NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 36 (2007) 522–531

Functional neural dynamics underlying auditory event-related N1 and N1 suppression response

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Received 4 December 2006; revised 7 February 2007; accepted 13 March 2007
Available online 30 March 2007

Presenting tone triplets of identical stimuli preceded by silent intervals of 30 s produces a series of three N1 averaged event-related potentials (ERPs), the first being of greater amplitude (non-suppressed N1) than the second and third ones (suppressed N1). Maximal statistically independent components (ICs) of single-trial multi-electrode scalp EEG responses to triplets were obtained by ICA algorithm, and then each IC was searched for underlying brain structures by LORETA inverse solution, and for oscillatory contributions by time–frequency analysis. Non-suppressed N1 cortical mechanisms were broken down into five ICs, grouped in two time-windows (early-onset and late-onset) involving the participation of temporal, frontal and parietal structures, and sub-serving EEG oscillatory contributions of power enhancement and putative phase concentration of mainly theta, alpha and low beta bands. Suppressed N1 was due to the modulation of two above-mentioned early-onset ICs, involving temporal structures only, and mainly sub-serving oscillatory contributions of phase concentration of theta and alpha. Present results, showing quantifiable changes of IC descriptors – i.e. time window of activation, implied structures and oscillatory contributions – extracted from two distinct brain functional situations (non-suppressed *versus* suppressed N1), give support to the view that ICA is not merely a statistical "latent variables" model when applied to ERPs, but could help to capture underlying specific function subunits of brain dynamics.

Introduction

Brain electrical responses time-locked to events (stimulus, response or behavioural task) have been studied for decades by averaging the event-locked single trials to obtain event-related potentials (ERPs). Although averaged ERPs resemble basic waves, they undergo complex neural dynamic activity that is likely to arise from multiple temporarily and spatially distributed specialized brain sources (Bressler and Kelso, 2001). Hence, it has been suggested that large-scale interaction of these neural contributions to ERPs gives rise to their functional integration, which might lead to support of specific function activities (Friston, 2005). In addition, the relevance of oscillatory activity as a framework for the functional integration of a distributed neural activity has been pointed out (Fries, 2005). Indeed, converging recent evidence showed that a distributed functionally conformed network of neurons might be transiently linked by reciprocal dynamic connections (Varela et al., 2001), thus resulting in multiple feedback loops that give rise to oscillatory neural-based behaviour (Bressler, 2002). Therefore, based on these arguments, underlying neural functional properties given by an ERP are unlikely to be captured solely by studying the representation of the temporal course and scalp features of the averaged electrical activity, but might require identification of their related temporal evolution, cortical topography and oscillatory behaviour (Fogelson et al., 2006), which can only be captured at the single-trial level.

The concept of ERPs as being composed of orchestrated clusters of distributed neural contributions, which transiently integrate to support specific functional activities, has been recently enlarged on the basis of ICA (Independent Component Analysis) results on multi-electrode EEG data (Makeig et al., 2002; Penny et al., 2002). Accordingly, ERPs could be broken down into maximal statistically independent contributions (independent components, ICs), which might be characterised by specific temporo-structural (Makeig et al., 2002; Marco-Pallarés et al., 2005) and frequency domain features (Makeig et al., 2004a). This leads to the proposition that the properties of maximal statistical independence and the multifaceted physiological characterization (in the time-, space- and frequency-domains) of each IC strongly suggest that they might also pick up specific functional brain subunits. However, at present, there is no direct evidence that neural activity identified by an IC intrinsically modulate to functional experimental manipulations, though this would, unequivocally, transfer meaningful functional entity to the given neural activity.

The first objective of this study was to provide evidence that separate specific functional activity of brain computing captured by ICs and their descriptors (i.e. time–structures–frequency) show quantifiable changes in distinct functional situations. To this end,

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Available online on ScienceDirect (www.sciencedirect.com).

1053-8119/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2007.03.027

we selected auditory N1, which in front of identical external repeated stimulation shows reduced amplitude (attenuation or repetitive suppression) (Näätänen, 1992; Friston, 2005). This reduced amplitude is associated with the prevention of the inflow of redundant information from the environment into daily life (Näätänen, 1992). The advantage of this experimental paradigm resides in that, as the stimuli of the sequence are physically identical, functional changes sub-serving N1 amplitude reduction other than the ones experienced by its intrinsic neural substrate can be discarded.

The second objective of this work is to advance on the characterization of functional neural dynamics underlying auditory event-related N1 and N1 suppression response. Auditory N1 ERP involves a complex neural network of several dynamic properties described by temporal, spatial and spectral contributions. Hence, in the time domain, scalp electromagnetic (MEG) (Loveless et al., 1996; McEvoy et al., 1997) studies showed distinct sequential N1 contribution activations, referred to as "early" (~80 ms) and "late" N1 (~130 ms) (Näätänen, 1992). Further, in the spatial domain, N1 are sub-served by a multi-generator process (Naatanen and Picton, 1987), involving temporal (Hari et al., 1980), frontal (Knight et al., 1980), cingulate (Tzourio et al., 1997) and parietal regions (Knight et al., 1980). And, in the frequency domain, the study of the underlying auditory N1 neural oscillatory activity showed the involvement of a multi-frequency phenomenon enclosing enhanced spectral power and phase-resetting of theta and alpha frequency bands at scalp EEG (Jansen et al., 2003; Fuentemilla et al., 2006). In addition, it has been argued that suppressed N1 might be due to the functional modulation of basic N1 processes, such as distinct EEG recovery cycles of N1 "early" and "late" contributions (Loveless et al., 1996), to decreased auditory cortical neuron activity (Rosburg et al., 2006) or to a reduction in scalp theta and alpha phase synchrony together with a disappearance of a concomitant spectral power modulation (Fuentemilla et al., 2006). However, to date, no integrated approach has made a comparative study of auditory N1 and N1 suppressed addressing the behaviour of time–structure–frequency IC descriptors relating to N1 and N1 repetitive suppression, though it could provide new insights in the study of N1 functional neural dynamics.

Here, we tackle these objectives by applying a 3-step approach analysis. The first two steps were based on the combined Independent Component Analysis (ICA) (Bell and Sejnowski, 1995; Jung et al., 2001)+Low-Resolution Tomography (LORETA) (Pascual-Marqui et al., 1994; Pascual-Marqui, 1999) proposed by Marco-Pallarés et al. (2005). ICA has been used to "blindly" identify neural modes describing activity in concurrent electromagnetic activity that is spatially fixed and temporally independent (Makeig et al., 1996), while LORETA analysis of the spatial maps associated with each IC provided solutions to the inverse problem of the neural source location of each component (Marco-Pallarés et al., 2005). In addition, the spectral content of each IC will be studied by computing a single-trial time–frequency analysis (Makeig et al., 2004b).

Material and methods

Subjects

16 right-handed healthy subjects (7 female), 25.4±1.6 years (range, 20–28 years), after complete description of the work, gave their written consent to participate in the study. All subjects had no history of head injury, neurological disease, audiological problems, severe medical illness or drug abuse. The experiment complied with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and was approved by the Ethics Committee of the University of Barcelona.

Stimuli and procedure

Stimuli paradigm consisted of trains of three pure sine-wave tones (1000 Hz, 90 dB, 10 ms rise/fall) where, first two tones (S1 and S2) were standard sounds (75 ms duration) and third tone was randomly ($P=0.5$) a standard (S3) or deviant sound (Dev) (25 ms duration). Intra-train interval was 584 ms and inter-train interval was 30 s. Only those stimuli trains containing three standard tones were analyzed in this study.

Participants sat in a comfortable chair in a dimly lit and electrically and acoustically shielded booth. During the EEG recording, each subject was instructed to perform a visual irrelevant task (reading) to ignore the auditory stimuli and to avoid extra eye movements and blinking.

EEG recording

EEG activity (0.1–70 Hz bandpass; 50 Hz notch filtered) was acquired by a 32-channel amplifier (Synamps, Neuroscan Inc.) at a sampling rate of 500 Hz. EEG electrodes followed the 10–20 position system (FP1, Oz, FP2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6) with ten additional electrodes (FC1, FC2, FT3, FT4, M1, M2, IM1, IM2, TP3, TP4, CP1 and CP2) referenced to the tip of the nose. Impedances were maintained below 5 kΩ during experiment. Ocular movements (EOG) were registered from two electrodes at the outer canthus of each eye. A single ground electrode was attached at AFz.

Event-related potential data analysis

3000-ms EEG epochs were averaged off-line, which included 1000-ms pre-stimulus as a baseline period and S1, S2 and S3 standard tone responses. Exceeding ±100 μV in EEG and/or EOG epochs were excluded automatically. No digital off-line band-pass filter was used for ERP extraction. A total of 823 trials were obtained for the analysis, in which each subject contributed with 69±14 trials (mean±SEM).

Auditory N1 was identified as the largest negative contribution between the 80 and 180 ms time window of the ERPs to the three standard sounds. In each case, the baseline-to-peak value was taken as the magnitude (μV) of the response.

N1 statistical analysis (one-way analysis of variance (ANOVA)) was carried out on mean N1 amplitude measurements at midline frontal (Fz), central (Cz) and parietal (Pz) electrode locations plus left (C3) and right (C4) central electrodes with respect to the pre-stimuli baseline (1000 ms). N1 suppression was assessed by the repeated-measures ANOVA calculation to N1 amplitudes after S1, S2 and S3, in which the factors Electrode (Fz, C3, Cz, C4 and Pz)×Condition (N1 to S1, S2 or S3) to the N1 peak values were compared. Greenhouse–Geisser correction to P values was used when appropriate. Post-hoc comparisons by Student's t-test for paired samples were made to N1 peak values (S1, S2 and S3) within each elec-

trode when the within-subject Condition factor was statistically significant.

Independent component analysis tomography imaging

A ICA-LORETA analysis was applied to the data as proposed in Marco-Pallarés et al. (2005). To that, firstly, data was demeaned and whitened and then the Infomax algorithm was used in independent component analysis of concatenated single-trial data from all subjects (Makeig et al., 1996) and, separately, to each single-subject trials. IC extraction was performed using the EEGLAB (v4.5) software under Matlab 7.0, as described by Delorme and Makeig (2004), to EEG epochs of −100 to 200 ms of each S1, S2 and S3 stimuli. An IC was considered responsible for N1 generation following these constraints: (a) it had a sequence of at least 12 consecutive sampling points (24 ms) (Guthrie and Buchwald, 1991; Grau et al., 1998; Marco-Pallarés et al., 2005) that exceed the threshold cut-off values after computing bootstrap distributions ($P<0.05$), extracted randomly from baseline data and applied 200 times were used, and (b) the activated window ($P<0.05$) coincided with N1 ERP latency range (80–180 ms) of any of the three standard sounds (S1, S2 or S3) responses.

Second, a LORETA analysis was performed with the scalp maps associated with selected ICs that passed restrictions (a) and (b). Only the values greater than 2.5 times the standard deviation of the standardized data (in the LORETA spatial solution) were accepted as being activated (Marco-Pallarés et al., 2005; Gomez et al., 2006).

Event-Related Spectral Perturbations (ERSPs) and Inter-Trial Coherence (ITC)

In a third step of the analysis, for each IC extracted previously, a trial-by-trial time–frequency analysis was computed (1000 ms before S1 to 2000 ms after) by using a sinusoidal moving Hanning-windowed wavelet with linear increased cycles, from 2 cycles for the lowest frequency (3.9 Hz) to 13 cycles to the highest frequency (48.8 Hz) analysed.

Changes in event-related spectral power response were computed by the Event-Related Spectral Perturbation (ERSP) index (Makeig, 1993) (1),

$$\mathrm{ERSP}(f,t) = \frac{1}{n}\sum_{k=1}^{n}\left(F_k(f,t)\right)^2 \quad (1)$$

where, for n trials, $F_k(f, t)$ is the spectral estimate of trial k at frequency f and time t. ERSP showed mean time–frequency values that exceeds significant cut-off threshold extracted from pre-stimulus baseline period.

Event-locked EEG partial phase coherence was computed by the Inter-Trial Coherence index (ITC) (2), analogous to the "phase-locking index" (Tallon-Baudry et al., 1996),

$$\mathrm{ITC}(f,t) = \frac{1}{n}\left|\sum_{k=1}^{n}\frac{F_k(f,t)}{|F_k(f,t)|}\right| \quad (2)$$

where || represents the complex norm. ITC values ranges from 0 to 1, wherein values near to 1 implies almost perfect phase coincidence across trials. To determine the threshold signification of both ERSP and ITC, bootstrap distributions ($P<0.01$), extracted randomly from baseline data and applied 200 times were used (Makeig et al., 2002). ERSP and ITC analysis was computed by using EEGLAB v4.5 (Delorme and Makeig, 2004) under Matlab 7 (The Mathworks, Inc.).

Results

Event-related potentials

All tones (S1, S2 and S3) elicited significant N1 ERP to all electrode locations studied ($P<0.001$). 4 subjects were excluded for the analysis due to technical problems on 4 electrodes (CP1, TP3, CP3 and TP4). Fig. 1 depicts the grand average of ERP waveforms to each stimulus across 12 subjects at Fz, C3, Cz, C4 and Pz electrodes and the scalp topography of the N1 peak amplitude to each stimuli. N1 attenuation was measured by N1 decreased amplitude across

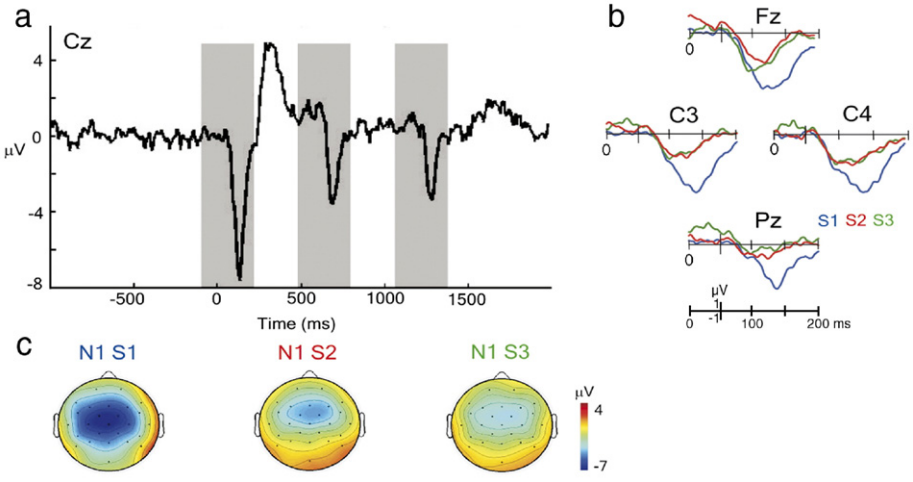

Fig. 1. (a) All subjects' EEG epoch (−1000 to 2000 ms) grand average epoch in response to S1 (red line), S2 (green line) and S3 (blue line) stimuli at Cz. Grey boxes at N1 responses correspond to the EEG time windows computed by ICA. (b) Grand average of Fz, C3, C4 and Pz after S1, S2 and S3 stimuli. (c) Scalp voltage plot of the grand average response after S1, S2 and S3 at N1 peak (identified at N1 vertex at Cz electrode). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

each electrode ($F(2,22)=15.16$, $P<0.001$) in which a main Electrode × Condition interaction effect was observed ($F(8,88)=3.46$, $P<0.05$). This suggested that decreased N1 amplitude was not equivalent at all electrode locations. Post-hoc comparisons were made at each repetition of N1 peak value (S1, S2 and S3) and electrode position. While N1 to S1 was higher than N1 to S2 and S3 ($P<0.01$) except S1 vs. S2 at Fz ($P<0.05$), no significant differences were encountered between N1 amplitudes to S2 and to S3 ($P>0.1$). These results are extended to all electrode locations (S1 vs. S2 and S3, $P<0.05$; S2 vs. S3, $P>0.1$).

Independent components of N1 and N1 suppressed: early and late onset N1 subcomponents

Three independent components (cFTl, cFa and cTl) activated in response to the S1 stimulus (Figs. 2 and 3), but not in response to repeated S2 and S3 stimuli, while two other components were present after all S1, S2 and S3 stimuli presentation (cTrl and cTr) (Fig. 3). IC contributions to ERP variance raised up to 76.3% (Fig. 4a).

Component cFTl (fronto-left temporal) (Fig. 2) showed a late-onset pattern and was significant from 144 to 174 ms stimulus onset ($P<0.05$), which encloses the second half of N1 to S1 stimulus, but was not significant after S2 and S3 stimuli ($P>0.05$). Brain sources underlying cFTl encompassed left temporal and right inferior frontal cortex ($P<0.05$), and its time–frequency analysis showed that theta, alpha and low beta frequency ranges (3.9–19.5 Hz) underlie this component, by both significant ($P<0.01$) enhanced spectral power and ITC increase after S1.

Component cFa (frontal anterior) (Fig. 2) manifested a late onset start and was significant after S1 stimulus onset from 129 to 162 ms ($P<0.05$), also contributing to the second half of the N1 latency range. No significant participation of this component was encountered in response to S2 and S3 stimuli ($P>0.05$). Brain sources of component cFa were placed in anterior cingulate and right inferior frontal cortex ($P<0.05$). cFa time–frequency analysis showed similar patterns as cFTl after S1, i.e., significant ($P<0.01$) enhancement to both spectral power and ITC within theta, alpha and low beta (3.9–19.5 Hz) frequency bands. Moreover, a small,

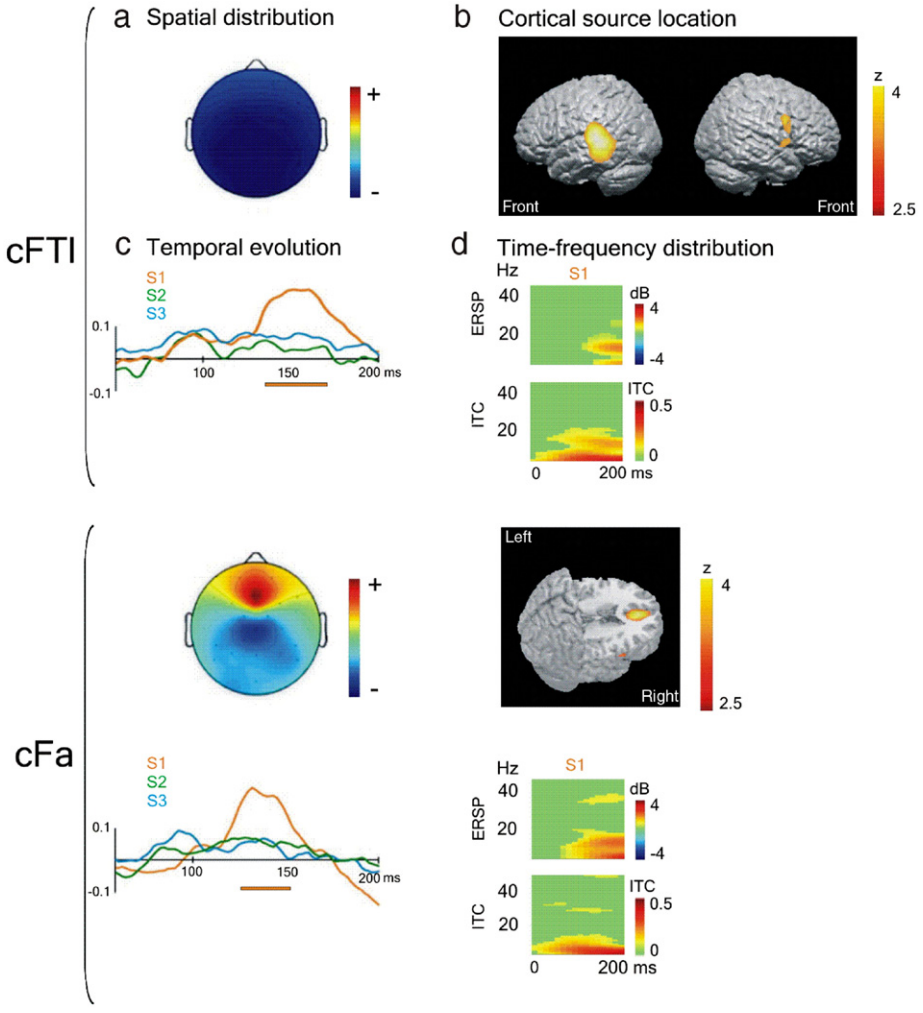

Fig. 2. Late-onset N1 ICs (cFTl and cFa). Each IC had: (a) its scalp spatial distribution, (b) the associated cortical source location ($P<0.05$), (c) its temporal evolution within N1 temporal window appearance – coloured bars below axis denote significant ($P<0.05$) activation, as compared to baseline period – and (d) its significant ($P<0.01$) spectral power (ERSP) and phase alignment (ITC) associated when it was significantly activated, as shown in (c). The apparent ERSP and ITC temporal non-coincidence could be due to a smearing effect of wavelet transformation (Lakatos et al., 2005). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

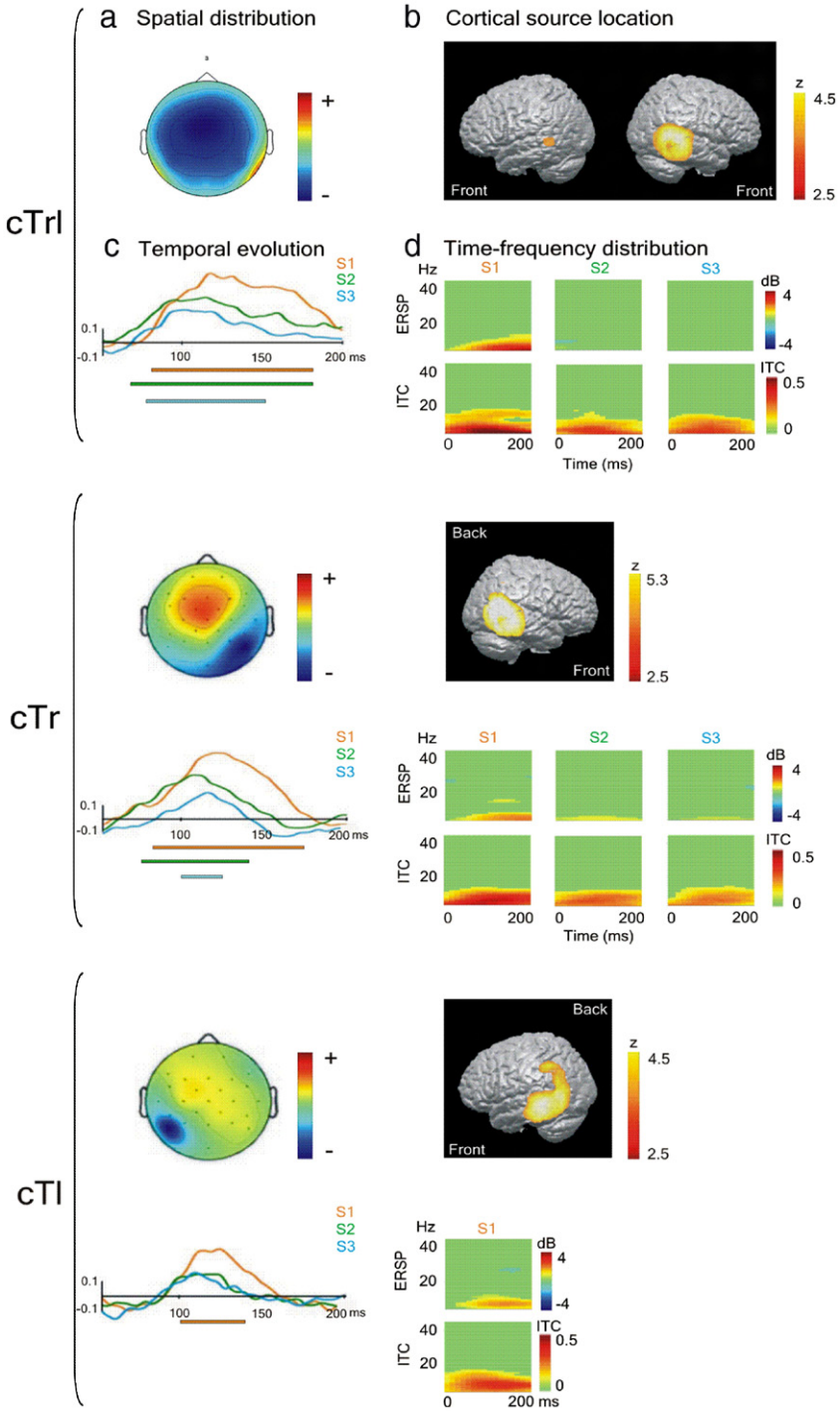

Fig. 3. Early-onset ICs (cTlr, cTr and cTl). Each component had: (a) its scalp spatial distribution, (b) the associated cortical source location ($P<0.05$), (c) its temporal evolution within N1 temporal window appearance – coloured bars below axis denote significant ($P<0.05$) activation as compared to baseline period – and (d) its significant ($P<0.01$) spectral power (ERSP) and phase alignment (ITC) associated when it was significantly activated, as shown in (c). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

but significant ($P<0.01$) induced spectral power enhancement at the gamma band (31.2–37.1 Hz) was also found.

On the other hand, cTrl (right and left temporal) and cTr (right temporal) were activated in response to all S1, S2 and S3 stimuli ($P<0.01$) while cTl (left temporal) was activated after S1 only (Fig. 3). All of the three components showed a similar early-onset activation pattern after the stimuli, thus, emerging at early phase of N1 ERPs and remaining active during most of the N1 wave latency range (that is, cTrl for S1: 90–180 ms, for S2: 76–179 ms and for S3: 94–158 ms; cTr for S1: 91–172 ms, for S2: 80–146 ms and for S3: 98–158 ms; while cTl was active for S1 only: 104–138 ms). Analysis of the cortical sources underlying each component

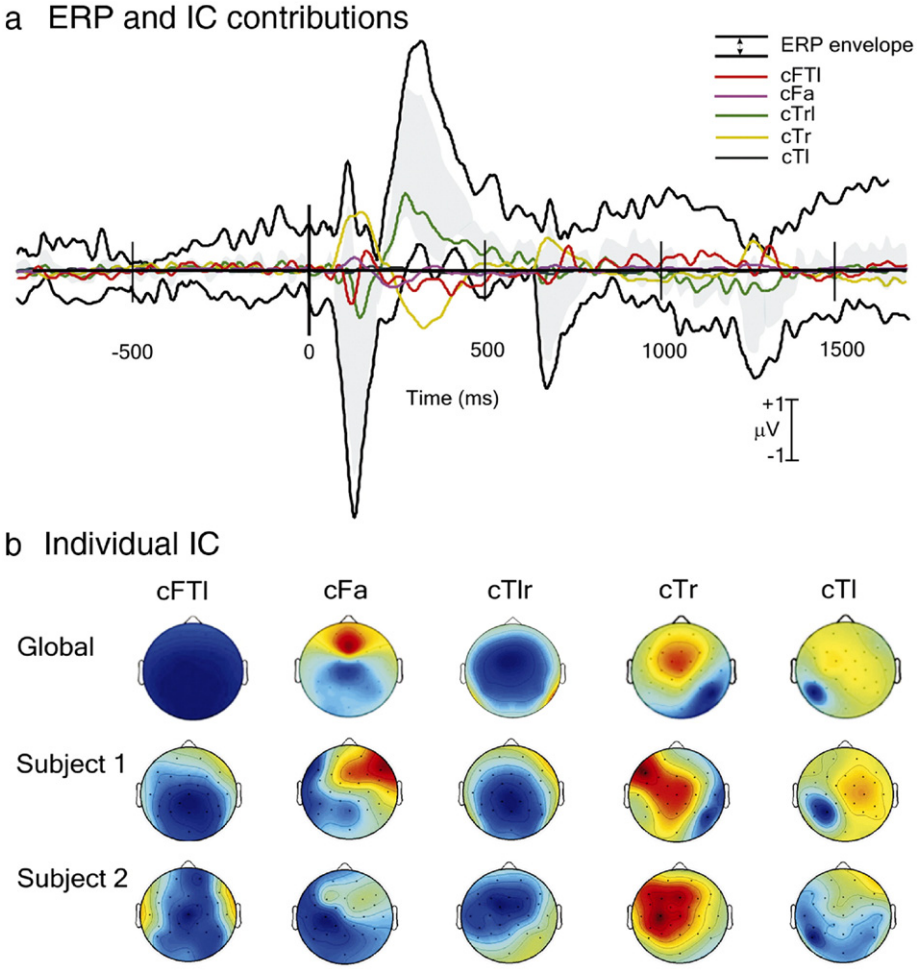

Fig. 4. (a) ERP amplitude envelope over all 30 electrodes of all subjects from −1000 to 2000 ms epoch including S1, S2 and S3 responses. Clear N1 ERPs could be observed after S1 (0 ms), S2 (584 ms) and S3 (1162 ms), and S2 and S3 N1 amplitude attenuation compared to S1 N1. Coloured traces show the projections (in μV) to the scalp of the 5 ICs contributing to a n ERP variance of 76.3% (blue fill). (b) Maps associated to IC weights for global data (all subjects), and the corresponding maps for two selected subjects. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

revealed that both cTrl and cTr originated from similar brain sources placed at right posterior temporal cortex, but cTrl also showed the activity of the left temporal cortex. cTl was found to be generated at left temporo-parietal cortical regions (Fig. 3). Moreover, cTrl, cTr and cTl spectral contents (Fig. 3) showed that theta–alpha (3.9–13.6 Hz) spectral power frequency ranges increased after S1 ($P<0.01$ to all three components).

However, differences were observed after repeated tone responses. Firstly, cTl not showed significant activation after tone repetition ($P>0.05$). Second, cTrl showed theta and alpha (3.9–13.6 Hz) ITC increase after S2 and S3 without any concurrent spectral power modulation (both $P<0.01$) and thirdly, cTr underwent also theta and alpha ITC enhancement (3.9–13.6 Hz) after S2 and S3 ($P<0.01$) but small theta spectral power (3.9–5.8 Hz) was also observed in both stimuli-related repeated tone responses ($P<0.01$).

Subject-by-subject ICA showed that all ICs detected in the global analysis (all subjects poll trials) were also present in the individual level, thus arguing that subject-by-subject spatial variance does not seem to alter global results. Hence, cFTl was identified in 11 of 12 subjects (91.6%), cFa in 8/12 (66.6%), cTrl in 11/12 (91.6%), cTr in 9/12 (75%) and cTl in 8/12 (66.6%) (Fig. 4b).

Discussion

This study puts forward an analysis of EEG data collected in an auditory attenuation paradigm, in which trials of three identical tones (S1, S2, S3), separated by brief intervals of 584 ms, were presented sequentially preceded by silent intervals of 30 s. N1 auditory ERPs were obtained in response to each stimulus, with S2 and S3 responses having less amplitude (attenuation) than S1. With this paradigm, according with the first objective of the present study, we demonstrated that ICs and their descriptors (i.e. time–structures–frequency), extracted from N1 and suppressed N1, showed quantifiable changes in these two different functional situations, thus providing direct evidence that each IC might capture specific functional brain subunits underlying N1 ERP, observed in both global (all subjects) and at the individual level. Hence, while non-suppressed N1 cortical mechanisms were broken

down into five ICs, suppressed N1 showed the disappearance of 3 of them and the modulation of the IC descriptors of the remaining two.

Moreover, in line with the second objective of the present study, the ICA+LORETA+Time–frequency analysis applied to N1 and suppressed N1 provides new insights into the neural dynamics sub-served within auditory N1 ERP. Two of the five identified ICs were maximal for S1, but changed after tone repetition (S2, S3). The remaining three were present after S1 only, but, whereas the activity of one IC started in the first half of the N1 appearance, two other ICs began ~50 ms later. Thus, three exclusive components can be described for non-suppressed N1, while two other components were present for all stimuli responses, but were modulated as a function of tone repetition (Figs. 2c and 3c). In addition, the study of IC source location showed that N1 generation sub-served frontal, temporal and parietal structures (Figs. 2b and 3b), while spectral content showed the involvement of theta, alpha and gamma neural oscillatory bands. However, suppressed N1 showed, on the one hand, the disappearance of frontal and parietal participation, and on the other, the modulation of the oscillatory neural mechanisms of the remaining bilateral temporal contributions by favouring phase-resetting of theta and alpha responses (Figs. 2d and 3d).

Functional neural dynamics of non-suppressed N1 (time-, space- and frequency-domains)

Our results showed that cortical dynamical modes reflected by non-suppressed auditory N1, obtained to S1 stimulus after a 30-s silent gap, involved the participation of five statistical maximal independent components. These components could be differentiated by their time-, space- and frequency-domain characteristics. Hence, regarding time-domain features, while cTrl, cTr and cTl were activated at 80–100 ms (early-onset components) and lasted until the second half of the N1 latency period, cFTl and cFa were activated at around 140 ms after stimulus (late-onset components), encompassing only the second half of the N1 appearance. This differentiation suggests that N1 generation relies on two time-domain "blocks" of activations, which would be in accordance with the "early" and "late" N1 contributions found with other brain recording techniques, such as MEG (Loveless et al., 1996; McEvoy et al., 1997) and fMRI (Jääskeläinen et al., 2004; Ahveninen et al., 2006). However, present results extended this, so that differences between each block focused on the temporal onset activations; thus, both time-domain activations (early onset and late onset) lasted, somehow, until the end of the N1 ERP time window appearance.

Moreover, present results showed that activation of the early-onset N1 components originated at both right and left temporal cortex (cTrl, cTr, cTl). Congruently, the involvement of both temporal lobes in early processing stages reflected by N1 has been stated by hemodynamic (Jääskeläinen et al., 2004) and electrical source current density (Mulert et al., 2004) studies. However, though our temporal source N1 location is consistent with that found previously, present data extend previous results by arguing that, within temporal cortex, several neural activity modes can be statistically disentangled. Hence, cTrl involved both right and left temporal lobes, cTl consisted of left temporal lobe and left inferior parietal cortex participation, while cTr encompassed the activity of the right temporal lobe alone.

Arguably, our finding of disentangled neural components in temporal cortex would be in accordance with those that stated that neural activity from this area (temporal cortex) could perform distinct task-related neural processes. As such, it has been argued that temporal areas are in charge of the analysis of the physical features of an auditory stimulus entry (Näätänen, 1992), gate sound to awareness (Jääskeläinen et al., 2004), are modulated by attention requirements (Petkov et al., 2004) and participate, differentially, in localization and identification of relevant auditory objects (Ahveninen et al., 2006).

Furthermore, it has been shown that these processes could take place in distinct neural sources within the temporal lobe. Hence, it has been proposed that, while analysis of the physical properties of a stimulus could be held by both hemispheres (Näätänen, 1992), attention influences, preferentially, the right temporal lobe (Petkov et al., 2004). As well as left and right hemisphere dominance in specific function activity, a distinct transient modulation of neural activity within the temporal cortex, based on the appearance of "early" and "late" traditional N1 contributions, has been also posited. Thus, this "early" contribution might originate in posterior areas of the temporal lobe, while "late" contribution might be located in a more anterior area (Sams et al., 1993; Loveless et al., 1996; McEvoy et al., 1997). In the present study, temporal lobe contribution to N1 was found to encompass two time-domain activations: early-onset (cTrl, cTr and cTl) and late-onset (cFTl). Accordingly, our finding that different statistically independent activity emerged from the temporal source could respond to these disentangled classical "early" and "late" contributions to N1, which might, presumably, show up different computational processes, implying distinct neural source locations within the temporal lobe separated by 7–10 mm (Hari et al., 1992; Tiitinen et al., 1993). However, present results showed that temporal lobe contributions to ICs seem to be, somehow, spatially overlapped (see Fig. 3b). This might be explained by the limited spatial resolution of the tomographic method used in the present study, which hindered the capacity of the fully separate neighbouring neural populations participating in distinct processing tasks, or by the contribution of intermixed neuronal populations located in the same brain structure performing different brain computation processes (Marco-Pallarés et al., 2005).

Notably, late-onset components showed that frontal source contribution started not at the initial part (~80–90 ms) of the N1 generation but ~50 ms later (~130–140 ms). This is in accordance with findings that described a frontal N1 generator to the N1 signal starting at about 140 ms (Alcaini et al., 1994). Functionally, a late frontal participation in N1 production has been attributed to a top–down mechanism, enabling enhancement of an auditory sound-features salience. Hence, after long "silent" intervals (30 s in our case), frontal source contribution to N1 has been suggested as eliciting an "attention switching" mechanism (Folk et al., 1992), which could trigger an attention-capturing signal for conscious perception of the stimulus (Naatanen and Picton, 1987; Giard et al., 1994). Additionally, present data showed the partial coincidence in time of right inferior frontal cortex and both left temporal cortex (cFTl) and anterior cingulated cortex (cFa) (see Fig. 2), which corroborates previous fMRI results showing that both right inferior frontal cortex and anterior cingulate cortex (Rinne et al., 2005 and Tzourio et al., 1997, respectively) were activated in the last stages of auditory stimulus response.

As well as time- and space-domain non-suppressed N1 component findings, our data provided evidence that some distinc-

tions could also be accounted for in their neural frequency-domain. Thus, while temporal cortical components (cTlr, cTr and cTl) showed a main oscillatory neural activity within theta and alpha range, frontal components (cFTl and cFa) seemed to also involve low beta and a slightly diffused gamma band power enhancement for the cFa component. In accordance with present oscillatory frequency range involvement, on the one hand, both visual (Makeig et al., 2002; Gruber et al., 2005) and auditory (Yardonova and Kolev, 1998) N1 oscillatory activity have been argued to lie within theta and alpha frequency range and, on the other, gamma band activity has been found in temporal and frontal sources with iEEG recordings in auditory stimulus task-responses (Lakatos et al., 2005; Canolty et al., 2006). Moreover, we found that in all aforementioned ICs, neural mechanisms of theta and alpha contributions in N1 to S1 encompassed both ERSP and ITC enhancement. This confirms previous results on scalp EEG (Fuentemilla et al., 2006) affirming that, within auditory non-suppressed N1, neural mechanisms involved the participation of an evoked mechanism without guaranteeing, quantitatively, the amount of partial phase alignment contribution. This is because, whenever an added neural activity (i.e. fixed-polarity and fixed-latency superimposed neuronal activity to background neural oscillations) is relatively phase-locked to stimulus, it will enhance both spectral power (ERSP) and phase synchrony measures (ITC), which makes the contribution of each mechanism less clear-cut (Klimesch, 1999; Shah et al., 2004; Yeung et al., 2004).However, a point that could not be clarified with our data should be noted: whether the presence of these rhythms is because the activity of a local neural network (e.g. neurons within left temporal cortex) or the interaction of distant sources (e.g. inferior frontal cortex and temporal cortex). A further step to tackle this problem would be to study independently the oscillatory neural activity of each neural source (Gomez et al., 2006), and the interaction between distant sources by directional coupling (Andrzejak et al., 2006), or to look for other neural oscillatory communication mechanisms, such as phase–amplitude interaction between distinct frequency ranges, as found recently in neocortex (Canolty et al., 2006). Further, it should be also noted, that our findings on theta, alpha and gamma oscillations in N1 ERP could not prove a causal relationship in N1 generation process. More experiments are needed to study oscillatory activity causality in ERP generation, i.e. manipulations of the experimental paradigm to modulate the physiological behaviour of the components described.

Functional neural dynamics of suppressed N1 (time-, space- and frequency-domain)

While non-suppressed N1 involved the contribution of five statistically independent components (cFTl, cFa, cTrl, cTr and cTl), after tone repetition just two of them remained active: cTrl and cTr.

Regarding time-domain features, when stimulus is repeated (S2 and S3), cTrl and cTr activity resembles the onset activity patterns that occurred in the non-repeated stimulus response (S1). However, while cTrl, which involves both temporal hemispheres, showed decreased activity than in the S1 response, starting at around 80 ms and disappearing at the end of N1 ERP emergence, cTr decreased its contribution, involving the right temporal cortex only, and revealed a slight temporal cut down of its offset activity (Fig. 3), thus reducing its activity to the first half of N1 temporal window appearance. This suggests that right temporal could also involve other neural functional activity that tended to disappear with tone repetition. In this respect, Teismann et al. (2004) showed that right and left temporal areas responded differently to repeated-word presentation (favouring preserved activity in left but not in right temporal areas), though they did not find differences on simple tone presentation. In addition, time activation differences encountered between ICs could be discussed in terms of those that described different "early" and "late" classical N1 contributions' reactivity to repeated stimuli presentation. Thus, when stimulus is repeated, "early" N1 contribution tended to adapt (i.e. decreasing its activity), while "late" contribution is suppressed more by stimulus repetition (Sams et al., 1993). Accordingly, our findings showed that, compared with the response to S1, cTr suppressed the contribution in the last half of the N1 time window appearance for S2 and S3 stimuli and cTrl showed similar recovery cycle after S3 stimulus.

In the space-domain, present findings showed that suppressed N1 responses involved the total suppression of frontal lobe activation (cFTl and cFa) and left temporo-parietal conjunction activity (cTl) and a decrease in the other two temporal hemisphere components activation (cTrl, cTr). This is consistent with the view that N1 suppression was reduced not only due to an auditory cortical source activity decrease but also to a distributed neural modulation of a cerebral multi-generator process (Naatanen and Picton, 1987).

Moreover, frequency-domain behaviour of cTrl and cTr after tone repetition provided evidence that, although spectral content involved in S2 and S3 responses resembled the oscillatory band appearing in S1 (i.e. mainly theta–alpha range with a decrease of ~0.1–0.2 ITC index), the mechanisms intervening in their neural oscillatory dynamics were modulated, thus involving phase realignment of oscillatory neural activity while concomitant evoked spectral power presence was partially (cTr) and/or totally (cTrl) abolished. Accordingly, the fact that phase resetting of theta and alpha rhythms appeared without concurrent spectral power modulation for cTrl after repeated tone presentation, supports the hypothesis that these neural mechanism responses are explained by an oscillatory-based approach (Makeig et al., 2004a), as was previously found in scalp EEG obtained under similar experimental conditions (Fuentemilla et al., 2006). Present results extend these findings by arguing that cortical sources underlying partial phase-resetting of oscillatory activity after a repeated tone presentation lay within the temporal cortex (Fuentemilla et al., submitted for publication). Hypothetically, changes in the oscillatory mechanisms underlying N1 responses due to transient N1 responses to repeated sounds suggest a sudden change in the strength of the neural network activity given by S1 entrance to the temporal neuronal sources (cTrl and cTr in our case), as has been stated in theoretical studies (David et al., 2005) and experimentally in hippocampus (Gasparini and Magee, 2006).

Identification of N1 and N1 suppression specific brain functional subunits

In the present study, specific brain functional subunits extracted from the ERPs are defined as the integrated activity characterized by maximal statistical independence properties and temporal, spatial and spectral features that showed changes in different functional situations.

Our results showed that ICs were modulated by an auditory N1 repetition suppression paradigm. Hence, while cFTl, cFa and cTl disappeared after S1 entrance, cTrl and cTr remained active in

S2 and S3. This suggests that the first three components are involved only in the specific functional mechanisms associated with S1 (e.g. attention and novelty processing). Moreover, when analysing the temporal, spatial and spectral properties of the two remaining ICs (cTrl and cTr) after tone repetition, we observed that, while similar temporal lobe structures participated in S1, S2 and S3 responses, there was a modulation of underlying time window of activation and neural oscillatory implied mechanisms. Thus, suggesting that they represent specific function activity needed for rising neural responses to all situations (e.g. sound feature analysis).

Present results, showing quantifiable IC changes in different functional situations, give support to the view that ICA is not merely a statistical "latent variables" model when applied to event-locked EEG activity, but that it could also help to capture the functional neural modes underlying it. In conclusion, maximal independent components of ERPs could be associated with concrete time-related behaviour, brain structures, frequency composition and functional modulation. This multifaceted IC characterization and, notably, its changes reflecting different functional neural states could have general relevance for Neuroscience, as they suggest that ICs capture specific brain-function subunits of brain dynamics.

Acknowledgments

The authors would like to thank Arnaud Delorme and Scott Makeig for their generous gift of software. This study was supported by grants to CG from the Generalitat de Catalunya to support NECOM group (SGR2005-00831), the Spanish Ministerio de Ciencia y Tecnología (SEJ2006-13998), the European Union (FP6-507231, SENSATION), and the Fundació Marató 2006-061632.

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