Mismatch Responses to Randomized Gradient Switching Noise as Reflected by fMRI and Whole-Head Magnetoencephalography

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Abstract: The central auditory system of the human brain uses a variety of mechanisms to analyze auditory scenes, among others, preattentive detection of sudden changes in the sound environment. Electroencephalography (EEG) and magnetoencephalography (MEG) provide a measure to monitor neuronal cortical currents. The mismatch negativity (MMN) or field (MMNm) reflect preattentive activation in response to deviants within a sequence of homogenous auditory stimuli. Functional magnetic resonance imaging (fMRI) allows for a higher spatial resolution as compared to the extracranial electrophysiological techniques. The image encoding gradients of echo planar imaging (EPI) sequences, however, elicit an interfering background noise. To circumvent this shortcoming, the present study applied multi-echo EPI mimicking an auditory oddball design. The gradient trains (SOA = 800 msec, 94.5 dB SPL, stimulus duration = 152 msec) comprised amplitude (−9 dB) and duration (76 msec) deviants in a randomized sequence. Moreover, the scanner noise was recorded and applied in a whole-head MEG device to validate the properties of this specific material. Robust fMRI activation patterns emerged in response to the deviant gradient switching. Changes in amplitude activated the entire auditory cortex, whereas the duration deviants elicited right-lateralized signal increase in secondary areas. The recorded scanner noise evoked reliably right-lateralized mismatch MEG responses. Source localization was in accordance with activation of secondary auditory cortex. The presented paradigm provides a robust and feasible tool to study the functional anatomy of early cognitive auditory processing in clinical populations such as schizophrenia. *Hum. Brain Mapping* 16:190–195, 2002. © 2002 Wiley-Liss, Inc.

Key words: functional magnetic resonance imaging; auditory stimulation; gradient switching; mismatch negativity

INTRODUCTION

Functional magnetic resonance imaging (fMRI) of the auditory system has a major restriction in the intrinsic acoustic noise of this technique [Talavage et al., 1999]. Despite this limitation, several studies have shown that auditory stimuli yield valid activation patterns at the level of the supratemporal plane [e.g., Gaschler-Markefski et al., 1998]. Nevertheless, unde-

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sired interactions cannot be excluded, e.g., reduction of response amplitudes [Hall et al., 1999] or masking of cochleotopic (tonotopic) organization [Le et al., 2001]. Thus, gradient switching, being the main source of scanner noise, has to be considered part of the “auditory scene” [Bregman, 1990] arising during fMRI measurements. To circumvent these shortcomings, gradient noise by itself might be used as a probe of the central-auditory system. This procedure has several advantages including undesired auditory interactions can be ruled out; the relative stimulation level is well controlled, e.g., differences between transfer of the stimulation sources and machine noise via bone conduction, are accounted for; and no external stimulation devices such as MR compatible headphones or speakers are required.

Mismatch negativity (MMN) is a widely studied phenomenon in electrophysiological research. The present study used gradient switching noise to compare the hemodynamic and neuromagnetic correlates of this auditory evoked response. As a rule, any series of discrete acoustic events reliably elicits middle- and long-latency electroencephalographic (EEG) deflections [Näätänen, 1992]. This pattern of event-related potentials (ERP) comprises a positive peak at about 50 msec after stimulus onset (P50), a consecutive negative one (latency of about 100 msec, N1) as well as various subsequent responses. Deviant rare sounds within a series of standard events (“oddball design”) elicit an additional net inward current at the auditory cortex [Javitt et al., 1994]. During EEG recordings, these synaptic currents give rise to an increased negativity at frontal electrodes at a latency of about 170 msec. MMN, conceivably, reflects the comparison of the rare incoming stimulus events with the sensory memory trace engraved by the frequent stimulus [Näätänen and Winkler, 1999]. This component, therefore, is assumed to indicate early cognitive stimulus processing at a preattentive level. The present study used gradient switching as auditory source. Primary stimulus processing such as adaptation or feature mapping should not affect the mismatch responses. Thus, the imaging sequence contained softer (amplitude) as well as shorter (duration) deviants in a randomized fashion.

MATERIALS AND METHODS

Subjects

Eleven right-handed volunteers participated in the fMRI study and 12 in the following MEG experiment. None of them had impaired hearing sensitivity or

reported any history of relevant neurological, psychiatric, or medical disorders.

Imaging procedure

Magnetic resonance imaging was performed using a 1.5 T clinical MR scanner (Sonata, Siemens, Erlangen, Germany). First, a T1-weighted anatomical image (FLASH-3D) was obtained from each subject. Subsequently, functional imaging was conducted. A single-shot multi-echo EPI sequence applied a 32×64 matrix to achieve a read-out time of 19 msec per echo (non-linear sampling on sinusoidal gradient ramps, bandwidth = 50 kHz, field of view = 250×250 mm², slice thickness = 6 mm, slice gap = 1.2 mm, voxel size = $3.9 \times 3.9 \times 7.2$ mm³). Acquisition of eight echoes per slice (duration = 152 msec) represented the frequent events occurring at a stimulus onset-asynchrony (SOA) of 800 msec. Strength of the imaging gradients was lowered by a factor of 0.35 for amplitude deviants (−9 dB sound pressure level, 7.5% of the events). The sound of the reading of 4 instead of 8 echoes yielded a duration mismatch (76 msec, 7.5% of the events; see Fig. 1). Sound pressure level of the gradient switching noise amounted to 94.5 dB at the head (about −28 dB dampening due to standard noise canceling headphones). During distinct blocks, one, two, or four imaging slices were acquired covering the supratemporal plane (STP) and Heschl’s gyrus in parallel orientation to the Sylvian fissure. Number of stimuli (= number of slice acquisitions) amounted to 512 using one, two, or four slices (TR = 800, 1,600, or 3,200 msec, respectively). Slices encoded during deviant events (15%) were discarded from statistical analysis. A multi-echo sequence was applied, first, to achieve acoustic stimulation of a suitable duration and, second, to increase the sensitivity to the blood oxygen level dependent (BOLD) effect [Posse et al., 1999].

MR data analysis

Analysis of the multi-echo MR data required pre-processing prior to application of the standard statistical parametric mapping (SPM99) [Friston and Turner, 1999] procedures. Differential weighting of the eight successive echoes optimized signal-to-noise (SNR) or contrast-to-noise ratio (CNR), respectively. To maximize SNR, each of the acquired echoes ($i = 1, \dots, 8$) was weighted with $[\exp\{-TE_i/80 \text{ msec}\}]^2$ (TE_i = echo time of i -th echo) before averaging. These images will be referred to as SNR-images. For optimal CNR of the BOLD effect, the echoes were averaged using the weight factors $[TE_i \cdot \exp\{-TE_i/65 \text{ msec}\}]^2$

Figure 1.

Scheme of (image encoding) gradient switching using amplitude (green) and duration (red) deviants. Hemodynamic response functions (hrf) succeed the events.

(CNR-images). Realignment and normalization of images were performed using the parameter estimates obtained from the SNR-images. Motion correction was restricted within the acquisition plane [Mathiak and Posse, 2001]. Statistical parametric maps (SPM) were obtained by applying a general linear model on the signal intensities of the normalized and smoothed (12 mm full width at half maximum GAUSS-kernel) CNR-images. The convolution of the bi- γ function and the indicator function of the respective rare events served as reference vector for the paradigm, i.e., the modeled hemodynamic response function (hrf) (Fig. 1). In case of four-slice acquisition, analysis was repeated for each slice separately applying the respective time delay; then, the calculated statistical maps were combined accordingly. During the entire session subjects were watching a silent movie (Charlie Chaplin). They were naive with respect to the experimental paradigm.

MEG recording and data analysis

Auditory evoked magnetic fields were recorded by means of a 151-channel whole-head MEG (CTF System Inc., Vancouver, Canada) within an electromagnetically shielded room (sampling rate = 250 Hz, anti-aliasing filtering = 80 Hz). Two sessions comprised 450 sweeps each (sweep length = 600 msec, pre-stimulus baseline = 148 msec, inter-stimulus-interval = 610 msec) including 20% randomly interspersed deviants (about 90 of the 450 sweeps). Recorded gradient switching noise served as auditory stimuli. In accordance with the fMRI experiment, subjects were

watching a silent movie and instructed to ignore the acoustic stimulation. MEG data analysis followed standard procedures in line with previous studies [e.g., Mathiak et al., 2001].

Figure 2.

Significant BOLD responses (Z-score overlay thresholded at corrected $P < 0.05$) to amplitude (a) or duration (b) deviants of gradient switching noise. Whereas, amplitude changes induce significant changes over both hemispheres in primary and secondary auditory areas, duration affects, in particular, the right secondary auditory cortex. The inserted crosses mark the respective dipole localizations as obtained with MEG recordings: P50m component (a) and mismatch field (MMNm; b). The white lines within the two upper panels depict representative slice positions.

Figure 3.

(a and b) Relative effect size (± 1 SD) within for primary (A1) and secondary (A2) auditory cortex (coordinates defined a priori in Talairach space) in the left (LH) and right (RH) hemisphere. The upper row (a) displays effect sizes estimated for each of the 11 individuals. In the middle row (b), the estimates were pooled across the group. Amplitude mismatch (left column) yielded a generally larger effect that might be, in part, due to adaptation affecting the succeeding frequent stimuli as compared to the duration deviants (right column). The latter activation exhibited a lateralization to the right side in the secondary areas. (c) Left panel: a point-source model for each auditory cortex delivered current moments for each auditory area separately. Neuromagnetic responses over the left (straight line) and the right (dashed line) hemisphere were obtained in response to frequent (blue) and deviant (green) scanner sounds. Right panel: within the time window (160–200 msec), amplitudes of mismatch fields, i.e., the difference between deviant and frequent response, over each hemisphere were quantified across the group.

RESULTS

MR analogue to mismatch negativity

As concerns the amplitude mismatch, group analysis (all $P < 0.05$, corrected) revealed activation within STP of the right (cluster size $k_E = 778$) and left hemisphere ($k_E = 738$; Fig. 2a), respectively. In response to the duration deviants, the left hemisphere failed significant activation whereas the right corresponding areas showed signal changes above threshold ($k_E = 148$; Fig. 2b). No reliable frontal activation was observed within the covered area.

Quantitative estimates of the BOLD effect were obtained in primary (A1) and dorsal secondary (A2) auditory cortex as defined a priori by Talairach (x, y, z) coordinates: A1 = ($\pm 45, -16, 4$) and A2 = ($\pm 56, -26, 7$) mm. All 11 subjects exhibited a significant activation in one of the areas at the (arbitrary) level of $P < 0.01$ (corrected for sampling points). Across group, A2 responses were larger as compared to signal increase in A1. Hemodynamic activation of A2 was larger at the left side in case of amplitude changes and

vice versa for duration deviants (all $P < 0.001$; see Fig. 3a,b).

Mismatch fields to scanner noise

In accordance with the literature, the N1m source exhibited a more anterior, lateral and superior source location as compared to its P50m cognate [Pantev et al., 1995].

In eight and six out of the total of 12 subjects ($P < 0.05$) a significant MMNm emerged at latencies of 160–200 and 240–280 msec post-stimulus onset, respectively. As concerns both time windows, a significant effect across the group as a whole could be documented ($P < 0.001$). Right-hemispheric responses were larger than their opposite counterpart (LH = -42.0 ± 9.2 nAm, RH = -53.1 ± 15.3 nAm; paired t -test of stratified and resampled side-differences: $P < 0.05$; Fig. 3c).

The early mismatch field (160–200 msec) showed a more superior source localization as compared to the P50m component (1.2 cm, $P < 0.05$). As concerns later time domains (240–280 msec), dipole analysis sug-

gested a more inferior location (0.8 cm, $P < 0.05$). The inserts in Figure 2 depict projections of the dipole sources into Talairach space.

DISCUSSION

Magnetic mismatch to scanner noise

In most subjects, the recorded scanner sound elicited robust mismatch fields in agreement with standard paradigms. Dipole source analysis indicated a more inferior (caudal) location of mismatch generators as compared to P50m sources. Because middle latency components (e.g., P50m) are assigned to the Heschl's gyrus [Borgmann et al., 2001], these findings suggest the mismatch response to arise more posterior-inferior locations, i.e., at the secondary auditory cortex. The observed lateralization effects might reflect a higher sensitivity of the right auditory cortex to environmental noise [compare Kasai et al., 2001; Mathiak et al., 2000, 2002].

fMRI mismatch paradigm

The measured BOLD response reflects differential hemodynamic activation integrated across seconds. Thus, neither early against late components nor processing of a deviant vs. its succeeding frequent stimulus can be separated on basis of this procedure. Amplitude changes elicited primary responses due to deviant detection as well as, conceivably, adaptation effects. Accordingly, both primary as well as secondary auditory cortices were responsive. Primary areas exhibited only small effects to duration deviants. This might indicate that the duration mismatch avoids changes in adaptation, as sound pressure level remains constant. Moreover, the right-sided lateralization pattern parallels the neuromagnetic mismatch responses to the noise stimuli. The fMRI and MEG experiments yielded a distinct topography and lateralization pattern in response to amplitude changes. As a possible explanation, later components might be integrated into the BOLD response whereas the mismatch field is restricted to the given temporal domain. Variation of the stimulus and deviant frequency within the present design can give further insights in the spatio-temporal characteristics of the neuronal response.

The present study failed to document any involvement of frontal structures within the covered cerebral region. In contrast, previous fMRI studies employing an oddball design revealed distributed activation during attentive conditions [Hall et al., 2000; Yoshiura et

al., 1999]. The comparison with ERP recordings suggests that distinct networks participate in preattentive processing and target detection [Opitz et al., 1999]. Nevertheless, even under preattentive conditions intracranial recordings support the involvement of prefrontal structures [Liasis et al., 2001]. Mismatch responses reflect, among others, the temporal and spatial structure of the auditory signal [e.g., Yabe et al., 1997]. Thus, this auditory evoked component might be compromised by interference of scanner and stimulation noise. Our procedure allows to examine a "pure" stimulation condition with gradient generated noise within the MR device. The role of attention for frontal activations remains to be clarified.

Clinical applications

From the literature on electrophysiological findings, clinical relevance of the investigated paradigms is well known; alteration of phenomena related to gating mechanisms were found, e.g., in patients suffering from schizophrenia [Javitt et al., 1996]. The method presented allows for a more precise delineation of the underlying neuronal networks. Moreover, this activation technique is easy to handle because no additional stimulation devices are required and it does not rely on attention and cooperation of the subjects.

CONCLUSION

The implementation of the classical neurophysiological paradigm 'mismatch negativity' using randomized gradient switching noise as stimuli allows for easy and reliable studies on the auditory cortex using fMRI. The multi-echo EPI approach renders the mismatch procedure highly sensitive. In addition, EEG and MEG experiments can be run using the same acoustical stimuli. It provides a tool for investigations on the neuronal basis of mismatch negativity and, thus, of automatic mechanisms of attention shifting and imaging of neuro-regulative dysfunctions, such as in schizophrenia, that are known to exhibit disrupted suppression of irrelevant stimuli.

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