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The Neural Circuitry of Pre-attentive Auditory Change-detection: An fMRI Study of Pitch and Duration Mismatch Negativity generators

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Electrophysiological studies have revealed a pre-attentive change-detection system in the auditory modality. This system emits a signal termed the mismatch negativity (MMN) when any detectable change in a regular pattern of auditory stimulation occurs. The precise intracranial sources underlying MMN generation, and in particular whether these vary as a function of the acoustic feature that changes, is a matter of some debate. Using functional magnetic resonance imaging, we show that anatomically distinct networks of auditory cortices are activated as a function of the deviating acoustic feature — in this case, tone frequency and tone duration — strongly supporting the hypothesis that MMN generators in auditory cortex are feature dependent. We also detail regions of the frontal and parietal cortices activated by change-detection processes. These regions also show feature dependence and we hypothesize that they reflect recruitment of attention-switching mechanisms.

Keywords: auditory, change-detection, fMRI, MMN, pre-attentive

Introduction

The pre-attentive detection of change in the environment is an essential element of perception and cognition in humans. Such mechanisms mediate the seemingly automatic shift of attention to new and potentially important information, whilst operating without drawing upon limited attentional resources. A well-established dependent measure of pre-attentive auditory change-detection is found in the mismatch negativity.

The mismatch negativity (MMN) is an electrical brain response that is elicited by any discriminable change in the regularity of the acoustic environment. The MMN is typically measured under conditions in which participants are instructed to ignore the auditory stimulation and read a book or watch a movie. Given that the MMN can be elicited in the absence of attention, when attention is directed toward an unrelated and demanding task (Alho *et al.*, 1994a; Woldorff *et al.*, 1998), and even when subjects are sleeping (most reliably during the REM stage of sleep) (e.g. Atienza and Cantero, 2001; Atienza *et al.*, 2002), the MMN system is considered to operate pre-attentively. The system underlying generation of the MMN is considered to maintain a representation of acoustic regularities of the recent past (Cowan, 1984; Cowan *et al.*, 1993), with the MMN elicited when this representation is updated (Winkler *et al.*, 1996; Näätänen, 1992); that is, when there has been a change.

MMN generation is typically studied using an oddball paradigm in which, in its simplest rendition, an infrequent tone (termed the 'deviant') is interspersed at random intervals within a train of frequent tones (termed the 'standard'). The scalp-recorded MMN, best viewed by subtracting the response to the standard from the response to the deviant, is a negative fronto-centrally distributed wave that often inverts at temporal sites around the mastoids, and peaks 100–200 ms post-deviance onset. The principal neural source of the MMN has been determined to be located within the supratemporal plane in or near primary auditory cortex on the basis of dipole analysis of magnetic recordings (Sams and Hari, 1991) and electrical recordings (Giard *et al.*, 1990; Scherg and Berg, 1991) obtained from the scalp of humans, complemented by intracranial recordings in cat (Csépe *et al.*, 1987) and macaques (Javitt *et al.*, 1992, 1994).

An important theoretical question that remains is whether there is a single neural network in auditory cortex that is responsible for generating the MMN regardless of the acoustic dimension that has changed or whether the MMN network differs depending upon the nature of the acoustic change. For example, does a different circuit generate the MMN for a change in frequency versus a change in the duration of a repeating tone? Several models of the MMN have assumed the latter (Näätänen, 1992; Winkler *et al.*, 1996), and there are data from dipole source modeling and scalp topographic mapping consistent with the notion that the neural networks underlying the generation of the MMN vary based upon the characteristics of the eliciting stimuli. For example, Paavilainen *et al.* (1991) found slightly different ERP topographies, all consistent with generators in auditory cortex, for MMNs elicited by frequency, intensity and duration deviants. This finding is supported by those of Giard *et al.* (1995), who localized the source dipoles of MMNs elicited by the same three types of deviants to different locations within auditory cortex. Likewise, in MMNm (the magnetic counterpart of the MMN) studies, source modeling has shown different cortical loci on the superior temporal plane for MMNms elicited by inter-stimulus interval deviants (that is, changes in presentation rate) and duration deviants (Levänen *et al.*, 1996), and for MMNms elicited by frequency, duration, and intensity deviants (Rosburg, 2003). In contrast to the above findings, however, other studies using dipole-modeling techniques have failed to find significant differences in the loci of MMN generators for different acoustic features [Sams *et al.* (1991) and Schairer *et al.* (2001) both examine frequency, duration and intensity MMNs].

While the methods of source modeling and scalp topographic mapping are highly useful tools to estimate the location of the neural sources underlying a given electro-magnetic scalp topography, they only provide general estimations, and have shown mixed results concerning the question of interest. Therefore, in the present study, we used the substantially better anatomical localization afforded by functional magnetic resonance imaging (fMRI) to test the hypothesis that the neural network that generates the MMN response depends upon the characteristics of the eliciting stimuli.

To our knowledge, only two previous imaging studies have investigated the anatomy of the neural networks underlying MMNs to changes in different acoustic features. Unfortunately, in one of these an alternative explanation may account for findings of different neural networks underlying different MMNs (Mathiak *et al.*, 2002), and in the other the question could not be addressed because no MMN-related activations were detected for one of the two deviants that were tested (Doeller *et al.*, 2003). Mathiak *et al.* (2002) examined fMRI MMN activations to intensity and duration deviants, compared with activity elicited by standard stimuli. Whereas an infrequent decrease in stimulus intensity activated bilateral primary and secondary auditory cortices, only right hemisphere secondary auditory areas were activated by an infrequent decrease in stimulus duration. While this finding generally supports the notion that the neural generator of the MMN is dependent on the acoustic feature that is varied, differences in intensity maps within auditory cortex (Clarke and Rivier, 1998; Schreiner *et al.*, 1992) could well account for the greater MMN-related activation in the intensity compared with the duration conditions. In a separate study, Doeller *et al.* (2003) used fMRI to examine MMN activations as a function of changes in both tone frequency and tone location. While frequency deviants resulted in significant changes in the BOLD signal within the right STG, the authors failed to find any MMN activations for the location condition. This was the case despite reliable location-MMNs being elicited in the same set of subjects during a separate ERP recording session.

In the present study we used a MMN paradigm designed specifically to eliminate a problem inherent in many of the previous imaging studies of the MMN (Celsis *et al.*, 1999; Opitz *et al.*, 1999; Wible *et al.*, 2001; Müller *et al.*, 2002; Sevostianov *et al.*, 2002; Liebenthal *et al.*, 2003). In these studies, all of which employed frequency deviants, activations elicited by blocks of stimulation comprising both standard and deviant tones were compared with activations elicited by blocks of stimulation in which only the standard tone was presented. Any differences in observed patterns of activations resulting from these two conditions were interpreted as reflecting MMN-related activity. However, due to the tonotopic organization of primary and secondary auditory cortices (Merzinich and Brugge, 1973; Kaas and Hackett, 1998; Schonwiesner *et al.*, 2002), the reported differences in activations might well be explained by differences in the sensory stimulation given during oddball and control blocks. That is, in the oddball (standard and deviant) blocks of these studies, two tones of different frequencies are presented and thus two distinct regions of tonotopic auditory cortex will necessarily be activated, resulting in a larger overall area of activation. On the other hand, in the control condition, only the standard tone is presented and as such only one tonotopic region is activated. Thus, in the control condition, one class of generators would be activated (i.e. those associated with the specific frequency of the standard), whereas in the oddball condition, three classes of generators are putatively activated; those associated with the frequency of the standard, those associated with the frequency of the deviant and those associated with the MMN. Problematically, there is no way to precisely determine the extent to which the additional activations of the oddball condition are due to frequency specific activation associated with the deviant versus activation associated with the MMN. Similar considerations apply to event-related fMRI designs, in that the standard will elicit activity associated with its frequency and the deviant will elicit activity associated with its frequency as well as activity associated with the MMN (Opitz *et al.*, 2002; Doeller *et al.*, 2003).

We have surmounted this problem in the present design by using a sequencing technique that equates for stimulus energies across both MMN and control blocks. Using this modified design, we show that separable neural circuits within auditory cortices underlie the MMN to frequency change and duration change. Further, our data strongly suggest that the neural circuitry activated by the duration-MMN and subsequent processing, recorded while subjects ignore auditory stimulation and watch a silent video, engages much of the neural circuitry activated by active processing of temporal information, as seen in unrelated studies on temporal processing (Schubotz and von Cramon, 2001; Macar *et al.*, 2002; Lewis and Miall, 2003; Coull *et al.*, 2004).

Materials and Methods

Subjects

Twenty subjects participated (age 27 ± 8, 14 female). All were right-handed and neurologically normal. Subjects provided written, informed consent according to institutional guidelines, and were paid for their participation. The Institutional Review Board of the Nathan Kline Institute approved all procedures.

Stimuli

Tones differing in frequency or duration served as stimuli. The stimuli were presented at a comfortable listening level that was clearly audible above the MRI scanner noise; intensity level was adjusted on an individual subject basis (~90 dB). Tone 1 was a 500 Hz tone of 100 ms duration, tone 2 was a 400 Hz tone of 100 ms duration and tone 3 was a 500 Hz tone of 50 ms duration.

Procedure

Subjects were fitted with pneumatic ear inserts, and their ears were then covered by custom-built foam and plastic earmuffs that served to further attenuate magnet noise while allowing for delivery of auditory stimulation. Once subjects were placed in the bore of the magnet a test scan was acquired to check the audibility of the auditory stimuli over the scanner-generated noise, and to ensure that the stimuli were presented at a comfortable listening level. Subjects were instructed to watch a movie (without sound) presented on a custom designed LCD screen and to ignore all tone events.

In devising the MMN and control blocks it was essential to match overall sensory stimulation. We took advantage of an MMN paradigm in which two tones are presented equiprobably and the order of their presentation varied (Sams *et al.*, 1983; Giese-Davis *et al.*, 1993). In this paradigm tones are arranged to compose alternating 'mini-sequences' of tones 1 and 2. The number of trials in a given mini-sequence varies such that the occurrence of a switch from tone 1 to tone 2 (and vice-versa) is irregular. As such, the switch trial tone is a 'deviant' and elicits the MMN, and the repeating tone is the 'standard'. This basic stimulation paradigm, which has proven to elicit robust MMNs, was used for the MMN condition (Sams *et al.*, 1983; Giese-Davis *et al.*, 1993). For the matched control condition to the aforementioned MMN condition, the same two tones were alternated sequentially to form a regular pattern, such that no MMN would be elicited. In this way, the frequency specific activations of tonotopic cortices produced by the two tones occur in both conditions and activity specific to the MMN generators and MMN related processes can be readily discerned.

During a single fMRI scanning session, five stimulation conditions ('frequency MMN', 'frequency control', 'duration MMN', 'duration control' and 'rest') were administered in a block fashion during two separate scans. Both MMN blocks consisted of alternating 'mini-sequences' of two tones: mini-sequences were 2, 3, or 4 repetitions of a single tone (each sequence length was represented equiprobably) followed by a mini-sequence of the other tone, and so on. The first tone in a sequence was expected to generate a MMN; this was confirmed by

an electrophysiological pilot study in which the MMN was elicited using the same stimuli and stimulus paradigm as in the fMRI study. A constant SOA of 500 ms was employed for both the MMN and control conditions. Control blocks consisted of two tones alternating in a regular fashion (e.g. T1, T2, T1, T2, etc.). Figure 1 provides a schematic of the experimental paradigm.

Each subject participated in one 'frequency scan' and one 'duration scan'. Each scan lasted 10.5 minutes. In the frequency scan, MMN-generating mini-sequences (described above) of tone 1 (T1) and tone 2 (T2) (same duration but differing in frequency) were presented in 32 s blocks that were alternated with control blocks consisting of regular sequences of T1 and T2. Each of these blocks was presented five times over the course of a scan and was interspersed with 32 s rest blocks during which no auditory stimulation was delivered through the ear inserts. Siémilarly, during the 'duration scan' mini-sequences of T1 and T3 (same frequency but varying in duration) were alternated with control blocks of sequentially alternating presentations of the same two tones and interspersed with rest blocks. Half of the subjects participated in the duration scan first.

Data Acquisition and Analyses

T2*-weighted echo-planar images (EPI/T_E/flip angle = 2 s, 64 ms, 90°; voxel size = 4 × 4 × 5 mm; matrix size = 64 × 64) were acquired on a 1.5T Siemens VISION scanner. The T_Rs were evenly distributed across the acquisition cycle so that auditory stimulation from the scanner was continuous during the scan. This resulted in a streaming into the background of the continuous scanner noise such that it clearly segregated from the auditory stimuli presented over the headphones. During each scan, 320 volumes were acquired in the axial plane, on each of 22 contiguous slices covering the entire brain. The first five images were discarded to allow for stabilization of the blood oxygenation level dependent (BOLD) signal.

For anatomical localization, high-resolution (1^3 mm) T1-weighted images of the whole brain were acquired using a standard three-dimensional magnetization prepared rapid gradient echo (MPRAGE) pulse sequence. Anatomical images were normalized into Talairach coordinates (Talairach and Tournoux, 1998) and the functional data were registered to the normalized anatomical data.

All data processing and analysis was conducted using the AFNI image-analysis software package (Cox, 1996). Images were realigned to an image at approximately the mid-point of the time-series acquisition. In all subjects, head motion never exceeded 0.75 mm along any axis. Prior to statistical analyses the images were spatially smoothed (FWHM 6 mm) to compensate for individual variation in cortical anatomy, and normalized into Talairach coordinates (Talairach and Tournoux, 1998). Data acquired from each of the two types of scans (frequency and duration) were analyzed separately. To estimate the BOLD response associated with each condition, regressors representing the timing of each stimulation epoch were convolved with a canonical hemodynamic response function and used in a multiple regression analysis.

Functional Auditory ROI

For both the frequency and duration scans, regression coefficients were modeled separately for the MMN, control, and rest blocks of each scan. For each participant, a general linear test (GLT) contrasting activity associated with the control condition with that associated with rest was performed. The linear coefficient values from these contrasts were entered into a groupwise *t*-test and compared against the null hypothesis. A single functional auditory region of interest (ROI) was generated by combining all voxels that were significantly activated ($P < 0.05$) during the control condition (relative to rest) in both scans (frequency and duration).

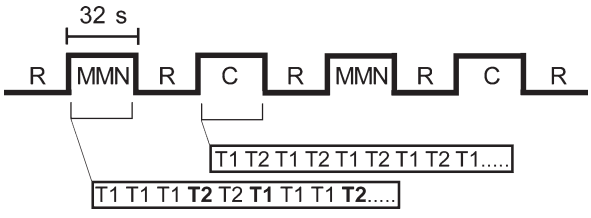

Figure 1. Schematic of the experimental paradigm: alternating MMN and control (C) blocks are interspersed with rest (R) blocks. Examples of the sequential ordering of tone 1 (T1) and tone 2 (T2) for MMN and control blocks are shown. For the MMN block, the 'deviant' stimulus is bolded.

Change-detection Related Activations

In our principal analysis we sought to compare functional activity in auditory cortex associated with the MMN response (and related auditory change-detection processes) as a function of the acoustic feature of the eliciting deviant. As such, we used linear regression to model the regressor coefficients for MMN, control and rest conditions for each of the two scan types. Regressor coefficients for MMN and control conditions were contrasted, on an individual subject basis, in a GLT. The resulting linear coefficients were entered into separate *t*-tests and tested, across subjects, against the null hypothesis. These *t*-tests considered only those voxels falling within the groupwise functional ROI (above). The results from both *t*-tests were further constrained to include only clusters of four or more neighboring voxels with *t* values equivalent to $P < 0.05$.

As a secondary analysis, and to provide a more thorough description of the group data, the linear coefficients from the MMN versus control contrasts (for frequency and duration scans) were entered into two additional *t*-tests where the ROI constraint was lifted. For this more liberal analysis only significantly activated voxels belonging to clusters of eight or more were considered.

Results

Sensory Auditory Activation: Control Blocks versus Rest Blocks

There was a significant increase in the BOLD response in auditory cortices for the control auditory stimulation blocks when compared with the rest blocks. This activation extended throughout much of the superior temporal plane of the right and left hemispheres, extending anteriorly into the posterior portion of the frontal lobes and posteriorly into the posterior portion of the superior temporal sulcus. This pattern of activation was similar for both the frequency and duration scans. The functional auditory ROI used in the group analysis is shown in Figure 2 shaded in green.

MMN Blocks versus Control Blocks

The ROI analysis revealed a significant increase in the BOLD response for MMN compared with control blocks for both the duration and frequency scans. In the right hemisphere these activations were situated within the superior temporal gyrus (STG), in primary auditory cortex for the frequency scan, and in secondary auditory cortex for the duration scan. Consistent with findings from the majority of ERP and MEG studies (Levänen *et al.*, 1996; Frodl-Bauch *et al.*, 1997; Rosburg, 2003), MMN-related activation in the duration-MMN scan was located posterior to that obtained in the corresponding frequency-MMN scan (see Fig. 2), In the left hemisphere these activations were found in the transverse temporal gyrus (in secondary auditory cortex) for the duration scan, and in the posterior STG for the frequency scan. In contrast to the right hemisphere, the frequency-MMN activation was more posterior than the duration-MMN activation. In both hemispheres, the duration-MMN activations were slightly lateral to the frequency-MMN activations. The data from this analysis clearly show that anatomically distinct regions of auditory cortex are involved in the generation of duration- and frequency-MMNs. Table 1 presents the Talairach coordinates of these activations.

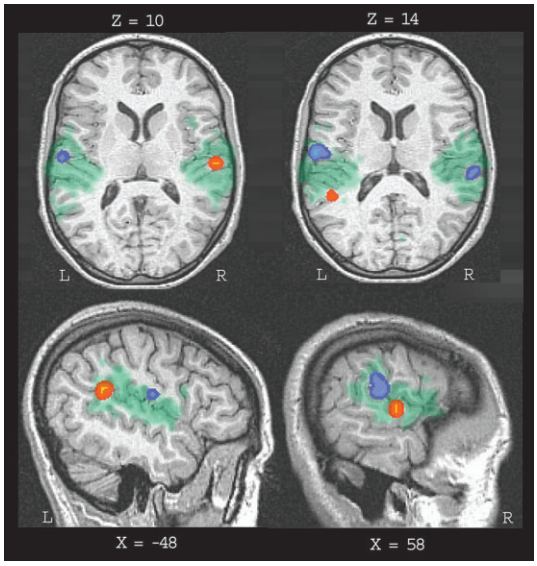

Figure 2. MMN generators in auditory cortices: significant duration-related MMN activations are shown in blue and frequency MMN activations are shown in orange. The larger extent of auditory cortices activated by simple sensory stimulation is shown in the shaded green. This region served as the region of interest (ROI) within which subsequent tests for MMN activity were conducted. For both this and Figure 3, the functional data have been transformed into Talairach and Tournoux coordinates and are displayed on the brain of an individual subject that has been similarly transformed.

Table 1
MMN activations within the ROI

	Brain region	Center of mass Talairach coordinates: *x*, *y*, *z*	Volume, Ml	*T*(1,19)	*P*
Duration	R superior temporal gyrus	64, −26, 15	320	2.13	0.047
	L transverse temporal gyrus	−57, −14, 11	320	2.70	0.010
Frequency	R superior temporal gyrus	56, −17, 6	256	2.45	0.025
	L superior temporal gyrus	−45, −44, 19	256	2.38	0.028

A second statistical analysis, in which the entire brain volume was considered, revealed additional extra-auditory cortical activations related to change-detection processes, mainly in frontal and parietal regions (see Fig. 3). These were found for both the duration and frequency scans. For the duration MMN versus control contrast there were significant bilateral increases in superior frontal cortices, the middle temporal lobes, and the inferior and precuneus regions of the parietal lobes. There were right hemisphere unilateral MMN-related activations of the middle frontal gyrus (including the supplementary motor area and right dorsal premotor cortex), the middle temporal gyrus, and the anterior cingulate; and in the left hemisphere of the inferior frontal gyrus and the post central gyrus of the parietal lobe. Comparing the frequency MMN condition to its corresponding control condition yielded significant enhancements in the BOLD signal within the inferior and middle frontal gyrus, inferior parietal lobule, and middle occipital gyrus of the right hemisphere. In the left hemisphere only the superior frontal gyrus contained any significant clusters of activation. Table 2 presents Talairach coordinates of these activations.

Discussion

Here we show that the neural generators underlying the auditory pre-attentive change-detection system vary as a function of the characteristics of the eliciting stimuli: infrequent changes in the frequency of a repeating tone resulted in differential patterns of MMN-related activation in auditory cortex compared with infrequent changes in the duration of a repeating tone. Thus the MMN system indicates not only that a change has occurred, but also the nature of the change. Our finding supports a model of the MMN in which it functions to update feature-specific sensory memories of acoustic regularities in the environment. Information about the nature of the change may help with the rapid evaluation of the significance of the change.

Our finding of MMN-related activation in the STG is generally compatible with those seen in previous imaging studies (Celsis *et al.*, 1999; Opitz *et al.*, 1999, 2002; Dittmann-Balçar *et al.*, 2001; Wible *et al.*, 2001; Mathiak *et al.*, 2002; Müller *et al.*, 2002; Sevostianov *et al.*, 2002; Doeller *et al.*, 2003; Liebenthal *et al.*, 2003; Schall *et al.*, 2003), even though in the majority of these studies the comparison condition did not fully account for sensory stimulation. This is not surprising since at the cortical level, MMN generation is largely achieved in the auditory cortices, and the basic processing of auditory stimuli at the cortical level is, of course, also achieved in the auditory cortices. Thus the inability to separate activations related to basic auditory processing from MMN-related processing was not expected to result in an altogether different pattern of activation. One would predict more extensive 'MMN-activations' in studies where overall stimulation was not matched across conditions. It is not surprising then that most imaging studies that have compared MMN and control (standard only) blocks, or used an event-related design in which the response to the standard is compared with the response to the frequency-deviant, have indeed shown activations in auditory cortex that are more extensive than we find here. It is also worth noting that there has been a relatively high degree of variance in the cortical location of the frequency MMN across previous studies, most of which used fixed-effects designs and are therefore not generalizable to the population at large (Desmond and Glover, 2002). On the other hand, a remarkably consistent location is found in right auditory cortex between the three studies to date — including this one — that have employed large subject populations and random-effects designs (Opitz *et al.*, 2002; Doeller *et al.*, 2003, in which there was no corresponding activation in the left STG; the present study).

In addition to MMN activations in auditory cortex, there were frontal and parietal activations related to change-detection processes for both the frequency and duration scans (see Fig. 3). Numerous studies have demonstrated that elicitation of the MMN draws attention to the deviant stimulus (Schröger, 1996; Escera *et al.*, 1998; Schröger and Wolff, 1998), and it is likely that this frontal and parietal activity is in part related to attention switching mechanisms that follow elicitation of the MMN. This activity may be related to generation of the electrophysiological component, the P3a, which often follows the MMN, has neural sources in frontal and parietal cortices (Soltani and Knight, 2000) and is considered to be related to the involuntary switching of attention to the deviant (Escera *et al.*, 1998; Schröger and Wolff, 1998). In addition, a right frontal MMN generator has been hypothesized by Giard *et al.* (1990) based on scalp current density maps of the MMN (see also Deouell *et al.*, 1998) and receives some support from human lesion studies (Alho *et al.*, 1994b; Alain *et al.*, 1998) and imaging studies (Celsis *et al.*, 1999; Dittmann-Balçar *et al.*, 2001; Müller *et al.*, 2002; Opitz *et al.*, 2002; Schall *et al.*, 2003). Thus frontal

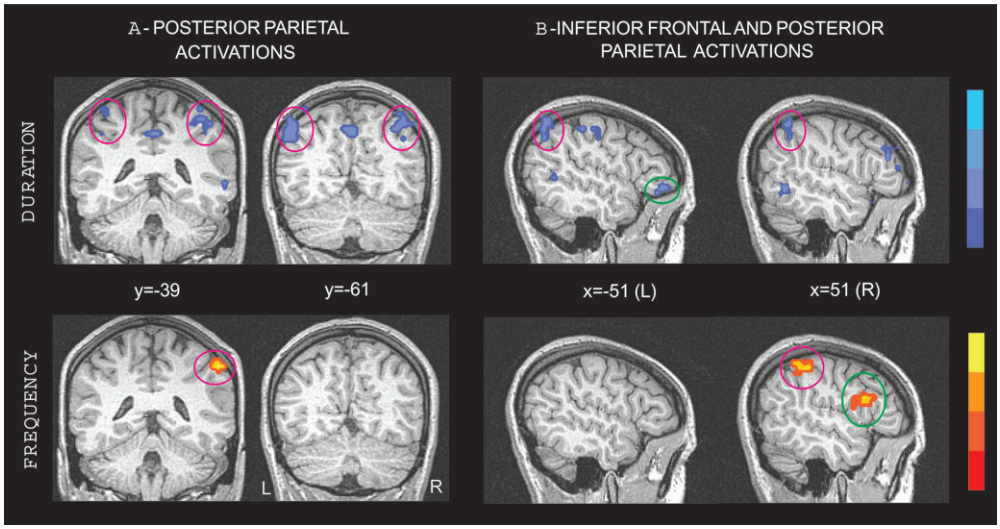

Figure 3. Frontal and parietal generators: activations induced by auditory 'change-detection' processes outside of auditory cortices are shown in the top two panels for the duration condition (in blue) and in the bottom two panels for the frequency condition (in orange). (*A*) Coronal slices show activations in posterior parietal cortex (circled in magenta), which are bilateral and more extensive for the duration condition (top) than the frequency condition (bottom). (*B*) Sagital slices show activations in the left frontal operculum for the duration condition (top panel — circled in green) and in the right inferior frontal gyrus for the frequency condition (bottom panel — also circled in green). The right parietal activation for the frequency condition can also be seen in this view (circled in magenta).

Table 2
MMN versus control activations

	Brain region	Center of mass Talairach coordinates: *x*, *y*, *z*	Volume, Ml	*T*(1,19)	*P*
Duration	L inferior frontal gyrus	−52, 35, −4	1856	2.80	0.012
	L superior frontal gyrus	−6, 60, 23	1600	2.83	0.011
		−41, 39, 28	512	2.31	0.033
	R inferior parietal lobe	42, −51, 50	3904	2.50	0.022
	R parietal lobe, precunius	18, −72, 40	768	2.47	0.024
	R middle frontal gyrus	49, 33, 26	896	2.42	0.026
		33, 1, 62	512	2.46	0.024
	R frontal lobe, medial frontal gyrus	1, −13, 70	1856	2.33	0.031
	R superior frontal gyrus	14, 50, 33	1024	2.25	0.037
		8, 12, 57	576	2.48	0.023
	L parietal lobe, precunius	−1, −50, 39	3328	2.92	0.009
	L parietal lobe, postcentral gyrus	−46, −25, 42	1920	2.65	0.016
	L inferior parietal lobe	−51, −59, 44	2368	2.82	0.010
	L parietal lobe, postcentral gyrus	−2, −50, 68	512	2.42	0.026
	R anterior cingulate	1, 40, −4	576	2.6	0.018
	R middle temporal gyrus	56, −50, −5	1216	2.53	0.021
	L middle temporal gyrus	−56, −53, 6	512	2.44	0.025
Frequency	R middle frontal gyrus	33, 39, 23	1344	2.67	0.016
		33, 12, 26	640	2.44	0.026
		42, 2, 53	512	2.30	0.033
	R inferior frontal gyrus	52, 10, 18	960	2.19	0.042
	L superior frontal gyrus	−20, 23, 51	512	2.73	0.014
	R inferior parietal lobule	53, −38, 45	1152	2.74	0.014
	R middle occipital gyrus	41, −75, 6	832	2.28	0.035

activations may also be partially related to MMN generation. Such a frontal generator has been interpreted as the part of the MMN system that initiates the involuntary switching of attention following the initial MMN response to the deviant (Giard *et al.*, 1990; Näätänen, 1992), or alternatively as an enhancing mechanism for small/difficult to detect changes (Opitz *et al.*, 2002; Doeller *et al.*, 2003). Some studies have localized the frontal activity to the inferior frontal gyrus (Opitz *et al.*, 2002). In the present study activation of the right IFG was seen in the frequency condition, whereas there was activation of the left IFG in the duration condition.

While frontal and parietal change-detection activations were seen in both the duration and frequency scans, there were notable differences in terms of extensiveness and hemispheric dominance. There was a bias to the right hemisphere for frequency activations, whereas duration activations were bilateral or biased to the left hemisphere. These differences in lateralization correspond well with the notion that the right hemisphere is more involved in the processing of tonal information (frequency differences) while the left hemisphere is more involved in the processing of temporal information (duration differences) (Zatorre *et al.*, 1994; Fiez *et al.*, 1996; Platel *et al.*, 1997; Belin *et al.*, 1998; Coull and Nobre, 1998; Nobre, 2001; Zatorre and Belin, 2001). In the inferior parietal lobe, duration change-detection activations were bilateral, whereas frequency change-detection activations were limited to the right hemisphere. In frontal regions, change-detection activations were more extensive for duration than for frequency, with duration showing activations in both the right and left hemispheres, and frequency change-detection activity seen mostly in the right hemisphere. Different regions of the IFG, which has previously been associated with MMN processes, were sensitive to change-detection processing in the duration and frequency scans. In this study, duration-related activation was limited to the left hemisphere and was seen in the frontal operculum. The location of this activation was very similar to that in a PET study by Dittmann-Balçar *et al.* (2001) that looked at duration MMN activations, except that the latter were seen in the right instead of the left hemisphere. The frontal operculum has been associated with temporal perception in a number of studies (Schubotz and von Cramon, 2001; Lewis and Miall, 2003; Coull *et al.*, 2004). In contrast, activation of the IFG for frequency change-detection was specific to the right hemisphere, in a region consistent with the MMN-related activations observed in Opitz *et al.* (2002) and posterior to that seen in the duration scan of the present study. Frontally there was also activation of right dorsal premotor cortex for duration change-detection (Tailarach coordinates: 33, 1, 62), a region that has been shown to correlate with attention to a temporal judgment task (Coull *et al.*, 2004), and the

supplementary motor area (Tailarach coordinates: 1, –13, 70), which is also associated with temporal processing (Macar *et al.*, 2002).

To conclude, using an experimental paradigm that controlled for stimulation across comparison conditions, we found that MMN generators in auditory cortex vary as a function of the nature of the deviating stimulus. Thus the MMN system exhibits feature specificity. Such specificity suggests that the MMN response indicates not only that a change has occurred, but also the nature of that change. The activation of frontal and parietal regions by change-detection processes in both the frequency and duration scans was consistent with the recruitment of attention switching processes.

Notes

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