

Abnormal gating of somatosensory inputs in essential tremor

Domenico Restuccia^{a,*}, Massimiliano Valeriani^{a,b}, Carmen Barba^a, Domenica Le Pera^a,
Annarita Bentivoglio^a, Alberto Albanese^a, Marco Rubino^a, Pietro Tonali^a

^aDepartment of Neurology, Catholic University, Policlinico A. Gemelli, L.go A. Gemelli 8, 00168 Rome, Italy

^bDepartment of Neurology, Pediatric Hospital 'Bambino Gesù', Rome, Italy

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Abstract

Objective: To study whether sensorimotor cortical areas are involved in Essential Tremor (ET) generation.

Background: It has been suggested that sensorimotor cortical areas can play a role in ET generation. Therefore, we studied median nerve somatosensory evoked potentials (SEPs) in 10 patients with definite ET.

Methods: To distinguish SEP changes due to hand movements from those specifically related to central mechanisms of tremor, SEPs were recorded at rest, during postural tremor and during active and passive movement of the hand. Moreover, we recorded SEPs from 5 volunteers who mimicked hand tremor. The traces were further submitted to dipolar source analysis.

Results: Mimicked tremor in controls as well as active and passive hand movements in ET patients caused a marked attenuation of all scalp SEP components. These SEP changes can be explained by the interference between movement and somatosensory input ('gating' phenomenon). By contrast, SEPs during postural tremor in ET patients showed a reduction of N20, P22, N24 and P24 cortical SEP components, whereas the fronto-central N30 wave remained unaffected.

Conclusions: Our findings suggest that in ET patients the physiological interference between movement and somatosensory input to the cortex is not effective on the N30 response. This finding thus indicates that a dysfunction of the cortical generator of the N30 response may play a role in the pathogenesis of ET. © 2002 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Somatosensory evoked potential; Generator source; Tremor; Dipolar analysis

1. Introduction

Essential tremor (ET) probably represents the most common movement disorder; its overall population prevalence ranges from 0.3 to 1.7% (RautaKorpi et al., 1984; Salemi et al., 1994). Although some reports describe clinical presentations that partially overlap other movement disorders (Marsden, 1984; Deuschl et al., 2000), the definite form of ET is characterized by visible and persistent postural tremor at 5–8 Hz involving hands and forearms, absent at rest, without parkinsonian, cerebellar, nor other neurological signs (Findley, 1996). The origin of ET is still unknown. Previous literature provided evidence that alterations in a central oscillator, rather than abnormalities of peripheral reflex mechanisms, are mainly involved in its generation (Elble, 1996). The simplest paradigm to address the periph-

eral or central origin of a tremor is represented by techniques that attempt to reset a tremor by stimulating peripheral or central CNS structures. ET, as expected in a tremor driven by a central oscillator, is easily reset by transcranial magnetic stimulation (Britton et al., 1993); however, the precise localization of such oscillator remains a matter of debate. So far, many findings converge towards the demonstration that this oscillator may be identified with the inferior olivary nucleus. Firstly, animals treated with harmaline show a tremor very similar to ET (Lamarre, 1975), together with increased rhythmicity and neuronal entrainment throughout the olive (Llinás and Yarom, 1986). Moreover, a significant association between typical tremor and abnormalities of cerebellar function has been recently demonstrated in advanced stages of ET (Deuschl et al., 2000). Besides these findings, which support of the afore-said theory, it has been suggested that other structures of the central nervous system (CNS) are involved in ET generation. Both positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) demonstrated overactivity of a number of brain structures in ET patients,

* Corresponding author. Tel.: +39-6-3015-4435; fax: +39-6-3550-1909.
E-mail address: drestuccia@rm.unicatt.it (D. Restuccia).

including not only the cerebellum, but also the globus pallidus, the thalamus, the red nuclei, and the primary sensorimotor cortex (Jenkins et al., 1993; Wills et al., 1994, 1995); in particular, both PET and fMRI failed to find a significant intrinsic olivary activation (Wills et al., 1994; Bucher et al., 1997). With regard to the sensorimotor cortex, its possible role in generating ET has been recently supported by the finding of coherence between the EEG signal and tremor-related electromyographic activity (Hellwig et al., 2001).

Somatosensory evoked potentials (SEPs) are a useful and non-invasive method to assess the functions of the somatosensory cortex. Mild SEP abnormalities have been demonstrated not only in direct focal lesion of the cortex, but also as a consequence of lesions of other brain structures functionally linked to sensorimotor cortical areas (Restuccia et al., 2001). Therefore, we tested the ability of SEPs to reveal functional modifications of primary sensorimotor areas in ET patients. For this purpose, in 10 ET patients we recorded median nerve SEPs after stimulation of the right upper limb, in 4 different conditions: (1) rest; (2) tremorgenic posture; (3) passive movements of the hand at rest; (4) voluntary, rapid movements of the hand at rest. Moreover we compared these data with those obtained from a population of healthy volunteers. This latter part of the study was performed by right median nerve stimulation in 3 different conditions: (1) rest; (2) antigravitary posture; (3) mimicked tremor. Finally, to improve the spatial resolution of the SEPs, raw data were further submitted to brain electrical source analysis (BESA), which has proven useful in separating the activities of neighboring cerebral structures (Scherg et al., 1989; Scherg, 1990; Franssen et al., 1992).

2. Material and methods

2.1. Patients and controls

We studied 10 patients (7 women, 3 men; age range 27–68, mean 49.7 years) suffering from definite ET (Findley and Koller, 1995). Two of them were positive for a family history of ET. All patients presented with bilateral, postural and longstanding (over 5 years) tremor of the hand. Neurological examination did not show any other abnormal sign. None of them was exposed in the past to tremorgenic drugs, or to trauma of the central nervous system. The tremor frequency ranged from 4.5 to 8 Hz, as determined by surface EMG. Scalp SEPs were recorded after stimulation of the right median nerve at wrist, in 4 different conditions: (a) upper limb at rest; (b) upper limb maintaining the tremorgenic posture; (c) upper limb at rest, rapid passive movements of the metacarpophalangeal joints of the II, III, IV and V finger produced by an experimenter, at about 4–8 Hz of frequency; (d) upper limb at rest, patient asked to perform rapid (about 4–8 Hz) flexion movements of the hand. Due to the clear difficulty to perform the whole procedure in the same session, the first 5 patients underwent stimulation in

conditions a, b and c, while the remaining 5 patients underwent stimulation in conditions a, b and d.

Moreover, we performed right median nerve stimulation in 5 healthy volunteers (2 men, 3 women; age range 25–42, mean 29 years). None of them had a history of neurological disease nor of exposition to tremorgenic drugs. Scalp SEPs were recorded in 3 different conditions: (a) upper limb at rest; (b) upper limb extended against gravity; (c) upper limb extended against gravity, when mimicking a 4–8 Hz tremor of the right hand. Tremor frequency was first assessed by surface EMG, then the volunteers were asked to maintain the same flexion-extension movement of the hand with the same frequency. The median nerve was stimulated at wrist. Stimulation (1.5 Hz frequency, 0.2 ms duration) was adjusted to the intensity sufficient to evoke a small twitch of the thumb. All subjects gave their consent according to the declaration of Helsinki.

2.2. SEP recording

For SEP recording, subjects lay on a couch in a warm and semi-darkened room. Disk recording electrodes (impedance below 5 k Ω) were placed at 19 locations of the 10–20 system (excluding Fpz and Oz). The reference electrode was at the lobe of the right ear and the ground at Fpz. The analysis time was 64 ms, with a bin width of 250 μ s. The amplifier band pass was 10–3000 Hz (12 dB roll off). An automatic artifact-rejection system excluded from the average all runs containing transients exceeding ± 65 μ V at any recording channel. In order to ensure baseline stabilization, SEPs were digitally filtered off-line by means of a digital filter with a bandpass of 40–2000 Hz. Two averages of 1500 trials each were obtained and printed out by the computer on a desk-jet printer. Frozen maps showing the distribution of the responses over the scalp were obtained by linear interpolation from the 4 nearest electrodes.

2.3. Data analysis

SEPs were identified on the basis of latency, polarity and scalp distribution. Amplitudes and peak latencies were measured on the average of the two runs. We evaluated the main scalp components. To avoid possible confusion due to the variability of the SEP labeling in previous literature, we identified SEP components as follows: parietal N20 (negative deflection at about 20 ms latency recorded in parietal regions contralateral to the stimulus), frontal P20 (positive deflection recorded on frontal regions contralateral to the stimulus at about the same latency as the N20; according to earlier literature, N20 and P20 should represent the opposite projections of the same dipolar source; Desmedt et al., 1987; Allison et al., 1991), central P22 (positive deflection at about 22 ms latency recorded on central regions contralateral to the stimulated side; Deiber et al., 1986), parietal P24 (positive deflection at about 24 ms latency recorded on parietal regions contralateral to the stimulated side), frontal N24 (positive deflection recorded on frontal

regions at about the same latency as the P24; according to earlier literature, N24 and P24 could represent the opposite projections of the same dipolar source; Garcia-Larrea et al., 1992; Valeriani et al., 1998); fronto-central N30 (large negativity at about 30 ms latency, widely distributed on frontal and central regions; Desmedt et al., 1987; Garcia-Larrea et al., 1992; Valeriani et al., 1998). Amplitude evaluations were performed on N20, P22, N24, P24 and N30 components. Amplitudes were measured from the baseline; all components except the N30 fronto-central response were evaluated at the recording location where the response to be analyzed was maximal. With regard to the N30 fronto-central response, although it usually reaches its maximal amplitude at frontal locations, we preferred to evaluate its amplitude at Cz location. In fact, it has been demonstrated that at frontal location this wave is largely contaminated by the activity of the N24 wave (Valeriani et al., 2000). Since absolute amplitude values are extremely variable among subjects, amplitude fluctuations across the various stimulation protocols were expressed as percentage changes referred to SEPs obtained at rest, which have been considered as 100%. When more than two conditions were taken into consideration, comparisons were performed by means of analysis of variance (ANOVA); when statistical significance was reached, a post-hoc analysis was performed by means of paired Student's *t* tests. When only two conditions were taken into consideration, comparisons were performed by means of paired Student's *t* tests. Latency values between different conditions were compared by paired *t* tests.

2.4. Brain electric source analysis

A detailed description of BESA is reported elsewhere (Scherg, 1990). The BESA program calculates potential distributions over the scalp from preset voltage dipoles within a 3-shell model of the head. It also evaluates the fit between the recorded and the calculated field distributions. The percentage of data that cannot be explained by the calculated field distribution is expressed as residual variance (RV). The lower the RV the better the dipolar model: in an ideal case, the RV should only be due to the recorded noise. In general, RV values lower than 10% are considered acceptable, particularly when obtained from individual recordings. However, even RV = zero is not enough to prove that a model is correct, on account of the infinite number of solutions to the 'inverse problem' of deriving intracranial sources from the extracranial potential field. BESA uses a spherical 3-shell model with an 85 mm radius and assumes that the brain surface is at 70 mm from the center of the sphere. The spatial position of each dipole is described on the basis of 3 axes: (1) the line through T3 and T4 (*x*-axis); (2) the line through Fpz and Oz (*y*-axis); (3) the line through Cz (*z*-axis). The 3 axes have their intersection point at the center of the sphere. The spatial orientation of the dipoles is described by two angles: (1) θ is the angle in the *x*-*y* plane

measured counter clockwise from the nearest *x*-axis; (2) φ is the vertical angle that is measured from the *z*-axis and is positive for the right hemisphere. The strength is expressed in ' μV_{eff} ', $1 \mu V_{\text{eff}}$ being the strength of a horizontal dipole, located at $y = 50$ mm, which produces a voltage difference of $0.5 \mu V$ between C3 and C4.

Dipole strengths in different conditions were expressed as percentages of the strengths measured from SEPs obtained at rest, which have been considered as 100%. When more than two conditions were taken into consideration, comparisons were performed by means of ANOVA; when statistical significance was reached, a post-hoc analysis was performed by means of paired Student's *t* tests. When only two conditions were taken into consideration, comparisons were performed by means of paired Student's *t* tests.

3. Results

3.1. SEP data

In all our subjects, we could identify all SEP components in parietal, central and frontal traces.

In SEPs recorded at rest, the N30 response was well identifiable over the central and frontal locations. It was always preceded by a negative N24 frontal wave, which appeared as a shoulder on the rising phase of the N30 potential in 4 controls and in 5 ET patients. Parietal N20 and P24 responses had their maximal amplitude at P3, while a P22 central response was maximal at C3. The N24 frontal wave was well evident at all frontal locations. Its mean amplitude was higher at F3 and Fz. The N30 mean amplitude was slightly higher at Fz. Across the different conditions, evoked responses reached their maximal amplitudes at the same scalp locations. For this reason, amplitude comparisons were performed on P3 traces for the N20 and P24 responses, on C3 traces for the P22 response, on F3 traces for the N24 response. Concerning the N30 wave, we compared the amplitudes of responses recorded at Cz (see above).

By comparing SEP amplitude percentages in controls at rest and during mimicked tremor, we found a significant difference, caused by a clear-cut amplitude decrease during mimicked tremor, concerning all cortical components (Student's paired *t* test, $P < 0.05$; Fig. 1). The amplitude of the subcortical P14 response remained unaffected (Student's paired *t* test, $P > 0.05$). Comparisons between SEPs at rest and during antigravitary posture did not reveal any significant modification (Student's paired *t* test, $P > 0.05$ for any SEP components).

By comparing SEP amplitude percentages in ET patients at rest and during postural tremor, we found a significant difference, caused by the attenuation of N20, P22, N24 and P24 components (Student's paired *t* test, $P < 0.01$). The amplitude of both P14 and N30 response showed no statistically significant difference.

By comparing SEP amplitude percentages in the 5

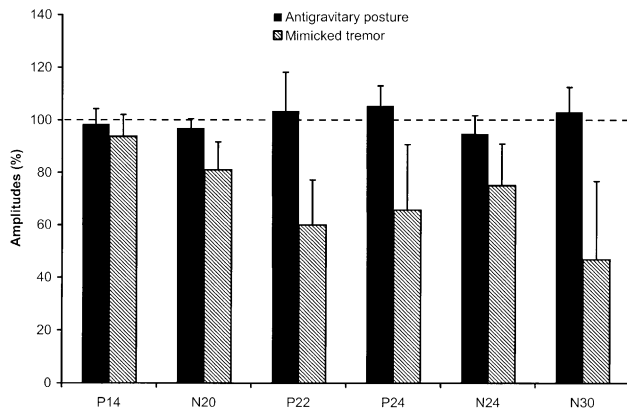


Fig. 1. Mean percentage amplitude of each scalp SEP component in 5 control subjects during antigravitary posture (black columns) and during mimicked tremor (hatched columns). Amplitudes obtained at rest are expressed as 100% (horizontal hatched line). Bars above each column represent standard deviations. No significant amplitude reduction was observed during antigravitary posture. By contrast, mimicked tremor induced a significant attenuation of all scalp components except the subcortical P14. Amplitude reduction was more evident for the P22 and N30 components.

patients who underwent SEPs at rest, during tremor and during active hand movements, ANOVA revealed a significant intergroup difference concerning all components, except the subcortical P14 wave ($P < 0.05$). Post hoc analysis showed significant difference between rest and tremor for all cortical components except the N30 (Student's paired t test, $P < 0.05$), and significant difference between rest and active hand movement for all cortical components

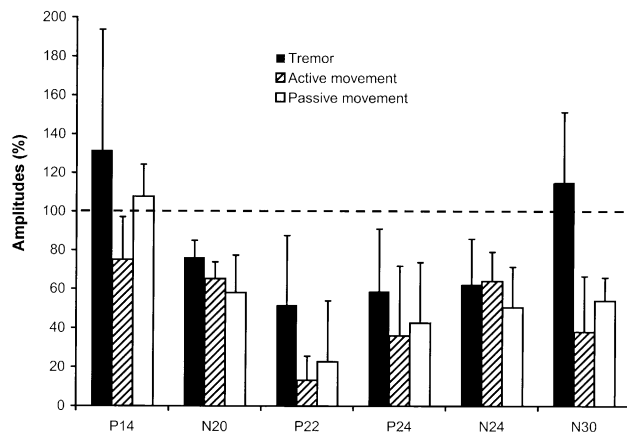


Fig. 2. Mean percentage amplitude of each scalp SEP component in ET patients, during postural tremor (black columns), during active hand movements (hatched columns), and during passive hand movements (white columns). Amplitudes obtained at rest are expressed as 100% (horizontal hatched line). Bars above each column represent standard deviations. No significant amplitude reduction was observed for the P14 component. During tremor, most of the scalp components (N20, P22, N24 and P24) showed a significant amplitude decrease, whereas the N30 wave remained substantially unchanged. Both active and passive hand movements induced a significant attenuation of all scalp components.

(Student's paired t test, $P < 0.05$). The amplitude decrease during active movement was more evident for the P22 and N30 responses (mean decrement 86.8 and 62% respectively; Fig. 2). By comparing SEP amplitude percentages in the remaining 5 patients, who underwent SEPs at rest, during tremor and during passive hand movements, ANOVA revealed a significant intergroup difference concerning all components, except the subcortical P14 wave ($P < 0.05$). Post hoc analysis showed significant difference between rest and tremor for all cortical components except the N30 (Student's paired t test, $P < 0.05$), and significant difference between rest and passive hand movement for all cortical components (Student's paired t test, $P < 0.05$). During passive movement, the amplitude decrease was more evident for P22, N24 and P24 responses (mean decrement 77.3, 49.5 and 57.4%, respectively; Fig. 2). Although less evident, the mean amplitude decrease of the N20 wave was stronger during passive movements than during active ones (41.9 and 34.8% respectively). SEPs at rest, during tremor and during passive hand movement in one of our patients are illustrated in Fig. 3.

3.2. Dipolar analysis

With regard to dipolar source modeling, to build the dipolar models we used a 'sequential strategy,' as described in

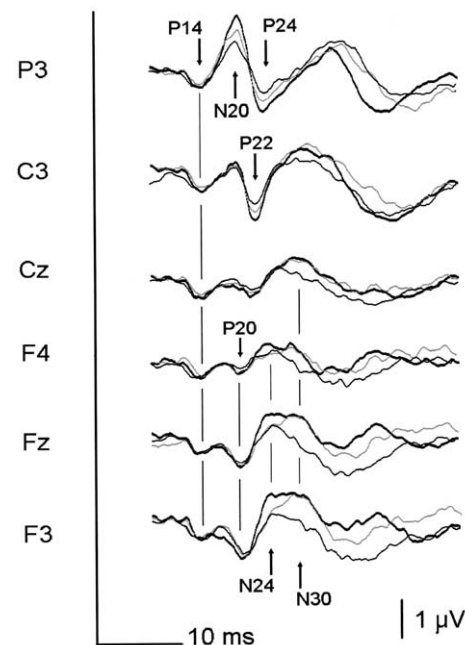


Fig. 3. Right median nerve SEPs from one ET patient. SEPs recorded at rest (black thick traces), during postural tremor (gray traces), and during passive hand movement (black thin traces) are superimposed. The subcortical P14 wave remained unchanged across the 3 different paradigms; by contrast, the parietal N20 and P24, central P22 and frontal N24 showed an evident attenuation during tremor and during passive hand movements. The N30 component, which can be evaluated in frontal as well as in central traces, is markedly reduced by passive hand movements but is clearly unaffected by postural tremor.

detail elsewhere (Valeriani et al., 1998; Restuccia et al., 2001). We divided the analysis time (from the subcortical P14 to the N30 response) into two intervals, choosing the peak of the N20 response as the division point. In the earlier interval, which was analyzed first, one subcortical and two cortical dipolar sources were activated. In particular two cortical sources were reputed necessary on the basis of previous results showing the contribution of two different cortical generators to the SEP topography in the 20 ms latency range. When we added the later interval to the analysis, another dipole was needed to explain the scalp SEP topography. This 4-dipole model explained well the SEP distribution in traces obtained from median nerve stimulation at rest (individual RV values ranging from 2.5 to 6.7%). Then, we applied the same 4-dipole model to traces issued from the remaining two stimulation paradigms (arm extended against gravity and mimicked tremor). Dipole locations and orientations were maintained unmodified through the 3 different types of stimulation. We obtained RV values quite similar to those obtained from median nerve traces at rest (antigravitary posture, individual RV values ranging from 2.71 to 8.3%; mimicked tremor, individual RV values ranging from 3 to 9.4%).

The first dipole (no. 1), whose peaking activity had the same latency as the P14, was placed at the base of the skull; the other 3 dipoles had perirolandic locations. Dipole no. 2 was oriented tangentially and was activated at the latencies of both the N20/P20 and, with inverted polarity, the P24/N24 potentials. Dipole no. 3 showed a constant peak of activity at the same latency as the P22 response. The 4th dipole (no. 4) reached a radial orientation and a medial location and showed a late peak of activity at the latency of the fronto-central N30.

When we compared the dipole strengths in controls, ANOVA showed a significant difference among dipole strengths across the 3 stimulation paradigms ($P < 0.05$). Post hoc analysis then revealed a significant difference between rest and mimicked tremor, concerning dipoles 2, 3, and 4 (Student's paired t test, $P < 0.05$). No significant difference was found between rest and antigravitary posture.

The 4-dipole model issued from control traces was applied also to SEPs obtained from patients. This 4-dipole model explained well the SEP distribution in traces obtained from median nerve stimulation at rest (individual RV values ranging from 3.5 to 8.7%). Then, we applied the same 4-dipole model to traces issued from the remaining two stimulation paradigms (postural tremor and active movement of the tremulous hand). In grand-average as well as in individual models, dipole locations were maintained unmodified through the 3 different types of stimulation, while dipole orientations were allowed to move freely. We obtained RV values quite similar to those obtained from median nerve traces at rest (postural tremor, individual RV values ranging from 3.69 to 8.8%. Active hand movements, individual RV values ranging from 3.96 to 10.3%; passive hand

movements, individual RV values ranging from 4.51 to 10%).

When we compared the dipole strengths, paired t tests showed a significant difference between stimulation at rest and during postural tremor (Fig. 4). The strength reduction was significant for dipoles 2 and 3 ($P < 0.05$), while the dipole 4 remained unmodified. By comparing dipole strength at rest and during active and passive hand movements, the strength reduction was evident for all cortical dipoles including the dipole 4 (Student's paired t test, $P < 0.05$). Fig. 5 illustrates the dipolar model issued from the grand-average of SEP data in the 5 patients who underwent stimulation at rest, during tremor and during active movement. Fig. 6 illustrates the dipolar model issued from the grand-average of SEP data in the remaining 5 patients who underwent stimulation at rest, during tremor and during passive movement.

4. Discussion

SEPs performed in our patients at rest did not reveal any abnormality. By contrast, SEPs recorded during tremor showed specific changes, consisting of the reduction of all cortical components, except the fronto-central N30 wave. This finding was confirmed by dipolar analysis, which showed a significant strength reduction of the dipoles 2 and 3, without significant involvement of the dipole 4. Previous studies demonstrated that the dipole 2 probably represents the generator of the N20/P20 and N24/P24 responses, whereas the dipoles 3 and 4 probably correspond to the generators of the P22 and N30, respectively (Valeriani

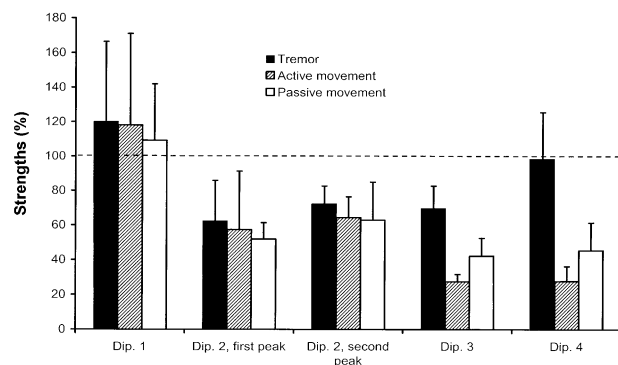


Fig. 4. Mean percentage strength of each dipole in ET patients, during postural tremor (black columns), during active hand movements (ragged columns), and during passive hand movements (white columns). Dipole strengths obtained at rest are expressed as 100% (horizontal hatched line). Bars above each column represent standard deviations. No significant amplitude reduction was observed for the first dipole, possibly corresponding to the P14 component. During tremor, most of the scalp dipoles (possibly corresponding to the N20, N24/P24 and P22 generators) showed a significant strength decrease, whereas the 4th dipole (corresponding to the N30 generator) remained substantially unchanged. Both active and passive hand movements induced a significant strength decrease of all cortical dipoles.

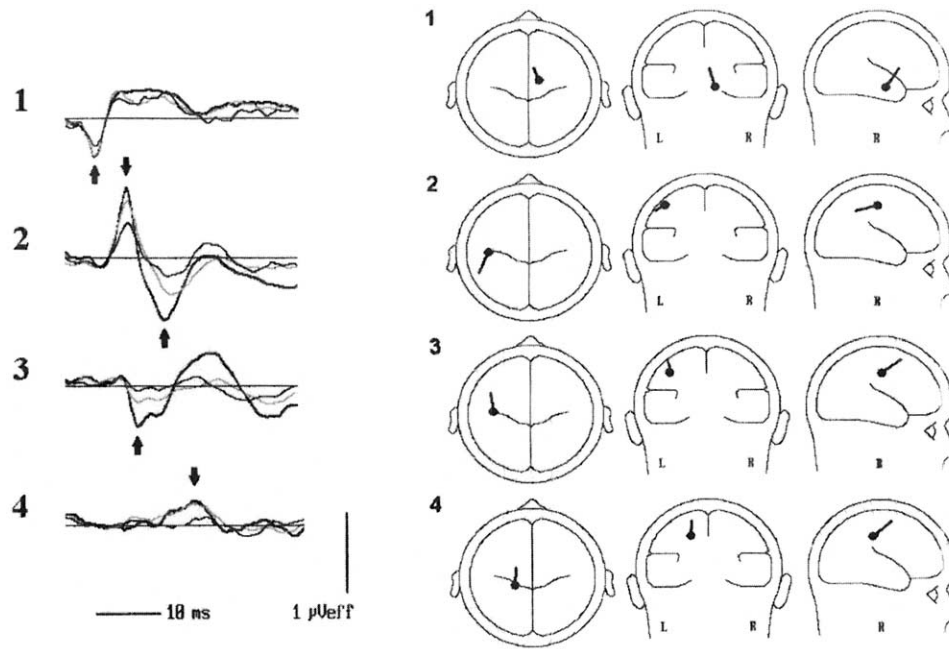


Fig. 5. Four-dipole spatiotemporal solution for median nerve SEPs; grand-average of 5 ET patients who underwent stimulation at rest, during tremor and during active hand movements. The source potentials of the dipoles are shown on the left (black thick traces: rest; gray traces: postural tremor; black thin traces: active hand movements). On the right, 3 views of the head illustrate the location and orientation of the dipoles. The top row shows source potential and location of the dipole at the base of the skull (dipole 1). Source potential and location of the tangential perirolandic dipole are shown in the 2nd row. The 3rd and 4th rows show source potentials and locations of the other two perirolandic dipoles. The strength of dipole 1 remains unchanged across the 3 different conditions. The strength of dipoles 2 and 3 is markedly reduced by tremor as well as by active hand movements. The strength of dipole 4 remains unchanged during tremor, while it is markedly reduced during active hand movements.

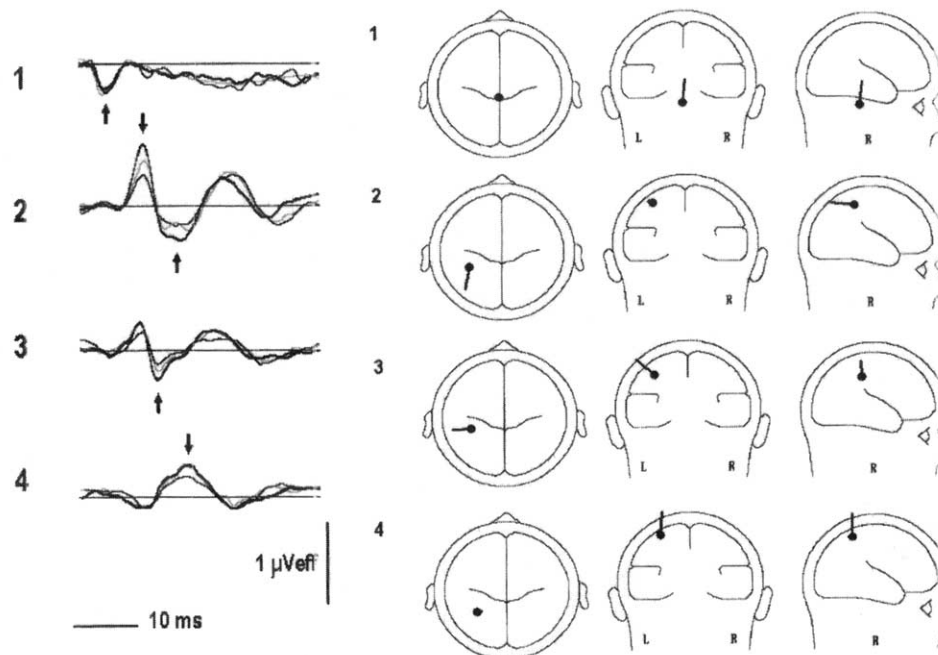


Fig. 6. Four-dipole spatiotemporal solution for median nerve SEPs; grand-average of 5 ET patients who underwent stimulation at rest, during tremor and during passive hand movements. The source potentials of the dipoles are shown on the left (black thick traces: rest; gray traces: postural tremor; black thin traces: passive hand movements). On the right, 3 views of the head illustrate the location and orientation of the dipoles. The top row shows the source potential and location of the dipole at the base of the skull (dipole 1). The source potential and location of the tangential perirolandic dipole are shown in the 2nd row. The 3rd and 4th rows show the source potentials and locations of the other two perirolandic dipoles. The strength of dipole 1 remains unchanged across the 3 different conditions. The strength of dipoles 2 and 3 is markedly reduced by tremor as well as by passive hand movements. The strength of dipole 4 remains unchanged during tremor, while it is markedly reduced during passive hand movements.

et al., 1998, 2000). However, to establish whether these SEP changes are specific of ET, we should exclude that they are merely caused by hand movement regardless of its central pathogenetic mechanisms. Theoretically, involuntary movement of the hand might interfere with SEP recordings. Movement-related SEP changes have been largely described in earlier literature, and they are usually explained by the so-called gating phenomenon (Jones, 1981; Cohen and Starr, 1987; Cheron and Borenstein, 1987, 1991; Jones et al., 1989; Rossini et al., 1996; Valeriani et al., 1999; Shimazu et al., 1999; for a review see Cheron et al., 2000). Cutaneous percepts as well as SEPs are inhibited during rapid hand movements, probably to prevent the processing of irrelevant tactile input (Schmidt et al., 1990). Such an interference acts at different levels of the central nervous system: as a matter of fact, sensory inputs triggered by the electrical stimulation and sensory inputs activated by the movement itself can mutually interfere at some point along the ascending somatosensory pathways ('peripheral' or 'centripetal' gating; Jones et al., 1989). Moreover, the central command that evokes movement can directly interfere with the processing of cutaneous inputs ('central' or 'centrifugal' gating; Jones et al., 1989). It is generally agreed that peripheral mechanisms mainly contribute to the gating effect caused by passive movements, while sensory gating following active voluntary movements implies a substantial contribution of both mechanisms. Finally, gating that occurs without movement or before its onset can be explained by pure central mechanisms. This type of gating, which has been evidenced by asking the subject to imagine hand movements (Cheron and Borenstein, 1992; Rossini et al., 1996), or by asking him to move his hands just after the electrical stimulation ('premovement' gating; Shimazu et al., 1999), has been explained by suggesting that the usual processes of movement preparation in the motor areas of the cortex ('motor subroutine'; Kaji et al., 1995) can interfere with somatosensory cortical processing. The question whether hand movements induced by tremor can fully explain the SEP pattern we observed in our patients can be solved by comparing SEPs during tremor with SEPs obtained during different movement paradigms. SEP modifications observed in our patients during active or passive hand movements, when the limb was not maintained against gravity, were very similar to those reported in previous gating studies in healthy humans. In our study, as well as in earlier ones, both active and passive hand movements did not affect subcortical SEPs, while cortical components were all affected in various degrees. Voluntary movements caused a more remarkable decrease of the N30 response (Jones, 1981; Cohen and Starr, 1987; Cheron and Borenstein, 1987, 1991; Jones et al., 1989; Rossini et al., 1996; Valeriani et al., 1999; Shimazu et al., 1999). Conversely, during passive movements cortical SEPs were less remarkably reduced, with a more evident involvement of the N20 component (Rossini et al., 1996; Valeriani et al., 1999). SEPs obtained from our control

subjects showed an evident attenuation of all cortical components very similar to the one usually observed during active hand movements, thus demonstrating that also a small amplitude movement such as tremor can induce, in physiological conditions, SEP changes which can be explained by a gating effect. Seen in this light, the attenuation during postural tremor in ET patients of most of SEP components (e.g. parietal N20, central P22, fronto-parietal N24/P24) may be interpreted as subsequent to the interference between an involuntary movement such as the tremor and the somatosensory input. By contrast, the finding of a centro-frontal N30 wave which is affected by passive movements, but not by tremor during antigravitary posture, requires a further explanation. In general, the interpretation of any abnormality of the N30 wave is difficult due to a number of uncertain details concerning its physiological meaning. N30 reduction with normal parietal N20 component was described in localized focal lesions of the frontal cortex (Mauguière et al., 1983) and of the internal capsule (Mauguière and Desmedt, 1991). This led to hypothesize that the N30 is generated by somatosensory input reaching precentral cortical areas by means of parallel and separate thalamo-cortical projections; moreover, a significant relationship between this wave and motor control was also supported by the finding of reduced N30 in movement disorders, such as Parkinson disease (Rossini et al., 1989) or Huntington's chorea (Topper et al., 1993). However, this hypothesis is not generally accepted, since other authors claimed for a postcentral location of the N30 generator (Allison et al., 1991; Ibañez et al., 1995), whereas others did not confirm the finding of reduced N30 in parkinsonian patients (Mauguière et al., 1993; Garcia et al., 1995).

Looking at our present data, the hypothesis of a direct anatomical lesion of the N30 cortical generator can be easily ruled out by the finding of a normal amplitude of this wave at rest. In the same way, we can exclude a persistent dysfunction of the N30 generator, since the abnormality we observed was evident only during postural tremor. The finding of a normal N30 at rest which does not change during tremor but is correctly gated by active and passive movements could be trivially explained by hypothesizing that the antigravitary posture produces an overflow of sensory input to the N30 generator. According to this hypothesis, the N30 gating during tremorgenic posture is actually correct, but it does not cause a measurable amplitude reduction of this wave, since a larger amount of proprioceptive afferents contributes to its building. On the other hand, antigravitary posture itself does not cause evident SEP changes in healthy subjects, rendering this hypothesis unlikely. Therefore, the more probable explanation for our present data is that, during ET, the central generator of the N30 is involved in a central oscillatory circuitry which is refractory to peripheral input; this input is therefore functionally 'switched off,' rendering impossible the classical gating of the electrical volley.

The existence of a thalamo-cortical loop selectively

involving the N30 cortical generator has been recently confirmed by a report, showing that deep brain stimulation (DBS) of the basal nuclei caused a selective enhancement of the N30 wave (Pierantozzi et al., 1999). In this study, the authors, according to earlier hypotheses about the frontal origin of the N30 wave, suggested that this thalamo-cortical loop mainly involves the frontal cortex and namely the supplementary motor area (SMA). Analogously, Murase et al. (2000) interpreted the finding of an incorrect N30 gating in dystonic patients by hypothesizing a dysfunction in prefrontal areas. These authors found that the N30 response, although showing normal amplitude values, was not modified by premotor gating. Since it has been proposed that dystonia can be caused by a fault in the usual processes of movement preparation in the motor areas of cortex (Kaji et al., 1995), Murase et al. (2000) suggested that the same frontal areas are not able to correctly process sensory inputs. Both explanations are substantially in agreement with other authors (Rossini et al., 1989) who localized the N30 generator within the SMA, which is possibly involved in the initiation and programming of voluntary movement (Goldberg, 1985); however, this hypothesis is still matter of debate, since other authors failed to find clear signs of SMA activation during upper limb stimulation (Ibañez et al., 1995; Barba et al., 2001). Nevertheless, whatever the exact location of the N30 generator, its refractoriness to proprioceptive inputs coming from a limb maintained in antigravitary posture is substantially in agreement with recent studies, which reveal a strict relationship between the N30 and the selective processing of proprioceptive input. In fact, N30 is lacking after pure cutaneous stimulation (Restuccia et al., 1999), and it is relatively more represented after pure proprioceptive stimulation (Restuccia et al., 2002). In conclusion, our present data suggest that the cortical N30 generator, whatever its location, is probably involved, during postural tremor in ET patients, in an oscillatory thalamo-cortical loop insensitive to peripheral proprioceptive input.

Several recent acquisitions in literature lend substance to this finding. Firstly, surgical lesions of the of the thalamus remove ET (Goldman et al., 1992), and tremor-related activity has been recorded in single neurons of the ventralis intermedius nucleus of the thalamus (Hua et al., 1998). Secondly, coherence has been found between an EEG component over the sensorimotor cortex contralateral to the tremulous limb and the tremor-related electromyographic activity (Hellwig et al., 2001). The existence of such a thalamo-cortical loop, however, does not necessarily rule out the classical hypothesis of an olivary oscillator accounting for the ET generation (Elble, 1996). It is well known that cortical manifestations of the tremor, such as cortical oscillations showing similar frequency and a fixed-phase relation with EMG-recorded limb tremor, could merely represent spread of the modulation along neuronal pathways from CNS structures functionally related to the somatomotor cortex (McAuley, 2001). In fact, several

studies provided strong evidence of a strict functional relationship between olivary nuclei and somatomotor cortex. Inferior olivary nuclei are known to respond to sensory inputs which are not self-generated or predictable; for instance, repetitive locomotion does not cause in physiologic conditions significant activation of olivary cells (for a review see Devor, 2002). Predictability of any sensory input is likely to depend on cortical processing, therefore the somatomotor cortex probably plays a major role in modulating the arrival of somatosensory information to the olives (Brown and Bower, 2000). As a matter of fact, a considerable share of data indicates that inferior olives receive inputs from sensorimotor cortex, either directly or via posterior column nuclei relays (Allen and Tsukahara, 1974; Andersson and Nyquist, 1983; Baker et al., 2001). Therefore, it is conceivable that an abnormality of the cortical processing of somatosensory information may influence the activity of the inferior olivary nuclei.

In conclusion, although the large clinical heterogeneity of ET patients and the intrinsic variability of the N30 wave suggest some precaution, our present data seem to indicate that somatomotor cortical areas play an important role in generating ET. This finding can be important in the future understanding of its pathophysiologic mechanisms, as well as in its management.

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