity ranging from 0.4 to 3 mA) to PMC (2 patients), MI (1 patient), SI and SMA through stereo-EEG electrodes; surface EMG was collected from both deltoids. The results showed that (i) the stimulation of PMC or MI could evoke a motor evoked potential (MEP) either at rest or during contraction, in this latter case followed by an SP; however, in two patients, at the lowest stimulus intensities (0.4 mA), 50% of stimuli could induce a pure SP, i.e. not preceded by an MEP; raising the intensity of stimulation (0.6 mA), the SPs showed an antecedent MEP in >80% of stimuli; (ii) the stimulation of SI at low stimulus intensities (from 0.4 to 0.8 mA) induced in two patients only SPs, never associated with an antecedent MEP, whereas in the third subject the SPs could be inconstantly preceded by an MEP; by incrementing the stimulus intensity (up to 3 mA), in all three patients the SPs tended to be preceded, although not constantly, by an MEP; stimulus intensity affected SP duration (i.e. the higher the intensity, the longer the SP), without influencing the latency of onset of the SPs; (iii) the stimulation of SMA induced only pure SPs, at all stimulus intensities up to 3 mA; as for SI, increment of stimulus intensity was paralleled by an increase in SP duration, without influencing the onset latency of SPs. We conclude that single electric pulse stimulation of PMC, MI, SI and SMA through stereo-EEG electrodes can induce pure SPs, not preceded by an MEP, which clinically appear as NM, suggesting therefore that these cortical areas may be involved in the genesis of this motor phenomenon. However, it must be pointed out that SMA stimulation induced only pure SPs, regardless of the stimulus intensity, whereas occurrence of pure SPs following stimulation of PMC, MI, and SI depended mainly on the intensity of stimulation.

Keywords: negative myoclonus; silent period; supplementary motor area; primary somatosensory cortex; intracerebral electrical stimulation

Abbreviations: DCR = direct cortical response; MEP = motor evoked potential; NM = negative myoclonus; NMA = negative motor area; MI = primary motor area; PMC = premotor cortex; PNP = primary negative potential; SI = primary somatosensory area; SMA = supplementary motor area; SP = silent period; TMS = transcranial magnetic stimulation

Introduction

Sudden, irregular lapses in the maintenance of postural tone were described in patients with hepatic encephalopathy by Adams and Foley (1949) under the term of asterixis. Lance and Adams (1963) reported lapses of postural control in the post-anoxic intention myoclonus syndrome as a result of a muscular silent period (SP), preceded or not by myoclonus, in relation to a spike and slow wave complex. Periods of muscular inhibition, strictly and only related to a diffuse or
focal spike, without preceding myoclonia, were defined as ‘spike-related epileptic silent periods’ (Tassinari et al., 1968; Tassinari, 1981). The catching term ‘negative myoclonus’ (NM), introduced by Shahani and Young (1976), encompass all the above-mentioned phenomena, and extends this definition to any brief, jerky interruption of tonic muscular activity, which causes a sudden postural lapse. As such, NM is an aspecific motor disorder that can be observed in a variety of physiological as well as pathological conditions. The EMG correlate of NM is a brief (<500 ms) muscular SP not preceded by any enhancement of EMG activity (Blume et al., 2001). Epileptic NM is defined as an interruption of tonic muscular activity, time-locked to a spike on the EEG, without evidence of an antecedent myoclonia (Tassinari et al., 1995). Although pathophysiology of NM is still incompletely understood, cortical as well as subcortical mechanisms are admitted (Obeso et al., 1995; Toro et al., 1995; Tassinari et al., 1995, 1998; Shibasaki, 2002). Regarding the cortical areas mediating NM, some evidences suggest a role of the perirolandic cortex (Ugawa et al., 1989; Artieda et al., 1992; Aguglia et al., 1995), whereas studies on epileptic NM showed that this phenomenon may be associated with epileptic activity in premotor cortex (PMC), including the supplementary motor area (SMA) (Rubboli et al., 1995; Baumgartner et al., 1996; Meletti et al., 2000), or in post-central somatosensory cortex (Tassinari et al., 1995; Noachtar et al., 1997).

Negative motor areas (NMA) have been identified in the lateral aspects of the frontal lobe (primary NMA) and in the frontomesial regions encompassed in the SMA (‘supplementary NMA’) (Luders et al., 1987, 1995; Lim et al., 1994). In epileptic patients undergoing presurgical evaluation, high frequency (50 Hz) cortical electrical stimulations of NMA through subdural electrodes produced sustained negative motor responses such as motor arrest, inability to perform a voluntary movement or to maintain a voluntary muscular contraction (Penfield and Welch, 1949, 1951; Luders et al., 1987, 1995; Fried et al., 1991; Lim et al., 1994; Hanakawa et al., 2001). On the basis of these findings, it has been hypothesized that NMCA may play a role in the pathophysiology of cortical NM (Tassinari et al., 1995; Baumgartner et al., 1996). This view has been challenged by other authors (Werhahn and Noachtar, 2000), who pointed out that the negative motor responses elicited by high frequency cortical stimulation were sustained and developed gradually over seconds, at variance with NM, which is a brief (<500 ms) (Blume et al., 2001) and sudden event; on the other hand, at present, no evidence that either repetitive (50 Hz) or single electric shock stimulation of NMA can induce brief, phasic SP such as in NM has been reported.

The aim of our study was to investigate the possible role of the PMC, the primary motor cortex (MI), the primary somatosensory area (SI) and the SMA in the generation of NM by delivering single electric pulses intracortically through intracerebral stereotaxic EEG (stereo-EEG) electrodes, during low frequency (1 Hz) electrical stimulation (Munari et al., 1993; Kahane et al., 1993), performed in drug-resistant epileptic patients undergoing functional cortical mapping for presurgical evaluation. We report evidences showing that single electric shocks delivered to PMC, MI and SI can induce brief contralateral ‘pure’ SPs, i.e. not preceded by a motor evoked potential (MEP), depending mainly on the intensity of stimulation: in fact, by increasing stimulus intensity, the SPs tended to be preceded by an MEP. On the contrary, single pulse stimulation of the SMA produced only pure SPs, i.e. never preceded by an MEP, regardless of stimulus intensity. We discuss the implications of our findings in the pathophysiology of cortical NM.

**Materials and methods**

We studied three patients (two females and one male; age range 13–32 years) with drug-resistant partial epilepsy undergoing presurgical evaluation for epilepsy surgery. Clinical features of the patients are reported in Table 1. Brain MRI (1.5 T) was unremarkable in Patients 1 and 3; in Patient 2, who suffered from post-traumatic epilepsy, it showed atrophy of the right frontal pole, extended to the right frontal horn, and gliosis of the corresponding white matter.

All three patients first underwent long-term video-EEG monitoring to record their spontaneous seizures. The data provided by video-EEG recordings were not considered sufficient to proceed to surgery; therefore, a video-stero-EEG evaluation was judged necessary to define the cerebral structures involved in the onset and propagation of seizure activity. Furthermore, the video-stero-EEG procedure, in addition to recording intracranially spontaneous seizures permits

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**Table 1** Clinical features of the patients

<table>
<thead>
<tr>
<th>Age (years) at epilepsy onset</th>
<th>Patient 1 (30/F)</th>
<th>Patient 2 (32/M)</th>
<th>Patient 3 (13/F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure type</td>
<td>13 Non-convulsive status ± SG</td>
<td>22 Left focal motor ± SG</td>
<td>9 Speech arrest, left limbs tonic-dystonic posturing</td>
</tr>
<tr>
<td>Seizure frequency</td>
<td>Weekly</td>
<td>4–6/month</td>
<td>Daily</td>
</tr>
<tr>
<td>Intercital scalp EEG</td>
<td>Vertex theta activity associated with spikes</td>
<td>Right frontocentral slow waves and spikes</td>
<td>Right frontocentral slow waves and spikes</td>
</tr>
<tr>
<td>Brain MRI</td>
<td>Unremarkable</td>
<td>Atrophy and gliosis of the right frontal pole extended to the right frontal horn</td>
<td>Unremarkable</td>
</tr>
<tr>
<td>Neurological examination</td>
<td>Unremarkable</td>
<td>Unremarkable</td>
<td>Unremarkable</td>
</tr>
<tr>
<td>Current treatment</td>
<td>CBZ, PB</td>
<td>CBZ, PB, CNZ</td>
<td>CBZ, TPM</td>
</tr>
</tbody>
</table>
performance of high frequency, (50 Hz) electrical stimulation and low frequency (1 Hz) electrical stimulation whose purposes are, respectively, to elicit some or all of the electroclinical seizures, and to map functionally eloquent cortical areas. Informed consent was obtained from all patients after the type and the purposes of the procedures were explained.

The stereo-EEG procedures were performed according to the Sainte-Anne School in Paris (Bancaud et al., 1965; Talairach et al., 1974; Munari et al., 1994) at the ‘C.Munari’ Epilepsy Surgery Center at Niguarda Hospital in Milan. All three patients were chronically implanted with semi-rigid platinum/iridium depth electrodes (0.8 mm in diameter) (DIXI, Besancon, France), featuring 5–15 contacts, 2 mm long and 1.5 mm apart. The number of the electrodes, their entry points and the target cerebral structures, were established on the basis of the clinico-EEG features of the seizures recorded during long-term video-EEG monitoring; anatomical landmarks (i.e. cerebral vessels) might represent additional constraints partially influencing the choice of the electrode entry point and trajectory to reach a specific target structure. For the aim of this study, we selected those patients in whom the stereo-EEG evaluation required the exploration of motor areas (either MI or PMC), SI and SMA. Patient 1 was studied with 20 electrodes exploring bilaterally homologous lateral and mesial frontoparietal cortices (Fig. 1). Patient 2 was implanted with 14 electrodes that explored both the convexity and the mesial aspects of the right frontal and parietal lobes, and the anterior portion of the right temporal lobe (Fig. 2).

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**Fig. 1** Stereotaxic schemes of Patient 1 and MRI images illustrating the trajectories of the electrodes N, Q and K. The upper panels show the stereotaxic schemes (right lateral and frontal views of the skull) showing the bilateral implantation (10 electrodes on each side). Upper left axial MRI slice: it shows the location of: electrode contacts N 5–6 in the precentral gyrus exploring PMC; electrode contacts Q 7–8, in the post-central gyrus, exploring SI; electrode contact K1, at the tip of electrode K, obliquely inserted, exploring SMA; CS: central sulcus. Upper right coronal MRI slice: the trajectory of electrode Q (featuring 15 contacts) is displayed: contacts 7–8 are located in the grey matter of the dorsal portion of the post-central gyrus. Note that the last four outer contacts are outside of the cortex. Lower left coronal MRI slice: it shows the trajectory of electrode K (featuring 10 contacts); the couple of contacts K 1–2 is placed in the grey matter of SMA. Lower right coronal MRI slice: it illustrates the trajectory of electrode N (featuring 15 contacts). Contacts 5–6 are positioned in the cortex of the precentral gyrus. The last four outer contacts are outside of the cortex.
Patient 3 was studied with 13 electrodes that recorded EEG activity from the convexity and the mesial aspects of the right frontal and parietal cortices (Fig. 3).

Significant interindividual anatomical variability has been reported in human brains, particularly in the precentral motor areas (Rademacher et al., 2001); furthermore, the exact boundaries between MI and PMC in the lateral aspects of the frontal lobe are still uncertain (Freund, 1996; Rizzolatti et al., 1998). Indeed, recent data indicate that most of the surface of the precentral gyrus belongs to area 6 and not to area 4 (Geyer et al., 1996; Rizzolatti et al., 1998).

To determine the precise sites of the recording/stimulating electrodes, as well as the locations of the discharges elicited by electrical stimulations, we first identified the cerebral structures explored by each stereo-EEG electrode through their entry point and target point as defined in the three-dimension proportional grid system devised by Talairach and Tournoux (1988). Then, to visualize with higher accuracy the exact locations of the electrode contacts we reconstructed the trajectories of the stereo-EEG electrode on the MRI images in each patient (Figs 1–3). Finally, we calculated the Talairach coordinates of the couple of electrode contacts of interest for this study, by superposing the X-ray of the skull of the patient with the electrodes implanted on the Talairach proportional grid system with a grid scale of 1 mm; the position of each couple of contacts was defined by the three axis coordinates ($x =$ anteroposterior axis; $y =$ lateral axis; $z =$ vertical axis) (see Table 2). For each electrode, the lowest numbers indicate the inner contacts whereas the highest numbers the outer contacts; electrodes on the left side are labelled with letters with apostrophe. In Patient 1, who underwent a
Fig. 3 The upper panels illustrate the stereotaxic schemes in Patient 3 (right lateral and frontal views of the skull). Upper right coronal MRI slice: it shows the trajectory of electrode Z (featuring 10 contacts) obliquely inserted. Contacts 1–2 are located in the cortex of SMA. Contacts 6–7 explore the upper portion of the precentral bank of the central sulcus belonging to MI, whereas contacts 8–9 are located in the dorsal part of post-central bank of the central sulcus, belonging to SI. In the scheme (modified from Talairach and Tournoux’s atlas) on the left of the coronal MRI image, we reconstructed on the axial plane the trajectory of the electrode Z, which crosses, from lateral to mesial, at first the post-central bank (SI), then the precentral bank (MI) of the central sulcus (CS), to reach with its tip the SMA. Lower axial MRI slices: they illustrate, on the left, the location of electrode contact Z 9 just on the cortical surface of the dorsal part of the postcentral gyrus; on the right, the location of electrode contact Z 6, more mesial with respect to Z 9, due to the oblique trajectory of electrode Z.
bilateral stereo-EEG exploration, we report the data obtained from stimulation of the right side electrodes, because they were more constant and replicable than their counterparts on the left side. For the aim of our study, we identified which electrodes explored M1 or PMC, SI and SMA. PMC was explored in Patients 1 and 2, M1 in Patient 3, SI and SMA in all three patients. Based on the Talairach and Tournoux’s atlas and on the reconstruction of the stereo-EEG electrodes trajectories on the MRI, PMC was explored: in Patient 1, by the middle contacts of electrodes N and H (Fig. 1); in Patient 2, by the middle contacts of electrodes N, H and M (Fig. 2); in Patient 3, by the middle contacts of electrodes Z and by the outer contacts of H (located in the precentral operculum) (Fig. 3). SI was explored: in Patient 1, by the outer contacts of electrode Q (Fig. 1); in Patient 2, by the outer contacts of electrode P (Fig. 2); and in Patient 3, by the outer contacts of electrodes Z and S (Fig. 3). The SMA was investigated: in Patient 1, by the inner contacts of electrodes K and M (Fig. 1); in Patient 2, by the inner contacts of electrodes M and Z (Fig. 2); and in Patient 3, by the inner contacts of electrodes K, F, M, J and Z (Fig. 3).

Stereo-EEG recordings were obtained with a bipolar montage from pairs of nearby contacts. As part of our standard procedure to detect possible motor phenomena induced by electrical stimulation, we collected EMG activity from both deltoids, other muscles were not recorded; therefore, we cannot provide information on the somatotomy of the motor effects. EKG was monitored applying two electrodes on the patients’ chest. Electrophysiological signals were recorded and digitized with a sampling frequency of 800 Hz with a 128 channel computerized video-EEG system for long-term monitoring (Telefactor Corp, West Conshohocken, PA). Bipolar high frequency electrical stimulation was performed by delivering 50 Hz trains of rectangular electrical stimuli of alternating polarity (IRES 600 CH electrical stimulator, Micromed, Italy) with pulse width of 1 ms through pairs of nearby contacts to reproduce ictal phenomena, in order to assess the participation of the stimulated brain structures in seizure semiology. Stimulation intensity ranged from 0.4 to 3 mA; the duration of the stimulation trains varied from 1 to 9 s. In Patient 1, analysis of one recorded episode of non-convulsive status and results of high frequency electrical stimulation were not unequivocal in defining the epileptogenic zone, therefore the patient is still under evaluation and has not been operated yet. In Patient 2, the analysis of one spontaneous and seven seizures induced by high frequency stimulation indicated that the epileptogenic zone extended from the right frontal pole to the orbital cortex, gyrus cinguli and mesial frontal regions (without involvement of the SMA), with a rapid spread of the epileptic discharge to the ipsilateral motor cortex. In Patient 3, based on 10 spontaneous seizures and on the results of high frequency electrical stimulation, we concluded that the epileptogenic zone involved the right posterior frontomesial cortex (including SMA), the middle portion of the gyrus cinguli and extended to the right dorsolateral superior frontal gyrus.

### Low frequency (1 Hz) electrical stimulation

Low frequency electrical stimulation for functional mapping of eloquent areas was performed by delivering monophasic rectangular electrical stimuli of alternating polarity (IRES 600 CH electrical stimulator, Micromed, Italy) with pulse width of 3 ms, at a frequency of 1 Hz for 5–25 s; the intensity could vary from 0.2 to 3 mA (Munari et al., 1993; Kahane et al., 1993, 1999). The stimulus marker was recorded in an additional channel included in the recording montage. For each stereo-EEG electrode, all contiguous couples of contacts were tested using a bipolar montage. Intensity of stimulation was raised with 0.2 mA steps. Data analysis was performed on a computerized polygraphic system (Scan 4.1, Neuroscan, Herndon, VA). Analysis window of the EMG activity was set from 100 ms prestimulus to 350 ms post-stimulus. Bandpass filters for analysis were set to 50–400 Hz. Rectification and average of the EMG activity, triggered from the intracerebral electrical stimulus, were performed. Number of averaged stimuli ranged from 5 to 20. For most of the stimulus intensities, once a motor phenomenon was noted for a given couple of contacts, at least two sessions of stimulation at the same intensity, delivering 5–20 stimuli for each session, were performed to replicate the observation. In Results, we report the findings obtained from the couple of contacts that, for each cortical area examined, provided the most constant and replicable results. In Table 2, we report the Talairach coordinates and the corresponding Brodmann areas of the most effective couple of contacts (see Results). The stimulation procedure started with the patient at rest, lying supine; after at least five stimuli were delivered with the patient in a relaxed condition, he/she was asked to raise both upper limbs while the stimulation continued, with the administration of at least five other stimuli. In both conditions of stimulation (relaxed/upper limbs raised), the patient was also asked to count aloud (to detect any modification of speech induced by stimulation).

Throughout both high frequency and low frequency electrical stimulation procedures, stereo-EEG was continuously monitored to detect any after-discharge or seizure activity.

### Statistics

Comparison of the durations of the SPs at different intensities of stimulation was performed by two-tailed one sample t-tests. Pearson correlation analysis was used to correlate stimuli intensities and the durations of the SPs. Statistical Package for Social Sciences (Version 8.0) was employed for computation.

### Results

**Low frequency electrical stimulation of PMC and MI** (Table 3)

Low frequency electrical stimulation of PMC and MI induced an MEP in the contralateral deltoid, either at rest or during

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**Table 2** Anatomical sites of the most effective electrode contacts in inducing SPs

<table>
<thead>
<tr>
<th>Patient</th>
<th>Electrode contacts</th>
<th>Talairach coordinates</th>
<th>Brodmann area</th>
<th>Gyrus</th>
<th>Side</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N/5–6</td>
<td>36 -12 56</td>
<td>6</td>
<td>Precentral</td>
<td>Right</td>
</tr>
<tr>
<td></td>
<td>Q/7–8</td>
<td>33 -35 60</td>
<td>3</td>
<td>Postcentral</td>
<td>Right</td>
</tr>
<tr>
<td></td>
<td>K/1–2</td>
<td>4 12 48</td>
<td>6</td>
<td>Superior Postcentral</td>
<td>Right</td>
</tr>
<tr>
<td>2</td>
<td>N/4–5</td>
<td>34 -12 65</td>
<td>6</td>
<td>Precentral</td>
<td>Right</td>
</tr>
<tr>
<td></td>
<td>P/8–9</td>
<td>32 -35 59</td>
<td>2</td>
<td>Postcentral</td>
<td>Right</td>
</tr>
<tr>
<td></td>
<td>M/1–2</td>
<td>6 8 47 32</td>
<td></td>
<td>Medial Frontal</td>
<td>Right</td>
</tr>
<tr>
<td>3</td>
<td>Z/6–7</td>
<td>16 -20 58</td>
<td>4</td>
<td>Precentral</td>
<td>Right</td>
</tr>
<tr>
<td></td>
<td>Z/8–9</td>
<td>45 -21 56</td>
<td>3</td>
<td>Postcentral</td>
<td>Right</td>
</tr>
<tr>
<td></td>
<td>Z/1–2</td>
<td>6 -22 53</td>
<td>6</td>
<td>Medial Frontal</td>
<td>Right</td>
</tr>
</tbody>
</table>
contraction; we did not observe any detectable change on the ipsilateral deltoid (Fig. 4). During contraction, the MEPs showed increased amplitude and were followed by an SP (Figs 4 and 5). In Patients 1 and 2, the most effective couples of contacts for PMC stimulation were N 5–6 and N 4–5, respectively, both couples located in Brodmann’s area 6, in the precentral gyrus (see Figs 1 and 2 and Table 2). In Patient 3, MI stimulation was achieved through electrode contacts Z 6–7, located on the precentral bank of the central sulcus (see Fig. 3 and Table 2). In Table 3, the results obtained with stimulation of PMC and MI during contraction of the upper limbs are reported. We consistently obtained MEPs at low stimulus intensities (i.e. 0.4 and 0.6 mA), which confirmed that we were stimulating PMC or MI, therefore we did not deliver stimuli at higher intensities (apart from Patient 2, to whom we delivered few stimuli at 0.8 mA; not reported in Table 3). Clinically, each single electric shock caused a muscle jerk that involved proximally the left upper limb. In Patient 2 (PMC stimulation), 100% of stimuli, at stimulation intensities of 0.4 and 0.6 mA, elicited

<table>
<thead>
<tr>
<th>Stimulation intensity (mA)</th>
<th>No of stimuli</th>
<th>MEP no (%)</th>
<th>MEP latency (ms)</th>
<th>SP no (%)</th>
<th>SP latency (ms)</th>
<th>SP duration (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PMC/MI stimulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pt.1 (N:5–6/PMC)</td>
<td>0.4</td>
<td>10</td>
<td>5 (50)</td>
<td>18 ± 7</td>
<td>10 (100)</td>
<td>37 ± 10</td>
</tr>
<tr>
<td></td>
<td>0.6</td>
<td>13</td>
<td>11 (85)</td>
<td>15 ± 6</td>
<td>13 (100)</td>
<td>40 ± 10</td>
</tr>
<tr>
<td>Pt.2 (N:4–5/PMC)</td>
<td>0.4</td>
<td>28</td>
<td>28 (100)</td>
<td>16 ± 2</td>
<td>28 (100)</td>
<td>52 ± 6</td>
</tr>
<tr>
<td></td>
<td>0.6</td>
<td>8</td>
<td>8 (100)</td>
<td>15 ± 4</td>
<td>8 (100)</td>
<td>53 ± 4</td>
</tr>
<tr>
<td>Pt.3 (Z:6–7/MI)</td>
<td>0.4</td>
<td>10</td>
<td>5 (50)</td>
<td>8 ± 4</td>
<td>10 (100)</td>
<td>32 ± 6</td>
</tr>
<tr>
<td></td>
<td>0.6</td>
<td>6</td>
<td>5 (83)</td>
<td>8 ± 4</td>
<td>6 (100)</td>
<td>34 ± 5</td>
</tr>
<tr>
<td><strong>SI stimulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pt.1 (Q:7–8)</td>
<td>0.5</td>
<td>18</td>
<td>–</td>
<td>3 (17)</td>
<td>48 ± 10</td>
<td>32 ± 3</td>
</tr>
<tr>
<td>Pt.2 (P:8–9)</td>
<td>0.6</td>
<td>32</td>
<td>10 (31)</td>
<td>22 ± 5</td>
<td>17 (53)</td>
<td>73 ± 19</td>
</tr>
<tr>
<td></td>
<td>0.8</td>
<td>10</td>
<td>4 (40)</td>
<td>29 ± 11</td>
<td>8 (80)</td>
<td>77 ± 11</td>
</tr>
<tr>
<td>Pt.3 (Z:8–9)</td>
<td>0.4</td>
<td>10</td>
<td>–</td>
<td>4 (40)</td>
<td>48 ± 5</td>
<td>34 ± 5</td>
</tr>
<tr>
<td></td>
<td>0.6</td>
<td>6</td>
<td>1 (17)</td>
<td>10</td>
<td>5 (83)</td>
<td>45 ± 5</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>5</td>
<td>2 (40)</td>
<td>20 ± 0</td>
<td>2 (40)</td>
<td>45 ± 5</td>
</tr>
<tr>
<td></td>
<td>1.2</td>
<td>8</td>
<td>2 (25)</td>
<td>15</td>
<td>4 (50)</td>
<td>39 ± 4</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>8</td>
<td>4 (50)</td>
<td>13 ± 4</td>
<td>6 (75)</td>
<td>73 ± 13</td>
</tr>
<tr>
<td><strong>SMA stimulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pt.1 (K:1–2)</td>
<td>0.4</td>
<td>8</td>
<td>–</td>
<td>4 (50)</td>
<td>54 ± 19</td>
<td>38 ± 6</td>
</tr>
<tr>
<td></td>
<td>0.6</td>
<td>8</td>
<td>–</td>
<td>4 (50)</td>
<td>63 ± 5</td>
<td>44 ± 4</td>
</tr>
<tr>
<td></td>
<td>0.8</td>
<td>10</td>
<td>–</td>
<td>2 (20)</td>
<td>63 ± 11</td>
<td>45 ± 0</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>10</td>
<td>–</td>
<td>5 (50)</td>
<td>58 ± 7</td>
<td>54 ± 5</td>
</tr>
<tr>
<td></td>
<td>1.2</td>
<td>11</td>
<td>–</td>
<td>6 (55)</td>
<td>57 ± 9</td>
<td>57 ± 8</td>
</tr>
<tr>
<td></td>
<td>1.4</td>
<td>13</td>
<td>–</td>
<td>13 (100)</td>
<td>59 ± 12</td>
<td>62 ± 10</td>
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<td>2 (20)</td>
<td>13 ± 4</td>
<td>3 (18)</td>
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<td>2.6</td>
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<td>9 (45)</td>
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<td>3</td>
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<td>50 ± 13</td>
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<td>10 (100)</td>
<td>56 ± 6</td>
<td>113 ± 12</td>
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</table>

*The data reported refer to stimulation during contractions of both deltoids.

Table 3 Results obtained by cortical stimulation of PMC, MI, SI and SMA
an MEP followed by an SP. In Patients 1 (PMC stimulation) and 3 (MI stimulation), at 0.4 mA, 50% of stimuli were effective in inducing an MEP, followed by an SP; the remaining 50% of stimuli could induce only a pure SP, not preceded by an MEP. In these two patients, at 0.6 mA, the percentage of stimuli effective in inducing an MEP was raised to 85% in Patient 1 and to 83% in Patient 3, constantly followed by an SP, whereas the remaining stimuli induced an isolated SP.

Therefore, in Patients 1 and 3, single electric pulses delivered, respectively, to PMC and MI at intensities of 0.4 and 0.6 mA could elicit either an MEP followed by an SP, or an isolated SP, not preceded by an MEP; by increasing the stimulus intensities, SPs showed more frequently an antecedent MEP. The latency of the MEPs ranged from ~15 ms (at 0.4 mA) to ~18 ms (at 0.6 mA) in Patient 1 whereas it was ~15 ms in Patient 2; in Patient 3, it was shorter,

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**Fig. 4** EMG tracing of both deltoids, at rest (left panel) and during muscular contraction (right panel) (the patient held his upper limbs raised and outstretched) during electrical stimulation of the right PMC (at 0.4 mA), SI (at 0.6 mA) and SMA (at 3.0 mA). The markers for each electrical stimulus at 1 Hz are shown above. PMC stimulation induced MEPs at rest, that increased in size during contraction, and were followed by an SP. SI stimulation did not evoke any MEPs at rest, but could induce an SP during muscular contraction, inconstantly preceded by an MEP. SMA stimulation did not induce any EMG phenomenon at rest, but evoked brief SPs, not preceded by an MEP, during muscular activation. These motor responses were observed only in the left deltoid, either at rest or during contraction; no effect was observed in the right one, ipsilateral to the stimulation. Asterisks indicate SPs not preceded by an MEP.
being ~8 ms. Latencies of SPs ranged from ~37 (at 0.4 mA) to ~40 ms (at 0.6 mA) in Patient 1, whereas in Patient 2 they were ~52 ms. In Patient 3, as for the latencies of MEPs, latencies of SPs were shorter, ~32–34 ms. On the whole, the only difference between MI and PMC stimulation was regarding latencies of MEPs and SPs, which were shorter for MI stimulation.

**Low frequency electrical stimulation of SI (Table 3)**

In Patient 1 and 3, low frequency electrical stimulation of SI at low stimulus intensities could evoke SPs not preceded by MEPs in the contralateral deltoid; no change of the EMG activity was visible on the ipsilateral deltoid (Fig. 4). The most effective contacts were located in Brodmann’s area 3, in the right post-central gyrus in Patient 1 (electrode contacts Q 7–8) (Fig. 1; Table 2) and in the post-central bank of the central sulcus in Patient 3 (electrode contacts Z 8–9) (Fig. 3; Table 2). SPs not preceded by MEPs were observed for intensities ranging from 0.4 to 0.8 mA in Patient 1, and at 0.4 mA in Patient 3. The optimal stimulus intensities for evoking pure SPs, never preceded by an MEP, were 0.6 mA in Patient 1, which was effective in 77% of stimuli, and 0.4 mA in Patient 3, effective in 40% of stimuli. Average of the EMG activity triggered from the stimulus did not show any enhancement of EMG activity that could indicate the occurrence of an antecedent MEP (Fig. 6). Raising the stimulation intensity, the SPs were preceded, although not constantly, by an MEP; these responses were observed in the contralateral deltoid, whereas in the ipsilateral one no clear modification of EMG activity was detectable. Indeed, for each stimulation intensity that we tested, the number of evoked SPs exceeded consistently the number of MEPs. Only in Patient 3, at the highest intensity of stimulation (2.2 mA), each SP was associated with an antecedent MEP. The latency of the SPs did not change across the different stimulation intensities, regardless of the presence or not of an antecedent MEP. It was ~45 ms in both patients. On the contrary, the increment of the intensity of the stimulus was paralleled by an increase of
Fig. 6 Average of the rectified EMG activity from the left deltoid, triggered from the electrical stimulus. The results obtained from stimulation of SI and SMA in the three patients are illustrated. The tracings related to SI stimulation were obtained averaging only those SPs not preceded by an antecedent MEP. The superposition of two averaged trials (number of averaged SPs ranged from 5 to 15) are shown. No evidence of an antecedent MEP, preceding the SP was observed, confirming that stimulation of SI and SMA could induce pure SPs not preceded by an MEP.
the duration of the SP, showing a positive correlation (Patient 1: $r = 0.795$, $P < 0.001$; Patient 3: $r = 0.772$, $P < 0.001$) (Fig. 7).

In Patient 2, at all stimulation intensities that we tested, SPs in the contralateral deltoid could be preceded, although not constantly, by an MEP; no changes were observed in the ipsilateral deltoid. The electrode contacts (P 8–9) that provided the most replicable results were located in Brodmann’s area 2, in the right post-central gyrus (see Fig. 2).
and Table 2). We did not detect contact pairs that could elicit only pure SPs. As in the other patients, for each stimulation intensity, a number of evoked SPs were not preceded by MEPs, however, by incrementing the stimulus intensity, the probability to obtain an MEP preceding the SP tended to increase (Fig. 5). Average of the EMG activity triggered from the stimulus failed to show any MEP preceding the SP (Fig. 6). Latency of onset of SPs was not affected by stimulus strength, and was longer than in the other two patients (~75 ms). The duration of the SPs showed a linear correlation with the stimulation intensity ($r = 0.636$, $P < 0.001$) (Fig. 7).

**Low frequency electrical stimulation of SMA (Table 3)**

Low frequency electrical stimulation of SMA did not produce any effect at rest, either in the EMG tracing or in the description by the patients (Fig. 4). During contraction, 1 Hz electric pulses elicited, in the contralateral deltoid, brief SPs not preceded by MEPs; no interruptions or enhancements of the EMG activity were observed in the ipsilateral deltoid (Fig. 4). Clinically, they appeared as small twitches at the left upper limb proximally, which the patients themselves described as ‘small jerks’ or ‘loss of muscle tone’. The most effective couple of contacts were located in the mesial part of the superior frontal gyrus, corresponding to Brodmann’s area 6, in Patients 1 (electrode contacts K 1–2) and 3 (electrode contacts Z 1–2) (Figs 1 and 3; Table 2), and in the most caudal portion of Brodmann’s area 32, in the mesial part of the superior frontal gyrus, in Patient 2 (electrode contacts M 1–2) (Fig. 2; Table 2). SPs started to appear at stimulation intensity of 0.4 mA in Patient 1, 1.4 mA in Patient 2 and 0.6 mA in Patient 3. In Patient 1, the most effective intensity of stimulation was 1.6 mA, which evoked an SP in 100% of stimuli; higher intensities of stimulation were less effective. In Patients 2 and 3, the progressive increase of stimulus intensities was associated with an increment of the percentage of effective stimuli; indeed, in both patients, at the highest intensities employed, i.e. 3 mA in Patient 2 and 2.6 mA in Patient 3, 100% of stimuli evoked an SP. Remarkably, in all patients, regardless of the stimulation strength, SPs were never preceded by MEPs (Fig. 5). Average of the EMG activity triggered from the stimulus failed to show any enhancement of EMG activity, consistent with an MEP, preceding the SP onset, even at the highest and most effective intensities of stimulation (Fig. 6). Latency of onset of SPs did not show statistically significant differences at the different stimulation intensities. Furthermore, it was quite similar in the three patients, resulting ~60 ms in Patient 1, ~58 ms in Patient 2, and a little more variable in Patient 3, ranging from ~45 ms (at 0.8 mA) to ~62 ms (at 1.6 mA). Duration of SPs was affected by stimulus strength. Indeed, there was a positive correlation between the stimulus intensity and the duration of the induced SPs (Fig. 7): in Patient 1, ranged from 45 ± 4 ms (at 0.6 mA) to 60 ± 4 ms (at 3 mA) ($r = 0.458; P < 0.01$); in Patient 2, ranged from 50 ± 13 ms (at 1.4 mA) to 77 ± 18 ms (at 3 mA) ($r = 0.346; P < 0.05$); in Patient 3, varied from 74 ± 21 ms (at 0.8 mA) to 113 ± 12 ms (at 2.6 mA) ($r = 0.731; P < 0.001$).

**Discussion**

In our study, we could obtain pure SPs by stimulating PMC and MI in the precentral gyrus (Brodmann’s area 6 in Patients 1 and 2, and Brodmann’s area 4 in Patient 3) and SI in the post-central gyrus (Brodmann’s area 3 in Patients 1 and 3, and Brodmann’s area 2 in Patient 2); the same couple of contacts could produce either pure SPs or MEPs associated with SPs, depending on the stimulus intensity, i.e. the higher the intensity the higher the probability that the SP was preceded by an MEP. Stimulation of the SMA induced in all three patients only pure SPs, never preceded by an MEP, regardless of the intensity of stimulation. A role of the primary sensorimotor cortices in the genesis of NM has been previously suggested by recording pure SPs evoked by single electric shocks delivered through subdural electrodes to a cortical area, located immediately posterior to the central sulcus, in a region that roughly corresponded to the SI portion that we stimulated (Ikeda et al., 2000); in the same report, stimulation of the SMA was ineffective in producing any SP.

Electrical stimuli applied directly to the cerebral cortex elicit a potential (the ‘direct cortical response’, DCR) (Adrian, 1936; Ochs, 1968) in the immediate vicinity of the site of stimulus application. Taking into account that DCR characteristics depend significantly on a variety of parameters (such as stimulus frequency, electrode size, physiological state of the cortex, anaesthesia and absence or presence of epileptogenicity) (Goldring et al., 1994), stimulus strength is a crucial factor in influencing DCR components. In fact, at weak stimulus intensities, DCR is essentially composed of an initial negative potential (the ‘primary negative potential’, PNP) followed by a longer lasting positive deflection. PNP represents excitatory post-synaptic potentials (EPSPs) of apical dendrites (Li and Chou, 1962; Sugaya et al., 1964); it is likely to reflect inhibition occurring in deep cortical layers (Ochs and Clark, 1968; Barth et al., 1989; Barth and Sutherling, 1988; Harding, 1992). At progressively stronger stimulus intensities, PNP increases in amplitude; moreover, in motor and primary sensory cortex, it is preceded by short-latency bursts of positive potentials (BPP) (Stohr et al., 1963; Barth and Sutherling, 1988), which have been demonstrated to be correlated with motor output (Adrian, 1936). Indeed, Mingrino et al. (1963) showed that BPP were related to the I waves of Patton and Amassian’s pyramidal response (1954). In humans, DCRs have been recorded from PMC, MI and SI, with distinguishable characteristics among these different cortical areas (Goldring et al., 1994). We can speculate that the pure SPs that we observed at low intensity stimulation might depend on a cortical inhibitory process possibly related to the PNP of the DCR. By increasing stimulus intensities, the appearance of BPPs,
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The modulatory effect of the stimulus intensity on the probability of obtaining either SPs or MEPs has been described also in transcranial magnetic stimulation (TMS) studies (Wassermann et al., 1993; Davey et al., 1994). These findings have been explained admitting that low intensity TMS can induce brief pure SPs by activating selectively intracortical inhibitory interneurons, whereas at higher stimulus intensity intracortical cells synapsing on corticospinal neurons would be enrolled (Wassermann et al., 1993; Davey et al., 1994). However, the analogies between the SP obtained by TMS both in normal and epileptic patients and by intracerebral electrical stimulation, as in our cases, should be cautiously evaluated owing to the topographic limits of TMS, variabilities among different groups of epileptic patients, antiepileptic treatment, and above all to the complexity of the cortical SPs induced by TMS (Hallett, 1995).

Our findings are in agreement with previous data suggesting that activation of the perirolandic cortex can produce pure SPs (Ikeda et al., 2000); in addition they provide the first evidence of the capability of non-primary motor areas, such as PMC and SMA, to generate SPs. It is conceivable, therefore, that the areas that we investigated can be involved in the genesis of cortical NM. As reported above, the probability of obtaining pure SPs following PMC, MI and SI stimulation was higher at low intensity of stimulation. Cortical SPs may result from the activation of low threshold inhibitory neurons, widely located in cortical areas, projecting onto the pyramidal cells of the motor cortex (Krnjevic et al., 1964). A scattered distribution of excitatory and inhibitory responses, the latter consisting of transient inhibition lasting $10^{-2}–10^{-3}$ ms, has been observed with microstimulation studies of MI (Schmidt and McIntosh, 1990). Inhibitory motor phenomena induced by PMC stimulation might be mediated by the corticofugal projections that PMC sends to regions of medullary reticular formation (Kuypers and Brinkman, 1970; Wise, 1985) whose activation might be responsible for motor inhibition (Magoun and Rhines, 1946).

By increasing stimulus intensity, the SPs tended to be preceded more frequently by MEPs. In Patients 1 and 2, latencies of MEPs recorded in the deltoid muscle by stimulation of PMC were $10^{-1}–10^{-2}$ ms, longer than those obtained in the same muscle by direct cortical stimulation of MI with subdural grids (Ikeda et al., 2000) and by TMS (Rossini et al., 1994), and in keeping with recent data reporting longer latencies of the deltoid MEPs elicited by TMS stimulation of PMC (Fridman et al., 2004). PMC stimulation can conceivably evoke MEPs by itself through direct projections to spinal interneurons and alpha motoneurons (Murray and Coulter, 1981; Dum and Strick, 1991; He et al., 1993) or by engaging directly the motor cortex through corticocortical connections to the MI (Civardi et al., 2001; Munchau et al., 2002). In Patient 3, the MEP latency was $10^{-2}$ ms (she was a small sized, young girl) consistent with the MEP latencies reported in the deltoid with MI stimulation by direct cortical electrical stimulation (Ikeda et al., 2000) and by TMS (Rossini et al., 1994).

Low intensity stimulation of SI produced exclusively pure SPs in two patients, whereas in the third an MEP could inconstantly precede the SPs. These observations may be supported by experimental data in monkeys that demonstrate an inhibitory action of SI on the motor system by showing mainly inhibitory, or extremely weak, effects of electrical microstimulation of SI neurons on muscular activity as compared with MI neurons, even at high stimulus intensities (Widener and Cheney, 1997). Additional studies have emphasized the different functional properties of movement-related neurons in motor and sensory cortex concluding that SI neurons have a significantly lower motor output capacity with respect to MI neurons (Wannier et al., 1986, 1991). In our SI stimulation session, the increment of stimulus intensity resulted in the progressive appearance of an MEP preceding the SP. Motor responses induced by electrical cortical stimulation of the post-central somatosensory cortex were reported since the pioneering works by Penfield and Boldrey (1937), and Woolsey (1958), and later replicated by electrical cortical stimulation with subdural grids (Uematsu et al., 1992; Nii et al., 1996). However, because of the stimulation methods used in these studies (macroelectrodes or subdural grid electrodes, relatively high current levels), it cannot be ruled out that the observed results might depend on a current spread to adjacent motor areas. In fact, Uematsu et al. (1992) acknowledged the possibility that their stimulation procedure could activate a somewhat broad region, although, with low current densities. In our stereo-EEG stimulation procedure, the short distance (1.5 mm) between the two stimulating contacts should limit the spread of current; however, at the highest intensities of stimulation with a stimulus duration (3 ms) longer than the one usually employed in other studies, we cannot exclude that the appearance of MEPs might be related to a diffusion of current to the precentral cortex, or alternatively, to the activation of the corticocortical connections.
between SI and the adjacent, functionally related, MI (Jones et al., 1978; Asanuma and Bornschlegl, 1988).

In our study, stimulation of SMA with increasing stimulus intensities produced only pure SPs. This finding substantiates the hypothesis of a role of the SMA in the genesis of NM (Rubboli et al., 1995; Tassinari et al., 1995; Baumgartner et al., 1996), based on the evidence of a circumscribed NMA encompassed in the SMA, labelled as ‘supplementary NMA’ (Luders et al., 1987, 1995; Lim et al., 1994; Hanakawa et al., 2001), and on reports of patients with strokes in the mesial aspects of anterior frontal lobes showing non-epileptic NM in the contralateral upper limb (Degos et al., 1979; Santamarina-Cano et al., 1983; Young and Shahani, 1986; Kim, 2001). High frequency (50 Hz) trains of electrical stimuli delivered directly to the supplementary NMA can produce sustained negative motor responses, such as behavioural arrest, motor slowing and inability to maintain a tonic contraction (Luders et al., 1987, 1995; Lim et al., 1994). We can speculate that the pure SPs that we recorded by stimulating SMA may depend on a transient, stimulus-related activation of the same mechanisms that underlie the more prolonged negative motor responses induced by repetitive 50 Hz stimulation. Interestingly, by SMA stimulation, we obtained only pure SPs, never preceded by an MEP, even at the highest intensity of stimulation, suggesting that the portion of SMA that we investigated exerted mainly an inhibitory action on the motor system. A subdivision of the SMA in two separate areas, the pre-SMA and the SMA proper, with distinct functional properties (Rizzolatti et al., 1998) has been delineated; the supplementary NMA described by Luders et al. (1987, 1995) is roughly encompassed in the pre-SMA. In our study, the sites of the electrode contacts that resulted more effectively in inducing SPs varied from a position that could be consistent with the SMA proper (electrode M in Patient 2 and electrode Z in Patient 3) to a position that might correspond to the pre-SMA (electrode K in Patient 1). Although in humans the distinction between pre-SMA and SMA proper is still under debate, our findings may suggest that it is possible to elicit inhibitory responses by stimulating more caudally with respect to the supplementary NMA, in a region possibly pertaining to the SMA proper.

Epilepsy has been shown to modify cortical excitability in response to direct electrical stimulation of the cortex (Goldring et al., 1961, 1994; Wyler and Ward, 1981). In a penicillin model of focal epilepsy, the neuronal populations participating in the genesis of the DCR may pathologically synchronize depolarization, triggering interictal spikes in the neocortex (Barth et al., 1989, 1990). Goldring et al. (1961) reported an increased duration of the PNP of DCR. This finding might relate to TMS data showing a prolonged cortical SP in the epileptic hemisphere when the epileptogenic area included MI, suggesting an up-regulation of inhibitory mechanisms (Classen et al., 1995; Cincotta et al., 1998; Tassinari et al., 2003). On the other hand, the inability of the epileptic hemisphere, as compared with the unaffected one, to produce a linear progression of the SP duration in parallel with the progressive increment of the stimulus intensity has been explained admitting a failure of recurrent inhibition from the excited pyramidal neurons at higher stimulus intensity (Cicinelli et al., 2000). In our study, SP duration increased linearly with the increment of stimulus intensity, as it occurs in normal condition, suggesting that in our cases cortical inhibitory mechanisms were preserved, at least at the stimulus intensity that we used. We could not verify asymmetries of SP duration between the two hemispheres since, in the only patient with bilateral exploration (Patient 1), contralateral stimulation provided less constant findings possibly due to a certain degree of asymmetry in the implantation of the stereo-EEG electrodes, in the homologous cerebral structures.

In epileptic patients, motor system excitability can be modified by antiepileptic treatment (Michelucci et al., 1996; Ziemann et al., 1996; Tassinari et al., 2003). Cortical SP duration mainly reflects GABAA-mediated inhibitory mechanisms (McCormick, 1992). Cortical SP duration as evaluated by TMS.

The discrepancies between our results and those reported by Noachtar et al. (1997) and Ikeda et al. (2000), who failed to obtain NM by stimulating, respectively, SI and SMA, might depend on technical reasons. Direct cortical stimulation by means of subdural electrodes activates only the cortical surface just beneath the electrodes with a significant dispersion of the current due to a shunting effect through the CSF (Nathan et al., 1993). On the contrary, bipolar electrical stimulation with stereo-EEG electrodes tends to activate a limited amount of tissue, close by the two electrode contacts, using lower currents, with the significant yield of allowing the exploration of areas of cortex deeply situated inside cerebral sulci, providing, therefore, a more complete and accurate investigation of cortical functions (Yeomans, 1990).

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