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Giant somatosensory evoked potentials in different clinical conditions: scalp topography and dipole source analysis

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Introduction

A peculiarity of somatosensory evoked potentials (SEPs) recorded in some patients affected by myoclonus is the extreme enlargement of cortical components elicited by stimulation of median nerve. Such a phenomenon was first observed in 1947 by Dawson [1], whose pioneer studies opened the pathway for subsequent investigations of SEPs in humans. Since then, a number of papers reporting the features of SEPs in patients with cortical myoclonus have considerably improved our knowledge of the pathophysiological mechanisms underlying such 'giant' evoked potentials. It has been demonstrated that the sources of giant SEPs reside in the primary sensorimotor cortex [2], where they reflect cortical hyperexcitability related to the pathological dysfunction of an inhibitory mechanism [2,3]; such a dysfunction may be modality specific, insofar as giant SEPs can be elicited by both cutaneous and muscular afferents inputs, or by cutaneous stimuli alone [4,5]. The components most often affected lie in the 20–100 ms latency range (usually sparing the N20 component) and their amplitude can reach ten times the values observed in normal subjects [6].

The majority of reports on giant SEPs deal with patients affected by cortical myoclonus, nonetheless pathological enhancement of cortical SEPs has been found in a variety of clinical conditions, including space occupying lesions [7,8], stroke [9–11], fragile-X syndrome [12], hyperekplexia [13] and Rett syndrome [14]. In addition, SEPs of enormous amplitude (up to 400 μV; 'extreme' SEPs) have been described in children with tactile-evoked spikes in their EEG [15]. Giant SEPs have also been observed in neurologically normal subjects as a consequence of pharmacological manipulations [16]. Overall, giant SEPs have been investigated less in conditions other than cortical myoclonus.

A series of remarkable papers by Shibasaki and coworkers has emphasized the fact that, in patients with cortical myoclonus, giant SEPs originate from extreme enhancement of the very same components which contribute to normal SEPs [2,17,18]. The enlarged components can be those with either a tangential or radial field, or both. As an important corollary to these observations, it appears that the study of giant SEPs can be of relevance to the loca-

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lization of cortical generators of normal SEPs: giant evoked potentials provide, in effect, a kind of 'magnifying glass' for the cortical responses, allowing a better differentiation of SEP components whose sources overlap considerably in space and time.

The present study examined giant SEPs in patients with cortical myoclonus and in individuals with non-myoclonic conditions. The aim was to compare the features of giant SEPs in these two groups of patients, and in relation to SEPs obtained in a population of normal subjects, in order to determine whether the observations on giant SEPs reported by Shibasaki and collaborators in cortical myoclonus hold true also for other clinical conditions associated with giant SEPs. To achieve an optimal identification of different SEP components, the scalp topography of median nerve SEPs was investigated with a spline estimate of both voltage and current source density (CSD). In addition to this, a spatio-temporal dipole modelling procedure was applied to both normal and giant SEPs to localize generators in the somatosensory areas. Dipole source analysis identifies the activity of a group of neurones generating an evoked potentials by localizing a single (or many) equivalent dipole(s) in a model of the head.

Materials and methods

Patients

A total of 14 patients with 'giant' SEPs was studied, of whom 12 were examined in Troina and two (patients 2 and 5) in Florence. The clinical characteristics of the patients are summarized in Table 1: their ages ranged from 4 to 71 years and they could be divided on clinical grounds as falling into a myoclonic or a non-myoclonic condition.

Six patients (1–6) showed postural and/or action myoclonus in the upper limbs, judged to be of cortical origin according to standard criteria [19]. Pre-myoclonus spike was detected by jerk-locked back-averaging in all of them and in 4 an enhancement of long-loop reflex (C-reflex) was also observed. They are referred to as myoclonic patients. Two out of 6 patients suffered from progressive myoclonic epilepsy (PME) of unknown origin while 4 (three belonging to the same family) had cortical tremor, a variant of cortical reflex myoclonus [20]. Five of these patients were under antiepileptic drug therapy.

The remaining eight patients (7–14) had giant SEPs but did not present with myoclonus, either spontaneous or reflex, at the time of the investigation and no history of limb jerking was reported: therefore they are referred to as non-myoclonic patients. They included one patient with fragile-X syndrome (diagnosis confirmed by molecular analysis for the FMR-1 gene), two patients with benign childhood epilepsy with centrotemporal spikes (BCECS), two with Down's syndrome (diagnosis confirmed by karyotyping), 3 with congenital hemiplegia due to perinatal hemispheric infarction. Three patients were on antiepileptic drugs.

Control subjects

In order to provide an adequate control population, SEPs were recorded in 23 neurologically normal volunteers, 10 females and 13 males, aged 5–74 years. Eight were in the paediatric age (5–11 years), and 15 were adults (22–74 years).

All the subjects and patients gave informed consent for the experiments according to the procedures required by the Ethical Committees of IRCCS ('Oasi', Troina) and of the University of Florence.

SEP recording procedure

SEPs were recorded in a quiet room with the patient/subject on a reclining armchair. The median nerve was stimulated at the wrist with square wave electric pulses of 0.2 ms in duration at a rate of 0.5 Hz with an intensity sufficient to produce a moderate twitch of the thenar muscles. SEPs were recorded from 19 Ag/AgCl scalp electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2 of the 10–20 system), mounted on an elastic cap, with reference to linked earlobes. Particular care was taken as to obtain electrode impedances below 5 kΩ and similar impedances between homologous electrodes, including the two earlobe electrodes. The scalp activity was amplified (Synamps Amplifiers, Neuroscan, Inc.) with a filter bandpass of 1–1500 Hz (3 dB), digitized with a sampling rate of 512 points every

TABLE 1
CLINICAL CHARACTERISTICS OF THE PATIENTS

Patient	Sex	Age	Diagnosis	Enhanced components of giant SEPs
1	F	15	Cortical myoclonus (progressive myoclonic epilepsy with unknown etiology)	N30/P27 tangential N33 radial P45/N45 tangential
2	F	30	Cortical myoclonus (progressive myoclonic epilepsy with unknown etiology)	N30/P27 tangential N33 radial
3	F	48	Cortical myoclonus (cortical tremor)	N30/P27 tangential P45/N45 tangential
4 daughter of patient 3	F	26	Cortical myoclonus (cortical tremor)	N30/P27 tangential P45/N45 tangential
5 son of patient 3	M	25	Cortical myoclonus (cortical tremor)	N30/P27 tangential P45/N45 tangential
6	F	71	Cortical myoclonus (cortical tremor)	P22 radial N33 radial
7	M	7	Fra-X syndrome	N60 tangential
8	M	12	Benign childhood epilepsy with centrotemporal spikes (BCECS)	N60 tangential
11	F	7	Congenital hemiplegia	P22 radial N33 radial
12	F	5	Congenital hemiplegia	P22 radial N33 radial
13	F	12	Down's syndrome	N30/P27 tangential P22 radial
14	M	10	Down's syndrome	N30/P27 tangential P22 radial

epoch, and averaged over an interval of 150 or 205 ms after the stimulus. Responses contaminated by artifacts larger than 200 μV were automatically rejected by the computer. At least two averages of 256 responses were acquired from each arm to check for reproducibility.

Data analysis

Signals were read into a FOCUS program (Megis, Munich) for further processing. It is important both for mapping procedures as well as for dipole modelling to have an optimal signal-to-noise ratio and to ensure baseline stabilization. After having verified by FFT analysis that the frequencies contributing to SEPs were below 300 Hz, individual SEPs were digitally filtered at 10–300 Hz (12 dB, zero phase shift). In addition, different SEP series obtained from each arm were combined into grand averages. SEP latency and amplitude were measured for

controls. Amplitudes were measured at the location where they were maximal, for each peak from the preceding peak of opposite polarity: the upper limit of the normal range of amplitude was computed as mean ± 3 SD. Differences in peak amplitude between controls and patients were evaluated by means of Z statistics.

Topographical mapping

The scalp distribution of median nerve SEPs was analysed by voltage maps as well as by CSD maps. Maps of instantaneous voltage distribution were calculated by linear interpolation among the 4 neighbouring electrodes and by spline interpolation. CSD maps were obtained using the method proposed by Perrin et al. [21], using spline interpolation and the Laplacian transformation of the potential values. CSD fields correspond to scalp sites where current flows out of ('source') or enters ('sink') the scalp, and have some advantages over potential fields in that they are computed without taking the reference electrode into account. Thus they represent an absolute quantity and show more localized electrical activity, allowing better spatial resolution and detection of minor topographical differences.

Dipole modelling

To localize the dipoles a spatio-temporal dipole method was used (Brain Electric Source Analysis, BESA 2.0, Megis, Munich). BESA estimates the number of active brain sources, provides locations and orientations of EDs within a spherical head model and depicts the time-varying amplitudes of the dipoles (dipole source potentials, DSP). Any ED is characterized therefore by its location, orientation and strength (dipole moment). BESA iteratively determines the position and DSP of a dipole until the residual variance (RV: the percentage of the recorded data not explained by the solution) reaches a minimum value, which identifies the optimal solution. The head model we used consisted of a 3 concentric shell sphere, with a radius of 85 mm.

In our attempt to model equivalent dipoles of normal and 'giant' SEPs we adopted the strategy proposed by Buchner et al. [22]: briefly, regional dipole sources were fitted independently in different SEP epochs, as defined by Global Field Power (GBF) [23]. In normal subjects, the model obtained included three sources: a brainstem dipole explaining the activity in the first 16–17 ms; a tangential dipole and a radial one, subtending the activities in the 18–45 ms range.

Results

SEPs in normal subjects

In adult controls a sequence of cortical peaks having a modal latency of 20, 22, 27, 30, 33, 45 and 60 ms followed contralateral median nerve stimulation (Fig. 1). Parieto-occipital electrodes recorded an earlier negativity (N20: mean latency 19.4 ms) and a later positivity (P27: 27.4 ms). A positive peak (P20: 19.7 ms) and a negative peak (N30: 28.7 ms) were observed at the frontal area. Central electrodes picked up a positivity (P22: 22.3 ms), a negativity (N33: 33.8 ms) and a later positivity (P45: 45.3 ms). A negative component was recorded over the central-parietal area (N60: 59.8 ms).The comparison of voltage and CSD maps allowed grouping of these peaks into two frontal-parietal dipolar complexes (P20-N20, N30-P27), three peri-rolandic unipolar components (P22, N33, P45) and one central-parietal unipolar component (N60). Peak amplitudes were (μV mean $\pm$ SD): N20 = 2.5 $\pm$ 1.3; P22 = 2.0 $\pm$ 1.0; 2.2; N60 = 5.2 $\pm$ 3.1. Paediatric SEPs showed the same components, with similar topography but with shorter latencies.

SEPs in patients

The latencies and amplitudes of N20-P20 were within the normal range in all patients. Later components were abnormally enlarged., with selective involvement of specific peaks depending on the patient (Table 1).

All components observed in normals up to 40 ms were clearly identifiable in patients with cortical myoclonus. In PME patients (1 and 2), two components were enlarged, the tangential N30-P27 and the radial N33. In patient 6 affected with cortical tremor the 'giant' components were the two radial peri-rolandic components, P22 and N33, whereas in the 3 patients with familial cortical tremor (3, 4 and 5), it was the tangential component N30-P27 which was abnormally enlarged. In addition, a later frontal-parietal dipolar component (P45-N45: mean latency 45.8 ms), never observed in normal controls, showed a large amplitude in patients 1, 3, 4 and 5 (Fig. 3).

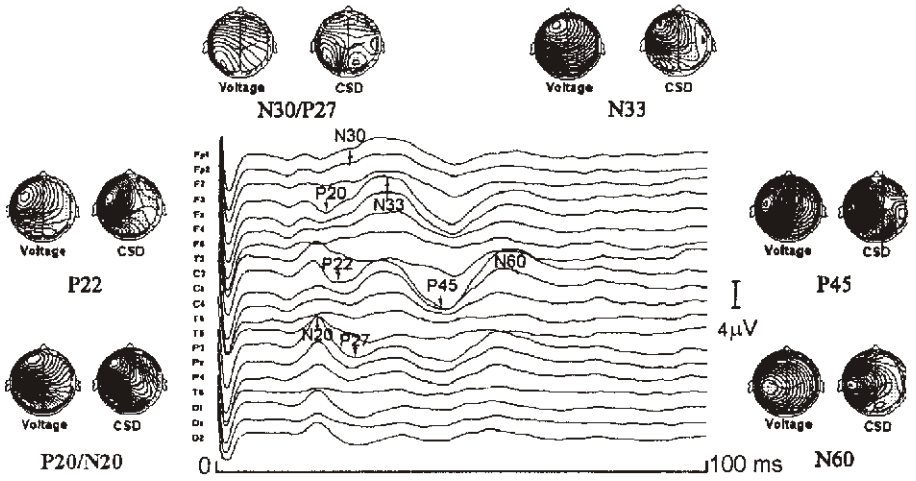

Fig. 1. Grand average of right median nerve SEPs across 4 normal adult subjects. Topographic maps compare voltage responses and current source density (CSD) responses. Maps display equipotential contours of the potential distribution at the scalp calculated on the basis of spherical spline. CSD estimation is based on a Laplacian montage calculated by spherical spline interpolation. Hatched areas superimposed on the equipotential lines define negative voltage values in potential maps and an inward current (sink) in CSD maps. Frontal-parietal P20-N20 and N30-P27 complexes represent tangential dipoles across the central fissure. P22, N33, P45 arise from radial peri-rolandic dipoles, whereas N60 corresponds to a radially oriented dipole at the central-parietal cortex.

In the non-myoclonic group, patients with congenital hemiplegia (10, 11 and 12) showed enlarged radial P22 and N33 components on the non-affected

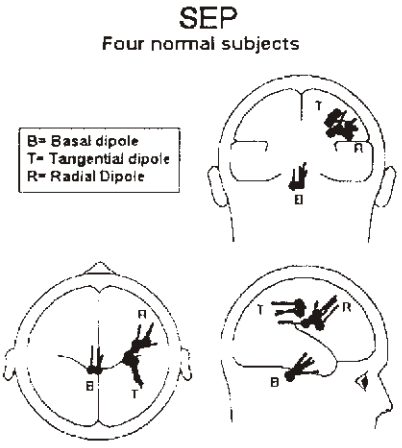

Fig. 2. Estimated locations of spatio-temporal dipoles of left median nerve SEPs obtained in 4 normal subjects. The residual variance is below 6.5%. The 3 head views illustrate the location and orientation of the dipoles. The dots indicate the locations of the dipoles; the bars their orientation. The early SEPs were modelled by 1 brain-stem dipole (B) and by 2 cortical dipoles tangentially (T) and radially (R) oriented. Dipole T explained P20-N20 and N30-P27 tangential complexes. Dipole R modelled peaks P22, N33 and P45.

hemisphere, while radial P22 and tangential N30-P27 were abnormally enlarged in Down's syndrome patients (13 and 14). SEPs in patients 7, 8 and 9 were characterized by an enormous component (up to 100 μV: 'extreme' SEPs) peaking at around 60 ms. Its potential field had a dipolar configuration with the negative and the positive maxima located, respectively, in the temporal and frontal-mesial area contralateral to stimulation (Fig. 5). Such a topographic pattern was at variance with that of component N60 observed in normals, which showed a unipolar central-parietal distribution.

Dipole modelling in normal subjects and in patients

In normals all the cortical components peaking within 50 ms post-stimulus were optimally explained by two EDs. A tangential dipole, modelling both P20-N20 and N30-P27, was located close to the posterior bank of the central sulcus; a radially oriented dipole, explaining the P22 and N33 peaks, was situated in the peri-rolandic cortex (crown of pre or post-central gyrus) (Fig. 2). The residual variance (RV) was always below 6.5%. Owing to their much greater strength, EDs of 'giant' SEPs

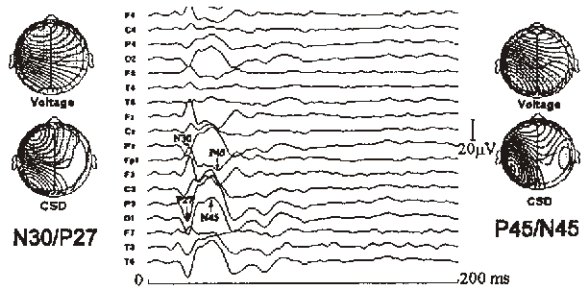

Fig. 3. Right median nerve SEPs in patient 3 affected with cortical myoclonus. Negativity upward. Frontal-parietal N30-P27 is greatly enhanced. In addition, a very large tangential component is observed with a maximum of negativity (49.6 μV) in the parietal area and a latency of around 45 ms. Such a component was never recorded in our normal subjects and is indicated as P45-N45. The voltage and CSD maps clearly show the dipolar distribution of these giant components.

were more easily modelled than those of normal SEPs and the RVs obtained were substantially lower, always below 2%.

The tangential and radial dipoles obtained in normals were observed in all the patients except those with 'extreme' N60. The tangential dipole accounted not only for the 'giant' N30-P27, but

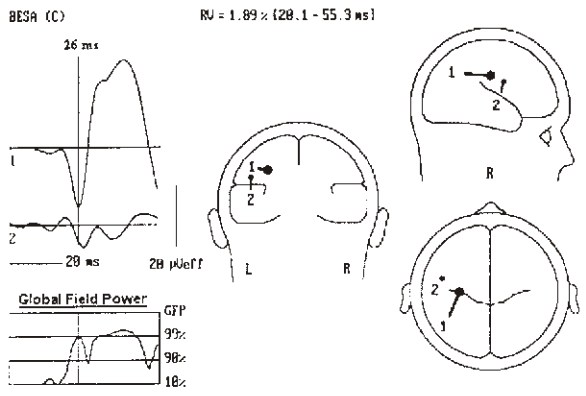

Fig. 4. Two dipole solution for right median nerve SEPs recorded from patient 3. On the left, the dipole source potentials are shown. On the right, location of the equivalent dipoles. Dipole 1 is tangential, located close to the central sulcus and much bigger in strength than dipole 2: it models giant N30-P27 and N45-P45. Dipole 2 is radially oriented and corresponds to peri-rolandic components P22 and N33. Global Field Power (bottom left) defines signal epochs for dipolar source analysis.

5 of cortical myoclonus; the radial ED fitted the enhanced P22 and N33 or just one of them (as in patients 1 and 2). The extremely enhanced component peaking at around 60 ms in BCECS patients and in the fragile-X patient was explained by two EDs located in proximity to the central sulcus: a mostly tangential one, with a temporal-frontal orientation; a radial one, with a central-lateral orientation (Fig. 6).

None of these dipoles was observed in normal SEPs, in which the N60 component, showing a central-parietal unipolar field, was subtended by a radial dipole with an entirely different orientation

Discussion

In the giant SEPs of all the patients examined (with the exception of the three individuals presenting with 'extreme' middle latency SEPs) it was possible to identify the same components observed in normal SEPs. The detailed analysis of scalp topography performed in the present study significantly improved the modelling of SEPs. These findings extend the observations of previous reports [2,16,18,24] insofar as our group of patients also included a series of cases not affected by cortical myoclonus. A fact worth emphasizing is that, depending on the patient, each tangential and radial component could be selectively and independently enhanced, leading to a great variability in the morphology of giant SEPs. This implies that the neuronal hyperexcitability leading to giant SEPs can affect each SEP generator independently, as already suggested by Ikeda et al. [18]. Another remarkable finding is the tangential frontal-parietal P45-N45 recorded in some patients with cortical myoclonus: this component was never observed in our normal controls. However, a recent paper [25] indicated that such a component can be identified in normal SEPs provided a high resolution technique is used. It is our impression that this component, of low amplitude in normal conditions, can become manifest when there is a selective increase of excitability of its generator, as is the case with giant SEPs. Such a finding corroborates the view that analysis of giant SEPs can help in elucidating

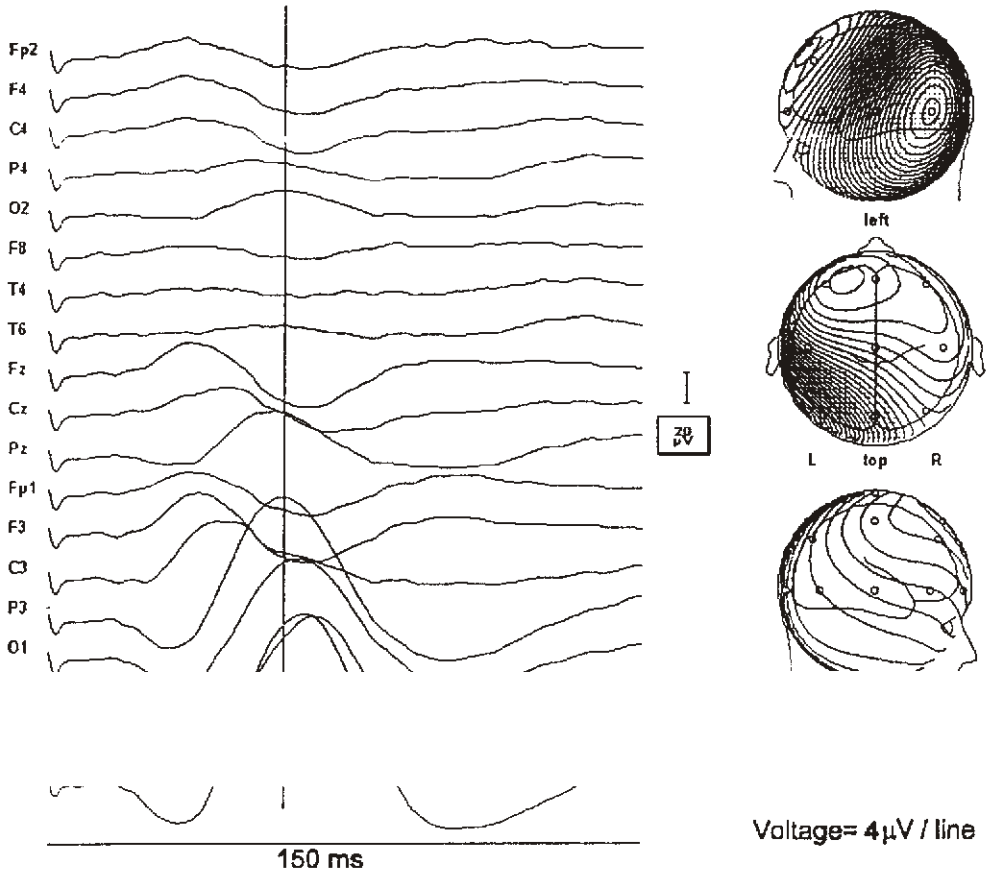

Fig. 5. Right median nerve SEPs in patient 9 affected with BCECS. On the left are SEP traces. A very much enlarged ('extreme') negative component (105 μV) is observed at a latency of about 60 ms with a temporal-frontal dipolar configuration (frozen map on the right). Such a tangential orientation is different from the radial field of component N60 observed in normal SEPs, but is similar to the scalp distribution of the rolandic spikes recorded in this patient.

those features of normal SEPs that are not easily seen in normal subjects. One previous study analysed scalp topography and dipole modelling of giant SEPs in cortical myoclonus [24]. The authors concluded that only the initial components (within approximately the first 30 ms) correspond to the physiological potentials recorded in normals, while later components were explained in terms of hyperpolarization of cortical neurones, similar to that associated with interictal epileptic spikes. Nonetheless, it is clear from their figures that a component quoted as Np/Pf corresponds to component P45-N45 observed in some of our myoclonic patients, with regard to both its scalp field configuration and dipole position. This finding confirms our hypothesis that all the components of giant SEPs originate from an abnormal enhancement of normal SEPs.

Spatio-temporal dipole modelling of giant SEPs allowed better differentiation of cortical generators which are closely located and whose activity can produce similar potential fields. As an example, tangential components P20-N20, N30-P27, P45-N45 all arise from tangential dipoles across the central sulcus, most likely located in area 3b. They partly overlap in time, but can be differentiated on the basis of spatio-temporal modelling.

A word of caution is required in analysing the results in the paediatric patients because of the maturational changes occurring in SEP patterns

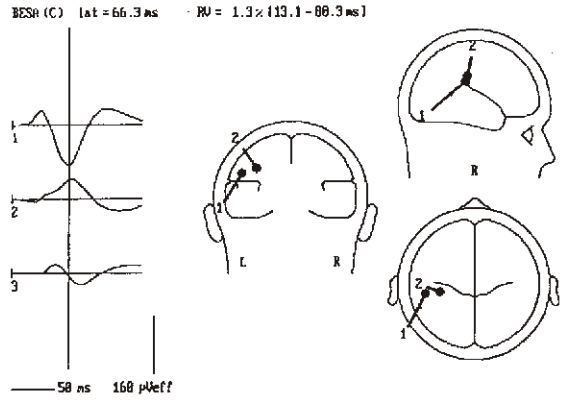

Fig. 6. A two dipole model of 'extreme' median nerve SEPs

locations on the right. Dipole 1 is mostly tangential, with a temporal-frontal orientation; dipole 2 is radially oriented. Both dipoles are located on the posterior bank of the central sulcus.

and of the small sample of our normal paediatric

normal children. The peak at 60 ms had an amplitude far greater than other giant SEPs: it was qualified as 'extreme' [15] and its scalp topography and dipolar modelling were different from those of component N60 recorded in normal SEPs. Its features were those of the spontaneous and tactile-evoked spikes and therefore could be attributed to a cerebral source non-active in normal SEPs.

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