The Functional Neuroanatomy of Novelty Processing: Integrating ERP and fMRI Results

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Recent research indicates that non-tonal novel events, deviating from an ongoing auditory environment, elicit a positive event-related potential (ERP), the novel P3. Although a variety of studies examined the neural network engaged in novelty detection, there is no complete picture of the underlying brain mechanisms. This experiment investigated these neural mechanisms by combining ERP and functional magnetic resonance imaging (fMRI). Hemodynamic and electrophysiological responses were measured in the same subjects using the same experimental design. The ERP analysis revealed a novel P3, while the fMRI responses showed bilateral foci in the middle part of the superior temporal gyrus. When subjects attended to the novel stimuli only identifiable novel sounds evoked a N4-like negativity. Subjects showing a strong N4-effect had additional fMRI activation in right prefrontal cortex (rPFC) as compared to subjects with a weak N4-effect. This pattern of results suggests that novelty processing not only includes the registration of deviancy but may also lead to a fast access and retrieval of related semantic concepts. The fMRI activation pattern suggests that the superior temporal gyrus is involved in novelty detection, whereas accessing and retrieving semantic concepts related to novel sounds additionally engages the rPFC.

Introduction

The ability to respond actively to novel events serves to facilitate adaptation to a rapidly changing environment (Sokolov, 1963). The underlying novelty detection mechanisms require that the incoming information be compared with a relevant memory template (Rolls *et al.*, 1982). Based on recent PET studies, Tulving *et al.* (Tulving *et al.*, 1996) have proposed the novelty/encoding hypothesis, according to which encoding as well as the long-term storage of incoming information depends on its novelty. An important issue in the neuroscience of memory is which regions in the human brain subserve the different facets of novelty processing.

Studies investigating novelty processing in the brain usually include two varieties of novel information, namely generic and episodic novelty. Generic novelty is provided by stimuli that have never before been experienced by the subjects. A traditional index of the response to such stimuli is the autonomic galvanic skin response (van Engeland *et al.*, 1991; Knight, 1996). The same kinds of stimuli that elicit autonomic skin responses cause an involuntary attentional shift when they occur outside the current focus of attention because of their potential behavioral significance [orienting response (Knight, 1984; Näätänen, 1990)]. Converging evidence suggests that the neurophysiological mechanisms underlying the orienting response are reflected in the event-related potentials (ERPs) as a frontally distributed, positive-going deflection that peaks around 300 ms, the so-called novel P3 (Courchesne *et al.*, 1975; Woods, 1990). This ERP component is usually elicited by unexpected non-tonal environmental sounds that are embedded in a train of frequent standard and rare deviant stimuli. When novel events are repeated and thus are categorizable into a discrete group of events there is a change from a frontal to a more posterior scalp distribution of the novel P3 (Priedman *et al.*, 1998).

Several divergent methods have been employed to delineate the sources of late positivities in the ERP (Rogers *et al.*, 1993; Mecklinger *et al.*, 1998). Electro- as well as magnetoencephalographic scalp recordings have shown that the scalp novel P3 reflects the activity of a widespread neuronal network including frontal and parietal lobes as well as lateral and medial temporal lobe structures (Mecklinger and Ullsperger, 1995; Alho *et al.*, 1998). Additionally, research on stroke patients with focal brain lesions (Knight, 1984, 1996) and on epileptic patients undergoing depth electrode measurements (Baudena *et al.*, 1995; Halgren *et al.*, 1995a,b) also suggested that the novel P3 reflects the activity of a distributed network, with major components in the hippocampus, the temporal lobes and dorsolateral prefrontal cortex.

Conversely, episodic novelty is provided by stimuli that are familiar in general but occur in a specific task situation for the first time. This is the situation in recognition paradigms in which subjects are required to decide whether or not a given stimulus has occurred previously in the experimental setting. In positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies, the difference in brain activation between new stimuli and previously presented, i.e. old stimuli (NEW minus OLD subtraction) allows the brain regions involved in novelty processing to be examined. There is converging evidence from these studies that novelty processing activates a large cortical and subcortical network including temporal, parietal and frontal regions, irrespective of whether visual words (Kapur *et al.*, 1995), pictures (Tulving *et al.*, 1996) or auditory sentences (Tulving *et al.*, 1994) are used as stimulus materials. Tulving *et al.* (Tulving *et al.*, 1996) assume that this transmodal novelty network realizes two subprocesses: novelty assessment, subserved by subcortical and temporal as well as parietal cortical regions, and novelty encoding, subserved by the frontal lobes.

These studies show that novelty is a broad concept that embraces a number of separable processes and brain regions. In a recent study, brain responses to two forms of auditory generic novelty – namely meaningful and non-meaningful novel sounds under attend and unattend conditions – were examined (Mecklinger *et al.*, 1997). This study revealed that only meaningful novel events for which a conceptual semantic representation can be assumed elicited a negative ERP component subsequent to the novel P3. In light of the topographical and functional similarities of this negative component with N4 components evoked by lexical-semantic aspects of language processes (Kutas and Hillyard, 1983) it was suggested that it reflects conceptual-semantic processes, i.e. the retrieval of semantic concepts expressed by the sounds.

The present study aims at identifying the spatial–temporal

characteristics of brain activation underlying the processing of identifiable (meaningful) and non-identifiable (non-meaningful) novel events by combining ERP and fMRI measures. The ERP approach to novelty processing is necessarily approximate in its capability of identifying functionally relevant brain regions, because neuronal sources can only be estimated from the two-dimensional scalp topography using inverse methods like dipole fitting algorithms [for an overview see Scherg (Scherg, 1990)]. Conversely, neuroimaging methods, despite their capability of localizing brain structures underlying cognitive functions with a high spatial resolution, in most cases do not provide the temporal resolution required to make inferences about the subprocesses involved in novelty processing that operate in the millisecond range.

In an effort to overcome the intrinsic limitations of both approaches, in the present study parallel ERP and fMRI recordings were conducted in separate sessions using the same subjects and stimulus materials, i.e. identifiable and non-identifiable novels sounds embedded in a train of tonal events. Because some aspects of novelty processing are considered as an automatic, biological response that operate independently of attentional processes, the experiments included two attentional conditions in which the subjects either attended to or ignored the stimulus train. Both the electrophysiological and hemodynamic measures were integrated by means of a neuroanatomically constrained source analysis. The fMRI provides the number and locations of possible generators of scalp-recorded ERP components that are active in specific time intervals. Therefore, equivalent current dipoles were kept fixed in location according to fMRI results and their orientations were modeled in order to fit the topographic distribution of specific ERP components. Although the fMRI constrained source analysis has a physiological basis, there is some disagreement between electrophysiological and hemodynamic measurements because fMRI and ERP measure physiologically different aspects of brain activity. Therefore, it is possible that changes in the hemodynamic signal will not have an ERP correlate unless they involve synchronous modulation of an neural population in the 'open field' configuration (Nunez, 1981). These cases could be easily identified in that neural generators located in these areas will not fulfill the electrophysiological constraints of limited activation strength (Nunez, 1990; Opitz *et al.*, 1999). Conversely, neural activity as reflected in the ERPs might not have a detectable hemodynamic counterpart. Considering the amount of experimental variance unexplained by the generator model, one can approximately estimate the likelihood of such activity; the more variance remains unexplained, the more likely are missing sources. Nevertheless, this approach enables us to describe temporal aspects of neural activation in a distributed network underlying novelty processing.

Materials and Methods

Subjects

We measured the electrophysiological and hemodynamic brain response in 16 paid healthy volunteers (ages 20–28 years, median 22 years, six male). Due to coarse movement artifacts in the fMRI session, two subjects had to be excluded from all analyses.

Stimuli

The stimuli used in this study were pure sine tones and unique environmental sounds. The frequencies of the pure tones were 600 and 1000 Hz. The environmental sounds (hereafter referred to as novels) were the same as used previously by Mecklinger *et al.* (Mecklinger *et al.*, 1997). Novel sounds were divided into two groups: identifiable novel sounds, which were reliably identified by subjects, and non-identifiable novels, which were not. This separation was based on a pilot study in which 15 subjects that did not participate in the main experiment were asked (i) to write down the first word that came to mind after hearing the sound, and (ii) to indicate how certain they were about their judgment on a four-point rating scale ranging from very uncertain (0) to very certain (3). Based on this rating the two groups of 50 novels each were selected out of 165 novel sounds. The confidence ratings were 1.98 for identifiable and 0.34 for non-identifiable novels. All stimuli had a duration of 200 ms (including 10 ms rise and 40 ms fall time) and were matched for mean intensity (85 dB/SPL). The stimuli were delivered to the subjects using speakers (EEG-session) or non-magnetic air-conducting headphones (fMRI session).

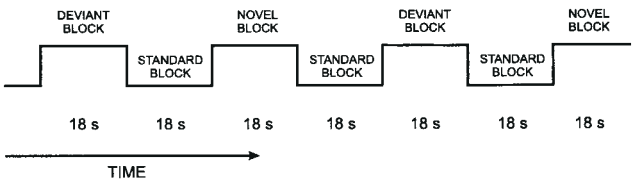

Figure 1. A schematic illustration of the temporal order of the novelty oddball task. During an experimental run 12 standard, 6 deviant and 6 novel blocks were presented. All blocks were comprised of 24 stimuli and had a duration of 18 s.

Procedure

The experiment included separate EEG and fMRI sessions 4 weeks apart, each of which consisted of two tasks: a two-tone auditory oddball task and a novelty oddball task. In the two-tone oddball task subjects were presented with series of low and high tones. Following the two-tone oddball task both sessions continued with the novelty oddball task, including low and high tones as well as novel auditory stimuli. The present report focuses on the novelty oddball task as the results of the two-tone oddball task were reported elsewhere (Opitz *et al.*,1999).

In order to guarantee an optimal comparison of fMRI and ERP data, stimuli were grouped in a blocked design with three block types: standard, deviant and novel blocks. Standard blocks comprised 24 low tones (standard tones) while deviant blocks comprised 16 low-frequency standards and 8 high-frequency, deviant tones. Each novel block contained 16 low tones and 8 novel sounds. The interstimulus interval (ISI) from offset to onset was 550 ms. A complete experimental run consisted of 24 blocks, including 12 standard, 6 deviant and 6 novel blocks, yielding a probability of a deviant tone or a novel sound of 0.083 across all 24 blocks. Standard, deviant and novel blocks alternated in a fixed order, as shown in Figure 1. To control for attentional aspects of deviancy and novelty processing in each session there were two separate runs of 24 blocks each. During the first run, subjects were instructed to watch carefully a silent cartoon video (unattend condition), which was not timelocked to the auditory stimulation, whereas during a second run they had to fixate the center of the black screen and silently count the high tones designated as task relevant targets (attend condition). Subjects were not informed that the novel stimuli would be presented, and if they asked, they were reminded to respond only to the target tones. The order of experimental runs was constant across subjects, with the unattend condition being performed before the attend condition.

MR Procedures

Imaging was performed at 3 T on a Bruker Medspec 30/100 system. The standard birdcage head coil was used. Subjects were supine on the scanner bed, with cushions used to reduce head motion. For each subject high-resolution, whole-brain images were acquired, to assist localization of activation foci using a T_1-weighted three-dimensional segmented MDEFT (128 slice sagittal, 1.5 mm thickness, 256 × 256 pixel matrix). To align the echo planar functional images to the three-dimensional images conventional anatomical images in plane with the functional images were acquired as an intermediate step using an IR-RARE sequence (T_E = 20 ms, T_R = 3750 ms, matrix 512 × 512). Finally, functional images were acquired using a gradient EPI sequence (T_E = 40 ms) sensitive to BOLD contrast. Data were collected from seven axial slices, parallel to the AC–PC line at a rate of 2 s/image. Slice thickness was 6 mm and interslice distance was 2 mm. The field of view (FOV) was 250 mm with a matrix of 128 × 64.

fMRI data were processed using the BRIAN software package (Kruggel and Lohmann, 1996). Prior to any statistical analyses movement artifacts were detected by thresholding the ratio of foreground (brain) and background intensity for each timestep. Timesteps at which this ratio was <12.5 were classified as artifacts (Kruggel *et al.*, 1998). Markov random fields (Chalmond, 1988; Kruggel *et al.*, 1998) were used for signal restoration in spatial and temporal domain. For each subject voxel-wise Pearson correlations of fMRI time series with a box car reference waveform were calculated to contrast activation related to the processing of both novel events with the standard tones. The box car function resembled the blocked design and was delayed for 4 s to account for delay in the hemodynamic response (Buckner *et al.*, 1998). The correlation statistics were normalized to *Z*-scores. A significance level threshold [$P < 0.05$, corrected for multiple spatial comparisons (Friston *et al.*, 1994)] was used to determine the presence of significant activation foci. Activation maps were registered with individual high-resolution three-dimensional datasets and transformed into stereotactic Talairach space (Friston *et al.*, 1995; Kruggel, 1995). Multisubject averaging was used to enhance the signal-to-noise ratio.

For each subject clusters of activation of interest were determined by identifying all contiguous voxels within a distance of 15 mm from the center of the averaged activation that reached the significance level. The mean value of the number of activated voxels of these clusters across the two hemispheres was calculated for each individual subject separately for identifiable and non-identifiable novels and subjected to a Wilcoxon signed-rank test to assess significant overall differences in brain activation between both novel types. In a second analysis, the left–right difference of the number of activated voxels was estimated for either novel type and subjected to a Wilcoxon test to evaluate novel type-specific lateralization of brain activity.

EEG Recordings

EEGs and EOGs were recorded continuously with a bandpass filter of 0.1–70 Hz and were digitized at a rate of 250 Hz. EEGs were recorded from 128 electrode sites using an Electrocap. Vertical and horizontal EOGs were recorded from three electrode pairs placed on the infra- and supraorbital ridges of the left and the right eye and the outer canthi of the two eyes. All leads were referenced to nosetip. Electrode impedance was kept <2 kΩ. ERP data were epoched off-line for a 1000 ms period (including a 200 ms prestimulus baseline). Prior to averaging, epochs were scanned for eye movement and other artifacts. Whenever the standard deviation in a 200 ms interval exceeded 40 μV an epoch was excluded from averaging. ERPs were computed separately for standards, deviants and both groups of novel sounds. For analogous comparison with fMRI data, only difference waveforms were analyzed. These difference waveforms were derived by subtracting the standard from the deviant or novel ERPs separately for both conditions.* The latency of ERP components was measured relative to stimulus onset.

For statistical analyses the ERPs to novel stimuli were quantified as mean voltages in an early (320–360 ms) and late (400–440 ms) time interval. To minimize type I error due to a large number of statistical tests of multi-electrode and multi-time window data, analyses were carried out for topographical regions (Oken and Chiappa, 1986). Six regions, comprised of six electrodes each, were defined over left, medial and right frontocentral and parietal scalp sites where the ERP effects of interest were largest. Repeated-measure ANOVAs were used to compare the ERPs to both novel types in the attend and the unattend condition. Factors were novel type (two levels), region (six levels) and time interval (two levels). Huynh–Feldt correction was used where appropriate. Uncorrected degrees of freedom and corrected *P*-values are reported in the Results.

Dipole Modeling

In order to assess temporal aspects of the processing network identified in fMRI activation maps a neuroanatomically constrained source analysis was utilized. For source localization purposes realistically shaped head models were developed using the boundary element method (BEM). Three compartments of the head were taken into account: the brain (including cerebrospinal fluid), skull and scalp (Cuffin, 1990). The conductivities were set to 0.33 S/m for the brain and the scalp and 0.0042 S/m for the skull. The head model was derived from 50 averaged, Talairach normalized MRIs, stored in a local brain database.

All estimations related to fMRI or EEG measurements were carried out in the reversed head system (Wieringa, 1993). The *y*-axis runs through the preauricular points from right to left and the *x*-axis runs perpendicular to the *y*-axis towards the nasion. The *z*-axis points to the vertex. On the MRI the nasion and both preauricular points were identified. Thus the MRI could be transformed to the head system using these markers.

Dipole locations were kept fixed according to the fMRI activation foci averaged across subjects. Orientations of dipoles were fitted with the ASA software (ANT Software BV, Hengelo, The Netherlands) using the average reference ERP data. The obtained model was subjected to further evaluation. First, explained variances were determined to assess the goodness of fit. Second, we evaluated whether the fitted dipole parameters, orientation and strength fulfill neuroanatomical and electrophysiological constraints, i.e. best-fitting dipole orientations were expected to be perpendicular to local cortical gray matter and the dipole strength should be in accordance with the characteristics of neural currents (Freeman, 1975; Nunez, 1990). Finally, the specificity of the dipole model to a particular ERP component was estimated by keeping dipole location and orientations fixed and calculating the time course of dipole strength and goodness of fit over the period from 100 ms before to 600 ms after stimulus onset.

Results

ERP

Unattend Condition

Figure 2 shows the ERP waveforms averaged across 14 subjects in the unattend condition. Deviant stimuli evoked a mismatch negativity (MMN), i.e. an enhanced negativity at frontal electrode sites, with polarity reversal at mastoid sites (Näätänen *et al.*, 1978). Using a repeated-measure ANOVA with the two-level factor stimulus type this observation was confirmed by significant differences between deviants and standards in the 120–160 ms time interval at Fz [–1.82 μV, $F(1,13) = 8.25$, $P < 0.001$) and mastoid recording sites (1.39 μV, $F(1,13) = 9.75$, $P < 0.001$). No further systematic differences between standards and deviants were obtained.

Both novel types elicited a frontocentrally distributed novel P3, peaking around 260 ms (measured at the Fz electrode). A repeated-measure ANOVA, with factors stimulus type (three levels) and region (six levels), revealed a main effect of novel type [$F(2,26) = 16.66$, $P < 0.0001$]. *Post-hoc* analyses exhibited larger positivities for both types of novels as compared to the standards [all $F(1,13)$ values > 22.27, $P < 0.0005$]. In an additional analyses no significant effect of novel type [$F(1,13) = 1.03$, $P > 0.33$] and no interaction between novel type and region [$F(5,65) = 1.10$, P 0.37] were observed.

* Since the fMRI data were obtained by block comparisons it could be argued that forming ERPs for all stimulus classes within a block (standards and novels in the novel blocks and standards only in the standard blocks) would yield a more valid comparison between ERP and fMRI data. But one should keep in mind that the ISI between two successive novel stimuli was rather short (mean ISI = 2.05 s). Thus, due to its temporal extent the hemodynamic responses to two successive novel stimuli will overlap in time and add in a linear fashion (Dale and Buckner, 1997). In contrast, the ERP waveforms to successive novel sounds do not summate. Contrasting novel blocks with standard blocks will reveal fMRI activation specific to the processing of novel sounds, but averaging ERPs across all stimulus classes within a block will not. Therefore, and for reasons of comparability with former ERP studies, we computed ERPs separately for each stimulus type.

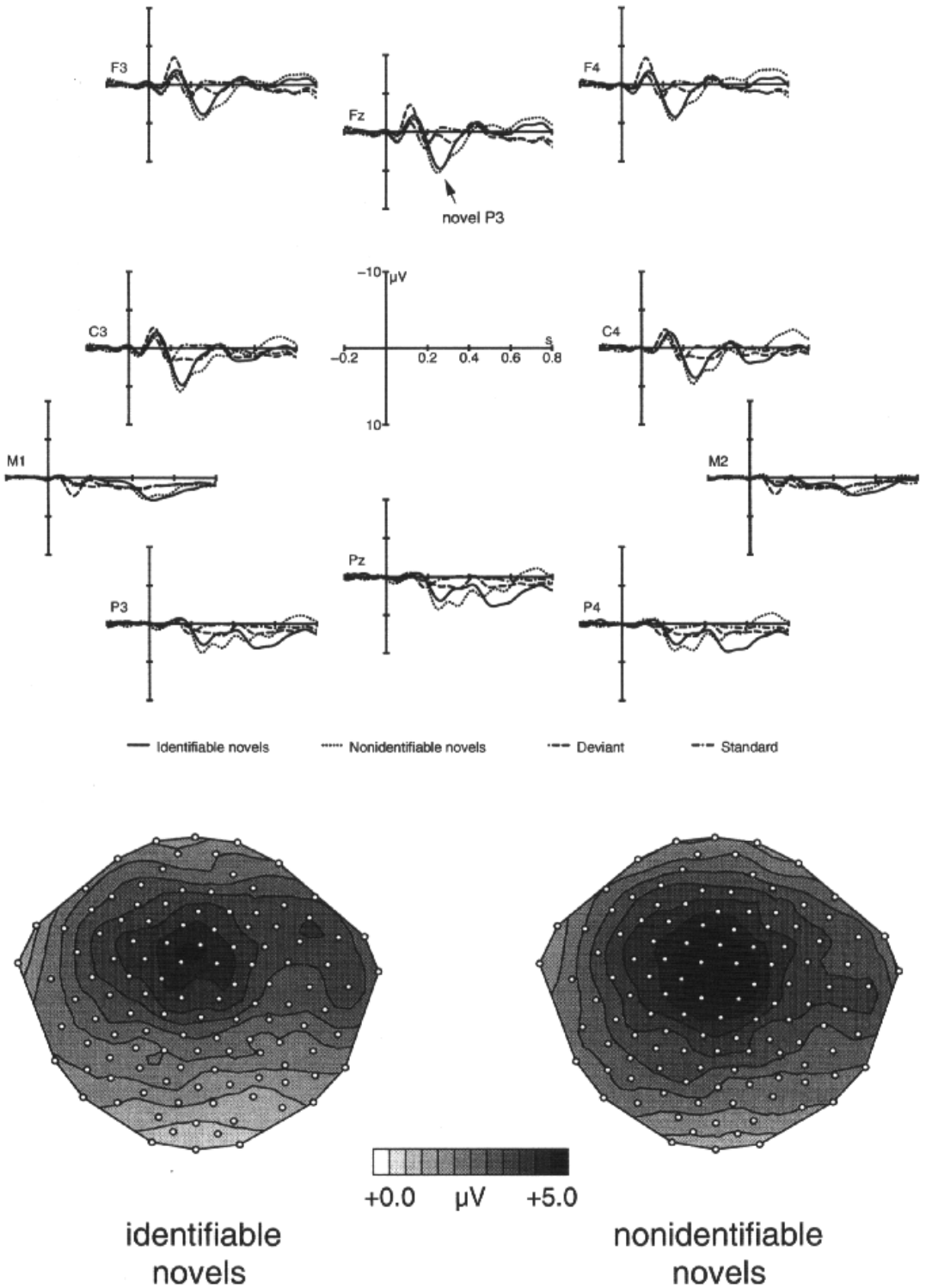

Figure 2. Unattend condition. (Upper panel) Grand average waveforms obtained for the standard, deviant and both novel stimuli. The waveforms are displayed for selected electrodes of the 10–20 system. (Lower panel) Scalp distribution of the difference novel – standard waveforms separately for identifiable and non-identifiable novels in the 320–360 ms time interval. Dark areas indicate positive differences. In this and following figures nose is plotted up.

Attend Condition

Task performance was high across subjects, with a mean error rate of 2.1%. In this condition, the deviants evoked a frontally focused MMN complex. Contrasts between standards and deviants yielded larger negative deflections at Fz for deviants than for standards [−2.42 μV, $F(1,13) = 5.54$, $P < 0.001$]. As revealed by an ANOVA contrasting the mean voltages between 120 and 160 ms in both conditions (unattend versus attend) the attention manipulation did not affect the MMN component [$F(1,13) = 0.90$, $P > 0.36$]. The subsequent P3b component to

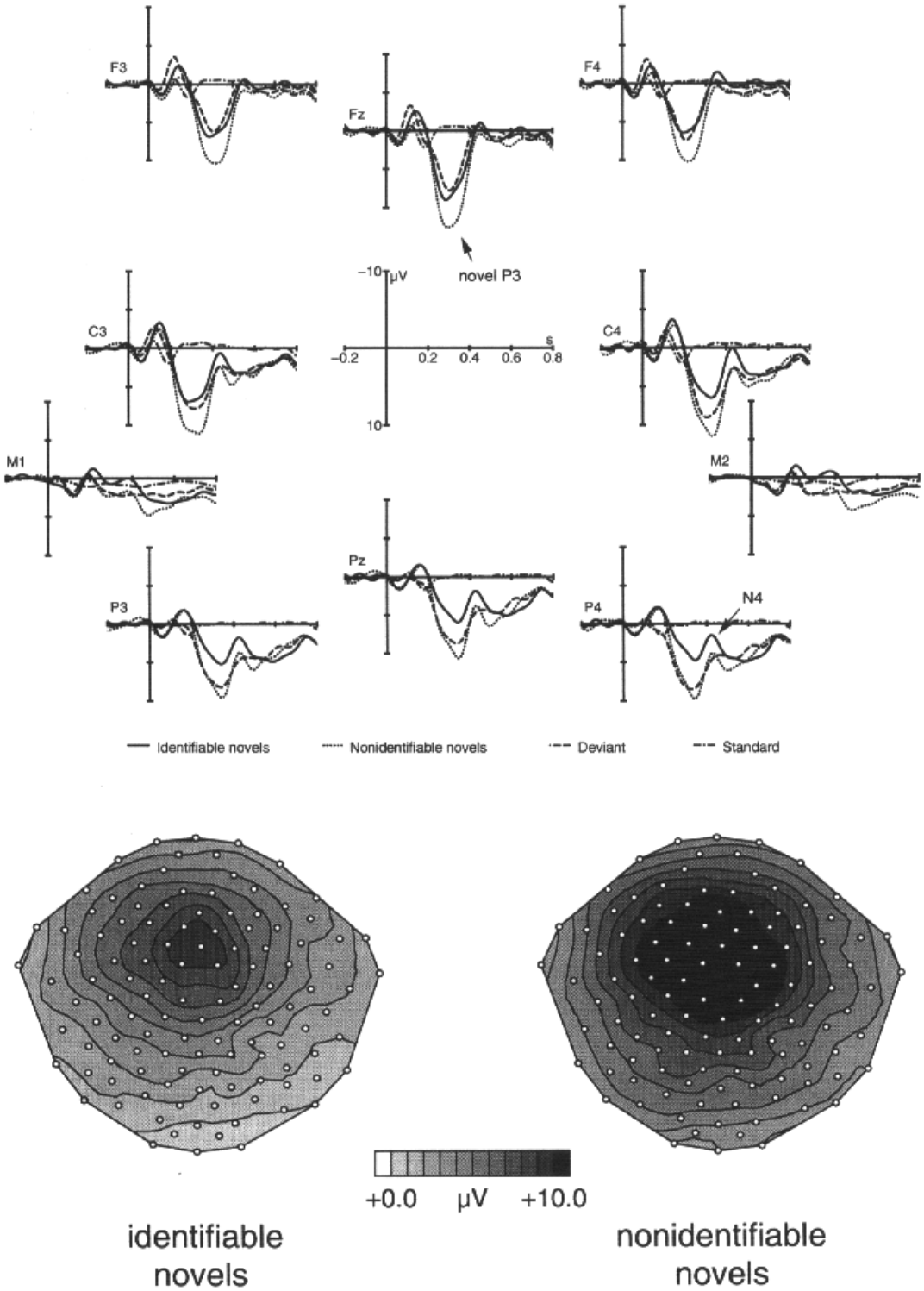

Figure 3. Attend condition. (Upper panel) Grand average waveforms obtained for the standard, deviant and both novel stimuli. (Lower panel) Scalp distribution of the difference novel – standard waveforms separately for identifiable and non-identifiable novels in the 320–360 ms time interval. Dark areas indicate positive differences. Note the different scaling of potential maps compared with Figure 2.

deviants showed a parietal maximum with a peak latency of 364 ms (at Pz electrode, Fig. 3).

As in the unattend condition, both types of novels elicited frontocentrally focused novel P3s (peaking around 280 ms). This observation was confirmed by an ANOVA with the three-level factor stimulus type, which revealed a significant main effect stimulus type [$F(2,26) = 36.75$, $P < 0.0001$]. Tested separately, both novel types showed more positive going waveforms than standards [all $F(1,13)$ values 33.5, $P < 0.0001$]. The novel P3s of both types of novels in the attend condition were larger than in

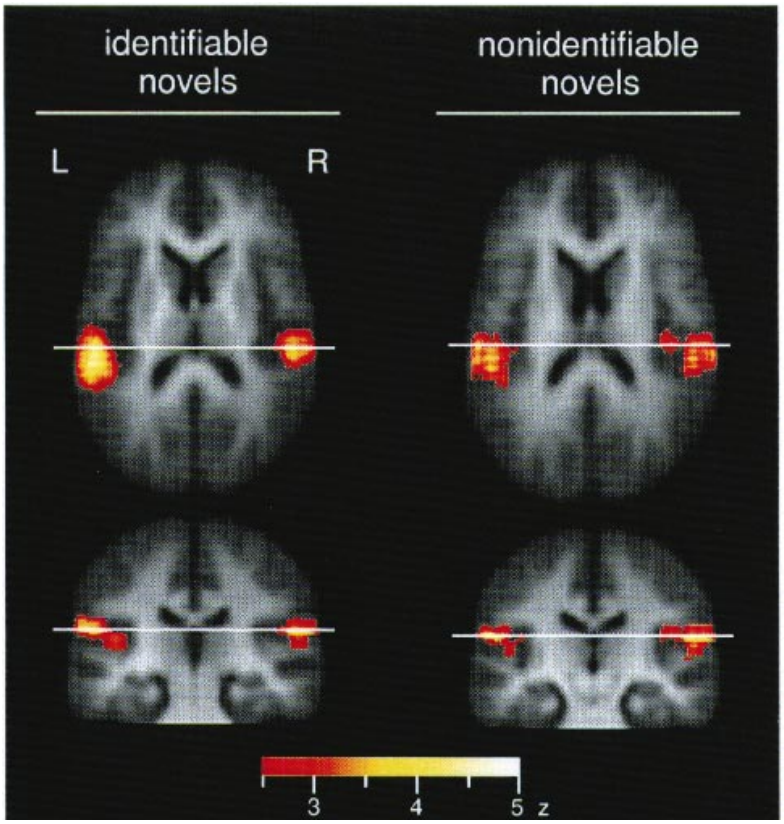

Figure 4. Unattend condition. Signal increases are shown for the novel versus standard blocks. Statistical maps were superimposed on an average structural MRI in Talairach space. Bright colors represent more significant activation, as indicated by the scale bar. (Left panel) Identifiable novels. (Right panel) Non-identifiable novels. The white lines on axial slices indicate the coronal section and vice versa.

Table 1
fMRI activation peaks associated with processing of novel stimuli in the unattend condition

Novel type	Peak location			*P*-value at peak	Size (mm^3)	Cortical region
	x	*y*	*z*			
Identifiable	49	–28	15	0.001	4096	superior temporal gyrus R
	–48	–30	17	0.001	4924	superior temporal gyrus L
Non-identifiable	49	–28	15	0.0005	5847	superior temporal gyrus R
	–47	–30	16	0.0005	4374	superior temporal gyrus L

The *x*, *y* and *z* coordinates are those of the Talairach and Tournoux system (Talairach and Tournoux, 1988).

the unattend condition as indicated by a significant main effect of attention [$F(1,13) = 11.15$, $P < 0.005$]. Notably, identifiable and non-identifiable novel sounds evoked different ERP patterns. The repeated-measure ANOVA for both time intervals of the attend condition revealed a significant main effect of novel type [$F(1,13) = 5.93$, $P < 0.05$] and significant interactions of novel type × region [$F(5,65) = 5.97$, $P < 0.01$] and novel type × time interval [$F(1,13) = 5.75$, $P < 0.05$]. For the early time interval a significant main effect of novel type [$F(1,13) = 8.13$, $P < 0.05$] was observed, indicating that the frontally focused novel P3 was more pronounced for non-identifiable than for identifiable novels. Second, for non-identifiable novels an additional parietally focused P3 component was obtained. This P3 component had a similar scalp distribution as the P3b to deviants. This result will hereafter be referred to as the parietal P3 effect (cf. Fig. 3). In contrast, identifiable novel sounds evoked a parietal negative-going deflection peaking around 420 ms. In light of the temporal and topographical similarities with the N4 component usually evoked by semantically unexpected language materials (Kutas and Hillyard, 1983), we will refer to this negativity as a N4-like component. An ANOVA performed separately for the late time interval revealed a significant effect of novel type [$F(1,13) = 4.95$, $P < 0.05$] and a marginally significant novel type × region interaction [$F(5,65) = 2.58$, $P < 0.1$]. These results suggest that the two novel types are processed differently.

To summarize the ERP results, both novel types (identifiable and non-identifiable) elicited a frontocentrally distributed novel P3 in both the attend and the unattend condition. There was a significant effect of attention on the amplitude of the novel P3, with the novel P3 being larger in the attend condition. Only in this condition did the ERPs to both novel types differ. At frontal recording sites the non-identifiable novels evoked larger novel P3s, whereas at posterior electrodes a parietal P3 effect for non-identifiable novels and a subsequent N4-like effect for identifiable novels were obtained.

fMRI

Unattend Condition

The statistical parametric maps, representing the BOLD response to both novel stimuli in the unattend condition, revealed two significant clusters of activity in the left and right superior temporal gyri (STG) (see Table 1 and Fig. 4). A Wilcoxon signed-rank test at an α-level of 0.05 did not reveal any significant differences in fMRI activation between identifiable and non-identifiable novels (Wilcoxon $t = 0.30$), nor was there a significant difference in

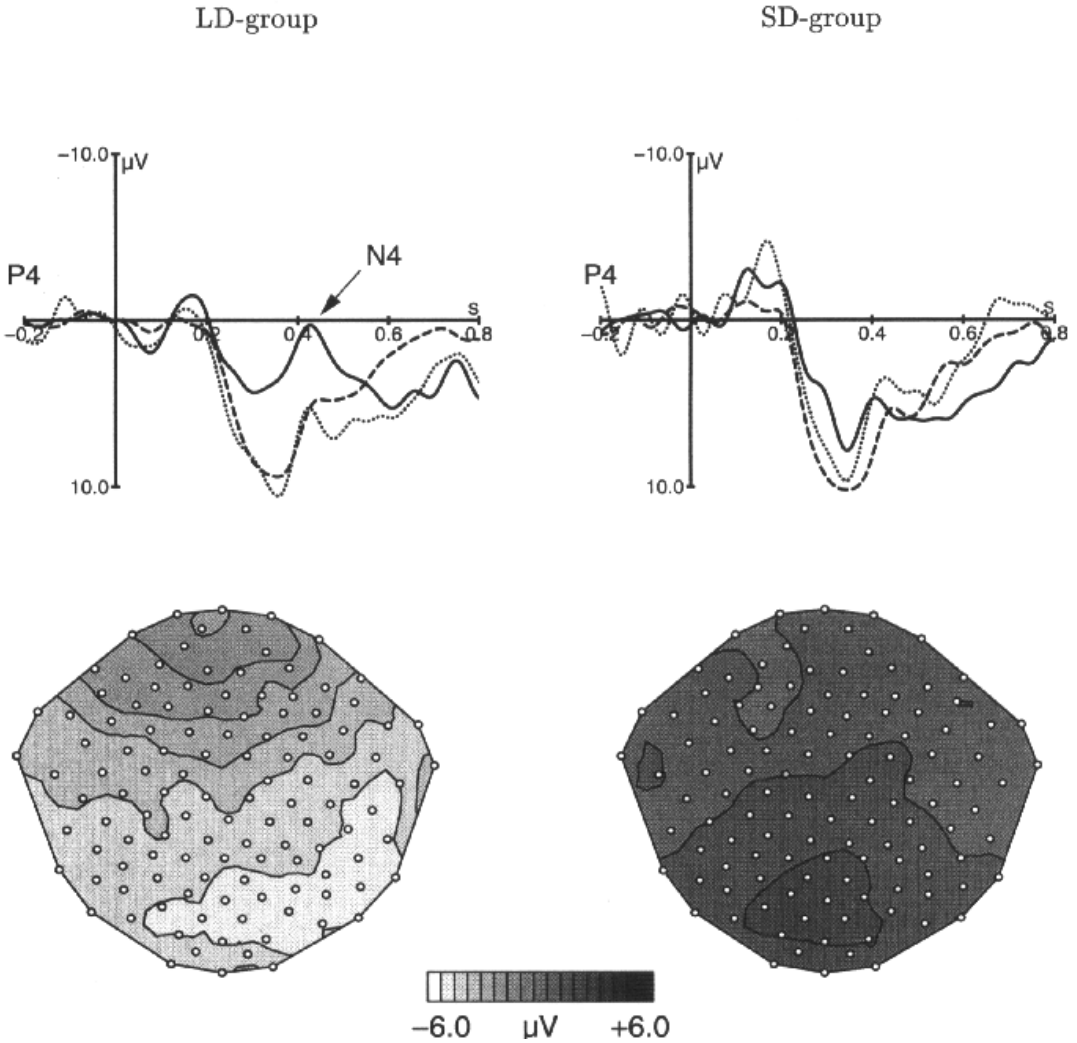

Figure 5. Attend condition. ERP waveforms for a representative electrode of the right parietal region (upper panel) and the scalp distribution (lower panel) of the N4-effect for the LD (left) and SD groups (right) are shown. Dark areas in the potential maps indicate positive and light areas negative differences between identifiable and non-identifiable novel sounds. Note the right lateralized effect for the LD group.

lateralization between the two novel types (Wilcoxon $t = 0.66$, $P > 0.51$).

Attend Condition

In this condition the fMRI activation pattern again was comprised of two significant clusters of activity in the left and right STG (see Table 2 for Talairach coordinates), which were almost identical in size and location to those obtained in the unattend condition. As in the unattend condition, a Wilcoxon signed-rank test at an α-level of 0.05 did not reveal any significant differences in mean fMRI activation size between identifiable and non-identifiable novels (Wilcoxon $t = 0.34$). Furthermore, no specific lateralization could be obtained for either novel type (Wilcoxon $t = 1.09$, $P > 0.27$).

Given the differential ERP waveforms obtained for identifiable and non-identifiable novels, the absence of any differences in the fMRI activation pattern was surprising. Therefore, in a *post-hoc* analysis we conducted a median split of the sample according to the most salient ERP differences between identifiable and non-identifiable novels, namely the N4-effect, which was only obtained for identifiable novels. Subjects showing a large N4-effect will be referred to as the large difference group (LD-group), while the other subjects, with a weak or no N4-effect, formed the small difference group (SD-group). The ERP waveforms of both novel stimuli at a representative electrode from the right parietal region and the scalp topography of the N4-effect for both groups are displayed in Figure 5. When the N4-effect in the late time interval (400–440 ms) was tested separately for each group, a significant effect of novel type [$F(1,6) = 6.35$, $P < 0.05$] and a significant novel type × region

Table 2
fMRI activation peaks associated with processing of novel stimuli in the attend condition

Novel type	Peak location			*P*-value at peak	Size (mm^3)	Cortical region
	x	*y*	*z*			
Identifiable	47	–31	13	0.001	3174	superior temporal gyrus R
	–45	–28	14	0.0005	4296	superior temporal gyrus L
Non-identifiable	46	–28	14	0.0001	5896	superior temporal gyms R
	–43	–29	14	0.0005	3758	superior temporal gyrus L

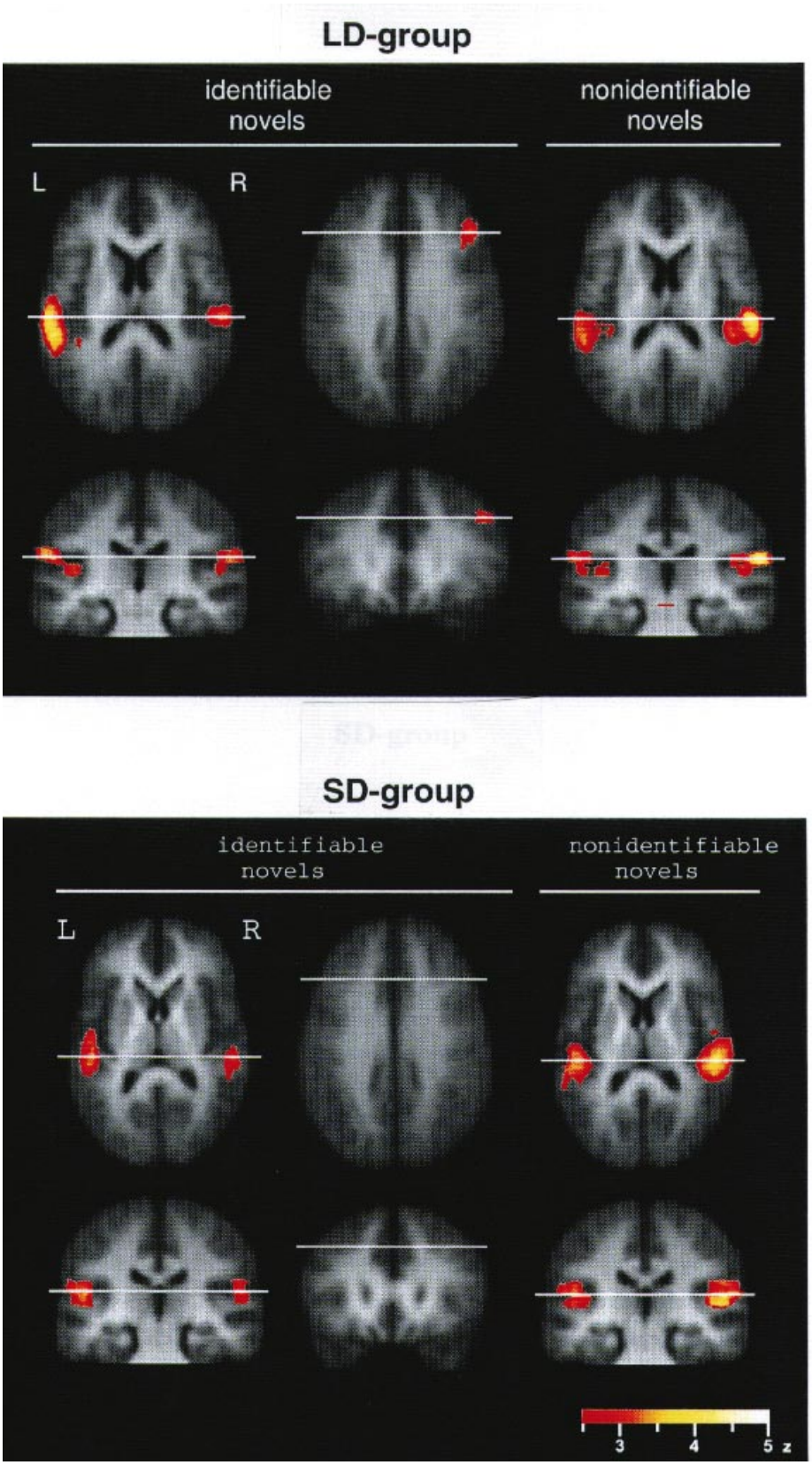

Figure 6. Attend condition. fMRI results for the novel versus standard block comparisons obtained by averaging across groups. (Upper panel) LD-group. (Lower panel) SD-group. Note that the slices where right frontal activation was obtained for the LD-group are also shown for the SD-group although no activation was present. The color scale is identical to that in Figure 4. The white lines on axial slices indicate the coronal section and vice versa.

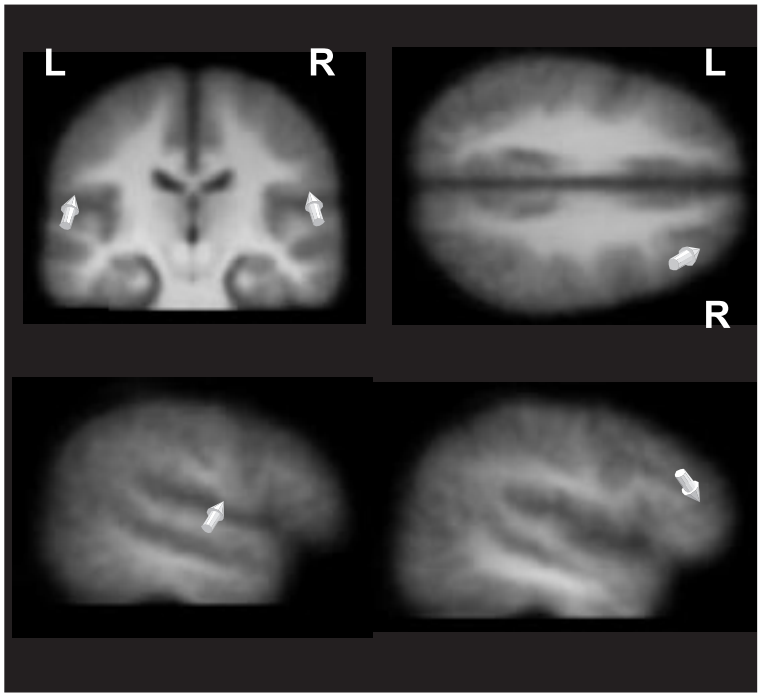

Figure 7. Best-fitting dipoles for the identifiable novels were superimposed on an average structural MRI in Talairach space. Two dipoles were placed bilateral in the superior temporal gyrus (left panel) and one dipole in the right inferior frontal gyms (right panel). Both sagittal views show the right hemisphere.

interaction [$F(5,30) = 9.32$, $P < 0.001$] were found only for the LD-group. Tests performed separately for single regions revealed larger N4-like components in right and medial parietal regions [$F(1,6)$ values > 8.27, $P < 0.05$], but not in other regions (all P-values > 0.5) for the LD-group.

In the early time interval (320–360 ms) the ANOVA was restricted to the three frontal-central regions of the initial design to contrast the novel P3 elicited by identifiable and non-identifiable novels for each group. Neither the main effect group [$F(1,12) = 1.55$, $P > 0.37$] nor the novel type × group interaction [$F(1,12) = 0.42$, $P > 0.53$] were significant, indicating that the novel P3 did not differ between groups. Thus, the two groups mainly differ in the presence and absence of the N4-effect.

When the fMRI data analysis was conducted separately for the LD- and SD-groups, the activation pattern for identifiable and non-identifiable novels was clearly dissociable for the LD-group, but not for the SD-group (Fig. 6).

In the LD-group bilateral activation of the midportion of the STG was obtained for the non-identifiable novels. The same part of the STG was activated by identifiable novels (see Fig. 6, upper panel and Table 3). In this group an additional right frontal activation for identifiable novels was found (peak at x,y,z = 36,23,34; $P < 0.01$). For the SD-group a similar pattern of STG activation was found for both types of novel stimuli (see Table 3), whereas no activation of the right frontal area even at low ($Z < 1$) thresholds was obtained. This between-group difference in right prefrontal activation was confirmed using an ANOVA contrasting the Z-scores of this region of both groups [$F(1,12) = 3.52$, $P < 0.005$].

Table 3
fMRI activation peaks associated with processing of novel stimuli in the attend condition for both groups

Group	Novel type	Peak location			P-value at peak	Cortical region
		x	y	z		
LD	identifiable	36	23	34	0.01	inferior frontal gyms R
		46	–27	13	0.005	superior temporal gyms R
		–45	–29	14	0.001	superior temporal gyrus L
	non-identifiable	45	–24	12	0.001	superior temporal gyrus R
		–44	–28	12	0.005	superior temporal gyrus L
SD	identifiable	46	–31	13	0.005	superior temporal gyms R
		–45	–30	12	0.001	superior temporal gyrus L
	non-identifiable	45	–27	12	0.001	superior temporal gyrus ll.
		–42	–30	12	0.005	superior temporal gyrus L

Modeling

Based on these results it can be hypothesized that (i) bilateral activation of the middle STG accounts for the generation of the novel P3, whereas (ii) an additional right frontal generator might contribute solely to the ERP waveforms for identifiable novels. To test these hypotheses we modeled the scalp ERP distribution of the LD-group, for which reliable ERP differences between both novel types were obtained, using dipole source locations in both STGs as derived from functional images. The obtained best-fitting orientations for the identifiable novels were superimposed on an averaged MRI (Fig. 7). As is apparent from the figure, the modeled dipole orientations were almost perpendicular to the gray matter.

Examination of the time course of dipole activation in the LD-group revealed that the dipole solution for identifiable as well as non-identifiable novels explained >90% of the signal variances in the time range 260–360 ms (Fig. 8, left panel). Furthermore, the left and the right STG dipoles showed similar activation time courses for identifiable and non-identifiable novels, with their maximal activity within the novel P3 latency range (Fig. 8, right panel). These results support the view that the middle STG is one of the contributors to the scalp-recorded novel P3.

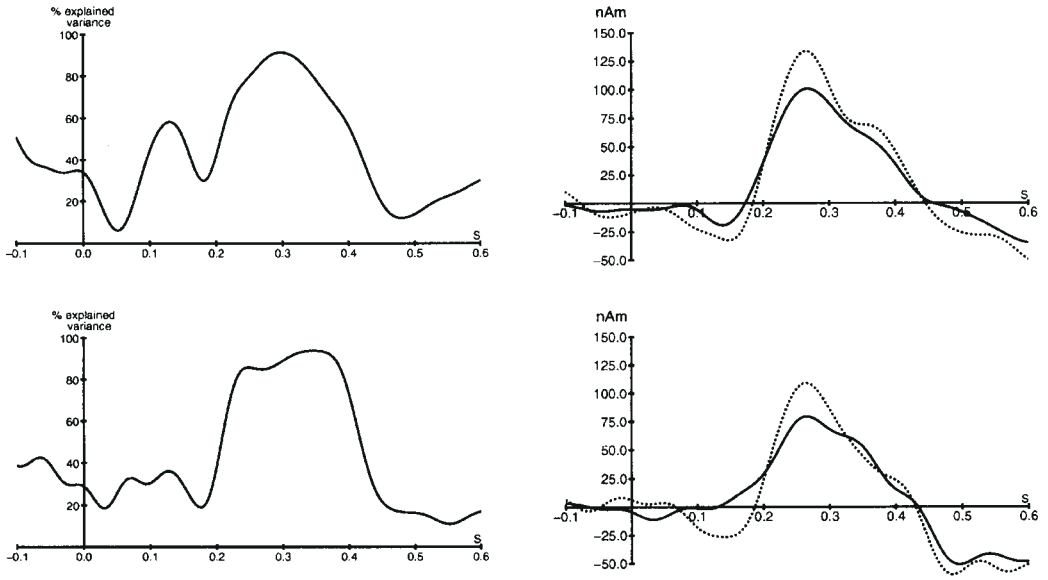

Figure 8. Percent explained variance (left) and dipole strength (right) of the two dipole solution of the novel P3 for identifiable (upper panel) and non-identifiable novels (lower panel) in the LD-group. The solid traces in the right panel indicate left hemispheric dipoles, dotted traces right hemispheric dipoles.

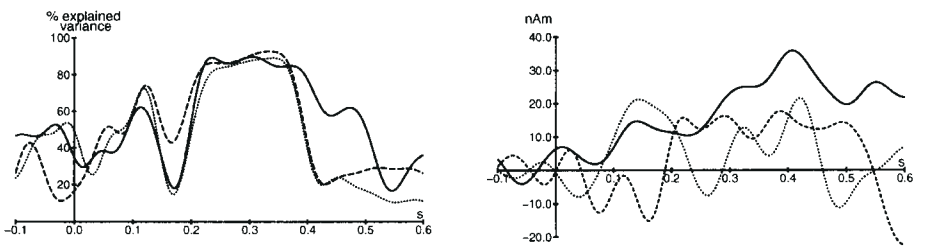

Figure 9. Percent explained variance (left) and the time course of dipole strength (right) of a constrained right frontal dipole for identifiable (solid line) and non-identifiable (dotted line) novels and an unconstrained dipole initially placed in the left hemisphere for identifiable novel sounds (dashed line). Note the clear activation peak and the larger amount of explained variance around 400 ms for identifiable novels only.

In a second step we added a dipole placed in the right frontal area that was activated by identifiable novels. The location of this additional dipole is illustrated in the right panel of Figure 7. In order to evaluate the reliability of this constraint the same analysis with identifiable novel stimuli was carried out using an unconstrained dipole initially placed in left frontal brain regions. Moreover, the constrained right frontal dipole was also used to model the waveforms to non-identifiable novels. The corresponding time courses of dipole activation strength for all three models are shown in Figure 9. Consistent with the ERP data, a clear maximum of dipole strength was obtained subsequent to the novel P3 for identifiable but not for non-identffiable novels. Furthermore, in case of the unconstrained dipole a weak dipole strength was obtained in the time interval from 200 to 550 ms, indicating a rather unspecific activity.

In addition, the three dipole model for identifiable novels, including two bilateral STG dipoles and one right frontal dipole, explained more of the signal variances in the late time interval 400–440 ms than did the corresponding two-dipole model. The third dipole in this model accounted for 47% of the variance in the ERP evoked by identifiable novels but only 15% in the ERP evoked by non-identifiable novels (see Fig. 9, left panel). The unconstrained dipole did not substantially increase the goodness of fit, again pointing to unspecific contributions to the ERP waveforms. This further strengthens the observation that the right frontal BOLD response is apparent for identifiable but negligible for non-identifiable novels.

Discussion

In the present report ERP and fMRI results obtained with the same subjects in separate but identical sessions were integrated in order to investigate the functional neuroanatomy underlying novelty processing. Based on prior studies that revealed different ERP patterns elicited by identifiable and non-identifiable novel sounds (Mecklinger *et al.*, 1997), our analysis focused on both electrophysiological and hemodynamic activity associated with these two kinds of sounds. In the ERP domain both types of novels elicited frontally focused novel P3s, independent of whether or not the subjects paid attention to the stimulus stream. This result confirms the view that novelty detection is not reliant on attention, and rather is associated with an automatic orienting response (Kenemans *et al.*, 1989; Näätänen, 1992; Friedman *et al.*, 1998). Despite this, the amplitude of the novel P3 was modulated by the direction of attention, with larger amplitudes in the attention condition. This finding is consistent with results of recent ERP studies (Holdstock and Rugg, 1995; Friedman *et al.*, 1998) assuming further processing of novel sounds in the attend but not in the unattend condition. The distinct ERP patterns elicited by the two types of novels in the attention condition suggested different such processes as a

function of novel type. First, the novel P3 at frontal recording sites was more pronounced for non-identifiable than for identifiable novels. This finding can be interpreted in the light of recent findings by Cycowicz and Friedman (1998). The authors analyzed ERP responses to familiar and unfamiliar novels sounds at a first and second presentation. Similarly to the present study, a novel sound's familiarity was defined as the availability of a 'conceptual name' (Cycowicz and Friedman, 1998, p. 33). In their study familiar but not unfamiliar novels showed a reduction of the frontal novel P3 at second presentation. Given that in the present study the attend condition always followed the unattend condition, it is conceivable that the decreased novel P3 to identifiable sounds reflects a similar repetition-related modulation as in the Cycowicz and Friedman study. A second effect of identifiability of the novel sounds was found at posterior recording sites. While a posterior distributed P3 component was obtained for non-identifiable novels, identifiable novels evoked an N4-like component, subsequent to the parietal novel P3. Consistent with Mecklinger *et al.* (Mecklinger *et al.*, 1997) we take this component to reflect conceptual semantic integration processes, i.e. the identification of the mental concept expressed by these sounds.

By contrasting novel and standard blocks in the fMRI session a bilateral increased hemodynamic response in the middle part of the superior temporal gyrus was obtained for both novel types, demonstrating the involvement of this brain region in novelty processing.

At this point it remains unclear how and to what extent the ERP and fMRI findings obtained in the present study overlap. Combining ERP and fMRI results by means of neuroanatomically constrained inverse modeling suggested that the middle part of the STG substantially contribute to the generation of the novel P3. The sources of the novel P3 are located more anterior in the STG as compared with the sources of the auditory target P3 reported in a previous study (Opitz *et al.*, 1999). This could account for the distinctive scalp distribution of the novel P3. Consistent with this result, a contribution of anterior temporal cortex activity to the novel P3 has been observed in a MEG study (Alho *et al.*, 1998). Further evidence for temporal cortex contribution to the anterior P3 is also provided by intracranial recordings (Alain *et al.*, 1989; Halgren *et al.*, 1995a,b). Moreover, extensive temporo-parietal lesions centered in the superior temporal cortex attenuated the P3 to novel sounds especially at posterior recordings (Knight *et al.*, 1989).

Despite this converging evidence for a STG contribution to novelty processing there is a lack of consistency with respect to hippocampal involvement in these processes. Human lesion studies (Knight, 1996) as well as intracranial recordings (Halgren *et al.*, 1995b) have suggested an important role of the hippocampal/parahippocampal region in the processing of novel information. The patients investigated by Knight (Knight, 1996) showed heterogeneous hippocampal/parahippocampal lesions particularly extending laterally and anteriorly. As indicated in a recent single-neuron recording study in rhesus monkeys, the inferior temporal cortex appears to be critically involved in novelty processing (Miller *et al.*, 1991) and therefore might contribute to Knight's findings (Knight, 1996). Our data, however, did not reveal significant activation within or in the vicinity of this region. Other studies also failed to demonstrate hippocampal activity in similar task situations (Shallice *et al.*, 1994; Tulving *et al.*, 1994; Buckner *et al.*, 1995). There are at least two possible explanations for this discrepancy. First, the differences in medial temporal lobe activity between novel and standard blocks simply might have been too low to cause detectable changes in the BOLD response in the present study (Rugg, 1998). Second, Halgren *et al.* (Halgren *et al.*, 1995b), using depth electrode recordings in the medial temporal lobes in epileptic patients, did not find the typical local polarity inversions and assume that these potentials are generated in cortical regions of the superior temporal lobes, an argument compatible with our findings.

There may be some limitations of the utility of the fMRI data to constrain ERP source localization in the present study, as not all brain structures described in earlier studies to be critically involved in novelty processing could be imaged due to the limited slice nuinber. But the high amount of explained variances (>90%) in the novel P3 time interval suggested that the midportion of the superior temporal gyri are the major contributors to novelty detection processes, reflected in the novel P3.

Those subjects that showed an enhanced N4-response to identifiable novels in the ERP also yielded increased hemodynamic activity to these sounds in the right prefrontal cortex (rPFC). The involvement of prefrontal cortex in novelty processing was suggested by a SPECT study demonstrating a correlation of novel P3 amplitude and blood flow in the anterior cingulate cortex (Ebmeier *et al.*, 1995). Further evidence for the involvement of PFC in novelty processing was provided by neuropsychological studies showing a decreased ERP response to auditory and visual novel stimuli after unilateral prefrontal lesions including fiber pathways from dorsolateral as well as medial prefrontal regions (Knight, 1984, 1997). However, the lack of selective amplitude reduction of the novel P3 over the lesioned hemisphere led Knight (Knight, 1984) to conclude that the prefrontal cortex is not the primary generator of these brain potentials but rather modulates generators located elsewhere, e.g. in the superior temporal cortex. In patients with lesions centered in the temporal plane a selectively reduced novel P3 over the hemisphere ipsilateral to the lesion was observed, indicating a direct contribution of these brain structures to the novel P3 (Knight, 1997). Another line of evidence for the notion that the prefrontal cortex might act as an attentional control system was added by a recent study that compared the novel P3 in young and old adults (Friedman *et al.*, 1998). They examined the novel P3 in an attend and an ignore condition and found a reduced novel P3 for old as compared to young adults in the attend condition, but identical novel P3 for young and old adults in the ignore condition. This finding may also be taken to suggest that prefrontal activity during an attended novelty oddball task more likely reflects attentional modulations rather than a true generator of the scalp recorded novel P3. Under the assumption that such an attention modulating function of the prefrontal cortex is also engaged in the present study it might have been similarly involved in standard and novel blocks and thus not been observable in the present fMRI comparisons. This similarly high involvement of attentional processes in the two blocks may be caused by the high auditory background noise produced by the scanner. Moreover, unlike the present study, other studies only used one or a restricted set of novel stimuli, thus limiting the examination space of conceptual-semantic aspects of novelty processing. Furthermore, as none of these studies reported a specific lateralization of frontal lobe involvement in novelty processing, processes other than novelty detection seem to be reflected in lateralized PFC activity in general, and in the rPFC found in the present study in particular.

The results of the combined analyses suggest that the rPFC is

activated only for those novel events for which a semantic concept can be activated and that this activation is delayed relative to processes underlying novelty detection. In previous functional imaging studies rPFC activation of similar kind has been found when previously learned materials had to be retrieved from episodic memory relative to a comparable reference task [for an overview see Nyberg *et al.* (Nyberg *et al.*, 1996)]. These studies have led to the idea that the PFC, especially in the right hemisphere, is engaged in either post-retrieval monitoring (Rugg *et al.*, 1996) or in maintaining a retrieval set (Nyberg *et al.*, 1995). Similar suggestions have been made based on ERP recordings that showed a late developing sustained positive slow wave with a right frontal topography that is related to post-retrieval control processes (Wilding and Rugg, 1996; Mecklinger and Meinshausen, 1998). Based on these findings it is conceivable that accessing and retrieving a sound's meaning is associated with some sort of post-retrieval processing or with the activation of a retrieval set, and that these latter processes are mediated by the rPFC [similar arguments are given by Moscovitch (Moscovitch, 1992) and Fletcher *et al.* (Fletcher *et al.*, 1997)]. Conversely, recent brain imaging studies have suggested that the PFC plays an important role for the encoding of verbal and non-verbal memories with a left dominant activation for the verbal domain (Wagner *et al.*, 1998) and a right dominant activation for the non-verbal domain (Brewer *et al.*, 1998). In the latter study the magnitude of focal rPFC activation during the encoding of complex figures was predictive for the subsequent memory for these pictures. Thus, the rPFC activation might reflect more efficient encoding of semantically identified novel sounds. The absence of left PFC activation found for lexical-semantic processes may be related to the acoustic-conceptual rather than language-related character of the present stimuli. The notion that the rPFC activity reflects the efficiency of encoding operations is also consistent with the novelty/encoding hypothesis (Tulving *et al.*, 1996) that claims that temporal regions provide the input for frontal encoding networks.

The data presented, together with those of previous studies, point to differential brain activation networks for identifiable and non-identifiable novel sounds. From the combined analyses of ERP and fMRI data we, moreover, conclude that novelty processing consists of at least two sequential subprocesses: first an automatically operating novelty detection mechanism, subserved by cortical neural networks including the superior temporal gyrus, and second, further processes based on a novel sound's meaning, subserved by right frontal cortical areas. The precise nature of the psychological process reflected in this rPFC activation remains to be elucidated. Nevertheless our data indicate that rather different neuronal networks are active depending on the proportion of conceptual semantic and generic novel information carried by a stimulus.

Notes

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