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Sensory and cognitive mechanisms for preattentive change detection in auditory cortex

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Abstract

In order to react adequately to potentially relevant information outside the focus of attention, our brain preattentively scans the acoustic environment for irregularities. Two different mechanisms are currently discussed: (i) a sensory one based on differential states of refractoriness of neurons sensitive to the features of a regular event and of neurons sensitive to features of an irregular event; (ii) a cognitive one based on a comparison of short-lived memory representations encoding current stimulation and the invariance inherent in recent recurrent stimulation. Here, we identified regions that mediate either of the two mechanisms by combining functional magnetic resonance imaging with an experimental protocol controlling for refractoriness. The sensory mechanism was associated with activity in the primary auditory cortex, whereas the cognitive one revealed activity in nonprimary auditory areas in the anterior part of Heschl's Gyrus. Moreover, it turned out that in the traditional oddball paradigm both mechanisms contribute to irregularity detection.

Introduction

Our sensory systems are specialized in the detection of irregularities in an otherwise regular background as they represent potentially important information to the organism. One may, for example, consider the importance of noticing changes in the colour of a traffic light or of detecting a signal-horn while driving on a highway. In the auditory modality, this irregularity detection system has been investigated extensively with brain recordings in the classical oddball paradigm in which an isochronously presented constant sound ('standard' stimulus) is infrequently replaced by a sound differing in some aspect ('deviant' stimulus) while the subject is engaged in some task not related to the auditory stimulation. Although the sounds are ignored, deviants elicit the mismatch negativity (MMN) component of the event-related brain potential (ERP). It consists of a negative component peaking between 150 and 200 ms after onset of the deviation (Näätänen *et al.*, 1978). In numerous studies including ERP, MEG, PET, fMRI and intracranial recordings in humans, the neural generators of the MMN have been identified in auditory and prefrontal areas (Näätänen *et al.*, 2002). Including behavioural and peripheral psychophysiological measures, it has been revealed that the functional role of this brain response is to deliver a warning signal which may trigger a call for attention to the deviant (Escera *et al.*, 2000).

On the one hand, this preattentive deviancy-detection has been investigated in many studies, resulting in a broad spectrum of applications of the MMN in basic and in clinical research in, for example, coma monitoring (Kane *et al.*, 1996), impaired language development (Kraus *et al.*, 1996) and cochlear implant users (Ponton & Don, 1995). On the other hand, the neural mechanisms contributing to this brain response are still not fully understood. It is commonly agreed that the elicitation of the MMN depends on a memory comparison process involving (i) the neural representation of the regularity inherent to recent stimulation and (ii) a representation of the current auditory event (the cognitive mechanism – Näätänen, 1990; Schröger, 1997). This cognitive account has been demonstrated for MMN using higher-order and abstract feature changes, such as duration or intensity changes or tone reversals (Schröger, 1998). However, there is little compelling evidence that this holds for frequency changes. Alternatively, the sensory mechanism account, which is based on the finding that the auditory cortex reveals a tonotopic organization from cochlea throughout cortex (Romani *et al.*, 1982; Pantev *et al.*, 1989), posits that the deviance-related activity results from a differential state of refractoriness between neural populations being sensitive to the pitch of the standard and those specifically responding to the pitch of the deviant. As the presentation rate of standards and deviants is different, the state of refractoriness of frequency-specific neurons differs.

The present study combines a recently developed experimental protocol with event-related functional magnetic resonance imaging to disentangle the relative contributions of the cognitive and sensory mechanisms underlying preattentive deviancy detection and their neuroanatomical loci. To address these issues, the neural correlates of these mechanisms, which may both contribute to the detection of pitch change, were examined in a functional magnetic resonance imaging (fMRI) study. The classical oddball paradigm (with a frequent standard and an infrequent pitch deviant) cannot delineate the sensory and the cognitive mechanism. However, using the classical paradigm together with a recently introduced control paradigm comprised of 10 equiprobable tones differing in frequency (Jacobsen & Schröger, 2001) enables estimation of the relative contributions of the two mechanisms (see Näätänen & Alho, 1997). The memory-comparison-based part of the

deviance-related brain activity, i.e. the cognitive mechanism, is revealed by comparing the responses elicited by the deviant in the oddball paradigm and the responses elicited by the physical identical sound in the control paradigm. The part of the deviance-related brain activity that is due to refractoriness effects is revealed by comparing the responses elicited by the standard in the oddball paradigm and the responses elicited by the physical identical sound in the control paradigm.

Methods

Subjects

Sixteen paid right-handed healthy students (nine female and seven male, mean age 25 years) volunteered in this study. Informed consent was obtained from all participants after the nature and possible risks of the experiment were explained. The study was approved by the Leipzig University Ethics Committee.

Stimuli

Ten different sinusoidal tones with frequencies ranging from 300 to ∼ 700 Hz were used. The range of frequencies used involved 10% increments in frequency (see Table 1). These frequencies were chosen to minimize interference with the gradient switching noise mainly comprised of frequencies above 800 Hz. All stimuli had a duration of 100 ms including 10-ms rise- and fall-times, and were presented binaurally at 85 dB SPL via head-phones.

Procedure

The experimental procedure was adopted from Jacobsen & Schröger (2001). Participants were presented with a sequence of 3000 tones, one every 600 ms. The tones were grouped into two types of blocks of 10 sounds each. In the first type of block, the 'oddball' block, one deviant occurred at a pseudorandom position in the second half of the block, i.e. at one of the positions six to 10. Across all 150 oddball blocks, deviants occurred at each of these positions with equal probability. The deviant stimulus was a 300 Hz stimulus and the standard was 330 Hz. In the other 150 blocks, the 'control' blocks, all 10 stimuli were presented, with the constraint that the 300 Hz stimulus (serving as the deviant in the oddball blocks) appeared in the same positions as in the oddball blocks. This procedure allowed the comparison of physically identical tones with equal probability of occurrence within a block. Consequently, it controls for the refractoriness explanation of deviance detection, as neural populations responsive to controls do reveal the same degree of refractoriness as populations responsive to deviants in the oddball blocks. The order of blocks was randomized across subjects. The subjects were instructed to count every stimulus and to press a button when they reached 100. Afterwards they had to restart their count from zero. This task was chosen to control for attentional states that diminish the contribution of those brain regions, in particular the frontal lobes, presumably involved in initiating a call

TABLE 1. Frequencies of the 10 stimuli used in the oddball and control conditions

Condition	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10
Oddball	330	330	330	330	330	330 (A)	330	330	330	300 (B)
Control	585	363	532	399	440	330 (C)	484	707	643	300 (D)

A–D indicate the stimuli contrasted to evaluate: the deviance effect (B vs. A), the cognitive mechanism (B vs. D) and the sensory mechanism (A vs. C).

for attention to deviant sounds (see Escera *et al.*, 2000; Opitz *et al.*, 2002). However, in the present experimental protocol we do not expect processes to occur that would lead to the elicitation of N2b and P3b ERP-components under attention conditions, as deviants did not have to be discriminated from standards (Donchin *et al.*, 1997). But, it seems possible that deviants elicited a small P3a. Crucially, P3a is often assumed to be generated anterior to the area of the MMN and their neural generators do not overlap with the regions of our expected effects (Alho *et al.*, 1998; Opitz *et al.*, 1999a,b).

Image aquisition

Imaging was performed with a 3T Bruker Medspec 30/100 system. A standard birdcage headcoil was used. Subjects were supine on the scanner bed. Cushions and a stereotactic fixation system were used to reduce head motion. In a separate session high-resolution whole-brain images were acquired to assist localization of activation foci using a 3D MDEFT (128 slice sagittal, 1.5-mm thickness, 256 × 256 voxel, see Ugurbil *et al.*, 1993). For each subject, conventional T1-weighted anatomic images were acquired (MDEFT: data matrix 256 3256, TR 1.3 s, TE 10 ms, see Norris, 2000) in the plane of the echo-planar images, to align the functional images to the 3D images. Finally, event-related functional images were recorded using a gradient-echo EPI sequence with a TE of 30 ms, flip angle 90°, and TR of 1000 ms sensitive to blood oxygen level-dependent (BOLD) contrast. An acquisition volume consisted of eight axial slices parallel to the intercommissural plane and positioned to cover the temporal lobes (*z* from −12 to +32mm). The matrix had an in-plane resolution of 3 × 3 mm. The slice thickness was 5 mm with an interslice gap of 2 mm. Ten discarded volumes were acquired at the beginning of each run while tones were presented to allow stabilization of magnetization. Thus, a total of 1812 volumes were acquired asynchronously with the stimulation in two runs of 906 volumes each, and we thereby increased the effective sampling rate of the hemodynamic response (one sample every 200 ms) and achieving a robust paradigm for analysis within the general linear model.

Image analysis

The data processing was performed using the software package LIPSIA (Lohmann *et al.*, 2001). Prior to statistical analyses, motion artifacts were corrected using an affine rotation and translation correction. Then, low-frequency signal fluctuations were removed on a voxel-by-voxel basis. Finally, a spatial smoothing with a Gaussian kernel of 8 mm full width at half maximum was applied to emphasize spatially coherent activation pattern. The temporally overlapping haemodynamic responses to the deviants, standards and controls were modelled based on multiple regression within the general linear model using a synthetic haemodynamic response function and its first-order temporal derivative (Josephs *et al.*, 1997; Clark *et al.*, 1998). The inclusion of the derivative accommodates for small shifts in the onset of the haemodynamic response (Friston *et al.*, 1998). This approach allows for an estimate of the haemodynamic response to each stimulus kind within our rapidly presented, random design. Critically, the estimate could be obtained with no assumption about the specific shape of the response other than the assumption that responses summate in a linear fashion (see Miezin *et al.*, 2000). Three different pairwise linear contrasts of the parameter estimates were calculated using a subject-specific fixed-effect model. First, the contrast between the deviants and the standards within the oddball blocks reflects the analysis usually employed in change detection paradigms. Secondly, the contrast between deviants and their respective controls represents the cognitive mechanism by accounting for differential state of

refractoriness. Thirdly, the contrast between the standard tones in the control blocks and the oddball blocks specifically assesses the sensory mechanism. The subject-specific estimates derived from each of the contrasts were subsequently transformed into Talairach coordinate space (Talairach & Tournoux, 1988) and entered into a second-level group analysis treating subjects as a random effect, using a one-sample t-test against a contrast value of zero at each voxel (Holmes & Friston, 1998). Following Opitz *et al.* (2002), regions were considered reliable if they consisted of > 10 contiguous voxels exceeding an uncorrected threshold of $P < 0.001$. The contributions of the cognitive and the sensory mechanisms to auditory change detection were further explored within the primary auditory cortex and adjacent areas. Therefore, the classical deviant contrast was masked by the areas activated by the cognitive mechanism and areas exhibiting differential contribution of the sensory mechanism.

Results

The first contrast, usually used to deliniate areas activated by change detection processes (namely deviants vs. standards in the oddball blocks), yielded a bilateral activation pattern in the superior temporal plane (see Fig. 1A). The two temporal foci were centred on Heschl's Gyrus (co-ordinates: left HG, $x = -49$, $y = -14$, $z = 9$; right HG, $x = 53$, $y = -21$, $z = 10$) extending to the adjacent superior temporal gyrus. This region has been previously identified by neuroimaging techniques using the classical oddball paradigm (Opitz *et al.*, 1999a; Tervaniemi *et al.*, 2000; Mathiak *et al.*, 2002). Moreover, this contrast revealed bilaterally increased activity for deviant tones in the putamen (left, -17, 16, 2; right, 23, 5, 6). In line with findings by Kropotov *et al.* (2000), that ERPs to attended deviant and standard tones also showed differences in the basal ganglia–thalamic circuits, we argue that the activity in the putamen might reflect their involvement in attentive processing of auditory stimuli (see Opitz *et al.*, 1999a).

Regarding the cognitive mechanism emerging when comparing deviants of the oddball blocks with the physically identical tones from the control block, a more confined activation pattern was observed (Fig. 1B). Within the temporal lobes, activation foci spanned the middle portion of the anterior rim of HG (see Table 2), a brain region corresponding to the temporoinsular area of HG, a nonprimary auditory area rostrally bordering the primary auditory cortex (Morosan *et al.*, 2001; Rademacher *et al.*, 2001).

The third contrast between the standards in the oddball blocks and their physically identical counterparts in the control blocks was used to identify regions subserving the sensory mechanism of change detection. Crucially, the brain regions to be identified are susceptible to refractoriness effects. As predicted, standards in the oddball blocks exhibited decreased activity in the lateral aspect of the posterior rim of

HG bilaterally (see Table 2 and Fig. 1C) as compared to the same tones in control blocks. The highly symmetrical response pattern nicely corresponds to that in previous studies demonstrating the involvement of this brain region in the perception of auditory stimuli (Schönwiesner *et al.*, 2002; Lütkenhöner *et al.*, 2003). In further support of the present results, both studies congruently depicted the responsiveness of lateral portions of HG to lower frequencies in the range used in the present study. According to a recent study identifying the relationship between cytoarchitectonic and macroanatomical landmark (Rademacher *et al.*, 2001) we argue that this brain region houses primary auditory areas.

In order to estimate the contributions of the cognitive and sensory mechanisms to the classical change detection contrast, we calculated the overlap between activated areas by masking the first contrast with the other two. This analysis would reveal brain regions that are engaged in change detection processes by means of memory-comparison-based (cognitive) mechanisms and other deviance-related (sensory) processes. As apparent from Fig. 2, areas commonly activated by the classical deviance effect and the cognitive mechanism were confined to the anterior rim of HG bilaterally. In contrast, areas that exhibited a refractoriness effect, i.e. the sensory mechanism, but are activated in the classical oddball paradigm were observed more lateral on the posterior rim of HG. To further explore the spatial relationship between regions of the HG either mediating cognitive or sensory detection processes the respective activation foci were traced along the anterior and posterior rim of the individual HG (see Schönwiesner *et al.*, 2002). Figure 3 demonstrates that the pattern of activity associated with either the cognitive or the sensory mechanism described above comprises distinct processing domains.

Discussion

In the present experiment we set out to investigate the contributions of the cognitive (memory-comparison-based) mechanism and the sensory (refractoriness-based) mechanism to auditory frequency change detection. The sensory mechanism led to increased activity in the lateral aspect of the posterior rim of HG bilaterally, whereas the cognitive mechanism involved a nonprimary auditory area within the lateral temporal lobe. In agreement with the present results, previous studies using inverse source localization methods had identified nonprimary auditory areas as potential generators of the change detection signal in the ERP, the MMN (Scherg *et al.*, 1989; Alho *et al.*, 1998; Korzyukov *et al.*, 1999). In addition, intracranial ERPs recorded in neurological patients have shown a pitch-dependent response in the primary auditory cortex, whereas a change-detection (MMN) response has been observed in the auditory association cortex (Kropotov *et al.*, 2000). This further supports our view that the

TABLE 2. Coordinates and *Z*-scores for brain regions exhibiting differential BOLD response in the three contrasts investigated

| Mechanism	Contrast	Cortical region	Peak location			Z- score
			x	y	z	
Deviance effect	Deviant vs. standard	Heschl's gyrus L	−49	−14	9	5.81
		Superior temporal plane R	53	−21	10	4.61
		Putamen L	−17	16	2	4.23
		Putamen R	23	5	6	4.40
Cognitive mechanism	Deviant vs. control	Anterior rim of Heschl's gyrus L	−42	−13	6	4.19
		Anterior rim of Heschl's gyrus R	49	−12	7	3.58
Sensory mechanism	Standard vs. control	Posterior rim of Heschl's gyrus R	−51	−18	7	−4.81
		Posterior rim of Heschl's gyrus R	53	−19	4	−6.01
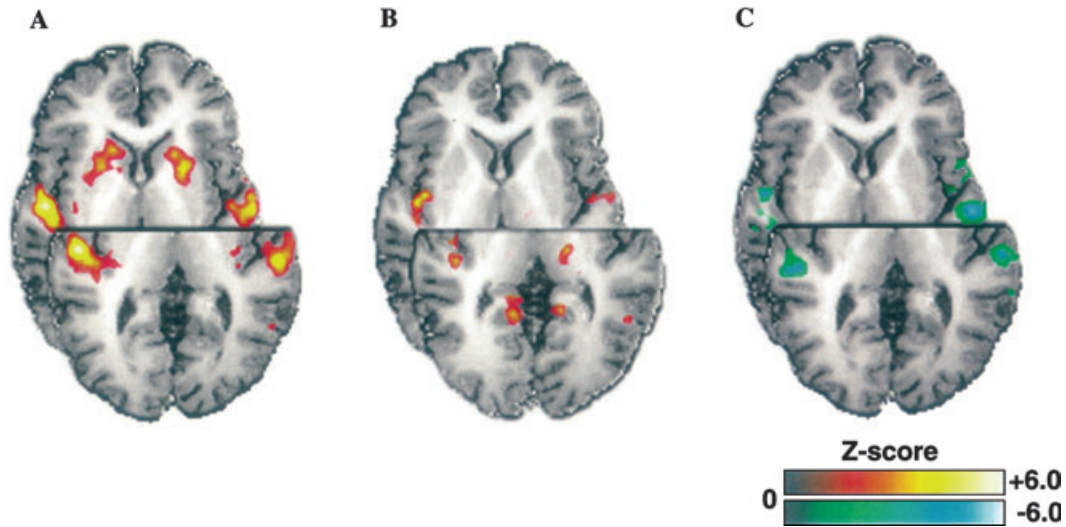
FIG. 1. Axial sections at $z = 8$ and $z = 12$ depicting areas of activation in the temporal cortex. (A) Contrast deviant vs. standard in oddball blocks. (B) Contrast deviant vs. control. Note, that both stimuli are physically identical. Therefore, this contrast reflects memory-comparison processes. (C) Contrast standard tone in the control blocks and the oddball blocks which specifically asseses the contribution of the refractory state. The Z-scores of the specific contrasts are colour-coded.

sensory and the cognitive mechanisms are subserved by primary and nonprimary auditory areas, respectively.

The present results further support previous source analyses estimating the generators of the MMN in the superior temporal plane about 1 cm anterior to the source of N1 component (Scherg *et al.*, 1989; Alho *et al.*, 1998; Escera *et al.*, 2000). A similar distribution of MMN and N1 generators on the rostral–caudal dimension has been described for the auditory cortex of the cat with the MMN potential arising rostral to the N1 component on the secondary auditory area AII

(Pincze *et al.*, 2001). Less consistent, however, are the findings with respect to medial–lateral location. Whereas Scherg *et al.* (1989), using inverse source analysis on the basis of EEG recordings, reported the MMN generator to be located more lateral as compared to the N1, Alho *et al.* (1998) observed more medial origins of the magnetic counterpart of the MMN. Although the present results support the latter findings a definite conclusion cannot be drawn given the differences in the methods used. On the other hand, there are also differences in the frequency range investigated. While the frequencies used in the present study and the work by Alho and colleagues were virtually identical, Scherg *et al.* (1989) employed much higher
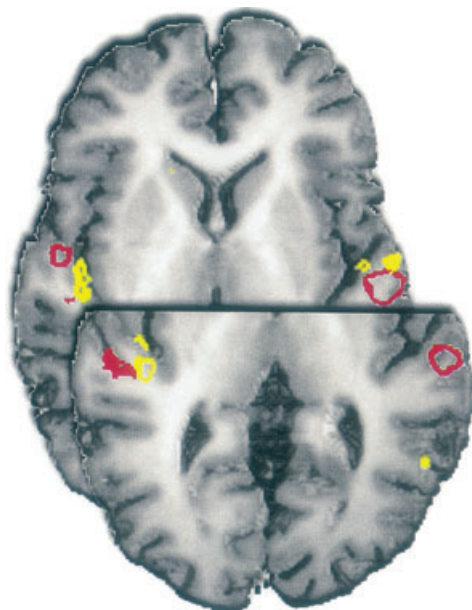

FIG. 2. Areas within the red border exhibited a refractoriness effect but are activated in the deviant–standard contrast. These include the lateral part of the posterior rim of Heschl's Gyrus bilaterally (left hemisphere, $x = -53$, $y = -18$, $z = 9$; right hemisphere, $x = 53$, $y = -21$, $z = 10$). Areas bounded by yellow are activated by the classical oddball contrast as well as by the deviant–control contrast and comprise the middle aspect of the anterior rim of Heschl's Gyrus (left hemisphere, $x = -46$, $y = -14$, $z = 8$; right hemisphere, $x = 48$, $y = -14$, $z = 8$).
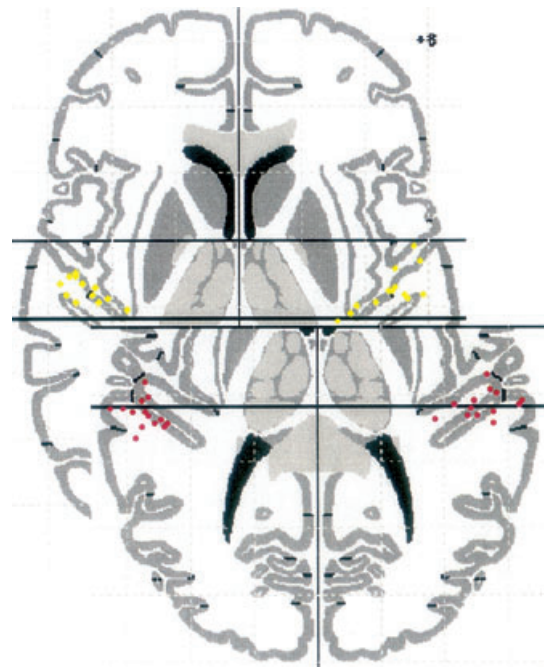

FIG. 3. The locations of the individual foci activated by the cognitive (yellow) and sensory (red) mechanism are shown on schematic outlines of the cortex based on the atlas of Talairach & Tournoux (1988). Axial sections are choosen to correspond to the sections of Figs 1 and 2.

frequencies. Given the medio-lateral gradient of neuronal responsiveness to high frequencies medially and low frequencies laterally (Schönwiesner *et al.*, 2002) one could argue that there is one nonprimary region within the temporal plane subserving the cognitive mechanism but several primary brain regions contributing to the sensory mechanism depending on the actual frequency used. Moreover, the MMN generator as estimated with inverse source analysis differs only in dipole orientation, but not location, when the absolute value of frequency is changed (Tiitinen *et al.*, 1993).

In conclusion, the present experiment combining event-related functional magnetic resonance imaging with an experimental protocol controlling for refractoriness effects (Jacobsen & Schröger, 2001) succeeded in deliniating the cognitive mechanism, based on memory-comparison processes, contributing to the MMN elicited by frequency changes from contributions of the sensory mechanism, i.e. a differential state of refractoriness. Whereas the latter mechanism is mediated by neurons in the primary auditory cortex, memory-comparison processes seem to be subserved by nonprimary auditory areas in the anterior part of Heschl's Gyrus. Its function might be the establishment of a sparse representention of simple and complex invariants inherent in the recent stimulation, thereby providing the neural basis for a memory comparison (Schröger, 1997). Crucially, both mechanisms appear to contribute to pitch change detection in the classical oddball comparison. This parallel usage of two different mechanisms for fulfilling the same function underlines the importance, in the human brain, of preattentively detecting changes in the acoustic environment.

Abbreviations

BOLD, blood oxygen level-dependent; ERP, event-related brain potential; fMRI, functional magnetic resonance imaging; MMN , mismatch negativity.

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