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Spatiotemporal dynamics of the auditory novelty-P3 event-related brain potential

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Abstract

The spatiotemporal dynamics of the cerebral network involved in novelty processing was studied by means of scalp current density (SCD) analysis of the novelty P3 (nP3) event-related brain potential (ERP). ERPs were recorded from 30 scalp electrodes at the occurrence of novel unpredictable environmental sounds during the performance of a visual discrimination task. Increased SCD was observed at left frontotemporal (FT3), bilateral temporoparietal (TP3 and TP4) and prefrontal locations (F8–F4 and F7–F3), suggesting novelty-P3 generators located in the left auditory cortex, and bilaterally in temporoparietal and prefrontal association regions. Additional increased SCD was found at a central location (Cz) and at superior parietal locations (P3–Pz–P4). The SCD of the nP3 was therefore generated at three successive, partially overlapping, stages of neuroelectric activation. At the central location, SCD started to be significant before the onset of the nP3 waveform, contributing solely to its early phase. At temporoparietal and left frontotemporal locations, nP3 electrophysiological activity was characterized by sustained current density, starting at about 210 ms and continuing during the full latency range of the response, including its early and late phases. At its late phase, the nP3 was characterized by sharp phasic current density at prefrontal and superior parietal locations, starting at about 290 ms and vanishing at around 385 ms. Taken together, these results provide the first evidence of the cerebral spatio-temporal dynamics underlying novelty processing.

Theme: Neural basis of behaviour

Topic: Cognition

Keywords: Novelty-P3; Involuntary orienting of attention; Spatiotemporal analysis; SCD

1. Introduction

In their seminal work, Squires et al. [36] described two varieties of long-latency positive EEG waves elicited by unpredictable auditory stimuli. These two waves differed in latency, scalp topography and psychological correlates. The authors used the term 'P3a' to refer to the earlier component elicited by infrequent, unpredictable auditory stimuli regardless of whether the subjects were attending to the auditory sequence or ignoring the tones while reading silently a book. Subsequent studies suggested that the P3a—often elicited by novel environmental sounds and therefore called the 'novelty P3' (nP3)—reflects the activation of a cerebral network involved in involuntary orienting of attention towards unattended changes and novelty in the acoustic surroundings [7,12,14,16,22,44].

The dipole localization of magnetoencephalographic (MEG) responses [1] has suggested the presence of neural generators of the nP3 in the supratemporal plane of the auditory cortex. These results have been supported by intracranial recordings in humans showing novelty-related activity in these areas [19]. The involvement of the superior temporal gyrus in auditory novelty processing has also been shown by fMRI studies [30]. Dipole modeling of

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EEG data in normal subjects [27] and studies of patients with cerebral lesions [8,22,46] has suggested that prefrontal and posterior association cortices are also involved in the generation of the nP3. Intracranial recordings in humans showing novelty-related activity over the dorsolateral prefrontal and posterior association cortices, as well as in cingulate and limbic areas, support the involvement of these brain areas in novelty processing [2,20]. A possible further contribution to the nP3 arises from the hippocampal region, as patients with unilateral lesions over the posterior hippocampus showed lower nP3 than normal controls [23]. Mapping of hemodynamic activity with functional magnetic resonance imaging (fMRI) [37] and positron emission tomography (PET) [41,42], and intracranial recordings in humans [17], also support the involvement of the hippocampal region in novelty processing. Taken together, these results indicate that a widely distributed cerebral network is involved in the generation of the nP3 event-related brain potential (ERP), and therefore in novelty processing.

In a recent study, Escera et al. [11] found that the nP3 was not a single ERP component but a composite response with two clearly separated subcomponents (see also Ref. [13]). These two subcomponents were disclosed on the basis of their respective latency, scalp distribution and psychological concomitants, just as the P3a was separated from the P3b in Squires et al.'s seminal study [36]. At an early latency (ca. 230 ms), the nP3 was maximally distributed over the central scalp, showing negative polarities over posterior inferior regions and at electrode locations below the Sylvian fissure. At a later latency (ca. 315 ms), the nP3 was more anteriorly distributed, showing a right frontal maximum. These two subcomponents were also disclosed on the basis of their sensitiveness to attentional manipulation: the later phase was much larger when the eliciting auditory stimuli were covertly attended than in a condition in which the sounds were ignored [11].

Though numerous studies have described the brain regions that contribute to the nP3, the specific temporal dynamics underlying the activation of this cerebral network remains unknown. In the present study, the millisecond accuracy of the ERP approach was improved with scalp current density (SCD) analyses. The SCD technique, although it does not provide with precise brain localization, allows to identify discrete generators of the electrophysiological responses, permitting the study of the spatiotemporal dynamics of the brain circuitry generating the nP3.

2. Materials and methods

Fourteen healthy, right-handed human subjects (mean age: 21.3±1.8 years; four males), with normal hearing and normal or corrected-to-normal vision gave written informed consent to participate in the study. Subjects were presented with 10 blocks of 200 stimulus pairs (trials) delivered at a constant rate of one pair every 1.5 s. Each trial consisted of an irrelevant auditory stimulus followed after 300 ms (onset-to-onset) by a visual stimulus. Auditory stimuli were a 600 Hz standard tone (probability=0.8), two different deviant tones (700 Hz or 514 Hz; probability=0.05 each), and novel sounds (total probability=0.1). Novel sounds were 60 different complex environmental sounds, such as those produced by a drill, hammer, rain, door, telephone ringing, etc. A particular novel sound was never repeated more than twice or three times in the whole experiment and never occurred twice in the same stimulus block. Auditory stimuli were delivered binaurally through headphones with a duration of 200 ms (including 10 ms of rise and fall times) and an intensity of 75 dB SPL (peak intensity between 70 and 80 dB SPL for novel sounds). The auditory stimuli were sequenced randomly, with the only exception that the trials in which the visual stimulus followed a deviant or a novel sound were always preceded by a trial in which the sound was a standard tone. The visual stimulus extending vertically 1.7° and horizontally 1.1° was either a digit (from 2 to 9) or a letter (A, E, J, P, R, S, U, or Y) presented equiprobably on a computer screen for 200 ms. Stimulus presentation and sequence control was carried out by means of Stim (NeuroScan, Inc.) software and hardware.

Subjects sat comfortably in a reclining chair in a dimly lit, electrically and acoustically shielded room. They were instructed to press one response button to letters with the right index finger of their dominant hand, and another response button to numbers with the right middle finger, and to ignore the auditory stimulation. Both speed and accuracy were emphasized. Response fingers were counterbalanced across subjects. Before the experimental session, subjects received two practice blocks in which the sounds were turned off. All subjects reached a hit rate of at least 85% in the practice blocks.

EEG (bandpass 0–100 Hz) was continuously digitized at a sampling rate of 500 Hz by a SynAmps amplifier (NeuroScan, Inc.), from 30 scalp electrodes: 18 of the 10–20 system (Fp1, Fp2, F7, F3, FZ, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6 and Oz), and 12 from the additional positions FT3 (halfway between F3 and T3), TP3 (halfway between T3 and P3), CP1 (halfway between P3 and Cz), FC1 (halfway between Cz and F3), the left mastoid (LM), IM1 (70% of the distance from the preauricular point to inion), and the homologous positions over the right hemisphere (Fig. 1a). Horizontal and vertical EOG were recorded with electrodes attached to the canthus and below the right eye, respectively. The common reference electrode for all EEG and EOG recordings was placed on the tip of the nose. ERPs were averaged off-line for each auditory stimulus class, for an epoch of 600 ms including a pre-auditory stimulus period of 100 ms. Epochs in which the EEG or EOG exceeded ±100 μV, as well as the first five epochs of each block, were auto-

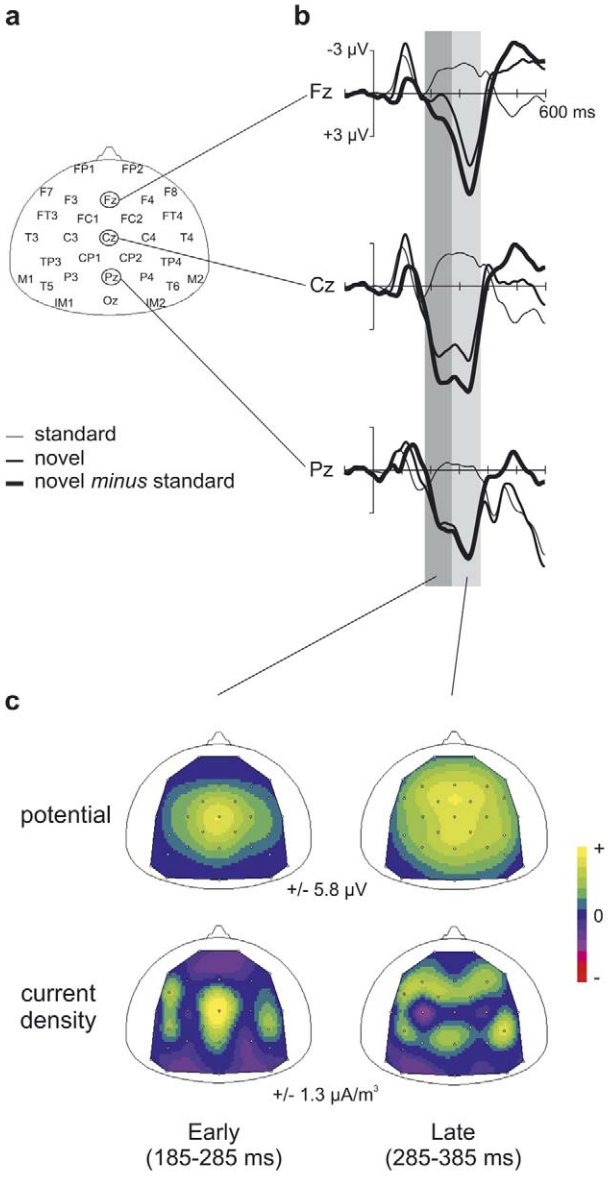

Fig. 1. (a) Distribution over the scalp of the 30 electrodes used in the EEG recordings. (b) Event-related brain potentials (ERPs) at midline electrodes elicited to standard and novel stimuli, and the corresponding difference waves. These revealed the nP3 response, which had two different phases of respective peak latencies at 235 and 335 ms. Gray shadows show the latency intervals used in nP3 analysis, i.e., 185–285 ms for its early phase (dark gray) and 285–385 ms for its late phase (light gray). (c) Scalp potential and current density distributions of the two phases of the nP3. Scalp potential maps show that the late phase of the nP3 was more anteriorly distributed than the earlier phase. Scalp current density analyses revealed positive currents over central, bilateral temporoparietal and left frontotemporal areas during the early nP3a, and over superior parietal, bilateral temporoparietal and frontal areas during the late nP3.

matically excluded from averaging. The standard-tone trials immediately following deviant-tone or novel-sound trials were also excluded from the averages. Frequencies >30 Hz were digitally filtered out from the individual ERPs.

A correct button press within 200–1100 ms after visual-stimulus onset was regarded as a hit, the mean reaction time (RT) being computed only for the hit trials. An incorrect button press during this period was classified as an error, and trials with no response as misses. Hits, errors, misses, and RTs were computed across letters and numbers. Reaction time and hit rate in standard and novel trials were compared by means of two-tailed *t*-test comparisons.

This report focuses only on the results obtained in novel trials, as the deviant-trial data have been reported elsewhere [45]. Novelty P3 was isolated in the difference waves obtained by subtracting the standard-tone ERPs from those elicited to novel sounds. The mean amplitudes of the two different phases of the nP3 identified in the difference waves were computed in 100-ms time windows around the peak of each phase (185–285 ms for the early phase, 285–385 ms for the late phase), as identified in the grand-average of the response across subjects. ERP scalp distribution analysis was performed on normalized mean amplitudes of the two nP3 phases at the F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, and T6 electrode locations (scalar normalization [26]) by means of analysis of variance (ANOVA) for repeated measures with frontality (three levels), laterality (five levels) and phase (early vs. late) as factors. Where appropriate, Greenhouse–Geisser correction of the degrees of freedom was applied, the uncorrected degrees of freedom and the corrected *P* values being reported.

The scalp potential distribution of the difference waves was reconstructed at each pixel by a spherical surface spline interpolation [32]. Scalp radial current density (SCD) curves and maps were obtained by computing the second spatial derivatives of the spline functions used for potential mapping. The SCD distributions, expressed in $\mu A/m^3$, show the scalp areas where the current either emerges (sources) from the brain into the scalp or enters (sinks) from the scalp into the brain. SCD analysis allows the spatial and temporal splitting of the smeared potential distributions due to simultaneously active generators, helping to disentangle the distribution of multiple generators overlapping in potential maps [33]. Compared with potential fields, SCD maps reflect mainly the activity of cortical generators located in the proximity of the recording electrodes, as their amplitude decreases with the depth of the generators in the brain [31,33]. For statistical analysis, the SCD waveforms were computed for all electrodes.

The statistical analysis of the SCD data was performed in two successive stages. First, the areas contributing to nP3 generation were determined by two-tailed *t*-test comparisons between the zero level and the mean amplitude of currents at sets of electrodes selected according to the sources observed in the SCD maps at the early (185–285 ms) and late (285–385 ms) phases of the nP3. In the second stage of the analysis, the temporal dynamics of the different currents at each of the sites found to be signifi-

cant in the previous analysis was analyzed by means of point-by-point two-tailed *t*-tests between the mean value of currents at each sampling point and the zero level, starting at 0 ms and up to 500 ms. The onset latency of a significant activation was defined as the starting point from which at least 12 consecutive points reached statistical significance at a conservative $P<0.01$ level or better [18].

3. Results

The overall performance level was high on both the standard and novel trials (94.3 and 94.2%, respectively). However, reaction time was significantly longer (on average by 13 ms) in novel than in standard trials ($t_{13}=-3.16$, $P<0.01$), revealing a significant distracting effect of novel sounds over the performance on the visual task. This result indicates that novel sounds activated the cerebral network underlying the orienting response.

Novel minus standard ERP waveforms revealed that novelty-related electrophysiological activity was characterized by an early negative response, resulting from combined N1 enhancement and mismatch negativity (MMN) activities (see Refs. [1,11]), and a large (about +7 μV at Cz) and long-lasting (from 200 to 400 ms from auditory stimulus onset) nP3 response. Two different phases of this response were evident in the waveform (Fig. 1b), with respective peak latencies at Cz of 235 and 335 ms. Scalp potential distribution mapping of the two phases of the nP3 showed that the early phase was maximal over the central scalp, whereas the late phase was distributed over frontal regions (Fig. 1c). ANOVA performed on normalized mean amplitudes computed at 185–285 and 285–385 ms latency windows for the early and late phases, respectively, showed a significant phase (early vs. late)×frontality (posterior vs. central vs. anterior) interaction ($F_{4,52}=12.71$, $P<0.001$), supporting the more anterior scalp distribution of the late phase of the nP3.

SCD analyses on the early phase of the nP3 revealed significant positive currents over central (Cz: +1.8 μA/m^3; $t_{13}=1.37$, $P<0.001$), left frontotemporal (FT3: +0.86 μA/m^3; $t_{13}=4.6$, $P<0.001$) and bilateral temporoparietal locations (TP3: +0.62 μA/m^3; $t_{13}=3.95$, $P<0.005$; TP4: +0.64 μA/m^3; $t_{13}=3.29$, $P<0.01$) (Fig. 1c). SCD analyses revealed that during the late phase of the nP3 significant currents were also elicited over left frontotemporal (FT3: +0.88 μA/m^3; $t_{13}=6.77$, $P<0.001$) and bilateral temporoparietal locations (TP3: +0.8 μA/m^3; $t_{13}=6.4$, $P<0.001$; TP4: +1.26 μA/m^3; $t_{13}=6.7$, $P<0.001$). During this late phase, further currents were also observed over superior parietal (P3–Pz–P4: +0.43 μA/m^3; $t_{13}=6.76$, $P<0.001$), and bilateral frontal locations (F3–F7: +0.45 μA/m^3; $t_{13}=5.26$, $P<0.001$; F4–F8: +0.54 μA/m^3; $t_{13}=6.2$, $P<0.001$) (Fig. 1c).

The spatiotemporal neurodynamics of the novelty-related electrophysiological activity, measured as increased SCD from 0 to 500 ms, is illustrated in Fig. 2 as the statistical significance of this activity at the highest temporal resolution (i.e., sampling rate). Early nP3 activity was found at central (Cz), left temporoparietal (TP3) and left frontotemporal (FT3) locations. At the central location (Cz), current started to be significant before the onset of the nP3 waveform, at 155 ms, and vanished at 295 ms,

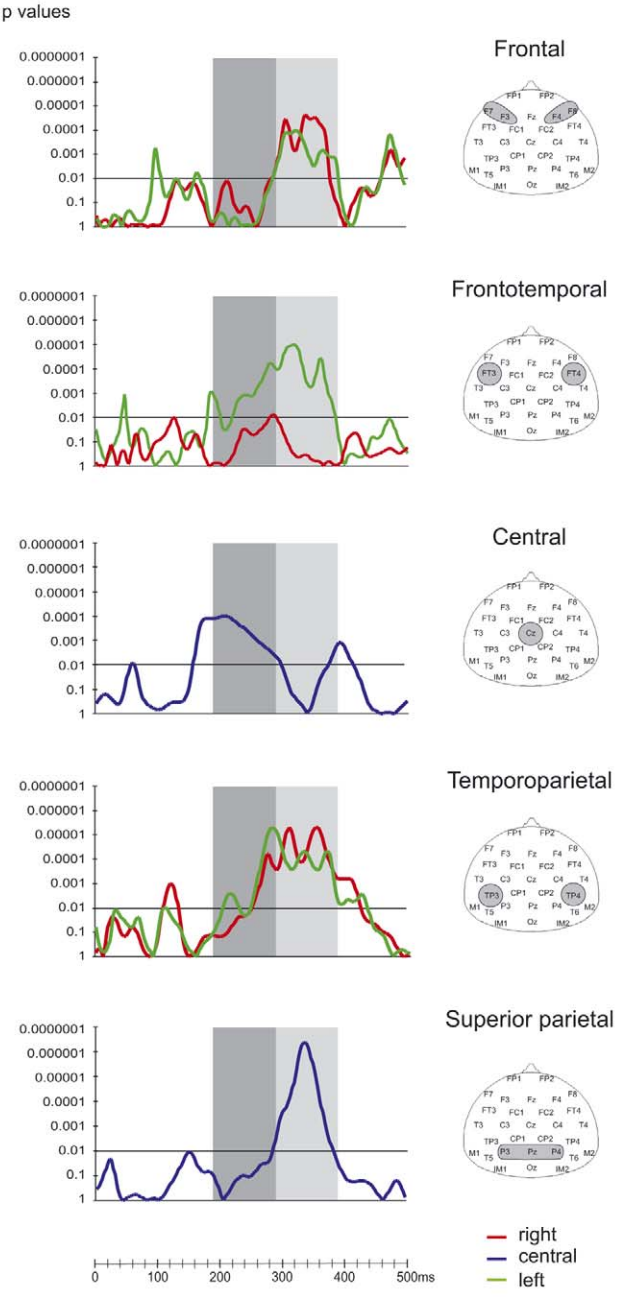

Fig. 2. Temporal dynamics, with a millisecond accuracy, of the statistical power of the increased SCD of nP3 at different scalp locations: frontal (right: F4–F8; left: F3–F7), frontotemporal (FT3, FT4), temporoparietal (TP3, TP4), central (Cz) and superior parietal (P3–Pz–P4) regions. Dark and light gray shadows show the early and late nP3, respectively. The horizontal line is plotted at the $P=0.01$ level.

Table 1
Onset and offset of the increased SCD of nP3 at different scalp locations

Scalp locations	Left		Central		Right	
	Onset	Offset	Onset	Offset	Onset	Offset
Frontal (F3–F7, F4–F8)	290	390	–	–	285	380
Frontotemporal (FT3, FT4)	220	385	–	–	–	–
Central (Cz)	–	–	155	295	–	–
Temporoparietal (TP3, TP4)	200	430	–	–	250	420
Superior parietal (P3–Pz–P4)	–	–	290	380	–	–

Latencies reported are taken from the first (onset) and last (offset) time point of the corresponding significant ($P<0.01$) latency intervals at each location.

contributing solely to the early phase of the nP3. At left temporoparietal (TP3) and left frontotemporal (FT3) locations, nP3 electrophysiological activity was characterized by sustained increased SCD, starting at about 210 ms and continuing during the full latency range of the response, including its early and late phases. Sustained increased SCD was also found at the right temporoparietal location (TP4), although this activity started a little later, at 250 ms, than that from the homologous location in the left hemisphere (TP3). Both the left and the right temporoparietal sources were still active even beyond the returning to baseline of the nP3, vanishing at 430 ms and 420 ms, respectively. Interestingly, the late phase of the nP3 was characterized by sharp phasic increase in SCD at frontal (F8–F4 and F7–F3) and superior parietal (P3–Pz–P4) locations, starting at about 290 ms and vanishing at about 380 ms. Table 1 summarizes onset and offset times of increased SCD at the different scalp locations.

4. Discussion

The results obtained in the present study demonstrate parallel contributions from multiple cerebral regions to the nP3, and therefore confirm that a widely distributed cerebral network underlies novelty processing. Increased SCD was observed at left frontotemporal areas, supporting that nP3 is generated in auditory cortex [1,30]. Indeed, MEG [1] and fMRI [10] studies have shown that the auditory cortex is involved in auditory novelty detection. Furthermore, in their MEG study, Alho et al. [1] reported that nP3 dipoles could be modeled more consistently over the left than over the right auditory cortex, in agreement with the present results showing left predominance of the auditory cortex contribution to nP3 generation. The left predominance of auditory cortex in nP3 generation may reflect an attempt to linguistically encode the novel sound, as it is well known that the left auditory cortex is more involved in encoding of linguistic material than the right one [4,29,35,38,48].

Increased SCD of nP3 was also observed bilaterally over temporoparietal areas, suggesting a cerebral contribution to nP3 from the temporoparietal region. The critical role of this brain region in the generation of the nP3 response has been previously shown in studies of patients with discrete unilateral lesions in the temporoparietal junction, in whom the nP3 elicited to auditory, visual and somatosensory novel stimuli was abolished over all recorded scalp locations [24,46,47]. In a recent fMRI study [10], the involvement of the temporoparietal junction in multimodal novelty detection has also been suggested, as activations in this brain region were found to stimulus changes in the auditory, visual and somatosensory modalities.

In the present study, increased SCD of nP3 was also observed bilaterally at frontal locations. The contribution of frontal regions to the generation of the nP3 has been previously indicated by dipole modeling data [27], as well as by studies showing attenuation of nP3 in patients with lesions to their dorsolateral prefrontal cortex [22,46]. Furthermore, intracranial recordings [2] in human subjects have shown novelty-related activity directly from the frontal cortex. It has frequently been reported that the frontal cortex is involved in directing the main focus of attention towards sensory events (e.g., Refs. [6,21,28,39]). Therefore, the frontal sources of nP3 observed in the present experiment may reflect the involuntary orienting of attention towards the novel sounds, which is also supported by the fact that the frontal component of the nP3 was found to be sensitive to the manipulation of the attentional load [11]. Moreover, ERP studies have shown impaired orienting responses in patients with frontal lesions [5,8], which indirectly supports the involvement of frontal areas in the control of attention.

The largest nP3 neuroelectric source, contributing solely to its early phase, was observed over the central region, at Cz (see Fig. 1c). It is apparently difficult to identify the underlying brain region generating this powerful current flow observed at the scalp, as anatomically the cerebral tissue below the electrode location Cz may correspond to areas surrounding the central sulcus [40]. This current flow may originate in the cingulate cortex, either anterior or posterior, as novelty-related activity in these brain regions have been observed in intracranial recordings in humans [2,19] and also in fMRI [3,10,43] and PET [41] studies. Alternatively, the current observed at Cz may originate in deeper structures, such as the posterior hippocampus, which could possibly contribute to the generation of the nP3 [23]. However, these assumptions should be carefully

considered since SCDs are particularly sensitive to shallow generators [31,33] and, consequently, the increased SCD observed at Cz appears to be too large to reflect deep neuroelectric activation such as that generated in the hippocampus.

Further increased SCD was observed over superior parietal locations, in agreement with human intracranial recordings showing novelty-related activities over the posterior and superior parietal lobe [19]. The observation of posterior and superior parietal contributions to nP3 contrasts, however, with results obtained in neurological patients, which suggested that lesions to the posterior parietal cortex had no effect on nP3 generation [46]. Nevertheless, lesions in that study were located at lateral portions of the parietal cortex, contrasting with the more probable superior parietal origin of the nP3 currents observed in the present experiment. Friedman and Simpson [15] have suggested that the late posterior parietal component of the nP3, named $P3_2$ by these authors, may reflect a secondary categorization of their novel stimuli, perhaps an attempt to encode linguistically novel events. Alternatively, with the present stimulus-task configuration, in which the sounds warned of the occurrence of the visual targets as shown by Escera et al. [11], the subjects may not have been able to fully disengage attention from the task-irrelevant auditory stimuli. Therefore, covertly monitored novel sounds may have been automatically analyzed up to the point to activate P3b-like generators in the posterior parietal cortex [19], which are thought to reflect memory updating of task-relevant stimulus features [5,9,36].

Although the spatial resolution of the methodological approach used in the present study is far from optimal, the agreement between the scalp locations which were observed to contribute to nP3 generation and the corresponding anatomical regions reported in the literature validates the SCD analysis to disclose specific brain generators of the nP3 component. Furthermore, the spatial limitations of the SCD approach contrasts with its powerful temporal resolution, in the millisecond domain. In comparison with SCD, MEG provides with better spatial accuracy and identical temporal resolution. However, only tangential dipoles to the scalp—ideally, those located in the supratemporal plane—are revealed with MEG, and are therefore not appropriate when studying multiple sources with different orientations as in this report. Thus, by combining the ability of SCD analysis to disclose multiple ERP generators with its temporal accuracy, the new result of the present study was that the neuroelectric contributions to the novelty P3 component of the ERPs had specific time patterns of activation. Currents observed at the central location contributed to the early phase of the nP3, whereas left frontotemporal and bilateral temporoparietal regions remained active during the full latency range of the response, and generators from frontal and posterior parietal regions showed a phasic pattern of activation, with sharp onset and offset, contributing solely to the late phase of the response.

A detailed examination of the temporal dynamics of the increased SCD showed that the nP3 was generated in three successive, partially overlapping, stages of neuroelectric activation: at an early latency, the central location contributed solely to the early nP3, even before the response could be observed in the potential recordings, followed by those at left temporoparietal and left frontotemporal regions, and finally by those at bilateral frontal and superior parietal regions. The specific reciprocal projections reported in monkeys between auditory cortex and prefrontal areas, which originate in caudal and rostral auditory cortex and target different regions in the frontal lobes [34], suggest that frontal regions may be triggered by the preceding temporal activations. A similar time sequence of novelty-related activations has been described by Halgren and co-workers [19,20] and Baudena et al. [2]. These authors found novelty-related activity at the anterior cingulate (at about 265 ms) shortly preceding activation of temporal (at about 280 ms) and parietal (at about 313 ms) regions. These results therefore suggest that the early nP3 current observed at the central location in the present study may indeed originate in the anterior cingulate region.

The specific spatiotemporal dynamics of activation of the cerebral network underlying nP3 generation may explain why lesions to the temporoparietal region eliminate the nP3 at all recorded scalp locations, whereas lesions over the prefrontal region only result in a reduction of its amplitude, mainly over ipsilateral frontal areas [22,46,47]. Therefore, frontal cortex lesions would impair only the last phase of the nP3, whereas lesions of the temporoparietal junction would affect the earlier nP3 generation, consequently preventing the whole nP3 response from being generated.

The data obtained in the present study have shown that the nP3 component of the ERPs is generated by the contribution of five distinct neuroanatomical regions, with specific patterns of temporal activation. By considering the functional role of the components of this cerebral network, we here suggest that novelty processing, as reflected in the nP3, may be carried out in a parallel distributed network at three different stages. Indeed, our results suggest that, as early as 155 ms from stimulus onset, novel sounds may activate cerebral structures of novelty detection, presumably in the cingulate cortex or in the hippocampus. Subsequently, with a slight delay of 65 ms, brain regions involved in novelty detection and encoding may be recruited in the left auditory cortex, and parallel processing may also be triggered over the temporoparietal region, probably reflecting the breaking of a multimodal template of the environment held in the posterior association cortex. At the third stage of processing, starting at about 290 ms after novelty onset, frontal mechanisms controlling the direction of attention may orient the focus of attention involuntarily towards the novel event, whereas a mul-

timodal template of the environment may be readjusted with fresh information, provided by the recently encoded novelty, in the superior parietal cortex. Although the present model of novelty processing is suggestive, further studies combining technologies of better spatial accuracy, such as fMRI, with the excellent temporal resolution of ERPs [25] are needed to disentangle the contribution of specific neuroanatomical regions, in a Talairach space, to the generation of the nP3 and to novelty processing.

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