Frontal phasic and oscillatory generators of the N30 somatosensory evoked potential

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The N30 component of somatosensory evoked potentials has been recognized as a crucial index of brain somatosensory processing and has been increasingly used clinically. Previously, we have shown that the N30 is accompanied by both an increase of the power spectrum of the ongoing beta-gamma EEG (event related synchronization, ERS) and by a reorganization (phase-locking) of the spontaneous phase of this rhythm (inter-trials coherency, ITC). In order to localize its sources taking into account both the phasic and oscillatory aspects of the phenomenon, we here apply swLORETA methods on averaged signals of the event-related potential (ERP) from a 128 scalp-electrodes array in time domain and also on raw EEG signals in frequency domain at the N30 peak latency. We demonstrate that the two different mechanisms that generate the N30 component power increase (ERS) and phase locking (ITC) across EEG trials are spatially localized in overlapping areas in the precentral cortex, namely the motor cortex (BA4) and the premotor cortex (BA6). From this common region, the generator of the N30 event-related potential expands toward the posterior part of BA4, the anterior part of BA6 and the prefrontal cortex (BA9). These latter areas also present significant ITC sources in the beta-gamma frequency range, but without significant power increase of this rhythm. This demonstrates that N30 results from network activity that depends on distinct oscillating and phasic generators localized in the frontal cortex.

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Introduction

The identification of distinct somatosensory evoked potentials (SEP) components represents an asset for accurate neurological diagnosis in patients with focal brain disorders (Amanatini et al., 2005; Logi et al., 2003; Mauguiere et al., 1983a, b). The origin and physiological role of subcortical SEP components have been reasonably well documented (Desmedt and Cheron, 1981a, b; Hashimoto et al., 1984) and successfully used in clinical investigations (Di Lazzaro et al., 1995; Valeriani et al., 1995). However, identification of particular generators of SEP components remains arduous and controversial once the afferent volley enters the cortex (Barba and Valeriani, 2004; Barba et al., 2008; Kanovsky et al., 2003).

According to a unifying model SEPs recorded over the anterior and posterior banks of the central sulcus reflect the activation of a single common generator situated in the parietal lobe (Allison et al., 1989; Allison et al., 1991; Broughton, 1969; Coff et al., 1977; Wood et al., 1988). In this line, the most consistent negative component, namely the frontal N30, has been considered as the mirror image of the parietal P25–27 component. This view has been challenged by a series of evidence demonstrating the specific involvement of basal ganglia circuitry in the modulation of the frontal N30 independently from the concomitant parietal components (Cheron et al., 2000, for a review). Notably, some studies have been shown that the amplitude of the frontal N30 component is specifically decreased in patients with Parkinson’s disease (Cheron et al., 1994; Rossini et al., 1993), though this has been debated (Garcia et al., 1995; Huttunen and Teravainen, 1993). Conversely, N30 amplitude has been found to be increased in dystonia (Kanovsky et al., 1997; Reilly et al., 1992). Moreover, there has been much discussion on the application of this SEP wave as a physiological index for modulatory loop control (dopaminergic dependent) exerted by the basal ganglia on the cortical mantle based on the reported effect of dopaminergic and deep brain stimulation treatments on N30 amplitude in Parkinsonian patients (Cheron, 1999; Cheron et al., 1994; Onofrj et al., 1995; Pierantozzi et al., 1999). Recent clinical data seem to corroborate this type of modulation (Arabata et al., 2007; Beniczky et al., 2007; Fukuda et al., 2003; Murase et al., 2000). However, two main uncertainties currently limit the clinical use of the N30, namely generation mechanism and generator source(s) location.

Recently, we have demonstrated that the N30 SEP component was accompanied by an increase of the power spectrum of beta-gamma rhythm peaking at 30 Hz and by a concomitant increase of the inter trials coherence (ITC) at this frequency band (Cheron et al., 2007). Pure phase-locking of the beta-gamma rhythm was found in a large
percentage of the trials. We also showed that concomitant flexion of the stimulated hand impinges such temporal concentration of the ongoing beta-gamma EEG oscillations and abolishes the N30 component throughout their wide topographical extent over the scalp (Cebolla et al., 2009). This phase-locking mechanism should thus be integrated in the search for generator source location.

The search for N30 generator(s) location has been undertaken through invasive recordings or dipole source estimation methods. However, none of these approaches has reached a definitive consensus. One of the crucial, disputed points concerning intracortical scalp (Cebolla et al., 2009). This phase-locking mechanism should thus be integrated in the search for generator source location.

The following points.

Motors Responses and Electric Stimulation. The SEPs were obtained by averaging at the latency and frequency information of the oscillations.

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The following points.

Materials and methods

Subjects and conditions

The data were collected from 13 normal volunteers (7 females and 6 males, mean age: 28.2 ± 7.6 years). They were in good health, free from neurological disease, and had given informed consent to take part in the study, which was approved by the local ethics committee. The SEPs were recorded at rest with the eyes closed.

Stimulation, recording parameters and SEP

The stimuli were 0.2 ms square electrical pulses delivered through a pair of Ag-AgCl electrodes cup to the left median nerve at wrist. The intensity was adjusted for eliciting visible small thumb twitches. Random stimuli intervals (0.5–2 s range) were used throughout the experiment.

EEG was recorded in 128 channels (ANT system, The Netherlands) at a sampling frequency of 2048 Hz and with a resolution of 22 bits (71.5 nV per bit). An active-shield cap using 128 Ag/AgCl sintered ring electrodes and shielded co-axial cables (5–10 electrode system placements) was comfortably adjusted to subject head. All electrodes were referred to the contralateral earlobe. Offline, data treatment was performed by means of ASA software (ANT system, The Netherlands) and in-house MATLAB-based tools. DC offset was firstly removed. Then ocular and any other remaining artifacts were rejected by carefully visual inspection. SEPs were obtained by averaging at around 400 trials per subject of 200 ms of duration each. The successive steps of the methodology used for the treatment of the data are illustrated in Fig. 1, which graphically summarizes the following points.

Time frequency analysis of EEG single trials

To detect and characterize EEG oscillations modulated by the electrical stimulation we applied Hilbert transform analysis (Bendat and Piersol, 2000) on the scalp signal. The Hilbert transform preserves both the latency and frequency information of the oscillations.

We first calculated the analytic signal: a complex spectro-temporal representation of the original signal that defines its amplitude A(t) and phase ψ(t) as a function of time and frequency. Thus, for an arbitrary signal s(t) the analytic signal H(t) for a centered frequency ω at time t is a complex function defined as:

\[ H(t) = s(t) + j\tilde{s}(t) \]

where \( s(t) \) is a band pass filtered version of \( s(t) \) at the centered frequency \( w \), \( j \) is the imaginary unit and \( \tilde{s}(t) \) is the Hilbert transform of the signal \( s(t) \) at centered frequency \( \omega \).

\[ \tilde{s}(t) = \int_{-\infty}^{\infty} \frac{s(t)}{t-t'} dt \]

Subsequently the instantaneous amplitude A(t) and the instantaneous phase ψ(t) are obtained as follows:

\[ A(t) = \sqrt{s(t)^2 + \tilde{s}(t)^2} \]

\[ \psi(t) = \arctan \left( \frac{\tilde{s}(t)}{s(t)} \right) \]

Eq. (1) was used to compute the baseline-normalized spectrogram or event-related spectral perturbation (ERSP) and the inter-trial coherence (ITC).

For ERSP measurements

ERSP may correspond to a narrow-band of event-related desynchronization (ERD) or synchronization (ERS). Hilbert transform was here applied in frequency bands of 2 Hz of width from 1 Hz to 50 Hz on each epoch. When instantaneous amplitude (Eq. (3)) is squared it becomes instantaneous spectral power. Normalization on each epoch by its respective mean baseline spectral value and then averaging across data trials were performed (Delorme and Makeig, 2004). Each trial consists of samples from -200 ms before up to 200 ms after the stimulus.

ERSP image provides a color code where each template pixel indicates the power (in μV²/Hz) at a preset frequency w and latency t relative to the stimulation onset. Typically, for n trials.

\[ ERSP(w, t) = \frac{1}{n} \sum_{k=1}^{n} H_k(w, t)H_k^*(w, t) \]

where \( H_k(w, t) \) is the analytical signal corresponding to the n-th trial at frequency w and time t computed using the Hilbert Transform and * indicates the complex conjugate.

For ITC measurements

ITC is a frequency-domain measure of the partial or exact synchronization of activity at a particular latency and frequency to a set of experimental events to which EEG data trials are time locked. This measure corresponds to the ‘phase locking factor’ described in (Tallon-Baudry et al., 1996). The term ITC refers here to its interpretation as the event-related phase coherence (ITPC), which is defined by:

\[ ITPC(w, t) = \frac{1}{|H_k(w, t)|} \sum_{k=1}^{n} \frac{H_k(w, t)}{|H_k(w, t)|} \]
where \( H_k(w, t) \) is the analytical signal corresponding to the \( n \)th trial at frequency \( w \) and time \( t \) computed using the Hilbert Transform and where \( || \) represents the complex norm. The ITC measure takes values between 0 and 1. A value of 0 represents absence of synchronization between EEG data and the time locking events; a value of 1 indicates their perfect synchronization.

The significance levels of the ITC and ERSP were fixed at 0.001 and assessed using surrogate data by randomly shuffling the single-trial spectral estimates from different latency windows during the baseline period, (EEGlab bootstrap method, (Delorme and Makeig, 2004). In ERSP 2D plots green color refers to absence of significant power perturbation \( (p>0.001) \) and progressive blue or red shades refer to significant ERD and ERS, respectively, for a determined frequency and time interval.

In ITC 2D plots, blue color refers to non-significant phase consistency \([0, 0.2\) values], and progressive green to red shades significant values \( (p<0.001) \) \([0.2, 1\) values] for a determined frequency and time interval (Delorme and Makeig, 2004; Makeig et al., 2004a, for a review).

Time domain source analysis of averaged activity

Among source reconstruction methods, the distributed inverse solution method is an interesting tool for modeling spatially distinct source activities without prior knowledge about the anatomical location of the generators. The Standardized Low Resolution Magnetic Tomography (sLORETA) method introduced by Pascual-Marqui in 2002 provides statistical parametric maps related to the reliability of the estimated current source density distribution. It shows exact topographic properties with zero-localization error for single dipoles in noiseless simulated data (for more specific details and experimental validation see (Pascual-Marqui; 2002; Pascual-Marqui et al., 2002; Wagner et al., 2004)). A recent version of the method, swLORETA (Standardized Weighted Low Resolution Electromagnetic Tomography) has enabled the accurate reconstruction of surface and deep current sources in simulated data even in the presence of noise and when two dipoles are simultaneously actives. This was achieved by incorporating a singular value decomposition based lead field weighting that compensates for the varying sensitivity of the sensors to current sources at different depths (Palmero-Soler et al., 2007). In order to map the generators of the N30 we computed the swLORETA solution for its time peak period. The swLORETA solution was computed using a 3D grid of points (or voxels) that represent possible sources of the signal. Furthermore, the solution was restricted to the grey matter by taking only voxels in which the probability of grey matter was unequal zero (based on the probabilistic brain tissue maps available from the MNI (Collins et al., 1994; Evans and Collins, 1993a; Mazziotta et al., 1995). Finally, the 2030 grid points (5.00-mm grid spacing) and the recording array (128 electrodes) were placed in registration with the Collins 27 MRI produced by the Montreal Neurological Institute (Evans and Collins, 1993b); The Boundary Element Model (BEM) was used for solving the forward problem (Geselowitz, 1967). The final coordinates \((x, y, z)\), Talairach coordinates) we provided for labeling the corresponding brain areas were based on Talairach atlas. These coordinates were obtained by placing the corresponding Talairach makers in the Collins brain using the ASA software. Doing so, it is possible to obtain the Talairach coordinates of every voxel inside the brain for later comparison with a Talairach atlas (Lancaster et al., 2000).
**Time frequency source analysis of EEG single trials**

After finding the frequency of interest using the ERPS and ITC analysis over the scalp signal, we focused our interest on the brain areas that exhibit an ERPS around the previous defined frequency. To this end the analytic signal at the target frequency was computed for each EEG sensor channel for the nth trial of the experiment. After that the swLORETA was applied to the analytic signals for each individual trial. The ERPS and ITC in brain space over the n trials were then calculated as (Lin et al., 2004):

\[
\text{ERPS}(w, t) = \frac{1}{n} \sum_{i=1}^{n} \text{diag} (H(w, t)H^*(w, t))
\]

\[
\text{ITC}(w, t) = \frac{1}{n} \sum_{i=1}^{n} \frac{H_i(w, t)}{H_i(w, t)}
\]

where \(H_i(w, t)\) is a row vector containing the analytic signal at time \(t\) and frequency \(w\) of the swLORETA estimates, \(n\) represents the number of trials, \(\text{ERPS}(w, t)\) represents the power spectrum of the swLORETA estimates, \(\text{diag}(M)\) is a vector formed by the diagonal elements of the matrix \(M\) and \(|A|\) indicate the norm of vector \(A\) and ITC represents the inter trials coherence of the swLORETA estimates.

**Statistical analysis**

To find the generators of the N30 components a rigorous method was used to establish a threshold value that helps in identifying statistical significance of the current density magnitude. To do so, a one-sample t-test (one-tailed t-test) with the null hypothesis of non-related mean current density related to the experimental manipulations was performed for all the subjects for each voxel of the source space at the N30 latency given a total of 2030 t-tests.

Because we are not protected from the effect of non-normality by the central limit theorem, and because it is difficult to give evidence that the modulus of the swLORETA solution follows a normal distribution, especially in experiments where there is a relative low degree of freedom it is necessary to use a statistical method that does not rely on the normality assumption. Moreover, since we are performing 2030 simultaneous t-tests (one for each voxel) we chose a method that controls for the false positives that may result from performing multiple hypothesis tests. Nonparametric permutation methods provide just such a framework and have been proposed and implemented by several authors in functional neuroimaging studies (e.g., (Arndt et al., 1996; Brammer et al., 1997; Holmes et al., 1996). The specific methods used here are fully explained in the paper of Nichols and Holmes (2002) so we shall only give a brief introduction here. In contrast to the parametric approaches where the statistic must have a known null distributional form, the permutation approach uses the data itself to generate the probability distribution for testing against the null hypothesis.

In our experiment this approach is implemented as follows: First we create a difference image by subtracting the modulus of the swLORETA solution at the time of the N30 component (active condition) and the modulus of the swLORETA solution at –200ms before stimulus onset and 5 ms of duration (baseline condition). From this difference image we compute T-image (T value per voxel) by performing a one-sample t-test (one-tailed) for each voxel of the source space. The null hypothesis is that the distribution of the voxel values of the subjects’ difference images has zero mean. However, instead of assuming a normal distribution to assess the statistical significance of the T score at each voxel, we use the permutation method. To do so, if we consider each voxel in the difference image, if the null hypothesis is true for that voxel (i.e. there is no significant group activation) multiplying any of the subjects’ values at that voxel by –1 will have no effect, the null hypothesis will still be true. Because there are N subjects in our study, there are \(2^N\) ways of choosing which values to be negated (relabeling). Using this relabeling we can create an empirical distribution test against the null hypothesis.

To create the empirical distribution for each relabeled \(i = 1, K, N\), the maximal statistic \(t^\text{max}\) is store in an histogram where \(t^\text{max}\) is define as: \(t^\text{max} = \max(t_i)\) for the \(i\) relabeling. These values give the permutation distribution for \(t^\text{max}\) named the maximal statistic. After 8192 relabeling the 95th percentile of the permutation distribution for \(t^\text{max}\) define the 0.05 level corrected significance threshold (Holmes et al., 1996). In other word we can reject the null hypothesis for any voxel with \(t\)-values of the un-permuted T image (all subject multiply +1) greater than the 95th percentile of the permutation distribution for \(t^\text{max}\) (Holmes et al., 1996). Region of interest (ROI) definition was based on the coordinates of the local maximum of the \(t\) values and a cube of 7 mm around that value as adapted from fMRI studies (Fox et al., 2009). The same statistical method was applied for time and frequency time source analysis.

**Results**

**Time domain source analysis of averaged activity**

The frontal N30 SEP component was easily identified in each of the 13 subjects (mean peak latency of 32.6±3.1 ms; mean peak amplitude of 5.4±2.1 μV). Fig. 2A (right) illustrates the scalp potential topography obtained with 128 electrodes array of the related N30 component (left) in one representative subject. This shows the classical mapping of this widespread negative component extending from the contralateral frontal pole toward ipsilateral central and parietal area (Desmedt and Cheron, 1980).

Figs. 3A and 4A illustrate the pattern of brain source activation found by swLORETA explaining the topographical distribution of the N30 ERP generators. This representation was supported by statistical nonparametric maps of inverse solution in time domain calculated for all subjects revealing significant contribution of precentral areas with two maxima at BA4 (55.8, −13.4, 41.0) and BA6 (34.3, 10.8, 47.5) and extending from BA4/BA3 border (57.8, −15.5, 28.4) to the prefrontal cortex (BA9) (37.1, 11.9, 38.6).

**Time frequency analysis of EEG single trials**

Time frequency analysis performed via Hilbert transform demonstrated that the frontal N30 was accompanied by a transient power increase and a significant ITC in the 30–45 Hz frequency band peaking at N30 peak latency (Fig. 2B, C right). This is consistent with previous findings (Cebolla et al., 2009; Cheron et al., 2007). Fig. 2B, (right) illustrates the topography of this frequency band behavior for one representative subject, indicating that for this subject the main power increase (ERS) was distributed in fronto-lateral areas contralateral to the stimulation. The maximal ITC was also present in the frontal pole, though its topography was more symmetric and confined to the anterior regions (Fig. 1C, right). It is important to note that at the scalp level there is a mixing of multiple processes caused by volume conduction (Makeig et al., 2004b) for which a power change may produce a phase-locking increase.

**Time frequency source analysis of EEG single trials**

In order to avoid this type of uncertainty swLORETA was separately applied on each EEG trial for the determination of the ERS and ITC source, respectively. The corresponding brain source localization solution to the dynamic behavior of the spontaneous EEG activity corresponding to the 30–45 Hz frequency band at the N30 peak latency is illustrated in Figs. 3B, C and 4B, C. As for the representation of the ERP generators (Figs. 3A, 4A), the ERS sources (Figs. 3B, 4B) and
the ITC sources (Figs. 3C, 4C) correspond to statistical nonparametric maps in frequency domain calculated with all subjects.

Concerning ERS sources, they are located in a more restricted precentral region than those corresponding to the ERP sources. There is a maximum situated at BA6 (39.7, −3.8, 48.2) and this cluster extends to BA4 (55.8, −13.4, 41.0). Concerning ITC sources, there is a rostro-caudal extension of precentral brain activation that resembles that of the ERP with two maxima situated at BA6 (46.8, −8.8, 36.4) and BA9 (37.1, 11.9, 38.6), and a significant activation of BA4 (55.8, −13.4, 41.0).

**Discussion**

**Motor (BA4), premotor (BA6) and prefrontal (BA9) cortex as N30 generators**

The presence of a N30 generator in the motor and premotor cortex is supported by a large set of evidences coming from experimental (Cheron and Borenstein, 1987, 1992; Desmedt and Cheron, 1980; Taylor and Murphy, 2008) and clinical studies (Mauguiere and Desmedt, 1991; Mauguiere et al., 1983a; Rossini et al., 1989; Slimp et al., 1986). Nevertheless, no consensus has yet been reached about the exact location of the N30 generator(s) (Barba and Valeriani, 2004; Barba et al., 2005; Kawamura et al., 1996).

According to the “mirror” concept of the SEP components the unique generator site is situated in the postcentral gyrus (Broughton, 1969; Goff et al., 1977; Wood et al., 1988), and the precentral areas are not involved in the generation of the N30. In the same line, (Allison et al., 1989; Allison et al., 1991) have confirmed the postcentral location of the N30 generator by combining cortical surface and transcortical recordings. In contrast, the intracerebral recordings performed in the pre-surgical phase of epilepsy surgery by (Kanovsky et al., 2003) support the existence of separate N30 generators within the premotor cortex either mesially or dorsolaterally (BA6, BA8 and their borders). Moreover, intracerebral SEP recordings performed at different locations

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**Fig. 2.** Time (A) and time-frequency analysis (B, C) of the SEP for a representative subject. A on the left side: event-related potential recorded from F4 channel during median nerve stimulation (open arrow) at the wrist with N30 component indexed by black arrow and P14 component indexed by small open triangle. A on the right side: Potential scalp distribution at the N30 peak latency (32.0 ms) from 128 channels. B on the left side: Event-related spectral perturbation for F4 channel. Note that main perturbation occurs in the beta-gamma range (30–45 Hz) and coincides with the N30 latency peak. B on the right side: event-related spectral perturbation topography at the N30 peak latency for the beta-gamma range (30–45 Hz) from 128 channels. The main perturbation occurs at fronto-lateral areas contralateral to the stimulation. C on the left side: Inter-trial coherence for F4 channel. Similarly to the ERSP the greatest values of ITC occur within the beta-gamma range (30–45). C on the right side: Inter-trial coherence topography at the N30 peak latency for the beta-gamma range (30–45 Hz) from 128 channels. The highest values of ITC are present in the frontal pole as ERSP, though their topography is more symmetric and confined to the anterior regions. Consider that at the scalp level there is a mixing of multiple processes caused by volume conduction (Makeig et al., 2004a) then power change may produce phase-locking increase.
within the depth of primary somatosensory and primary motor cortex did not support postcentral N30 generators (Balzano et al., 2004). These authors rather suggested that the recorded negative component peaking at 31 ms may reflect the activity of the lateral portion of the precentral gyrus (Balzano et al., 2004). These findings are in accordance with the present data and reinforce the idea that N30 component would reflect a more complex network than a single mirror image of a postcentral generator. Although the postcentral cortex has never been revealed as a maximum source by the successive analysis performed in the present study, the contribution of a dipolar source at 30 ms involved in the processing of the somatosensory input and situated in the primary somatosensory cortex (area 3b) (Allison et al., 1989; Allison et al., 1991) might not be entirely rejected on the basis of the present results. Indeed, the distinctive contribution of a tangential P30–N30 dipole situated in area 3b and the other oscillating generators of the N30 located outside of the somatosensory cortex and revealed in the present paper are not technically possible as LORETA selects the pattern of activation showing the smoothest solution which best matches best the whole topographical voltage distribution at the latency of the N30 phenomenon.

The present localization study corroborates the idea that the N30 wave reflects a first stage in sensorimotor integration processes (Cheron et al., 2000; Hallett, 2000; Rossi et al., 2002; Rossini et al., 1999). This hypothesis is also supported by a wealth of clinical reports (Abbruzzese and Berardelli, 2003; Berardelli et al., 1998; Cheron et al., 1994; Frasson et al., 2001; Murase et al., 2000; Reilly et al., 1992; Rossi et al., 2005; Rossini et al., 1998; Olivelli et al., 1999) and peculiar physiological behaviors of the N30 wave (Cebolla et al., 2005; Cheron and Borenstein, 1987, 1992; Rossi et al., 2002; Urushihara et al., 2006).

The precentral localization of the N30 may also be related to the nature of the peripheral inputs. In case of median nerve stimulation at the wrist, skin, joint and muscle afferents are stimulated and may potentially contribute to the N30 response. Goldring and Ratcheson (1972) have shown that in passive and active movement some neurons respond with a short latency in the motor cortex, indicating that joint and muscle afferent might contribute to the N30. As stimulation of the digital nerves avoiding muscle afferents evoked clear N30 component (Desmedt and Cheron, 1980) and as pure cutaneous afferent stimulation fails to evoke a robust N30 (Restuccia et al., 2002), the contribution of joint afferents appears as the more efficient input to evoke the N30. This idea is reinforced by anatomical studies showing that finger joint inputs reach not only in the sensory areas but also premotor cortex (Strick and Preston, 1982) and that neurons projecting from thalamus to precentral cortex respond most powerfully to joint movement or deep pressure rather than to cutaneous stimuli (Lemon and van der Burg, 1979). All these arguments indicate that the N30 component may reflect proprioceptive integration in precentral cortex.

ERS and ITC generators revealed by time frequency domain source analysis

A methodological key point of the present approach was the application of ERSP and ITC time frequency domain measurements in source localization with swLORETA. This approach was performed for the first time and has permitted to give a spatial identity to the two different mechanisms at the basis of the N30 emergence (Cebolla et al., 2009; Cheron et al., 2007). To some extent, the present results
confirm the relative functional independence of an oscillating mechanism with respect to a phasic mechanism. It is generally accepted, that if an ERP is generated by phase reset of ongoing rhythms, the neural sources of the ERP and those of ongoing rhythms generating it are the same (Sauseng et al., 2007). Here, this condition was thus respected for BA4, BA6 and BA9. However, BA9 was not implicated as an ERP source and could thus correspond to a pure phase-locking generator. In other paradigms, phase-locking phenomenon at the basis of the oscillating source is often supported by long range neuronal synchronization implicating communication between distinct areas (Singer, 1999). This is consistent with the findings of Kanovsky et al. (2003) describing separated generators within the frontal cortex (BA6 and BA8). These intracortical N30 recordings also reproduced previous gating protocols (Cheron and Borenstein, 1987, 1992). In particular, the mental movement paradigm inducing a blood flow increase in the SMA (BA6) (Roland et al., 1980) produced a specific gating of the N30 without affecting the postcentral components (Cheron and Borenstein, 1992). This specific N30 suppression reproduced by intracortical SMA recordings (Kanovsky et al., 2003) reinforces the present localization of a phasic and an oscillating generator in the precentral area.

The interpretation of the intracortical N30 recording is complicated by difficulties in recording polarity-reversal potentials in the frontal lobe (Barba et al., 2001; Barba et al., 2005; Barba et al., 2003). Because of the anatomic conformation of the cortex, the polarity-reversal recording may be highly difficult if not impossible. However, in addition to the gating approach a large set of evidence has been accumulated in favor of a precentral origin of the N30, namely (1) the N30 amplitude depends on motor cortex excitability (Rossini et al., 1991) which corroborates the present findings of N30 generators in BA4, (2) transcranial magnetic stimulation (TMS) of the premotor cortex at very low rate produced a specific N30 amplitude increase interpreted as an increase in premotor cortex inhibition (Hosono et al., 2008; Urushihara et al., 2006), corroborating BA6 as a N30 generator (3) basal ganglia stimulation induced selective increase of N30 amplitude in Parkinsonian patients (Pierantozzi et al., 1999) (4) apomorphine injection in some groups of Parkinsonian patients produced a specific increase of the N30 amplitude (Cheron et al., 1994; Rossini et al., 1995). However, this latter evidence has been contradicted by other studies which failed to find N30 reduction when comparing Parkinsonian patients with normal subjects or when comparing the N30 amplitude of the most and the less affected side in patients with hemiparkinsonism (Garcia et al., 1995; Huttunen and Teravainen, 1993; Mauguiere et al., 1993). In addition, eventual N30 increase associated with subcutaneous injection of apomorphine did not reach statistical significance in the study of Mauguiere et al. (1993). The same group (Onofri et al., 1995) also reported that in spite of positive clinical effects on motor performance of acute or chronic administration of L-DOPA and bromocriptine in Parkinsonian patients, the N30 amplitude remained unchanged.

The N30 amplitude increase in presence of increasing inhibition produced by TMS and conversely a N30 decrease in presence of increasing excitation of premotor and motor areas produced by movement execution (Cheron and Borenstein, 1987) or mental imagery (Cheron and Borenstein, 1992) may be explained by the inhibition-timing hypothesis of Klimesch et al. (2007). Although afferent input plays an important role in the control of intracortical inhibition of the motor cortex (Ridding and Rothwell, 1999), these authors have shown that motor imagery failed to produce change in cortical inhibition. This indicates that N30 amplitude decrease during movement and motor imagery could be induced by different mechanisms. Interestingly, TMS stimulation applied to the precentral
cortex also induced an increase in blood flow in the prefrontal cortex (Urushihara et al., 2006), indicating that the N30 oscillating source localized in this region may also contribute to the N30 plasticity.

The existence of beta and gamma oscillations in the sensorimotor cortex has been largely supported by neurophysiological experiments in monkey (Murthy and Fetz, 1992; Sanes and Donoghue, 1993) and in human (Jasper and Penfield, 1949; Conway et al., 1995; Salenius et al., 1997; Salmelin et al., 1995a; Salmelin et al., 1995b; Salmelin and Hari, 1994a, b). Interestingly, it has been shown in vitro that some beta oscillations originated from the cortical layer V of the sensory and motor cortex may be generated by non phasic–synaptic mechanisms (Roopun et al., 2006). This latter endogenous rhythm may be phase-locked by peripheral input acting on gap junction conductance inducing rapid switch from in to out of phase oscillation, a mechanism demonstrated in vitro by Hughes et al., 2004 and which may contribute to the N30 ITC generator.

The oscillating generators of the N30 located in the motor cortex (BA4), in the premotor cortex (BA6) and in the pre-frontal cortex (BA9), may be viewed as one part of the cortical network where phase locking of the ongoing oscillation involving the basal ganglia motor circuit (Alexander and Crutcher, 1990) is manifested. Phase resetting of both local field potential and single-unit activity representative of the ongoing motor cortical beta (15–30 Hz) rhythms has been demonstrated using pyramidal tract stimulation in monkeys (Jackson et al., 2002). In humans, this network has been investigated by electrical stimulation of the subthalamic nucleus (STN) in Parkinson’s disease which specifically increase the N30 amplitude (Pierantozzi et al., 1998) and leads to an increase in the SMA (BA6), pre-SMA (BA8) and cingulate cortex (Sestini et al., 2002). Interestingly, BA9 is an associative basal ganglia projection site positively activated (increased glucose metabolism) by STN stimulation in Parkinson patients (Hikker et al., 2004; Kalbe et al., 2009). In this context, resonance in the basal ganglionic-thalamo-cortical loop could be implicated in EEG oscillation triggered by sensory stimulation. Neuronal activity in the 30–80 Hz band acts as pacemaker for sensorimotor integration (Humphries et al., 2006) and is under the control of dopaminergic drive (Cassidy and Brown, 2001; Cassidy et al., 2002; McKay, 1997). In this theoretical framework, we may conclude that the present oscillating generators of the N30 component located in precentral (BA4 and BA6) and the prefrontal (BA9) cortex could be viewed as resulting from the phase-locking of the basal ganglionic-thalamo-cortical loop activity resonating around 30–45 Hz, upon which additional ERS generators located in more restricted parts of BA4 and BA6, (corresponding to recruitment of neurons population by the peripheral stimulus), significantly contribute to N30 genesis.

Conclusion

The present results demonstrate that the N30 phenomenon is produced by activation of BA4, BA6 and BA9. swLORETA applied on the ERS and ITC sources showed that BA4 and BA6 are involved in both ERS and ITC sources while BA9 contribute to the N30 generator only as an ITC source.

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