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## Prefrontal cortex involvement in preattentive auditory deviance detection: neuroimaging and electrophysiological evidence

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### Abstract

Previous electrophysiological and neuroimaging studies suggest that the mismatch negativity (MMN) is generated by a temporofrontal network subserving preattentive auditory change detection. In two experiments we employed event-related brain potentials (ERP) and event-related functional magnetic resonance imaging (fMRI) to examine neural and hemodynamic activity related to deviance processing, using three types of deviant tones (small, medium, and large) in both a pitch and a space condition. In the pitch condition, hemodynamic activity in the right superior temporal gyrus (STG) increased as a function of deviance. Comparisons between small and medium and between small and large deviants revealed right prefrontal activation in the inferior frontal gyrus (IFG; BA 44/45) and middle frontal gyrus (MFG; BA 46), whereas large relative to medium deviants led to left and right IFG (BA 44/45) activation. In the ERP experiment the amplitude of the early MMN (90–120 ms) increased as a function of deviance, by this paralleling the right STG activation in the fMRI experiment. A U-shaped relationship between MMN amplitude and the degree of deviance was observed in a late time window (140–170 ms) resembling the right IFG activation pattern. In a subsequent source analysis constrained by fMRI activation foci, early and late MMN activity could be modeled by dipoles placed in the STG and IFG, respectively. In the spatial condition no reliable hemodynamic activation could be observed. The MMN amplitude was substantially smaller than in the pitch condition for all three spatial deviants in the ERP experiment. In contrast to the pitch condition it increased as a function of deviance in the early and in the late time window. We argue that the right IFG mediates auditory deviance detection in case of low discriminability between a sensory memory trace and auditory input. This prefrontal mechanism might be part of top-down modulation of the deviance detection system in the STG.

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*Keywords:* MMN; deviance detection; superior temporal gyrus; inferior frontal gyrus; ERP; fMRI; dipole modeling

### Introduction

Infrequent tones (deviants) presented among frequent tones (standards) elicit an event-related potential (ERP) component, the so-called mismatch negativity (MMN; Näätänen et al., 1978). The MMN is assumed to be generated by a mismatch between the sensory input from a deviant stimulus and a neuronal sensory-memory trace representing the

features of a repeatedly presented standard stimulus (Näätänen, 1990; Näätänen and Winkler, 1999; Schröger, 1997). It has been proposed that this preattentive mismatch detection process plays an important role in initiating involuntary switching of attention toward an auditory stimulus change outside the focus of attention (Giard et al., 1990; Näätänen and Michie, 1979; Schröger, 1996). In accordance with this call for attention function, the MMN is often followed by a P3a component, indexing a switch of attention (e.g., Knight, 1996).

It is assumed that the transverse temporal gyrus (TTG)

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and the superior temporal gyrus (STG) subserve auditory change detection. This view is supported by electrophysiological measures (Giard et al., 1990), magnetoencephalography (MEG; Alho et al., 1998; Hari et al., 1984), functional imaging techniques (Mathiak et al., 2002b; Opitz et al., 1999b; Tervaniemi et al., 2000a), intracranial recordings (Javitt et al., 1992; Kropotov et al., 1995), and neuropsychological investigations (e.g., Woods et al., 1993). The precise location of the MMN generator within the temporal cortex depends on both the deviance domain (e.g., frequency, duration, or intensity; Giard et al., 1995) and the degree of deviance (Tiitinen et al., 1993, 1994).

An open issue concerns the involvement of the prefrontal cortex in auditory change detection. Recent neuroimaging studies, including positron emission tomography (PET; Müller et al., 2002), EEG/MEG (Rinne et al., 2000; Yago et al., 2001), and fMRI (Downar et al., 2001, 2002; Opitz et al., 2002), suggest that beyond the STG the inferior frontal gyrus (IFG) contributes to MMN generation. Müller et al. (2002) propose a two-stage model of auditory deviance detection. Processing of small stimulus changes relies upon a network of posterior STG and IFG, whereas analyses of large stimulus changes are more detailed and therefore additionally involve mid-dorsolateral prefrontal cortex. Rinne and colleagues (2000) found that the frontal component of the MMN was activated slightly later than the temporal one and argue that the frontal MMN generator supports switching of attention to changes in repetitive auditory stimulation. Right IFG was activated by visual and auditory deviant stimuli regardless of task relevance in two studies of Downar et al. (2001, 2002). The authors suggest that IFG plays a role in evaluating the potential relevance of stimuli. Opitz et al. (2002) presented three different pitch deviants (10%, 30%, and 100% pitch change compared to the standard stimulus) and observed significant activation for medium and large deviants in the STG bilaterally and in the opercular part of the right IFG. Temporal lobe activation was more pronounced for large than for medium deviants, whereas a reversed pattern was observed for the right IFG. In a parallel session ERPs were recorded using the same stimuli. The STG activation correlated with the change-related ERP signal between 90 and 120 ms (early MMN peak), while the IFG activation correlated with the MMN signal in a late time window (140–170 ms, late MMN peak). Opitz et al. (2002) propose that the IFG might be related to an involuntary amplification or contrast enhancement mechanism, tuning the auditory change detection system. Taken together these data suggest that the prefrontal cortex subserves auditory deviance detection in a later stage of processing, possibly by top-down modulation of early deviance processing. In contrast, using scalp current density mappings of activation elicited by pitch deviants, Yago and coworkers (2001) showed that a right frontal MMN generator was activated about 60 ms earlier than a right temporal generator. The authors propose that the early frontal MMN

proportion might reflect thalamic contributions to MMN generation via thalamo-cortical connections.

We used event-related fMRI and event-related brain potentials to investigate the role of the prefrontal cortex in auditory deviance detection in more detail. We presented three types of infrequent deviant stimuli on two dimensions, pitch and space. Recent evidence suggest that pitch and spatial auditory information is processed in distinct areas of auditory as well as prefrontal cortex (Rauschecker and Tian, 2000; Romanski et al., 1999; Zatorre et al., 2002). The degree of pitch deviance was physically equidistant with small, medium, and large deviants differing by 33% (667 Hz), 67% (833 Hz), and 100% (1000 Hz) from the standards (500 Hz). In the spatial condition stimuli differed from the standard tone (0°, forward direction; 500 Hz) as a function of spatial deviation, with an azimuthal (left-right) angle of 30° (small), 60° (medium), and 90° (large).

## Materials and methods

### Subjects

Eighteen subjects participated in the ERP study (aged 19–38, mean age 24 years; 9 males) and seven in the fMRI study (aged 24–32, mean age 26 years; 4 males; 3 subjects participated in both experiments). All subjects were healthy right-handed adults with normal hearing and were paid for participating. Informed consent was obtained before the measurements. All participants reported to be in good health with no history of neurological disease.

### Stimuli, experimental procedure, and design

Spectrally rich tones, which consisted of three sinusoidal partials were used as stimulus materials (see Tervaniemi et al., 2000b). The second and third components were 3 and 6 dB, respectively, lower in intensity than the first component. There were four different tones of 100-ms duration (including 5-ms rise and fall times) in the stimulus sequence of the pitch and space condition: a frequent ( $P = 0.88$ ) standard tone consisted of frequencies 500 (first component), 1000 (second component), and 1500 Hz (third component). In the pitch condition the infrequent tones ( $P = 0.04$  for each type) differed from the standard tone in frequency of all partials by 33% (667 Hz), 67% (833 Hz), and 100% (1000 Hz) change and are further referred to as small, medium, and large pitch deviants. In the space condition, deviant stimuli were defined in terms of interaural time difference (ITD) and interaural level difference (ILD). The tones also consisted of three sinusoidal partials. Spatial deviants differed from the standard tone (forward direction, ITD = 0  $\mu$ s, ILD = 0 dB) as a function of spatial deviation: The azimuthal (left-right) angle  $\theta$  was 30° (small deviant, ITD = 382  $\mu$ s, ILD = -2 dB), 60° (medium deviant, ITD = 661  $\mu$ s, ILD = -3 dB), and 90° (large deviant, ITD = 763  $\mu$ s, ILD =

–4 dB; Grantham, 1995; Kuhn, 1977; Stern and Trahiotis, 1995). In each condition, 2440 stimuli were delivered binaurally via headphones at 70 and 85 dB/SPL in the ERP and fMRI experiment, respectively. A standard electrostatic auditory stimulation system was used in the ERP experiment and a pneumatic system in the fMRI experiment. The standard and deviant stimuli were delivered in random order, except that each deviant tone was preceded by at least 6 and at most 10 standard tones. The stimulus onset asynchrony (SOA) for all stimuli (standards and deviants) was 500 ms, resulting in intervals between two deviants ranging from 3 to 6 s. Both conditions were presented in separated blocks. The sequence of blocks was balanced across subjects. Prior to statistical analysis electrophysiological and hemodynamic signals to standard tones were randomly selected so that their number equals the number of responses to the deviants. In both the ERP and fMRI experiment, subjects were instructed not to pay attention to the auditory stimuli. No additional task was conducted.

### *ERP procedures*

EEGs and EOGs were recorded continuously from 64 electrodes including the left and right mastoid using an Electrocap. All leads were referenced to the nose tip. The signals were online bandpass-filtered (0.1–70 Hz) and digitized at 1000 Hz. Vertical and horizontal EOGs were recorded from two electrode pairs placed on the infra- and supraorbital ridges of the right eye and on the outer canthi of the two eyes. Impedances were kept below 5 k $\Omega$ . ERPs of 500-ms length including a 100-ms prestimulus baseline were computed separately for all electrodes, conditions, and subjects. Prior to averaging epochs containing eye movements and other artefacts (threshold: standard deviation > 40  $\mu$ V; width of sliding window: 200 ms) were excluded from further analysis. Difference waveforms were calculated by subtracting the averaged ERPs to the standard stimuli from those to the deviants. The MMN was measured in the difference waveforms as the mean amplitude during the 90–200-ms time period from stimulus onset. Difference waveforms were selected for MMN measurement to allow a better comparison with the fMRI activation contrasts (see below). Based on a previous study (Opitz et al., 2002) the amplitude of an early and a late proportion of the change-related component were separately measured at electrode Fz as the mean voltage in 30-ms time windows around the first and second MMN peak, respectively. The latencies of these two peaks were defined in the grand average ERPs separately for both conditions. The two peaks were observable in most subjects, especially at electrode Fz (see Results section). Repeated-measures analyses of variance (ANOVA) with the factors deviance and time window were used to examine the difference signals elicited by the three deviant types in both time windows separately for both conditions at electrode Fz and mastoid recording sites (the average of the left and right mastoid electrode). Based on the phenomenon

of phase reversal of the MMN at frontal and mastoid recording sites, the analyses were restricted to these electrodes. In the following we will focus on ERPs at electrode Fz because the early and late MMN peaks were clear discernible at this recording site. The effect of deviance on the P3a component (defined as the mean signal between 230 and 270 ms at electrode Fz) was assessed by one-way repeated-measures ANOVAs with the factor deviance separately for both conditions. Greenhouse-Geisser correction was used where appropriate. Uncorrected degrees of freedom and corrected *P* values are reported. Wherever indicated additional one-tailed Student's *t* tests against zero level were used to determine the presence of an ERP component.

### *MR scanning parameters*

A Siemens VISION MR scanner (Erlangen, Germany) operating at 1.5 T with a standard circularly polarized whole head coil was employed to acquire both T1-weighted anatomical images and T2\*-weighted BOLD-sensitive functional images. Structural images were acquired using an isometric (1.17 mm<sup>3</sup> voxel size) MP-RAGE 3-D sequence (TR = 15 ms, TE = 7 ms, flip angle = 8°, IT = 300 ms; Mugler and Brookeman, 1990). Functional data were acquired using a gradient-echo echo-planar pulse sequence, with the following parameters: TR = 2.69 s, TE = 60 ms, flip angle = 90°, 24 contiguous axial slices parallel to AC-PC plane, in-plane resolution = 3.75 × 3.75 mm, slice thickness = 5 mm, interslice interval = 101.25 ms, FoV = 240 mm. Each condition (pitch and space) was conducted in a separate run with 457 volume acquisitions per run. The order of runs was counterbalanced across subjects.

### *Data preprocessing*

Analysis was performed with statistical parametric mapping (SPM99; Wellcome Department of Imaging Neuroscience, London, UK; Friston et al., 1995) implemented in Matlab6 (The Mathworks, Inc., USA). To account for the different sampling time of the slices, voxel time series were corrected using sinc interpolation and resampled using the first slice as a reference point. All functional volumes were motion corrected by spatial realignment to the first volume. Resulting volumes were normalized (Ashburner and Friston, 1999) to a standard EPI template based on the MNI reference brain (Cocosco et al., 1997), an approximation of the canonical Talairach-space (Talairach and Tournoux, 1988), using a 12-parameter affine transformation along with a nonlinear transformation using cosine basis functions. The normalized images were spatially smoothed with an isotropic 8-mm FWHM Gaussian kernel to compensate for residual between-subject variability after spatial normalization and permit application of Gaussian random field

theory. The time series in each voxel were high-pass-filtered to  $\frac{1}{120}$  Hz to remove low-frequency noise and proportionally scaled to a grand mean of 100 over voxels per run to remove effects due to global intensity fluctuations.

### Statistical analyses

Statistical analysis was performed in two stages in a mixed-effects model. Trials for all three deviants and standards were modeled separately for both the pitch and space condition by convolving an event train of  $\delta$ -functions, representing the onset of each stimulus with a canonical hemodynamic response function (HRF) and its temporal derivative (Friston et al., 1998). Effects were estimated using a subject-specific fixed-effect model. Furthermore, six covariates comprising the three rigid-body translations and three rotations determined from the realignment algorithm to capture residual movement-related artifacts and one covariate representing the mean over scans were included into the design matrix. Parameters for each covariate were estimated by a least-mean-squares fit of the model to the time series. Linear contrasts of these parameter estimates entered into a second-level analysis treating subject as a random effect, using a one-sample  $t$  test against a contrast value of zero at each voxel (Holmes and Friston, 1998). Based on previous fMRI studies (Opitz et al., 1999b, 2002) the specific differences in the superior temporal and inferior frontal gyrus reported below were considered significant when 100 or more contiguous voxels survived a threshold at  $P < 0.001$ . In addition to voxel-wise analysis, region-of-interest (ROI) analyses were conducted to quantitatively estimate the effect of experimental factors on the identified regions. For the ROI analyses, spherical regions of interest were identified by choosing all significant voxels within a 5-mm radius of the maximum identified in the group statistical map. Data for all three deviants were expressed in terms of mean percentage-change in hemodynamic signal relative to standards.

### Dipole modeling

To compare ERP and fMRI measurements, a dipole analysis constrained by fMRI data was performed (see Opitz et al., 1999a, 1999b). For source localization purposes realistically shaped head models were developed using the boundary elements method (Knösche, 1997). 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 B.V., Enschede, The Netherlands) to explain the average reference ERP data in both time windows of interest.

## Results

### ERP measures

Fig. 1 shows difference waves obtained by subtracting grand-average ERPs to standards from ERPs for all three deviants for the (a) pitch and (b) space condition. Small, medium, and large deviants for both conditions evoked a mismatch negativity, i.e., an enhanced negativity, peaking about 100–180 ms after stimulus onset at frontocentral electrode sites with polarity reversal at mastoid sites. The components to all deviants showed a double peak over frontal scalp locations, suggesting two subcomponents. As apparent from Fig. 2, mismatch responses were greater for pitch than for space deviants. Interestingly, the two subcomponents for all three spatial deviants peaked about 40 ms later compared to the pitch deviants. Therefore, the two time windows of interest differed between both conditions: in the pitch condition the early time window was set to 90–120 ms, the late time window was defined as the mean signal between 140 and 170 ms. In the space condition, the two time windows were set to 135–165 and 170–200 ms, respectively. In the early time window, the mean MMN amplitude increased as a function of deviance for both the pitch and space condition (see Fig. 2a). In the late time window, the pattern was different for pitch and space deviants: the MMN amplitude increased as a function of deviance in the space condition, whereas a U-shaped relationship between MMN amplitude and deviance could be observed in the pitch condition. Medium deviants elicited smaller MMNs compared to small and large deviants (see Fig. 2b).

In the pitch condition, two-way repeated-measure ANOVAs with the factors deviance (small, medium, large) and time window (early vs. late) were performed separately for the mean amplitude at electrodes Fz and the average of the left and right mastoid recording sites. These analyses revealed a main effect of deviance (Fz:  $F_{2,34} = 12.40$ ,  $P < 0.001$ ; mastoid:  $F_{2,34} = 13.57$ ,  $P < 0.001$ ), a main effect of time window (Fz:  $F_{1,17} = 7.74$ ,  $P < 0.05$ ), and a time window  $\times$  deviant type interaction (Fz:  $F_{2,34} = 5.43$ ,  $P < 0.05$ ). The data from the space condition were treated analogously. Results revealed a main effect of deviance ( $F_{2,34} = 5.72$ ,  $P < 0.01$ ) at the Fz recording site, but not for mastoid electrodes ( $F_{2,34} < 1$ ,  $P > 0.6$ ). At both electrodes, neither a main effect of time window nor a time window  $\times$  deviant type interaction was obtained in the space condition. Nevertheless, reliable MMNs were elicited at mastoid recording sites. Additional one-tailed Student's  $t$  tests were conducted for the mastoid recording sites, indicating that the difference waves were significantly different from zero between 135 and 200 ms for small ( $t = 5.16$ ,  $P < 0.0001$ ), medium ( $t = 6.63$ ,  $P < 0.0001$ ), as well as for large ( $t = 4.16$ ,  $P < 0.001$ ) deviants. Furthermore, a P3a (peaking around 250 ms) was elicited by small, medium, and large deviants in the pitch condition with a fronto-central maximum, indicating an involuntary switch of attention toward sound changes (Schröger and Wolff, 1998). A repeated-measure

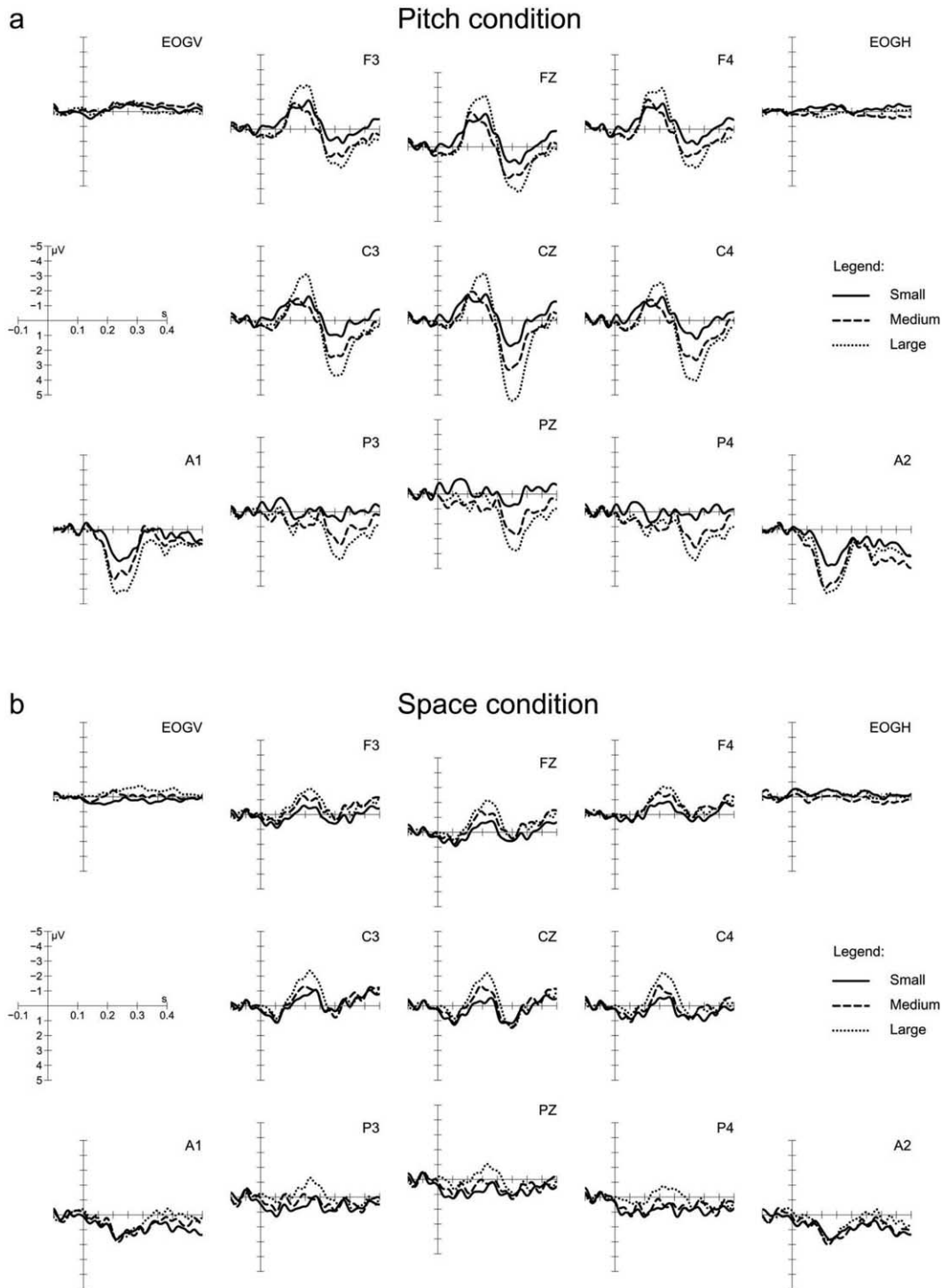


Fig. 1. Grand average difference waveforms (18 subjects) in the (a) pitch and (b) space condition obtained by subtracting ERPs to standard stimuli from those to deviant stimuli separately for small (solid), medium (dashed), and large (dotted) deviants for selected electrode sites of the 10–20 system.

ANOVA with the factor deviance for the mean amplitude at electrode Fz between 230 and 270 ms confirmed this observation ( $F_{2,34} = 3.72, P < 0.05$ ). No P3a was elicited in the space condition at Fz. One-tailed Student's *t* tests separated for all three deviants yielded no effect in the 230–270 time range (all *P* values  $> 0.3$ ).

*fMRI measures*

For the pitch condition, the functional imaging data revealed activation in the right superior temporal gyrus (STG) for each deviant type relative to the standard stimuli (Talairach coordinates *x, y, z* [mm]: 58, -20, 11 [small], 60,

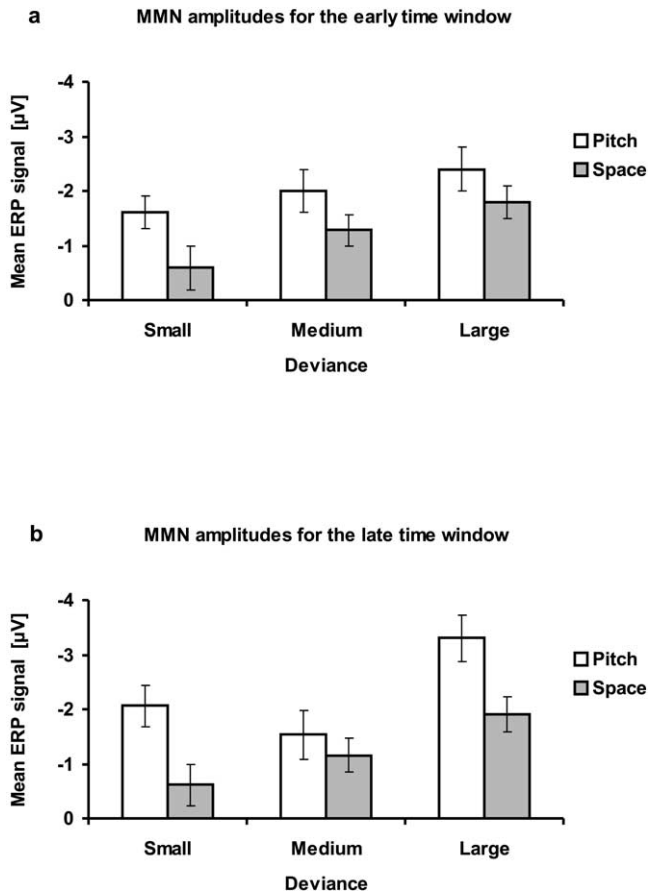


Fig. 2. Mean MMN amplitudes for the (a) early and (b) late time window plotted as a function of deviance for the pitch (white) and space (gray) condition.

–20, 10 [medium], 61, –20, 8 [large]). The statistical parameter maps separated for all three pitch deviants are given in Fig. 3a (thresholded at  $P < 0.001$  uncorrected for multiple comparisons, with a contiguous 100-voxel extent). Mean percentage BOLD signal change (relative to grand mean over voxels and scans) is depicted in Fig. 3b averaged over subjects for the spherical ROI based on the group statistical map in right STG separately for all three pitch deviants. As apparent from Fig. 3b, activity increased with the degree of deviance, i.e., large and medium pitch deviants showed greater activity than small pitch deviants. After lowering the statistical threshold (uncorrected  $P < 0.01$ ; contiguous 50-voxel extent), additional left STG activity for all three pitch deviants could be observed.

In addition, several direct contrasts between pitch deviants were conducted (threshold: uncorrected  $P < 0.001$ ; contiguous 100-voxel extent). Small pitch deviants elicited greater activity than medium pitch deviants in the right inferior frontal gyrus (IFG, BA 44/45; 54, 24, 6), extending over the opercular part and the dorsal portion of the triangular part of the IFG (see Fig. 4a). A small vs. large contrast (small > large; 50, 28, 22; see Fig. 4b) revealed a more dorsally shifted right-hemispheric activation cluster at the

junction between the most dorso-rostral portion of the opercular part of the IFG and the inferior part of the medial frontal gyrus (BA 46). As shown by Fig. 4c the inferior frontal gyrus (BA 44/45) was activated bilaterally to a larger extent by large pitch deviants than by medium pitch deviants (large > medium; 50, 24, 6 [right], –54, 26, 8 [left]). This activation pattern included the opercular part of the IFG. The activated region was greater in the right than in the left hemisphere (right: 529 voxels; left: 203 voxels). All remaining possible contrasts between different pitch deviants did not show reliable activations (even with an uncorrected statistical threshold of  $P < 0.01$ ; contiguous 50-voxel extent). Due to the different right-frontal activation pattern in the contrasts comparing small and medium and small and large pitch deviants, we recalculated the small vs. medium contrast with a marginal lower uncorrected threshold of  $P < 0.002$  and a contiguous 100-voxel extent. Additional activation in the most dorsal portion of the opercular part of the right IFG could be observed, similar to the activation in the small vs. large contrast.

Taken together the fMRI data for the pitch condition suggest that the right IFG is more involved in processing small pitch changes compared to medium and large changes, whereas bilateral IFG activation could only be observed for large compared to medium pitch deviants. In the space condition no significant activations were found for either the deviant-standard contrasts or the direct comparisons. However, the lack of activity is not due to the high statistical threshold used in the analysis. Even after lowering the threshold (uncorrected  $P < 0.05$ ; contiguous 10-voxel extent), no significant hemodynamic response for spatial deviants could be observed (see Discussion for further possible explanations for the absence of hemodynamic activation in the space condition).

#### Dipole analysis

To further examine the relationship between ERP and fMRI data, a dipole analysis constrained by fMRI activation foci was conducted. We modeled the scalp ERP difference waveforms for all three deviants relative to standards in the pitch condition within the early time window (90–120 ms), using dipole source locations in the right STG as derived from functional images. ERPs within the late time window (140–170 ms) were modeled with dipoles placed in the left and right IFG, respectively. By introduction of an additional dipole placed in the left STG in modeling the early time window, goodness of fit improved from 89% to more than 95%. Fig. 5 illustrates the obtained best-fitting orientations and the explained variance of the dipole model. The modeled dipole orientations were almost perpendicular to the gray matter. More than 95% of the signal variance was explained by the four dipoles between 90 and 170 ms. Outside this time range the fit was greatly reduced. As it is apparent from Fig. 5 the dipole strength for both STG dipoles increased as a function of deviance. In accordance

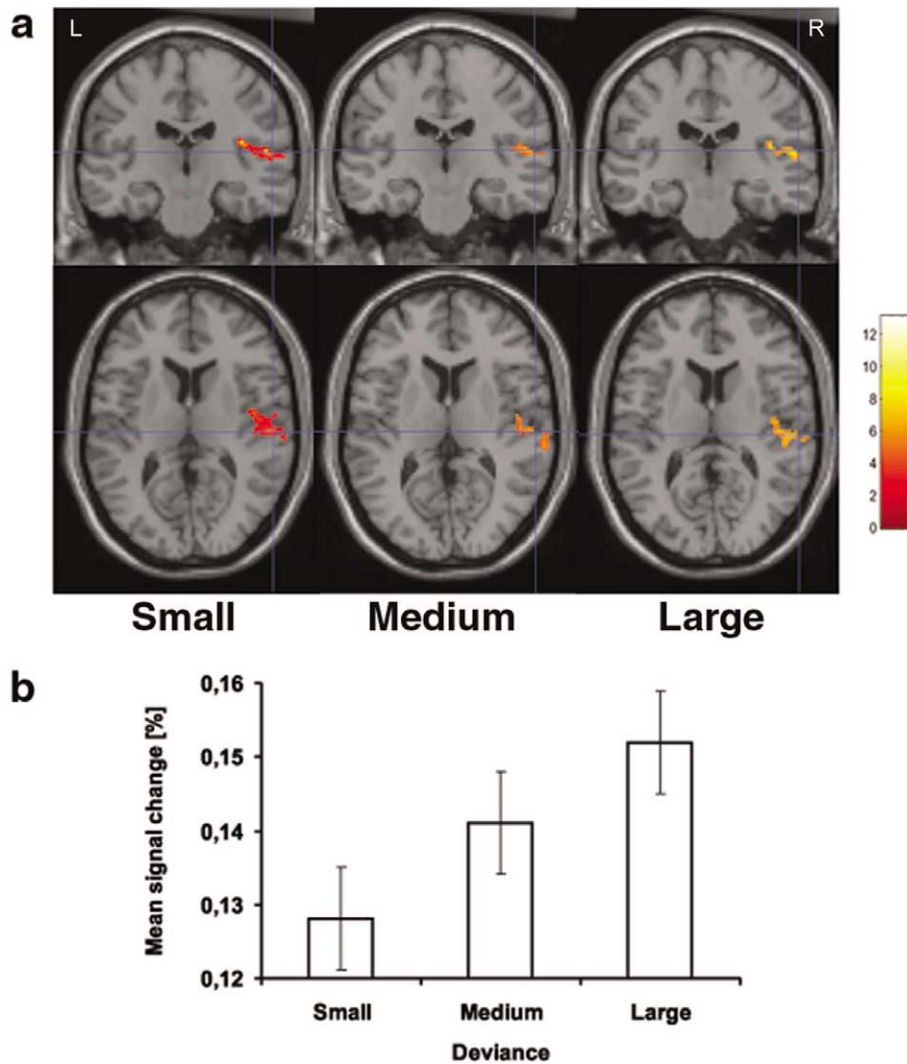


Fig. 3. (a) Significant BOLD signals in the right superior temporal gyrus (STG) to small ( $x, y, z: 58, -20, 11$ ; left panel), medium ( $x, y, z: 60, -20, 10$ ; middle panel), and large ( $x, y, z: 61, -20, 8$ ; right panel) deviants relative to standard stimuli in the pitch condition. Statistical parametric maps (SPMs, thresholded at  $P < 0.001$  uncorrected for multiple comparisons, with an extent threshold of 100 voxels) are superimposed on coronal (upper panel) and axial slices (lower panel) of the canonical T1-weighted image. (b) Mean percentage signal change of the averaged event-related BOLD signal (relative to grand mean over voxels and scans) for small, medium, and large pitch deviants relative to standards for the defined region of interest (ROI) within right STG.

with the fMRI data, right STG dipoles were more pronounced than left STG dipoles.

To investigate the contribution of the frontal dipoles in more detail and to emphasize the different involvement of the IFG, we calculated mean percentage change in dipole strength for the IFG dipoles relative to the corresponding STG dipoles. This analysis was conducted separately for left and right IFG/STG pairs and all three pitch deviants. As it is apparent from Fig. 5 a U-shaped relationship between the right relative IFG dipole strength and the degree of pitch deviance could be observed, by this resembling the right IFG activation pattern in the fMRI measurements. In the fMRI study left IFG was solely activated by large relative to medium pitch deviants. In accordance with this observation the left relative IFG dipole strength was more pronounced for large compared to small and medium pitch deviants.

#### Follow-up behavioral experiment

In the pitch condition the MMN amplitude in the early time window as well as right STG activity increased as a function of deviance. A U-shaped relationship between MMN amplitude and the degree of pitch deviance was observed in the late time window, by this resembling the right IFG activation.

MMN amplitudes for spatial deviants increased as a function of deviance in both time windows but no fMRI activity was found. Pitch deviants elicited MMNs with larger amplitudes and smaller latencies compared to spatial deviants. Given this, it is conceivable that the spatial deviants used in this study were harder to discriminate than pitch deviants. There is evidence that the MMN peak latency and the reaction time decreases monotonically as a function of pitch deviance (Tiitinen et al., 1994).

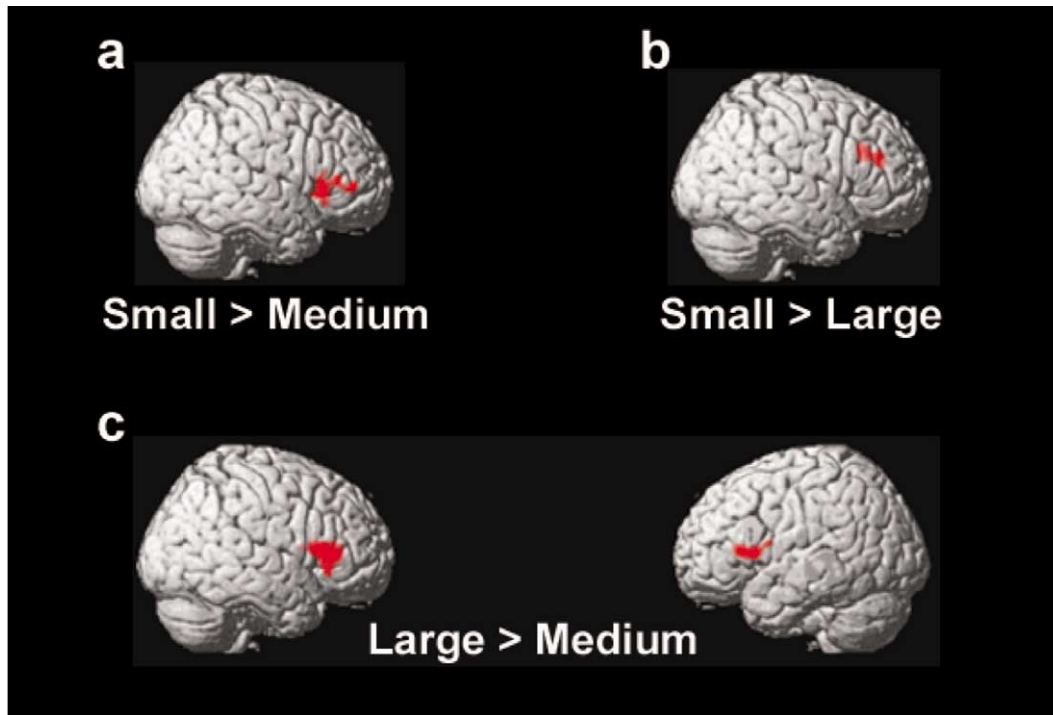


Fig. 4. Lateral views of significantly activated voxels within the prefrontal cortex overlaid onto the surface-rendered MNI standard brain for the contrasts comparing (a) small and medium deviants (small > medium;  $x, y, z$ : 54, 24, 6), (b) small and large deviants (small > large;  $x, y, z$ : 50, 28, 22), and (c) large and medium deviants (large > medium;  $x, y, z$ : 50, 24, 6 [right],  $x, y, z$ : -54, 26, 8 [left]) in the pitch condition. In all comparisons, SPMs were thresholded at  $P < 0.001$  uncorrected for multiple comparisons, with an extent threshold of 100 voxels (one-tailed  $t$  test).

We tested the hypothesis of lower detectability and discriminability of spatial deviants by conducting a follow-up behavioral experiment. We expected prolonged reaction times (RT) for spatial compared to pitch deviants (lower detectability). Furthermore, spatial deviants should be harder to discriminate from each other than pitch deviants (lower discriminability). Nineteen subjects (aged 20–34, mean age 24 years; 9 males; all 7 subjects from the fMRI experiment and 12 new subjects) participated in the experiment. Subjects were instructed to respond to all deviants by button press; 1220 stimuli were delivered in the pitch and spatial condition, respectively. All other parameters were held constant compared to ERP and fMRI recordings. Both conditions were presented in separated blocks. The sequence of blocks was balanced across subjects. For each participant, we calculated proportions of correct responses (PC) and mean RT as a function of deviance separately for both conditions. Performance was highly accurate for both conditions (pitch: 97.8%, space: 90.7%). As Fig. 6 shows, RT for spatial deviants were prolonged compared to pitch deviants for all three degrees of deviance. In contrast to the space condition, RT in the pitch condition decreased with increasing deviance. A one-tailed Student's  $t$  test for the mean RT difference between spatial and pitch deviants, collapsed across all three deviants, revealed a significant difference ( $t = 5.27, P < 0.0001$ ). Additional ANOVAs were run on mean RT separately for both conditions. Deviance effects were obtained in the pitch conditions ( $F_{2,36} =$

5.37,  $P < 0.01$ ), but not in the space condition ( $F_{2,36} < 2, P > 0.2$ ). This confirms the view of lower detectability and discriminability of the spatial compared to the pitch deviants.

## Discussion

The goal of the current study was to examine the functional roles of superior temporal and inferior frontal brain regions in auditory deviance detection using event-related functional magnetic resonance imaging and event-related brain potentials. In particular, we were interested in the issue of which deviant types activate the IFG. The results from the dipole analysis integrating the electrophysiological and hemodynamic measurements confirmed the previously proposed view that the mismatch negativity can be separated into two functional distinctive subcomponents, the early and late MMN, generated in the superior temporal gyrus and the inferior frontal gyrus, respectively (see Opitz et al., 2002). Right STG activity and early MMN amplitude increased as a function of pitch deviance, whereas a U-shaped pattern was observed in the right IFG and the late MMN amplitude, respectively. Large pitch deviants showed additional activity in left IFG. A post hoc behavioral study provides support for the view that the smaller MMN amplitudes and the absence of reliable BOLD activation in the space condition may result from the lower detectability and



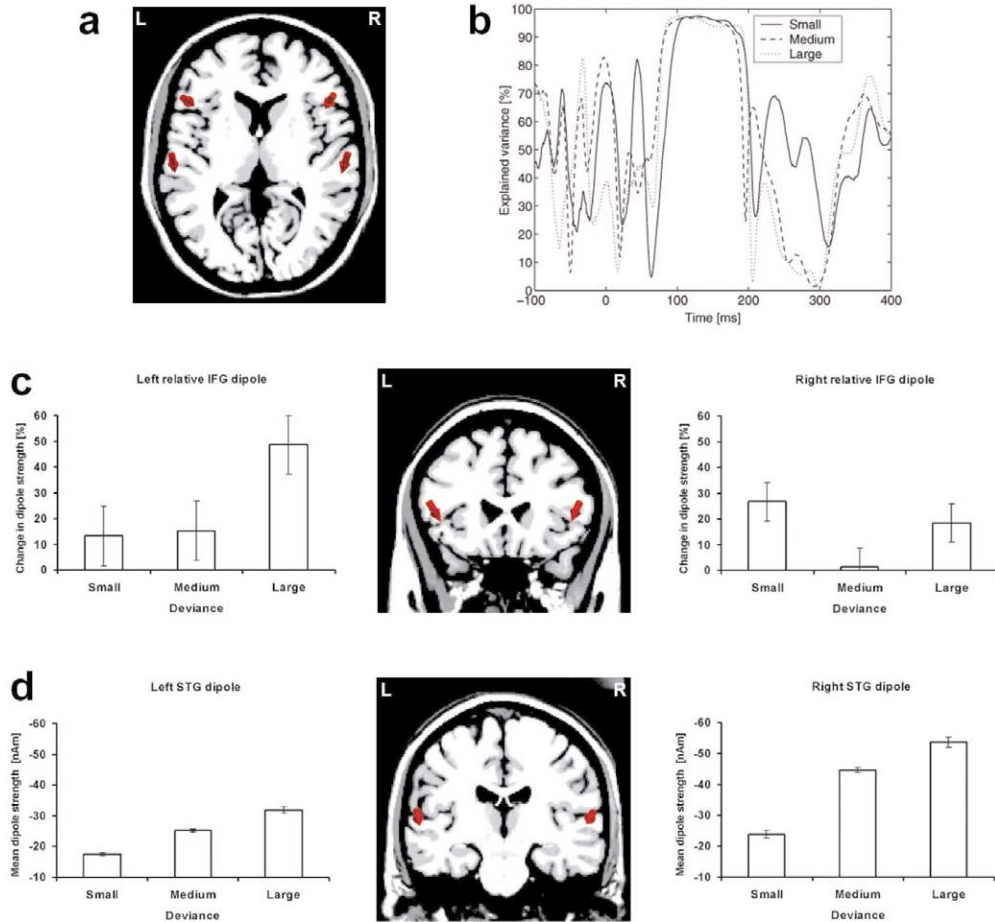


Fig. 5. (a) Best-fitting dipoles for change-related ERP signals for all three deviants within the early (90–120 ms; STG dipoles) and late (140–170 ms; IFG dipoles) time window in the pitch condition, superimposed on an axial section of an average structural magnetic resonance image in Talairach space ( $z = 10$ ). Dipoles are indicated by red arrows. (b) Explained variance of the dipole model separated for small (solid), medium (dashed), and large pitch deviants (dotted). (c) Mean percentage change in dipole strength for IFG as compared to STG dipoles is plotted as a function of pitch deviance for the left IFG (left panel) and right IFG (right panel) dipole, respectively. Both IFG dipoles are superimposed on a coronal section (middle panel;  $y = 24$ ). (d) Left STG (left panel) and right STG (right panel) dipole strength is depicted for small, medium, and large deviants. Both STG dipoles are superimposed on a coronal section (middle panel;  $y = -20$ ).

discriminability of the spatial deviants compared to the pitch deviants used in this study.

*Temporal cortex*

It could be hypothesized that the early MMN amplitude reflects an automatic change detection process, proportional to the degree of deviance. The ERP data in the pitch as well as in the spatial condition confirm this assumption: in both conditions, the early MMN amplitude increased as a function of deviance. In the pitch condition, these ERP data were paralleled by the fMRI data: right superior temporal gyrus activity increased with increasing pitch deviance. The right-lateralized pattern of activity in STG is in accordance with a model of auditory cortex function (Zatorre et al., 2002), suggesting that right auditory cortex is involved in pitch perception, whereas left auditory cortex is more concerned with the processing of temporal properties of auditory information. Zatorre et al. (2002) assumes that left auditory

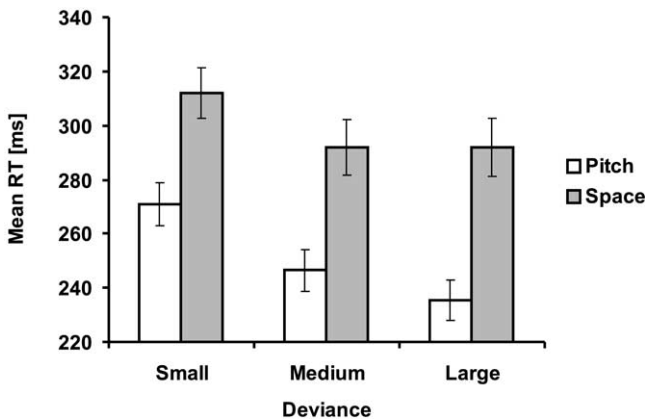


Fig. 6. Proportion of reaction times as a function of deviance for the pitch (white) and space (gray) condition in the follow-up behavioral experiment.

cortical areas have a higher degree of temporal sensitivity, optimal for speech discrimination, whereas corresponding right hemispheric areas have a greater spectral sensitivity, optimal for frequency processing (e.g., Johnsrude et al., 2000; Zatorre et al., 1992; Zatorre and Belin, 2001). This view is supported by two recent MEG studies (Mathiak et al., 2002a; Schneider et al., 2002). Using a dichotic listening paradigm, Mathiak and coworkers (2002a) found that right auditory cortex is more engaged in detection of pitch change than left auditory cortex. MEG and MRI-based volumetric data from Schneider et al. (2002) revealed larger dipole amplitudes in right than in left auditory cortex and larger gray matter volume in the anteromedial portion of Heschl's gyrus for musicians compared to nonmusicians during processing of sinusoidal tones.

In the space condition, deviants vs. standards elicited no significant BOLD signal in the STG. The smaller MMN amplitudes (see Deouell and Bentin, 1998) in the ERP experiment and the elevated reaction times in the behavioral study for spatial compared to pitch deviants in silent environment suggest that it was more difficult for the subjects to detect and discriminate the spatial deviants. Postexperiment debriefing of participants confirmed this observation in all three experiments. Due to scanner noise it seems to be problematic to study auditory processing of small stimulus changes with fMRI. Therefore, it is conceivable that spatial deviants, differing only by interaural time and level differences from the standards, were hardly detectable by subjects and elicit no reliable hemodynamic response compared to the standard tones. This difference in processing spatial and pitch deviants may be due to the specific stimulus parameters of the present study chosen for the experimental setup and not to a general processing difference, as in previous studies similar RT and hit rates were obtained for pitch and spatial deviants when perceptual differences were controlled for in terms of just notable differences (jnd; Widmann et al., 2000).

In the ERP experiment, early and late MMN amplitudes increased with the degree of spatial deviance. Confirming previous research on location MMN (Paavilainen et al., 1989; Schröger and Wolff, 1996; Winkler et al., 1998) these data demonstrate that MMNs to spatial deviants increase with increasing deviance similar to pitch deviants (Tiitinen et al., 1994). These data provide evidence for the view that the early deviance detection system as indexed by the early MMN peak and STG activity is a stimulus-driven bottom-up process that detects auditory mismatches in a fast and domain-general way.

### *Prefrontal cortex*

The present data show that auditory deviance detection depends on the interaction between auditory and prefrontal cortex. There is neurophysiological evidence that both areas have reciprocal interconnections. The auditory cortex of primates can be subdivided into distinct streams of process-

ing (Rauschecker and Tian, 2000; Tian et al., 2001), a spatial stream that originates in the caudal part of the superior temporal gyrus and projects to the parietal cortex, and a stream originating in the more anterior portions of the lateral belt. In contrast to the “where” path, the “what” path is reciprocally connected to prefrontal areas, e.g., ventral prefrontal regions (Romanski et al., 1999). In particular, the ventrolateral prefrontal cortex contains an auditory responsive domain (Romanski and Goldman-Rakic, 2001).

In the right prefrontal cortex the relationship between pitch deviance and hemodynamic response was reversed compared to the STG pattern: right prefrontal activation was greater for small than medium and large pitch deviants. Opitz et al. (2002) propose a contrast enhancement view concerning the prefrontal MMN generator. This view claims that the prefrontal MMN generator is activated in situations, when the temporal deviance detection system gets in difficulty in discriminating stimuli. Within the framework of the contrast enhancement model, it could be proposed that the late MMN amplitude and the prefrontal hemodynamic activity should be more pronounced for small than for medium and large deviants. In accordance with this view, small pitch deviants elicited greater MMN amplitudes than medium deviants in the late time window between 140 and 170 ms in the ERP study. Further support for the contrast enhancement view is provided by the present fMRI results. As predicted, both the small vs. large and the small vs. medium contrast (although at a marginal lower statistical threshold) revealed greater activity for the small deviants compared to medium and large deviants in the most dorsal portion of the opercular part of the right IFG. These results confirm that the proposed contrast enhancement mechanism (largest for small deviants) relies on the recruitment of the right inferior frontal gyrus, in particular the dorsal portion of the IFG.

However, contrary to the contrast enhancement model, in the late time window large deviants showed greater MMN amplitudes than small and medium deviants in both the pitch and space condition. In the same way, bilateral hemodynamic activation for large relative to medium pitch deviants could be observed in the ventral portion of the IFG. One post hoc interpretation for this unexpected result could be derived from music theory of pitch processing (Burns, 1999). Large pitch deviants differed from the standards by one octave, i.e., 100% change in frequency (octave equivalence). It is well established in music-theoretical perspective of pitch that tones belonging to the same pitch class, as standards and large deviants that differed by 100% in frequency, are musically more similar than tones differing by 33% or 67% in frequency. Thus, it could be assumed that large pitch changes were processed in a more complex manner than small and medium pitch changes, based on qualitatively different mechanism (Brattico et al., 2000).

Interestingly, in the small vs. medium contrast an activation of the ventral part of the right IFG was observed. This could be interpreted in a similar vein. A 33% change is

close to a perfect fourth musical interval. Given this, it could be speculated that in contrast to the dorsally organized contrast enhancement mechanism a more ventral portion of the IFG might be involved in processing of musical features. Several lines of evidence support the view that the IFG is involved in musical perception. In a recent MEG study, Maess and colleagues (2001) found that harmonic incongruities occurring within a major-minor tonal context elicit an early negativity similar to the MMN. Dipole solutions indicated that the generators of this negativity are located in the opercular part of the inferior frontal gyrus bilaterally. Furthermore, musicians showed increased gray matter density in Broca's area in the left inferior frontal gyrus compared to nonmusicians, as revealed by voxel-based morphometry (Sluming et al., 2002). Thus, it could be argued that beyond the physical characteristics additional musical features of deviants are processed and that the bilateral IFG might enable this specialized function. This, in turn, could result in qualitatively different and more complex processing of pitch changes when both the physical and the musical stimulus dimension are of relevance. This complex processing of pitch deviants should not necessarily alter the reaction times in the target detection task in the behavioral post study. However, further research will be required to disentangle the precise role of the left and right IFG and different portions within the IFG in auditory pitch discrimination.

In the present ERP experiment, deviants elicited a frontocentrally distributed positivity, the P3a. The P3a is considered to be a reflection of the attentional switch following mismatch detection (Näätänen, 1990). Previous data suggest that the P3a is diminished by prefrontal lesions, suggesting that prefrontal cortex is critical for orienting attention toward novel stimuli (Knight, 1984). However, the increase of the P3a as a function of deviance in the present ERP measurements is not in accordance with the PFC activation pattern in the fMRI study. Therefore the association between prefrontal cortex and involuntary switches of attention seems not to be supported by the present fMRI data. In addition, several fMRI studies of target detection using active oddball paradigms, where subjects are required to detect rare targets in the visual (Casey et al., 2001; Clark et al., 2000; Huettel et al., 2002; Kirino et al., 2000; Linden et al., 1999; McCarthy et al., 2000) as well as in the auditory (Kiehl et al., 2001; Linden et al., 1999) domain, showed target-related prefrontal activity, especially in the inferior and middle frontal gyrus. In ERP experiments, the detection of such task-relevant stimuli is accompanied by a parieto-central target P3, resp. P3b. Prefrontal areas seem to be activated by the same events that evoke P3b (see Kirino et al., 2000). As no P3b components were elicited by any deviants in the present study, a contribution of target-related processing to the present IFG finding seems to be rather unlikely.

To summarize, the results of this study are partly consistent with a contrast enhancement function of the right prefrontal cortex in auditory pitch discrimination, i.e., the

lower the discriminability between pitch deviants and standard tones the greater right IFG activity. In contrast, bilateral IFG was activated by large relative to medium pitch deviants, separated by one octave from the standard tone, presumably reflecting the preferential role of bilateral IFG in processing of additional musical features within the auditory stream. Therefore, we argue that preattentive auditory deviance detection critically depends on the interaction between right superior temporal gyrus and right inferior frontal gyrus, with an additional involvement of left IFG when musical stimulus features are processed.

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