Cerebral mechanisms underlying orienting of attention towards auditory frequency changes

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Brain mechanisms underlying detection of auditory frequency changes were studied with event-related potentials (ERPs) in 14 human subjects discriminating visual stimuli. Scalp-current density mapping revealed bilateral components of mismatch negativity (MMN) in frontal and auditory cortices. Deviance-related activations in frontal and temporal cortex began to be significant at 94 ms and 154 ms in the right hemisphere, and at 128 ms and 132 ms in the left hemisphere. The magnitude of MMN-neuroelectric currents from the left temporal cortex correlated significantly ($r = -0.56$, $p < 0.05$) with distraction caused by MMN-eliciting deviant tones. These results suggest a complex cerebral circuitry involved in frequency change detection and strongly support the role of this circuitry in driving attention involuntarily towards potentially relevant frequency changes in the acoustic environment.

Key words: Audition; Current density; Event-related brain potentials; Human; Mismatch negativity; Orienting response; Source analysis

INTRODUCTION

Detecting potentially relevant changes occurring in the unattended environment and the subsequent orienting of attention is a fundamental function for biological survival. In the auditory modality, a modality-specific change-detector mechanism has been proposed to play a crucial role in driving attention involuntarily towards unattended acoustic changes [1]. This mechanism is reflected in an event-related brain potential (ERP) called mismatch negativity [2] (MMN). MMN generation is based on a sensory memory system detecting acoustic irregularities by comparison of each new afferent stimulus with a neural trace of the preceding repetitive auditory stimulation [1]. The functional role of MMN generator processes in involuntary attention switching has been supported by recent studies showing deterioration of task performance, i.e. increased reaction time and decreased hit rate to target stimuli delivered after irrelevant MMN-eliciting deviant sounds occurring in a task-irrelevant sound sequence [3–5].

Source localization of electrically and magnetically recorded MMNs, as well as intracranial recordings in cats, monkeys, and humans have shown that MMN has bilateral generators in the primary auditory cortex or its vicinity (for a review, see [6]). In addition, scalp current density mapping of deviance-related negativities [7–9] has suggested a frontal contribution to MMN generation. A frontal contribution to MMN generation is also supported by studies showing attenuation of its amplitude in patients with lesions in the dorsolateral prefrontal cortex [10,11]. According to the current theory [1], the supratemporal MMN component is related to the analysis of the stimulus features and to the sensory memory trace processes involved in MMN generation [12,13], whereas the frontal MMN component is apparently a firm candidate to represent the neuroelectric signal triggering the attention switching response [1,7]. Recent evidence supports that frontal and temporal MMN generators may indeed have different functional roles [9,14]. These later authors found that increasing the standard stimulus probability enhanced the frontal component, whereas the temporal MMN component remained unaffected. This result suggests that the frontal component of MMN may be involved in the processing of the unfamiliarity of deviant stimuli, and thus in the initiation of attention switching. These assumptions on the functional roles of MMN subcomponents have been supported by a recent study of Rinne et al. [15] in which the temporal dynamics of the activations underlying MMN generation were addressed. By using minimum-norm estimate analysis of deviance-related EEG and MEG responses, these authors found that the frontal MMN generators to duration deviant tones activated on average by 8 ms after the supratemporal auditory cortex ones.

To further investigate the cerebral networks underlying
the detection of frequency changes in the acoustic environment, in the present study ERPs to distracting auditory frequency changes were recorded from 30 scalp electrodes while fourteen healthy human subjects performed on a forced-choice visual discrimination task [3,4]. Deviancere-related potentials were analyzed by means of scalp current density analysis (SCD) in order to reveal the distribution of sinks and sources of radial scalp currents disclosing multiple MMN generators and their temporal dynamics during the MMN latency range.

MATERIALS AND METHODS

Fourteen healthy, right-handed human subjects (mean age 21.3 ± 1.8 years; four males), with normal hearing and normal or corrected-to-normal vision gave their written informed consent to participate in the study. In a paradigm modified slightly from that used by Escera et al. [4], the subjects were presented with 10 blocks of 200 stimulus pairs (trials) delivered at a constant rate of one pair every 1.5 s. Each trial consisted of an irrelevant auditory stimulus followed after 300 ms (onset-to-onset) by a visual target stimulus. Auditory stimuli were a 600 Hz standard tone (probability 0.8), two different deviant tones with respective frequencies of 700 Hz and 514 Hz (p = 0.05 for each), and novel sounds (total p = 0.1) drawn from a pool of 60 natural complex sounds (e.g. a telephone ringing) so that a particular novel sound was repeated only twice or three times in the whole experiment and never occurred twice in the same stimulus block. All auditory stimuli were delivered binaurally through headphones with a duration of 200 ms (including 10 ms of rise and fall times) and an intensity of 75 dB SPL (peak intensity between 70 and 80 dB SPL for novel sounds). The auditory stimuli were sequenced randomly, with the only exception that the trials in which the visual stimulus followed a deviant or a novel sound were always preceded by a trial in which the visual stimulus followed a standard tone. The visual stimulus extending vertically 1.7” and horizontally 1.1” was either a digit (from 2 to 9) or a letter (A, E, J, P, R, S, U, or Y), presented equi-probably on a computer screen for 200 ms. Stimulus presentation and sequence control was carried out by means of Stim (NeuroScan, Inc.) software and hardware.

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

EEG (bandpass 0–100 Hz) was continuously digitized at a rate of 500 Hz by a SynAmps amplifier (NeuroScan, Inc.), from 30 scalp electrodes including the entire 10-20 system except O1 and O2 (FP1, FP2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, Oz) and the following additional positions: FT3 (halfway between F3 and T3), TP3 (halfway between T3 and P3), CP1 (halfway between P3 and Cz), FC1 (halfway between Cz and F3), at the left mastoid (LM), IM1 (70% of the distance from the preauricular point to the inion), and the homonymous positions over the right hemispher (Fig. 1a). Horizontal and vertical EOG were recorded with electrodes attached to the canthus and below the right eye, respectively. The common reference electrode was placed on the tip of the nose. ERPs were averaged offline for each auditory stimulus class, for an epoch of 600 ms including a pre-auditory stimulus period of 100 ms. Epochs in which the EEG or EOG exceeded ±100 µV, as well as the five first epochs of each block, were automatically excluded from averaging. The standard-tone trials immediately following deviant tone or novel sound trials were also excluded from the averages. Frequencies > 30 Hz were digitally filtered out from individual ERPs.

A correct button press within 1100 ms after visual stimulus onset was regarded as a hit, the mean reaction time being computed only for the hit trials. An incorrect button press during this period was classified as an error, and trials with no response as misses. Hits, errors, misses, and reaction time were computed across letters and numbers. Distraction effects caused by deviant sounds were analyzed by means of t-test comparisons between hit rate and reaction time to visual stimuli preceded by a standard tone and those preceded by a deviant sound.

This report focuses only on the performance and ERPs obtained in deviant trials, as the novel-trial data will be reported elsewhere. MMN was isolated in the difference waves obtained by subtracting the standard-tone ERPs from those elicited by deviant tones, and analyzed as the mean amplitude in the 50 ms (125–175 ms) time window around its peak, which was identified in the across-subjects averaged grand-average ERP. Scalp potential distribution of MMN was reconstructed at each pixel by a spherical surface spline interpolation [16]. Scalp current density (SCD) curves and maps (computed as the second spatial derivatives of the spline functions used for potential mapping) were analyzed to disentangle the distribution of multiple MMN generators overlapping in potential maps [17]. Currents were averaged across the electrode pairs F4-FC2, F3-FC1, M2-T6 and M1-T5 in order to estimate activity in the right frontal, left frontal, right temporal, and left temporal cortices, respectively. In order to compare different MMN-generator activities, ANOVA for repeated measures was performed on the current amplitudes with generator (frontal vs temporal) and hemisphere (right vs left) as factors. The time course of the deviance-related activations was analyzed with point-by-point t-test comparisons against the zero level starting at 0 ms up to 300 ms. The onset latency of a significant activation was defined as the latency point from which ≥12 consecutive points reached significance at the 0.05 level or better [18]. Point-by-point t-test of the amplitude of currents to standard tones was performed against the zero level from 0 ms up to 150 ms in order to disclose multiple generators of the N1 component. Correlations were calculated between MMN current amplitudes at each electrode location in the 125–175 ms time window and the difference in hit rate and reaction time between standard and deviant trials.

RESULTS

Deviant tones elicited a significant MMN (t(13) = 5.01, p < 0.001; at Fz) with an inverted polarity at mastoid sites and a peak latency of 150 ms (Fig. 1b,c). SCD analysis of
MMN measured as the mean amplitude around its maximum peak in the grand average (125–175 ms) indicated significant bilateral activation in the temporal areas (Fig. 1d), including negative currents (sinks) at the right (TP4: -0.18 μA/m^3; t(13) = -2.5, p < 0.05) and left (TP3: -0.29 μA/m^3; t(13) = -2.46, p < 0.05) temporal sites, and positive currents (sources) at the right (M2-T6: 0.16 μA/m^3; t(13) = 3.35, p < 0.01) and left (M1-T5: 0.18 μA/m^3; t(13) = 3.9, p < 0.005) electrode locations below the Sylvian fissure, suggesting activation of bilateral dipoles located in the supratemporal plane. Bilateral MMN current sinks were also found at the right (F4-FC2: -0.2 μA/m^3; t(13) = -4.04, p < 0.005) and left (F3-FC1: -0.18 μA/m^3; t(13) = -4.1, p < 0.01) frontal areas. ANOVA performed on the sink amplitudes with generator (frontal vs temporal) and hemisphere (right vs left) as factors showed no significant hemisphere differences nor interactions between factors, suggesting that MMN generators were similarly activated in both hemispheres.

Point-by-point t-tests run on the amplitude of deviant minus standard currents against the zero level revealed that the right frontal areas (F4-FC2) were significantly activated from 94 to 214 ms (Fig. 2), whereas currents in the left frontal areas (F3-FC1) showed significant activation from 128 to 182 ms. Temporal locations showed significant activations from 154 to 200 ms in the right hemisphere (M2-T6) and from 132 to 190 ms in the left hemisphere (M1-T5).

Point-by-point t-tests against zero level run on the currents to the standard tones from 0 ms to 150 ms revealed significant activations in the frontal cortex from 34 ms to 144 ms in the right hemisphere and from 42 ms to 144 ms in the left hemisphere, and in temporal cortex from 80 to 126 ms in the right hemisphere.

Reaction time increased to visual stimuli preceded by a deviant sound as compared to reaction time in standard trials, although the difference was only marginally significant (480 ms vs 474 ms; Wilcoxon Z = -1.66, p < 0.1). This distraction effect, measured as the difference in reaction time between standard and deviant trials, correlated significantly (r = -0.56, p < 0.05) with the amplitude of currents in the left auditory cortex (TP3) in the MMN latency range (125–175 ms). Reaction time increase in deviant trials did not correlate significantly with currents at any of the remaining electrodes.

**DISCUSSION**

In the present study, SCD mapping of activations elicited by irrelevant changes in sound frequency during performance of a visual discrimination task disclosed bilateral temporal and frontal MMN components. The bilateral temporal MMN currents were characterized by sinks (negative currents) over the superior temporal electrodes and by sources (positive currents) over positions located below the Sylvian fissure. These results suggest bilateral generators located in the supratemporal plane, and are well in agreement with the results reported in the literature [6]. Our results also revealed additional MMN generators located bilaterally in the frontal cortex, confirming the previous results reported by Deouell et al. [8] in the context of dichotic listening.

The novel result of the present study was the early deviance-related activation in the right frontal cortex, starting to be significant at 94 ms. Since the frequency changes used in the present study had a deviation of 16%, the earlier frontal deviance-related activation may be due to...
Temporal dynamics of MMN components

Fig. 2. Point-by-point representation of currents and p values from t-test comparisons of currents at each sampled point against the zero level (the horizontal line marks p < 0.05) at frontal (left: FC1-F3; right: FC2-F4; upper panel) and temporal (left: M1-T5; right: M2-T6; lower panel) areas. The vertical line marks the time point in which the right frontal generator became significantly activated.

to a less refractory state of neural populations representing the deviant frequency. Accordingly, this early frontal activation may correspond to an increase of the frontal component of the N1 response to deviant tones as compared to that of standard tones. This is supported by the generation of a frontal N1-related activation to standard tones during this same early latency range [19] (i.e. from 34 ms to 144 ms in the right hemisphere). Kropotov et al. [13] have suggested three different auditory cortex mechanisms involved in frequency detection in humans: an earlier one, involved in the analysis of the physical features of sound, and two later ones, which reflect sensory memory and mismatch detection processes, respectively, conforming the genuine MMN response. Therefore, the present results suggest an analogous model of frequency detection in the right frontal cortex, where the combined activation of N1 and MMN responses would reflect the analysis of sound frequency at an earlier phase (from about 94 ms to 144 ms) and the genuine mismatch response at a later phase (from about 144 ms to 214 ms), respectively.

Alternatively, the early deviance-related activity found in right prefrontal cortex may correspond to a genuine frontal MMN response. In this case, it is plausible that the frontal MMN component activates before the supratemporal MMN component by receiving in advance the thalamic contribution to MMN generation, through parallel thalamo-cortical projections [20]. Indeed, intracranial recordings in guinea pigs have revealed MMN-like activity to frequency [21] and phonemic [22] changes in the nonprimary subdivision of the auditory thalamus (medial geniculate nucleus), giving support to our interpretation. In these studies, MMN was generated in the thalamus only when the deviant sounds were presented in the context of standard stimulation, but not when they were presented alone, suggesting that thalamic MMN-like responses are not caused by frequency-specific refractoriness, but by a specific thalamic mismatch detection mechanism. In humans, the absence of MMN in patients with anteromedial thalamic infarctions also supports a thalamic contribution to MMN generation [23].

Whichever of these explanations finds empirical support in future studies, our findings contrast with those reported by Rinne et al. [15], who described an earlier activation of the temporal as compared to the frontal MMN generators. The discrepancies between the present results and those of Rinne and collaborators may account to the different type of auditory changes used in these experiments. Rinne and collaborators presented deviant tones differing from the standard tones in duration, whereas in the present study standard and deviant sounds differed in frequency. The involvement of frontal areas in the processing of sound frequency, as demonstrated in ERP [19] and functional neuroimaging [24] studies, suggests different brain mechanisms underlying the detection of changes in sound duration and frequency. Furthermore, in the study of Rinne and collaborators, subjects were instructed to ignore the auditory stimulation while watching a silent video-movie, whereas in the present study, the subjects, although instructed to ignore the auditory stimulation, possibly attended to the sounds covertly and used them as cues for responding to the subsequent visual target stimuli [4]. The early activation of right frontal areas found in the present study could be explained by covert orienting of attention towards the visual target triggered by the preceding deviant sound, as the prefrontal cortex is involved in directing attention at the occurrence of cues informing on location [25] or temporal moment of appearance [26] of a subsequent target.

The present results suggest deterioration of task performance after the occurrence of MMN-eliciting deviant sounds as revealed by an increase of reaction time to visual targets preceded by a deviant sound as compared to those preceded by a standard tone, in agreement with previous studies [3–5]. Furthermore, the amplitude of MMN-nerve impulses from the left auditory cortex correlated significantly with the reaction time increase to visual targets preceded by MMN-eliciting deviant tones. These results strongly support the involvement of MMN-generating mechanisms in directing attention involuntarily towards unexpected changes in the auditory environment.
CONCLUSION
The present study replicates previous findings by disclosing bilateral temporal and frontal generators of the frequency detection mechanism reflected in the MMN. The new finding was the early deviance-related activations at right frontal areas. Two possible explanations may account for this early frontal activation. First, the frontal deviance-related activation may represent specific N1 differences between standard and deviant sounds differing in tone frequency, due to refractoriness of neural populations responding to the specific deviant frequency. Alternatively, the early frontal activation may correspond to a genuine frontal MMN component, which may be fed earlier than supratemporal cortex via the thalamic contribution to MMN generation. Whichever of these explanations finds empirical support in future studies, the present results suggest a complex cerebral circuitry involved in frequency change detection and, given the correlation between distraction and MMN-related activity, strongly support the role of the neural mechanisms in this circuitry in driving attention involuntarily towards potentially relevant stimulus changes in the acoustic environment.

REFERENCES

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