Integration of fMRI and simultaneous EEG: towards a comprehensive understanding of localization and time-course of brain activity in target detection

Christoph Mulert, a,* Lorenz Jäger, b Robert Schmitt, a Patrick Bussfeld, a Oliver Pogarell, a Hans-Jürgen Möller, a Georg Juckel, a and Ulrich Hegerl a

fMRI and EEG are complimentary methods for the analysis of brain activity since each method has its strength where the other one has limits: The spatial resolution is thus in the range of millimeters with fMRI and the time resolution is in the range of milliseconds with EEG. For a comprehensive understanding of brain activity in target detection, nine healthy subjects (age 24.2 ± 2.9) were investigated with simultaneous EEG (27 electrodes) and fMRI using an auditory oddball paradigm. As a first step, event-related potentials, measured inside the scanner, have been compared with the potentials recorded in a directly preceding session in front of the scanner. Attenuated amplitudes were found inside the scanner for the earlier N1/P2 component but not for the late P300 component. Second, an independent analysis of the localizations of the fMRI activations and the current source density as revealed by low resolution electromagnetic tomography (LORETA) has been done. Concordant activations were found in most regions, including the temporoparietal junction (TPJ), the supplementary motor area (SMA)/anterior cingulate cortex (ACC), the insula, and the middle frontal gyrus, with a mean Euclidean distance of 16.0 ± 6.6 mm between the BOLD centers of gravity and the LORETA-maxima. Finally, a time-course analysis based on the current source density maxima was done. It revealed different time-course patterns in the left and right hemisphere with earlier activations in frontal and parietal regions in the right hemisphere. The results suggest that the combination of EEG and fMRI permits an improved understanding of the spatiotemporal dynamics of brain activity.

Keywords: fMRI; EEG; ERP; P300; Auditory-evoked potential; Target detection; Oddball

Introduction

For years, research in auditory target detection has been focused on event-related potentials. Using an oddball paradigm, a large positive component can be recorded after about 300 ms (the P300 potential), if a rare, task-relevant target has been presented. This component can be reliably found with largest amplitudes in parietal electrodes on the scalp. Major interest to this potential was caused by the finding that in several neuropsychiatric disorders, like dementia of the Alzheimer type or schizophrenia, attenuations of the amplitude and latency have been described (Frodl et al., 2002a; Hegerl et al., 1995; Polich and Pitzer, 1999; Winterer et al., 2001). However, the clinical benefit has been limited so far, since the finding of an attenuated P300 amplitude seems to be rather unspecific when looking at scalp-data. The topography on the scalp allows apparently only a rough distinction between a more frontally pronounced early P3a component and a more parietaally pronounced P3b component. The P3a has been described to be involved in automatic novelty detection and the P3b is more concerned with volitional target detection (Soltani and Knight, 2000). Using intracranial measurements, however, it could be demonstrated that a complex network of brain regions is involved in the generation of the P300 potential, including temporoparietal junction, posterior superior parietal regions, cingulate cortex, dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, and medial temporal regions (Kiss et al., 1989; McCarthy and Wood, 1987). Interestingly, these regions also show different time-course patterns (Baudena et al., 1995; Halgren et al., 1995a,b).

With regard to the meaning of a disturbed P300 in brain diseases, it became clear that the important next step would be to get similar information with high spatial and time resolution noninvasively, since intracranial measurements are usually not appropriate in a clinical setting. With the development of noninvasive hemodynamic-based brain imaging methods like fMRI, with its high spatial resolution in the range of millimeters, several studies have been undertaken to figure out brain regions involved in auditory target detection (Downar et al., 2000; Kiehl et al., 2001; Linden et al., 1999). Interestingly, beside the medial temporal region, all other brain regions that have been known from the intracranial measurements could be detected again using fMRI, suggesting that there is a high degree of concordance between the electrical signal and hemodynamic response. Concerning the disturbed P300 potential in diseases like schizophrenia, it was evident that a noninvasive investigation of disturbed brain function...
in target detection became possible now with high spatial resolution (Kiehl and Liddle, 2001).

However, the intracranial measurements by Halgren et al. had revealed clear differences in the time-course patterns of the involved brain regions with latency peak differences in the range of 100 ms and less. Therefore, it was also clear that hemodynamic-based methods would not have a sufficient high temporal resolution for a distinct analysis of the timing of brain activity in target detection. Thus, a combination of electrical activity- and hemodynamic-based methods is suggestive since these methods are complementary because of the good temporal resolution of EEG/ERP-based approaches and the good spatial resolution of fMRI. For such a combination approach, it would be critical that the signals generated by each method correspond to the same set of underlying generators (Horovitz and Poeppel, 2002). The good concordance of the intracranial measurements and the fMRI studies did already encourage this approach. Concerning basic research, important support came from recent physiological studies in monkeys (Logothetis et al., 2001), investigating simultaneously intracortical recordings of electrical neural signals and the blood-oxygen-level-dependent (BOLD) fMRI-responses in the visual cortex. Clear correlations were found between the local field potentials, which are mostly reflecting a weighted average of synchronized dendro-somatic components of the input signals of a neural population, and the BOLD responses. No such clear relationship could be found between multiunit spiking activity and the BOLD signal. Since the local field potentials are the physiological basis of the scalp EEG, this result is in favor to the hypothesis that the signals generated by EEG and fMRI might correspond to the same set of underlying generators.

In principle, there are three possibilities: Cerebral activity might be detectable only with EEG, only with fMRI, or with both methods. The first might be true if, for example, short-lasting neuronal activity, leading to a short ERP component, does not evoke a measurable (and significant) hemodynamic response. The second could occur if long-lasting neuronal activity would result in a large hemodynamic response but maybe only in a slow shift of the electrical baseline that is not detected in the classical peak picking approach. Finally, brain activity should be detectable with both methods in the case of a synchronous activity of a large number of neurons for some hundred milliseconds. Then, probably both a large ERP component and a significant BOLD signal would be expected. This could be true for the P300 component: An important study by Horovitz et al. (2002) could already show a close relationship between the scalp-P300 and the BOLD signal in an oddball paradigm. Manipulation of the task (probability of the occurrence of a target) was found to influence both the amplitude of the P300 component and the BOLD-signal changes in most of the involved brain regions in the same direction. So, an experimental condition that did result in an increased P300 amplitude at Pz did also result in an increased BOLD-signal change (e.g., in the supramarginal gyrus) and vice versa (Horovitz et al., 2002). EEG and fMRI measurement was done in separate sessions in this experiment.

Due to the technical challenge of a simultaneous measurement of EEG and fMRI, a combination of EEG and fMRI so far has mostly been done measuring with each method in separate sessions. Using such an approach, many additional variables are convoluted, such as attention, vigilance, familiarity with a task, which might not be the same in two separate data acquisition sessions, or experimental environment (lying inside a noisy and narrow scanner with dim lightning, or sitting comfortable in a quiet EEG lab with natural light). That in fact the arousal level of a subject is crucial for the activation of brain regions in cognitive tasks has recently been demonstrated by Matsuda et al. using a simultaneous EEG/fMRI study. Here, the authors could find significant activations in a smooth-pursuit eye movement task in brain areas like the parietal eye field and the supplementary eye field only during the high arousal level (Matsuda et al., 2002). Beside the possible implications of this finding in studies dealing with the comparison between healthy volunteers and patients with potentially disturbed vigilance/ arousal dynamics, it becomes clear that vigilance and arousal is a variable that could influence neural activity and therefore should be controlled if the interpretation of the results shall not be extremely limited. The only way to make results comparable in a way that differences between the results obtained by EEG or fMRI are based on the physiology and on fundamental properties of the methods and not on confounding variables would be to measure simultaneously with both methods. Thus, to get usable and interpretable results, it is worthwhile to make more effort concerning methodology. Simultaneous measurement of EEG and fMRI requires a special EEG hardware that can be used in the MRI scanner without making artifacts and with no safety risk. These efforts have been primarily undertaken in the analysis of epileptic activity (Jager et al., 2002). Obviously, epileptic activity is in fact a single event that cannot simply be repeated on demand and therefore a simultaneous measurement with both EEG and fMRI is especially important. However, the abovementioned influence of vigilance or arousal on activations in cognitive fMRI studies make a simultaneous data acquisition also necessary in target detection. We have therefore established an experimental set-up that allows a simultaneous measurement of EEG and fMRI data.

With this study, it was intended to answer three questions: (1) Is the EEG-signal (P300 potential), as measured inside the MR scanner, comparable to the signal outside the scanner, measured in a directly preceding session? (2) Are the same localizations for activated brain regions found with fMRI and EEG signals? (3) Do the involved brain regions differ with respect to the time-course of the neuroelectric activity?

Methods

Subjects

Ten healthy volunteers with no history of neurological or psychiatric disturbance or reduced hearing were recruited from an academic environment. One data set was later excluded due to technical problems. Finally, the data of nine subjects (six men, three women: range, 20–30 years old; mean age, 24.2 ± 2.9) were analyzed. The study was approved by the local ethics committee of the Ludwig-Maximilians-University of Munich and written informed consent was obtained from each subject.

Paradigm

Auditory stimuli were generated on a Personal Computer using the BrainStim software package (Brain Products, Munich, Germany) and conducted through a pair of plastic tubes into a set of headphones placed over the subjects ears. The auditory stimuli were a 800-Hz sinus-tone (nontarget, 80%) and a 1300-Hz sine-wave tone (target, 20%) at a sound pressure level of 95 dB. The tones were presented with an interstimulus of 3 or 6 s (mean: 4 s).
Fig. 1. Comparison between the auditory-evoked potentials recorded inside and outside the scanner. (a) Clearly attenuated N1/P2 potential inside the scanner (at Cz). (b) Only slightly reduced P300 potential inside the scanner (at Pz). Outside the scanner, a pronounced P3a component is evoked.

Fig. 2. Comparison between target and nontarget. (a) Inside the scanner: neither the target nor the nontarget stimulus evokes a pronounced P3a component. (b) Outside the scanner: both the target and nontarget stimulus evoke a P3a component.
Targets appeared in pseudo-random order. The volunteers had to press a button with the right index finger.

**Acoustic environment, sound system, and headphones**

For the measurement of the sound pressure level inside and outside the scanner, we have used the following equipment: A 1/2-in. microphone (B&K 4313, Brüel and Kjær, Denmark) attached with a preamplifier (B&K 2639) with extension cable (B&K A027) connected to a measuring amplifier (B&K) served as sound level recording unit. To enable offline recording, the AC output of the measuring amplifier was connected to the line input of a digital audio tape (DAT) recorder (SONY 300 ES, Japan). The measuring amplifier and the DAT recorder were placed outside the shielded MR room and the microphone cable was routed via an opening shielded by copper tubes to suppress radio frequency (RF) induction. Before the recordings, a calibration procedure was performed using an acoustic calibrator (B&K 4230). The signals were recorded at the position of the human head in the isocenter of the MR system and the second one, at 1.2 m in front of the opening of the MR. Due to the impulse characteristic of the MR noise, a large difference between averaging measurements applying “fast” time constant and peak detection occurred. The echo planar imaging (EPI) sequence used in our study produced a sound measured in sound pressure level (SPL) of 90.5 dB (dB = decibel) (fast) and of 106.5 dB (peak) inside the MR system. The basic noise (due to the vacuum pump) inside the MR system was 76 dB. At 1.2 m in front of the opening of the MR, a basic noise of 62 dB was measured. Binaural sound transmission was performed using an air tubing sound delivery system (Resonance Technology, Van Mays, USA). The personal computer was placed outside the shielded MR room. The sound delivery system was evaluated using standardized equipment (microphone 4144, preamplifier 2619, calibrator 4230, and artificial ear with 2-cm coupler 4152; Brüel and Kjær, Denmark). Because we combined an in-ear earphone with circum-aural ear muffs, a high attenuation against the noise of the MR (20 dB at low and 50 dB in the high frequencies) occurred. Due to the tube-based sound transportation and the sound driver characteristics, a rippled band pass frequency response occurred. Therefore, the desired level of 95 dB SPL was achieved by a digital attenuation to the correct intensity.

**fMRI setup**

Imaging was performed in a 1.5 T Siemens Magnetom Vision scanner with echo planar capability. For functional BOLD imaging, 10 slices with a T2-weighted EPI sequence (TR: 3 s; TE: 64 ms; FOV: 210/280 mm; matrix: 128 × 64; interleaved slice acquisition; slice thickness: 8 mm; interslice gap: 0.8 mm; resulting pixel size: 3.16 × 2.11 mm) were acquired in the same position as the anatomical images. Each functional time series consisted of 120 volumes each. Five functional time series were acquired. The...

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**Fig. 3.** Global field power of the target-specific activity (target minus nontarget) inside the scanner and outside the scanner. The shapes of both curves are highly corresponding. The target-specific brain activity is even more pronounced inside the scanner.
first two functional image frames of each time series were
discarded to allow for signal equilibration, giving a total of 590
frames used in analysis. For each subject, a three-dimensional
MPRAGE data set (T1-weighted) was acquired. The subject’s head
was immobilized during the whole experiment to minimize invol-
untary head movements.

Post-processing

The complete post-processing of the data including motion
correction, statistics, and transfer of the data into Talairach space
was done with the Brainvoyager software package, version 4.9
(Rainer Goebel, Maastricht, Netherlands). The first two scans of
each run have been excluded from further analysis because of T1
saturation effects. Motion correction was done using Trilinear
Interpolation on a reduced (12.5%) data set. Data smoothing was
performed as temporal data smoothing and linear trend removal.
No spatial data smoothing has been performed.

Functional data were transformed into Talairach space, aligned
with the three-dimensional anatomical volumes from the same
session, and interpolated to a resolution of 1 mm³. For further
statistical analysis, multiple regression analysis was performed on
the three-dimensional functional volume time courses (5 for every
subject with 118 time points each) using the General Linear Model
(GLM). The design matrix contained the idealized response func-
tions that corresponded to the signal time-courses (target, nontar-
get). For statistical analysis, any combination of predictors can be
used. Statistical maps were computed for analysis of individuals
(contrast: target vs. nontarget) and thresholded at \( P < 0.05 \) (cor-
rected for multiple testing). Additionally, to obtain information
about activation that are consistent for the entire group, a statistical
group analysis was performed, thresholded at \( P < 0.05 \) or \( P < 0.001 \)
(corrected for multiple testing), respectively (see figures and tables).

EEG

We used an EEG amplifier that cannot be saturated by any MR
activity (EMR; Schwarzer, Munich, Germany) and which has been
specifically developed for operation in the MR system. The EEG
recording was performed with 27 electrodes (sintered silver and
silver-chloride) referred to Cz and placed on the scalp according to
the international 10–20 system with the additional electrodes FC1,
FC2, FC5, FC6, T1, T2, CP5, CP6. Electrode skin impedance was
usually less than 5 kΩ. Data were collected with a sampling rate of
500 Hz and an analogous band-pass filter (0.16–30 Hz). Two
hundred milliseconds of prestimulus baseline and 575 ms post-
stimulus periods were evaluated for every sweep. For artifact
suppression, all sweeps were automatically excluded from averag-
ing when the voltage exceeded 100 ± \( \mu \)V in any of the 27 channels
at any point during the averaging period. For each subject, the
remaining sweeps were averaged after baseline correction. Only
wave-shapes, based on at least 40 averages, were accepted. The

![Fig. 4. Average (n = 9) three-dimensional maps of BOLD-signal increase for targets versus nontargets (P < 0.05, corrected for multiple testing) on the inflated hemispheres of a single subject. Lateral views.](image1)

![Fig. 5. Average (n = 9) three-dimensional maps of BOLD-signal increase for targets versus nontargets (P < 0.05, corrected for multiple testing) on the inflated hemispheres of a single subject. Medial views.](image2)
EEG recording was acquired and displayed using the BrainLab software (OSG, Rumst, Belgium). All data processing (artifact rejection and averaging) has been done using the BrainVision Analyzer software (Brain Products).

Peak detection has been done semiautomatically using the Analyzer software. The N1 peak has been defined as the most negative value between 80 and 150 ms, the P3 peak as the most positive value between 250 and 500 ms poststimulus. Differences between N1 and P3 peaks inside and outside the scanner have been compared with paired $t$ tests using the SPSS-software (SPSS 11.5).

**Parametrization**

According to the global field power time course (difference wave corresponding to the infrequent tone minus frequent tone), the timeframe 250–540 ms poststimulus has been chosen for further analysis (Fig. 3).

**LORETA**

Low resolution electromagnetic tomography (LORETA) assumes that the smoothest of all activity distributions is most plausible (“smoothness assumption”) and therefore, a particular current density distribution is found (Pascual-Marqui et al., 1994). This fundamental assumption of LORETA directly relies on the neurophysiological observation of coherent firing of neighboring cortical neurons during stimulus processing (Gray et al., 1989; Llinas, 1988; Silva et al., 1991) and therefore can be seen as a physiologically based constraint. However, this coherent firing has been described on the level of cortical columns, which have a much smaller diameter than the voxels used in the LORETA software; the empirical basis for coherent firing in the millimeter range is not strong enough to fully accept this constraint as a physiological one, even if it might help to produce useful results. The characteristic feature of the resulting solution is its relatively low spatial resolution, which is a direct consequence of the smoothness constraint. Specifically, the solution produces a “blurred-localized” image of a point source, conserving the

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**Fig. 6.** fMRI activations ($P < 0.05$, corrected for multiple testing) and EEG–LORETA current source density activations at corresponding slices ($Z = 8, 15, 22$). Good correspondence in the temporoparietal region, but not in subcortical regions (not covered by LORETA).

**Fig. 7.** fMRI activations ($P < 0.05$, corrected for multiple testing) and EEG–LORETA current source density activations at corresponding slices ($Z = 29, 36, 44$). Good correspondence in the midline and the right middle frontal gyrus.
location of maximal activity, but with a certain degree of dispersion. It should be emphasized that this solution will typically produce a “blurred-localized” image of arbitrary distributions due to the principle of superposition. However, some distributions of point sources may superpose in such a way that they actually cancel out on the scalp and therefore cannot be correctly localized by any method. The version of LORETA used in the present study used the digitized Talairach atlas (Talairach and Tournoux, 1988) available as digitized MRI from the Brain Imaging Center, Montreal Neurologic Institute, estimating the current source density (mA/mm²) distribution for either single time-points or epochs of brain electric activity on a dense grid of 2394 voxels at 7-mm spatial resolution (Pascual-Marqui et al., 1999). The solution space (the three-dimensional space where the inverse EEG problem is solved) was restricted to the gray matter and hippocampus in the Talairach atlas (anatomically based constraint). Localization concerning spherical and realistic head geometry was done using EEG electrode coordinates reported by Towle et al. (1993). A voxel was labeled as gray matter if it met the following three conditions: its probability of being gray matter was higher than that of being white matter, its probability of being gray matter was higher than that of being cerebrospinal fluid, and its probability of being gray matter was higher than 33% (Pascual-Marqui et al., 1999). LORETA has been widely used in the last years to localize electrical generators of scalp EEG data (Gallinat et al., 2002; Mulert et al., 2001, 2002, 2003; Park et al., 2002; Pizzagalli et al., 2001).

Table 1
Corresponding activations (target minus nontarget) in fMRI and EEG

<table>
<thead>
<tr>
<th>Region</th>
<th>fMRI</th>
<th>Number of activated voxels</th>
<th>EEG (LORETA)</th>
<th>Current source density [μV/mm² × 10⁻³]</th>
<th>Euclidean distance (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMA/gyrus cinguli</td>
<td>-10, 0, 43</td>
<td>7268 (***)</td>
<td>-3, -11, 64</td>
<td>5.21</td>
<td>21</td>
</tr>
<tr>
<td>TPJ left</td>
<td>-27, -27, 32</td>
<td>2301 (***)</td>
<td>-59, -25, 22</td>
<td>3.90</td>
<td>14</td>
</tr>
<tr>
<td>TPJ right</td>
<td>-24, -19</td>
<td>3214 (***)</td>
<td>60, -18, 15</td>
<td>3.17</td>
<td>7</td>
</tr>
<tr>
<td>Insula left</td>
<td>-38, -1, 7</td>
<td>7973 (***)</td>
<td>-38, 17, 1</td>
<td>2.69</td>
<td>17</td>
</tr>
<tr>
<td>Insula right</td>
<td>42, 4, 6</td>
<td>6777 (***)</td>
<td>53, 10, 8</td>
<td>3.82</td>
<td>12</td>
</tr>
<tr>
<td>STG left</td>
<td>-24, -24, 12</td>
<td>2390 (***)</td>
<td>-59, -32, -6</td>
<td>3.57</td>
<td>26</td>
</tr>
<tr>
<td>Lobulus parietalis inferior left</td>
<td>-39, -43, 46</td>
<td>1286 (***)</td>
<td>-45, -46, 50</td>
<td>4.19</td>
<td>8</td>
</tr>
<tr>
<td>Middle frontal gyrus right</td>
<td>37, 36, 23</td>
<td>104 (**)</td>
<td>53, 17, 22</td>
<td>3.47</td>
<td>24</td>
</tr>
<tr>
<td>Precuneus</td>
<td>-5, -70, 46</td>
<td>165 (*)</td>
<td>-3, -53, 57</td>
<td>4.96</td>
<td>20</td>
</tr>
<tr>
<td>Middle frontal gyrus left</td>
<td>-30, 39, 25</td>
<td>48 (*)</td>
<td>-31, 38, 36</td>
<td>4.08</td>
<td>11</td>
</tr>
</tbody>
</table>

SMA = supplementary motor cortex; TPJ = temporoparietal junction; STG = superior temporal gyrus; (***) number of voxels significant on a P value < 0.001 (corrected for multiple testing); (*) number of voxels significant activated on P value < 0.05 (corrected for multiple testing).
In the present study, LORETA-time-course peak detection (Table 3) has been done by visual inspection.

**Experimental procedure**

**Session in the scanner**

Five runs with 120 scans each have been performed. During each run, 15 target tones and 63 nontarget tones have been presented, resulting in 75 target tones and 315 nontarget tones for each subject. Between the end of the EPI sequence and the stimulus presentation, there has been a quiet period of 1 s. The EEG was recorded continuously during the entire experiment. After stimulus onset, additional 580 ms poststimulus EEG could be acquired until the next EPI sequence started.

**Session in front of the scanner**

Before the simultaneous EEG/fMRI measurement has been performed, the same experiment has been done in front of the scanner, using the same paradigm, the same number of stimuli, and the same EEG equipment. Between the two runs, there was a break of about 10 min.

In one subject, due to a technical problem of trigger marker coding, no averaging was possible. All together, nine subjects showed clear fMRI activations including the primary motor cortex on a $P$ value of 0.05, corrected for multiple testing, and were used for further analyses.

**Comparison between fMRI and EEG localizations**

This comparison has been done in calculating the Euclidean distances between the Talairach coordinates of the LORETA current density maxima and the Talairach coordinates of the BOLD centers of gravity in the same anatomical structures.

**Results**

**Comparison between the EEG inside and in front of the scanner**

There has been a clear difference in the amplitudes of the N1 component with higher amplitudes outside the scanner (mean: $10.15 \pm 5.70 \, \mu V$ vs. $5.06 \pm 2.58 \, \mu V, T = -3.37, P = 0.010$). However, no significant difference could be found between the P300 potential with a mean amplitude at Pz of $8.00 \pm 4.25 \, \mu V$ outside the scanner versus $6.60 \pm 3.98 \, \mu V$ inside, $T = 1.39, P = 0.202$ (Fig. 1). The N1 latency was longer outside the scanner (mean: $118 \pm 10$ vs. $109 \pm 9$ ms, $T = -3.130, P = 0.014$).

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**Table 2**

<table>
<thead>
<tr>
<th>Region</th>
<th>fMRI $X,Y,Z$ (Talairach)</th>
<th>Number of activated voxels</th>
<th>EEG (LORETA) $X,Y,Z$ (Talairach)</th>
<th>Current source density $[\mu V/mm^2 (\times 10^{-3})]$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor Cortex</td>
<td>$-35,-27,50$</td>
<td>9435</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Striatum left</td>
<td>$-25,-6,6$</td>
<td>4196</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Striatum right</td>
<td>$26,-5,6$</td>
<td>2642</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalamus left</td>
<td>$-8,-16,8$</td>
<td>2881</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalamus right</td>
<td>$10,-12,9$</td>
<td>1782</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precuneus</td>
<td>$0,-33,44$</td>
<td>142</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor Cortex</td>
<td>$-52,-4,-27$</td>
<td>3,53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gyrus temporalis inferior</td>
<td>$-53-13$</td>
<td>4.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gyrus temporalis medialis</td>
<td>$3.53-13$</td>
<td>4.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle frontal gyrus cinguli</td>
<td>$-45,10,29$</td>
<td>3.59</td>
<td></td>
<td></td>
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</tbody>
</table>

(♦) Region not covered by the fMRI slices.

In the present study, LORETA-time-course peak detection (Table 3) has been done by visual inspection.

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**Fig. 9.** Current source density time courses. Left hemisphere (Talairach coordinates are given in Table 3).
was no significant difference between the P3 latencies outside and inside the scanner (mean: 343 ± 73 vs. 326 ± 23 ms inside, \( T = -0.63, P = 0.55 \)). Both the frequent and the infrequent tone evoked a P3a outside the scanner, but the P3a component of both the frequent and infrequent tone inside the scanner was less distinct (Fig. 2). In order to analyze the brain activity specifically related to target detection, we have calculated difference waves (based on the potentials related to the infrequent tone minus the potentials related to frequent tone). Here, the specific target-related activity was similar inside and outside the scanner (mean difference wave amplitude at Pz inside the scanner 5.95 ± 3.99 vs. 5.45 ± 3.49 outside the scanner, \( T = -0.35, P = 0.73 \)). In addition, no significant difference in the difference wave latencies was detected (Fig. 3).

Comparison between fMRI and EEG localizations

fMRI activations were found in several brain regions including the supplementary motor cortex (SMA), the anterior cingulate cortex (ACC), the bilateral temporoparietal junction (TPJ), the bilateral insula, and the frontal regions such as the middle frontal gyrus (Figs. 4 and 5).

In the LORETA analysis, current density maxima have been found in similar regions (Figs. 6, 7, and 8). Additionally, LORETA-maxima were found in the left inferior temporal gyrus (Z = −27) and the right middle temporal gyrus (Z = −13). These regions have not been covered by the fMRI slices. In the comparison between the BOLD cluster centers of gravity and the LORETA-maxima, consistent spatial activation patterns were found with Euclidean distances between 7 and 26 mm (mean of 16.0 ± 6.6 mm, Table 1).

Table 2 shows the regions with no correspondence between fMRI and current source density including the motor cortex, the subcortical regions (thalamus, striatum). Subcortical regions are not included in the LORETA analysis, which is restricted on the cortical gray matter and the hippocampus. Two fMRI activations, one in the posterior cingulate and one in the precuneus, could not exactly be matched to a current source density maximum. One current source density maximum in the left middle frontal gyrus did also have no direct equivalence in the fMRI analysis.

Table 3

<table>
<thead>
<tr>
<th>Region</th>
<th>P300 peak (ms)</th>
<th>EEG (LORETA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>X, Y, Z (Talairach)</td>
</tr>
<tr>
<td><strong>Left hemisphere</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gyrus temporalis inferior</td>
<td>294</td>
<td>−52, −4, −27</td>
</tr>
<tr>
<td>STG</td>
<td>371</td>
<td>−59, −32, −6</td>
</tr>
<tr>
<td>TPJ</td>
<td>385</td>
<td>−59, −25, 22</td>
</tr>
<tr>
<td>Lobulus parietalis inferior</td>
<td>387</td>
<td>−45, −46, 50</td>
</tr>
<tr>
<td>Insula</td>
<td>388</td>
<td>−38, 17, 1</td>
</tr>
<tr>
<td>Middle frontal gyrus I</td>
<td>389</td>
<td>−45, 10, 29</td>
</tr>
<tr>
<td>Middle frontal gyrus II</td>
<td>390</td>
<td>−31, 38, 36</td>
</tr>
<tr>
<td>SMA/gyrus cinguli</td>
<td>396</td>
<td>−3, −11, 64</td>
</tr>
<tr>
<td>Precuneus</td>
<td>396</td>
<td>−3, −53, 57</td>
</tr>
<tr>
<td><strong>Right hemisphere</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gyrus temporalis medialis</td>
<td>345</td>
<td>53, 3, −13</td>
</tr>
<tr>
<td>Insula</td>
<td>356</td>
<td>53, 10, 8</td>
</tr>
<tr>
<td>TPJ</td>
<td>360</td>
<td>60, −18, 15</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>361</td>
<td>53, 17, 22</td>
</tr>
<tr>
<td>SMA/gyrus cinguli</td>
<td>396</td>
<td>4, −11, 64</td>
</tr>
<tr>
<td>Precuneus</td>
<td>396</td>
<td>4, −53, 57</td>
</tr>
</tbody>
</table>

Earlier activations in the right and the left insula, TPJ, and middle frontal gyrus. SMA = supplementary motor cortex, TPJ = temporoparietal Junction, STG = superior temporal gyrus.

Table 3: Time-course of the activations in the left and right hemisphere

Figs. 9 and 10 show the time course of brain activity in target detection in the left and right hemispheres. In Table 3, the exact peak latencies are given. There is early activity in the temporal lobes, with the temporoparietal junction being active afterwards and finally activation of frontal and supplementary motor regions. Peak activity in frontal regions has been earlier on the right than on the left, and also, activity in the insula was peaking earlier on the right.
Discussion

Comparison between the EEG inside the scanner and in front of the scanner

Clear differences between the amplitudes of the N1 component of the auditory-evoked potential inside the scanner and outside the scanner could be detected, but no significant difference for the P300 component. The N1 is a relatively early component and has strong generators in the auditory cortex (Naatanen and Picton, 1987; Picton et al., 1999). The noisy environment inside the scanner with the noise by the gradients has certainly an effect on the activation of the auditory cortex. The gradient noise can thus be seen as an additional auditory stimulus. In our study design, between the quiet interval between the end of the scanner gradient noise and the tone presentation was about 1 s. Therefore, the auditory cortex has been in a partial refractory period and therefore producing attenuated N1 amplitudes (Budd et al., 1998).

Outside the scanner, the same interstimulus interval of 3 or 6 s has been used, but not interrupted by scanner (gradient) noise. Therefore, both the infrequent and the frequent tone have evoked a strong P3a component, representing an orientation reaction (Friedman et al., 2001). No such clear P3a component has been evoked inside the scanner. With regard to the specific brain activity in target detection, which has been analyzed in comparing the difference waves of the potentials evoked by the infrequent minus the potentials evoked by the frequent tones, the related activity was quite similar inside and outside the scanner (Fig. 3). An effect of the recording order of the two conditions is less likely since there has been a break between the two runs and there is no learning effect in an oddball paradigm.

Comparison between fMRI and EEG localizations

Beside the activity in the motor cortex, which is not stimulus-locked and therefore not represented in the P300 potential, but represented largely in the fMRI signal, all major cortical regions have been well detected by the EEG-based LORETA analysis and the fMRI analysis independently, including the temporoparietal junction, the SMA/cingulate cortex, the insula, and the middle frontal gyrus with a right > left asymmetry (Downar et al., 2000; Halgren et al., 1998; Kiehl et al., 2001; Linden et al., 1999). Here, an additional LORETA-maximum has been detected in the left middle frontal gyrus with no correspondence in the fMRI signal. Two additional LORETA-maxima in the left inferior temporal and right middle temporal gyrus (Z = −13 and −27) have not been covered by our fMRI slices (covering about Z = 55 to −10). Finally, subcortical regions such as the thalamus and the striatum have been strongly activated in the fMRI analysis. However, thalamus and striatum are not included in the LORETA solution space.

The mean Euclidean distance between EEG- and fMRI-based localizations has been 16 mm, that is, in the range of the spatial resolution of LORETA, which is between 1 and 2 cm. Our finding is corresponding to a recent result of Vitacco et al. (2002) describing a mean distance of 14.5 mm between fMRI and ERP local maxima.

The results suggest that a close relationship exists between the electrical P300-signal on the scalp and the corresponding BOLD signal. Earlier studies, using from 19 to 124 electrodes (present study: 27) and the LORETA-method or similar approaches, have already described current source activity in parietal and frontal regions, suggesting that the topographical information on the scalp is sufficient for a plausible localization (Anderer et al., 2003; Moores et al., 2003; Wang et al., 2003). The present study demonstrates in addition a close relationship between EEG- and fMRI-based localizations. This finding is in accordance with the results of Horovitz et al. (2002) demonstrating a close correlation between changes in the P300 amplitude and BOLD-signal changes after manipulation of the experimental condition. The comparison of the localizations in this study has been performed based on current density images (ERP) and statistical images (fMRI). Beside the good correspondence of the localizations, it may be best to use similar methodology (e.g., the same kind of statistics) for the different data types in the future, which has not been possible with the applied software packages yet.

Time-course analysis of the current source density maxima

In both hemispheres, the activation sequence (within the P300 time range 250-540 ms) started in the temporal lobe with later activations of the temporoparietal junction (TPJ) and latest activity in frontal and supplementary cortex. Interestingly, the activity in several brain regions (insula, TPJ, and SMA) has been peaking earlier on the right than on the left side.

In comparison to the time-course patterns of the intracranial recordings (Halgren et al., 1998), several differences are obvious: In the present investigation, the time courses of the specific target-related brain activity was analyzed, that is, the difference wave between the potentials evoked by the infrequent versus frequent tone. Furthermore, our paradigm did not evoke a strong early (P3a)-component inside the scanner. Therefore, the time-course patterns in our analysis do not show different time courses contributing either to the P3a or P3b, but mainly different time-course patterns within the P3b. Here, further studies are necessary, using a paradigm that is evoking P3a and P3b inside the scanner separately (Comerchero and Polich, 1999).

Applications in neuropsychiatric research

Concerning the possible clinical impact of this approach, we suppose that a simultaneous measurement of EEG and fMRI, enabling us to analyze data with high resolution spatial and temporal information, should allow a distinct analysis of disturbed brain function in diseases like schizophrenia, dementia, or depression. In these conditions, with very different pathologies, attenuated P300 potentials can be recorded on the scalp (Polich and Herbst, 2000).

Our finding of asymmetric time course patterns with earlier activations in the TPJ, the insula, and the middle frontal gyrus on the right in healthy subjects might be worth to be further investigated. Several authors are describing asymmetric P300 amplitudes on the scalp in healthy subjects (Alexander et al., 1996; Bruder et al., 1998). With a simultaneous EEG/fMRI approach, this asymmetry could be further clarified, specifying the brain regions involved and their respective time courses. Furthermore, the relationship between P300 attenuations and psychopathology could be further elucidated: Several authors have described reduced P300 amplitudes in patients with distinct thought disorder (Frodé et al., 2002b; Higashima et al., 1998; Iwanami et al., 2000; Juckel et al., 1996). Here, the combination of EEG and fMRI might help to identify reduced activity in related brain regions and/
or a disturbed timing and synchrony of brain activity as a cerebral correlate.

Based on the fact that high quality EEG recordings are possible now in the scanner and that elimination of artifacts (originating, e.g., from MR gradients) from the EEG-signal has recently much improved (Allen et al., 1998; Goldman et al., 2000; Hoffmann et al., 2000; Sjibers et al., 1999), further applications of a simultaneous EEG/fMRI approach are appropriate. For example, it is obviously worthwhile to further investigate the relationship between electrical oscillations and the fMRI signal, since close relationships have been described between the energy consuming high frequency oscillations in the gamma (40 Hz)-range, and the BOLD signal (Logothetis et al., 2001) and gamma oscillations are also known to play a critical role in higher cognitive functions (Engel et al., 2001). Furthermore, the investigation of EEG coherence might improve our understanding of connectivity within the brain, expanding our methodology here beyond the analysis of hemodynamic-based connectivity approaches (Bokde et al., 2001; Buchel and Friston, 2001).

In summary, this study shows diminished N1 amplitudes and shorter N1 latencies inside the scanner but comparable P3 peaks and latencies inside and outside the scanner as well as a high degree of concordance between fMRI- and EEG-based localizations and distinct time-course patterns in the involved temporal, parietal, and frontal regions.

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References


