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Combined event-related fMRI and intracerebral ERP study of an auditory oddball task

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Event-related fMRI (efMRI) has been repeatedly used to seek the neural sources of endogenous event-related potentials (ERP). However, significant discrepancies exist between the efMRI data and the results of previously published intracranial ERP studies of oddball task. To evaluate the capacity of efMRI to define the sources of the P3 component of ERP within the human brain, both efMRI and intracerebral ERP recordings were performed in eight patients with intractable epilepsy (five males and three females) during their preoperative invasive video-EEG monitoring. An identical auditory oddball task with frequent and target stimuli was completed in two sessions. A total of 606 intracerebral sites were electrophysiologically investigated by means of depth electrodes. In accordance with the finding of multiple intracerebral generators of P3 potential, the target stimuli evoked MRI signal increase in multiple brain regions. However, regions with evident hemodynamic and electrophysiological responses overlapped only partially. P3 generators were always found within hemodynamic-active sites, if these sites were investigated by means of depth electrodes. On the other hand, unequivocal local sources of P3 potential were apparently also located outside the regions with a significant hemodynamic response (typically in mesiotemporal regions). Both methods should thus be viewed as mutually complementary in investigations of the spatial distribution of cortical and subcortical activation during oddball task.
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Introduction

Endogenous event-related potentials (ERPs) are thought to reflect the neurophysiological correlates of cognitive processes. The P3 component of ERPs, which is a target detection response, has been the one most studied. This large long-latency positive waveform is generally viewed as reflecting decision-making or cognitive closure of recognition processing. It has been mostly linked to both orienting and memory mechanisms (Paller et al., 1987; Squires et al., 1975). Some newer evidence nevertheless clearly supports the idea that P3 is actually a much more complex phenomenon. In addition to stimulus-related processing, it certainly also reflects response-related processing (Brázdil et al., 2003a; Verleger, 1997). The P3 potential is usually evoked in an oddball task by rare (target) stimuli. Previous ERP studies using electrodes implanted in the human brain unequivocally demonstrated multiple generators of P3 potentials in different cortical and subcortical brain structures (Baudena et al., 1995; Brázdil et al., 1999; Halgren et al., 1995a,b, 1998; Kiss et al., 1989; Kropotov and Ponomarev, 1991; McCarthy, 1992; McCarthy et al., 1989; Puce et al., 1989, 1991; Rektor et al., 2003; Seeck et al., 1995; Yingling and Hosobuchi, 1984). However, a complete list of them has yet to be determined. With the availability of modern imaging technologies, event-related fMRI (efMRI) has been repeatedly used to seek the neural sources of ERPs and to determine the brain regions involved in target detection (Ardekani et al., 2002; Brázdil et al., 2003b; Clark et al., 2000; Kiehl et al., 2001; Kirino et al., 2000; Linden et al., 1999; McCarthy et al., 1997; Menon et al., 1997; Mulert et al., 2004; Opitz et al., 1999; Stevens et al., 2000; Strange and Dolan, 2001; Yoshiura et al., 1999). Relatively homogenous findings from various authors who have detected significant hemodynamic changes within most brain regions that have been known from intracerebral measurements have suggested a high degree of concordance between electrophysiological and hemodynamic responses. At the same time, however, significant discrepancies between the efMRI data and the results of previously published intracranial ERP studies have also been revealed. Most hemodynamic studies have very rarely revealed any post-target activation within the mesiotemporal structures even though hippo-

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campal formation is now widely accepted as a powerful generator of P3 activity. Similarly, a more spatially extensive genesis of P3 potential has been proven within the anterior cingulate gyrus (ACC) in intracerebral ERP studies. Thus, the current question is not whether brain activity related to the target detection is detectable by both methods, but rather it is a degree of their sensitivity and mutual exchangeability in this task that should be clarified. To evaluate the factual capacity of efMRI to define the sources of the P3 component of ERPs within the human brain, in the present study both efMRI and intracerebral ERP recordings were performed in the same subjects. To the best of our knowledge, this is the first oddball task study directly combining event-related fMRI and intracerebral ERP methodology ever published.

Materials and methods

Subjects and study design

Eight patients (5 males and 3 females) ranging in age from 25 to 43 years (with an average age of 33.6 years), all with medically intractable epilepsies, participated in the study (Table 1). An identical auditory oddball task with binaural pseudorandom presentation of frequent (1000 Hz) and target stimuli (2000 Hz) was completed in two sessions (first, the "fMRI session"; next, the "electrophysiological session", which was performed 5 days later during preoperative invasive video-EEG recording). The duration of each stimulus was 200 ms. The minimum total of presented targets in each session was 23. The ratio of target to frequent stimuli was approximately 1:12, the interstimulus interval was fixed at 2760 ms, and the minimal delay between two subsequent target stimuli was 20 s. During the investigation, subjects were instructed to keep their eyes closed and to mentally count the target stimuli. After the investigation, participants were requested to report the number of targets. Informed consent was obtained from each subject prior to the experiment. The study received the approval of the local ethics committee.

fMRI

Imaging was performed on a 1.5-T Siemens Symphony scanner equipped with Numaris 4 System (MRease). Functional images were acquired using a gradient echo, echoplanar imaging (EPI) sequence: TR (scan repeat time) = 2760 ms (including 1 s of silence for stimulus presentation), TE = 40 ms, FOV = 230 mm, flip angle = 90°, matrix size 64 × 64, slice thickness = 5 mm with a 2-mm inter-slice gap (total space between two adjacent slices = 7 mm) 16 transversal slices per scan. A total of 384 functional (BOLD T2*-weighted) scans were acquired during each patient's imaging examination. Following functional measurements, high-resolution anatomical T1-weighted images were acquired using a 3D sequence that served as a matrix for the functional imaging (160 sagittal slices, resolution 256 × 256 interpolated to 512 × 512, slice thickness = 1.17 mm, TR = 1700 ms, TE = 3.96 ms, FOV = 246 mm, flip angle = 15°). The SPM 99 program was used to analyze the fMRI data (Friston, 1996; Horwitz et al., 2000). The following pre-processing was applied to each subject's time series of fMRI scans: realign to correct for any motion artefacts; slice timing correction; spatial normalization to fit into a standard anatomical space (MNI); spatial smoothing using a Gaussian filter with an FWHM of 8 mm; temporal smoothing with Gaussian filter (FWHM = 4 s) and high-pass filter of 100 s. The voxel size generated from the above acquisition parameters was oversampled to 3 × 3 × 3 mm. To determine the brain regions that showed significantly greater time-locked activation to targets, a general linear model (GLM), as implemented in SPM 99, was used. As a basis set for analysis, a canonical hemodynamic response function with time and dispersion derivatives was selected. Six regressors of interest (canonical hrf, its temporal and dispersion derivatives, for both frequents and targets) and 6 vectors of movement parameters (additional regressors) were used for estimating GLM parameters. Next, statistical parametric maps with F statistics were computed for the overall effect of targets compared to frequents (using F contrast −1 0 0 1 0 0; 0 −1 0 0 1 0; 0 0 −1 0 0 1). The analyses of individual subjects were performed at a higher voxel-wise significance threshold ($P < 0.0001$) to compensate partially for multiple comparisons. We used fixed-effect analysis to compute group activation, paying particular attention to the mean activation of these subjects. Group results were calculated at a significance threshold of $P < 0.01$, corrected for multiple comparisons.

Table 1
Patient characteristics

Subject no.	Sex	Age (years)	Dominant hand	Implanted sites[a]	No. of recording sites
1	M	37	R	LTF	86
2	F	43	R	LT, RTPO	86
3	M	28	R	RTFP	65
4	F	35	L	LTF, RT	86
5	F	25	R	LTF, RTF	86
6	M	26	R	LT	25
7	M	34	L	LT, RTF	86
8	M	41	R	LTF, RF	86

[a] T, temporal; F, frontal; P, parietal; O, occipital; R, right; L, left.

Electrophysiological recordings

Three days after fMRI investigation, depth electrodes were implanted in the patient to localize the seizure origin prior to surgical treatment. Each patient received 3–12 orthogonal platinum electrodes in the temporal and/or frontal, parietal, or occipital lobes using the methodology of Talairach et al. (1967). A total of 606 intracerebral sites were electrophysiologically investigated by means of 63 multicontact depth electrodes (42 temporal, 17 frontal, 3 parietal, 1 occipital). Standard MicroDeep semiflexible electrodes (DIXI) with diameters of 0.8 mm, contact lengths of 2 mm, and intercontact intervals of 1.5 mm were used for invasive EEG monitoring. Contacts at the electrode (5–15) were always numbered from the medial to the lateral side. Their positions were indicated in relation to the axes defined by the Talairach system using the "x,y,z" format where "x" = lateral, mm to midline, positive right hemisphere; "y" = anteroposterior, mm to the AC line, positive anterior; and "z" = vertical, mm to the AC–PC line, positive up. The exact positions of the electrodes and their contacts in the brain were verified using postplacement MRI with electrodes in situ (T2-weighted FLAIR images using turbo inversion recovery sequence, TR = 9000 ms, TE = 115 ms, FOV = 243.5 × 230 mm, voxel size 0.45 × 0.45 mm, slice thickness = 3.3 mm, 20–30 coronal slices according to subject's electrodes placement). The recordings from lesional anatomical structures and epileptogenic

zones were not included in the experimental analysis. The EEG signal was simultaneously recorded from various intracerebral structures and from the CPz scalp electrode (situated between Cz and Pz) using the 96 channel BrainScope EEG system (M and I). All recordings were monopolar, with a linked earlobe reference. EEGs were amplified with a bandwidth of 0.1–40 Hz at a sampling rate of 128 Hz. Artefact-free EEG periods of 2 s were averaged off-line using the stimulus onset as a trigger (−200 and +1800 ms from the stimulus). ScopeWin software was used for signal analysis. At least twenty-five sweeps were independently averaged for each type of stimulus-frequent and target. ERP components in the 250–500 ms latency range were identified by visual inspection and quantified by latency and amplitude measures. The most interesting results were intracerebral findings of polarity reversals or steep voltage gradients that uniquely proved the focal origin of the waveform (Vaughan et al., 1986).

Comparison between efMRI and intracerebral ERP findings

The concordance of significant hemodynamic and electrophysiological responses (in terms of apparent occurrence of P3 generators) in the investigated brain sites was evaluated in each subject separately (individual data analysis). Corresponding post-placement anatomical MRI scans with electrodes in situ served as a matrix for individual functional images in this step. The analysis was done by slice-to-slice and contact-to-contact inspection of the results.

Results

Behavioral data

Satisfactory cooperation of all subjects was observed in both parts of the experiment. In most experimental sessions, the subjects reported the number of targets correctly. The accuracy of the behavioral responses (reported number of targets) did not differ significantly between the fMRI and the electrophysiological sessions in any of the subjects.

fMRI results

Significantly greater fMRI activations to target stimuli (in comparison with frequent stimuli) were found in several brain regions, including the supramarginal gyri and inferior parietal lobules (BA 40), the anterior cingulate gyrus (BA 32), the inferior and middle frontal gyri (BA 6,9,10), the middle temporal gyrus (BA 21), the precentral gyrus (BA 4), and the subcortical grey matter (putamen and thalamus). Most of the activations were bilateral; however, obvious right-sided predominance was observed in most of the activated regions. The largest and most significant cortical activations were revealed in inferior parts of the parietal lobes and in the anterior cingulate areas. No significant efMRI activation was observed within the mesiotemporal regions (amygdala, hippocampus and parahippocampal or fusiform gyrus) in the group or in the individual data. Table 2 summarizes the anatomical areas, their MNI coordinates, and the number of voxels with significantly greater activation to target stimuli compared to frequent stimuli ($P < 0.01$ corrected; $Z > 5.65$). Fig. 1 presents composite maps of eight investigated subjects with a typical fitted BOLD response in one of the activated clusters.

Table 2
Brain areas that showed significantly greater activation to target stimuli based on an average across 8 subjects

ROI (Brodmann area)	MNI coordinates (x,y,z)		Size (voxels)	
	R	L	R	L
Supramarginal gyrus (40)	54, −45, 21	−57, −45, 24	683	183
Inferior parietal lobule (40)	51, −42, 48	−48, −42, 57	512	398
Anterior cingulate (32)	3, 24, 45		828	
Inferior frontal gyrus (44)	51, 27, 24	−51, 9, 27	374	123
Middle frontal gyrus (10)	42, 54, 3	−27, 51, −3	388	18
Middle frontal gyrus (9)		−30, 36, 36		97
Middle frontal gyrus (6)	27, 9, 57		58	
Precentral gyrus (4)		−48, −6, 54		41
Middle temporal gyrus (21)	60, −3, −6	25		
Putamen	33, 27, −3	−12, 6, −6	719	539
Thalamus	8, −15, −5		31	

The activations were significant at $P < 0.01$ ($Z > 5.65$) after correction for multiple spatial comparisons.
ROI, regions of interest; voxel size 3 × 3 × 3 mm.

ERP results

Intracerebral ERP recordings revealed prominent P3 potentials after target stimuli in many cortical areas in all of the investigated subjects. The responses mostly had the typical character of a broad monophasic potential with a longer latency (350–500 ms) or of a sharp triphasic, usually negative–positive–negative, waveform with a shorter latency positive component (at about 250–400 ms). Neither their character nor their anatomical distribution within the brain differed significantly from previous intracerebral ERP studies (see Brázdil et al. (1999) and Halgren et al. (1998)). Most of the positive observations of the P3 potentials arose from the investigation of the temporal, frontal, and parietal cortices (for details see Table 3). In accordance with previous studies, the focal origin of P3 waveform was repeatedly proven in mesiotemporal structures (with the hippocampus most frequently involved), anterior and posterior cingulate gyrus, prefrontal and inferior parietal cortices, and lateral temporal neocortex. No generators of the P3 potential were found within occipital and insular cortex in this study. As a control electrophysiological condition, simultaneous scalp ERP recordings were obtained in all investigated subjects; the mean latency of scalp P3 was 345.0 ± 33.38 ms, the mean scalp P3 peak-to-peak amplitude was 13.46 ± 7.484 μV.

Comparison between efMRI and intracerebral ERP findings

When evaluating the concordance of significant hemodynamic and electrophysiological responses in individual data, a partial overlapping of positive findings was systematically observed. A P3 generator was always found within a hemodynamic-active site, if this site was investigated by means of depth electrode. Typically, this condition was seen in the supramarginal gyrus and inferior parietal lobule, where electrophysiological proof of a P3 generator corresponded anatomically to the significant increase of BOLD response (Figs. 2 and 3). On the other hand, unequivocal local sources of P3 potential were apparently also located outside the regions with a significant hemodynamic response (Fig. 2). The most striking discrepancies of this sort were found in the mesiotemporal structures. Despite indubitable proofs of the P3 generators within the hippocampus (15×), the amygdala (4×), and the parahippocampal and fusiform gyrus (1× and 4×, respec-

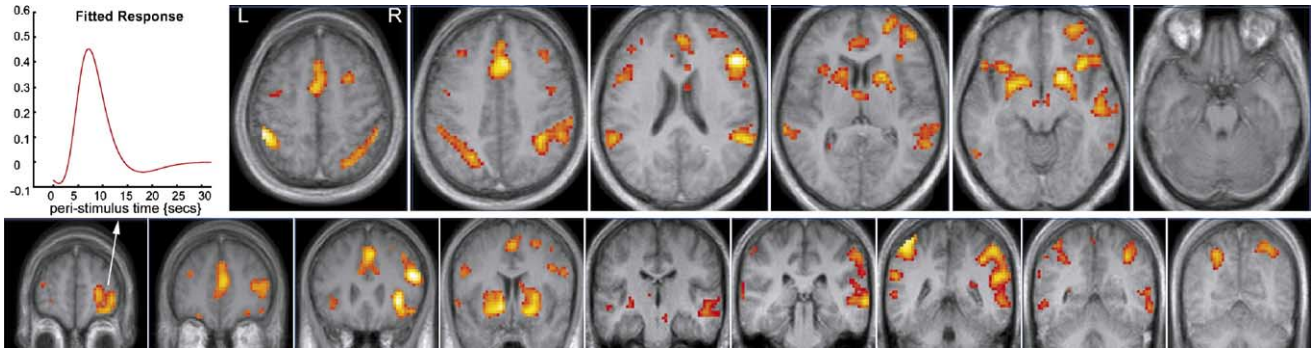

Fig. 1. Composite map of 8 subjects showing areas responsive to the target stimuli ($P < 0.01$ corrected). Axial and coronal slices. In the upper left part of the figure, a fitted BOLD response in the cluster of activation within the right inferior frontal gyrus is given.

tively), we observed no significant post-target BOLD effect, neither in the identical anatomical sites, nor in their nearby surroundings (Fig. 4). These observations did not change even if the significance level of the individual functional data was experimentally increased to $P < 0.001$ uncorrected. An imperfect concordance was revealed in the other investigated brain sites. Cerebral activation as proven by depth ERP recordings unambiguously exceeded the regions with significant BOLD response in many cortical areas. In the posterior cingulate gyrus, the rate of congruity was 50%; in the anterior cingulate, it was 22%. Similar findings were obtained from analysis of the prefrontal and lateral temporal cortices.

Discussion

The P3 component of event-related potentials does not represent a homogeneous phenomenon originating in a single brain structure. Instead, it reflects extensive neuronal activity within many cortical and limbic areas (Halgren et al., 1998). In scalp recordings, a P3 potential emerges as a sum of activity of multiple cortical and perhaps subcortical generators. Initial intracerebral ERP studies focused on the identification of P3 sources revealed its powerful generators in mesiotemporal structures (the hippocampus, the amygdala, and the parahippocampal gyrus) (McCarthy, 1992; McCarthy et al., 1989; Puce et al., 1991). These findings were not truly surprising because of the well-known role of mesiotemporal structures in memory functions (crucial for recognition of relevant stimuli in an oddball task). In contrast, apparent proof of the limited contribution of these large hippocampal P3 potentials to the genesis of the P3 in scalp recordings was rather astonishing (Johnson, 1988; Verleger, 1997; Wood et al., 1980). The anatomical relations between mesiotemporal areas and recording electrodes placed on the head surface, and an inconvenient spatial orientation of a P3 generating dipole, were considered as the most likely reasons for this result. Subsequent studies on the genesis of P3 potential revealed several other generators, most of them outside the temporal lobes: the lateral temporal–parietal junction (including the supramarginal and angular gyrus), the orbitofrontal, dorsolateral, and mesial prefrontal cortices, and the anterior and posterior cingulate gyri (Baudena et al., 1995; Brázdil et al., 1999; Halgren et al., 1995a, 1998; Kiss et al., 1989; Ojemann and Lettich, 1983; Seeck et al., 1995). The P3 generators were also demonstrated in the lateral temporal neocortex and within the pole of the temporal lobe (Brázdil et al., 1999; Halgren et al., 1995a,b). In addition, some invasive ERP studies revealed the presence of P3 potential within the subcortical grey matter–thalamus and basal ganglia (Kropotov and Ponomarev, 1991; Rektor et al., 2003; Yingling and Hosobuchi, 1984). The P3 potential measured at the scalp nevertheless seems to be largely determined by the parietal lobe generators and in particular by the activity in the temporal–parietal junction (see discussion by Ford et al., 1994; Halgren et al., 1995b; Knight and Scabini, 1998; Molnár, 1994; Verleger et al., 1994). The utilization of the intracerebral ERP methodology for identification of the P3 sources provides an outstanding view on the complexity of brain activation during a simple oddball task, unambiguously demonstrates a large-scale network of activated neuronal populations, and reveals obvious differences in the time-course patterns of activation within the involved brain regions. However, due to some method limitations, the intracerebral ERP recordings are unable to definitively set up a complete map of the activated brain regions. The most substantial limitation of the method is actually related to the fact that depth electrodes are only reasonably used in a presurgical investigation

Table 3
Occurrence of intracerebral P3 activity at different anatomical brain sites, including proofs of the focal origin of the ERPs

Anatomical site	Cerebral lobe	No of positive observations/no. of investigations	Steep voltage gradients or polarity reversals (indicating focal origin)
Hippocampus	T	17/19	15
Amygdala	T	6/9	4
Parahippocampal gyrus	T	2/3	1
Fusiform gyrus	T	5/8	4
Temporal pole	T	1/2	1
Medial temporal gyrus	T	11/26	6
Superior temporal gyrus	T	4/8	2
Inferior temporal gyrus	T	2/2	2
Anterior cingulate gyrus	F	12/12	9
Medial frontal gyrus	F	2/2	2
Middle frontal gyrus	F	5/8	5
Inferior frontal gyrus	F	7/9	5
Rectus gyrus	F	1/1	–
Posterior cingulate gyrus	P	2/2	2
Inferior parietal lobule	P	1/1	1
Supramarginal gyrus	P	1/1	1
Middle occipital gyrus	O	0/1	–
Insula	–	1/1	–

Group data across 8 subjects.

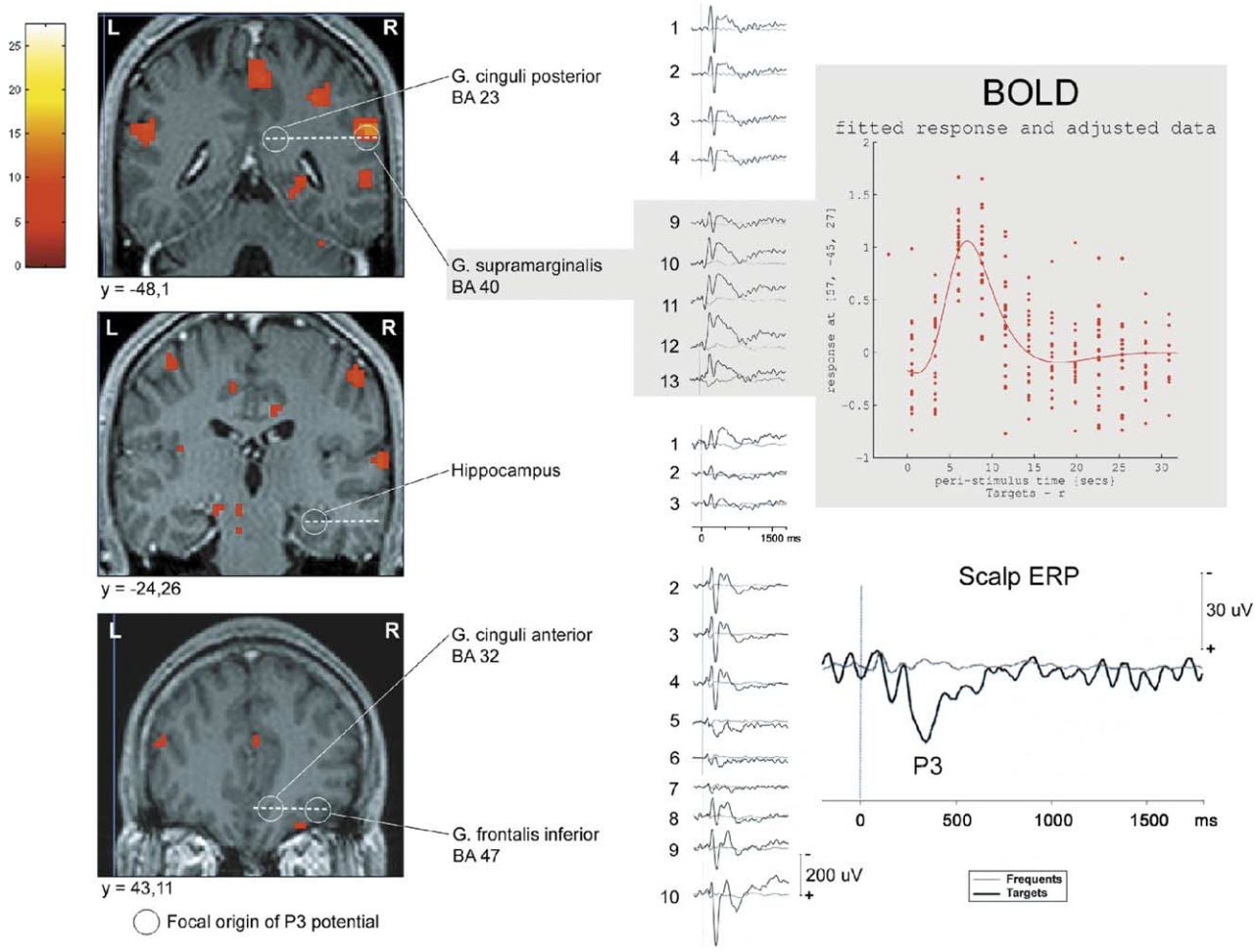

Fig. 2. Partial overlapping of electrophysiological and hemodynamic responses in individual data. Obvious generators of P3-like potentials (steep voltage gradients in adjacent contacts of the depth electrode) were proven in several investigated brain sites (indicated by circles in the coronal anatomical scans). A significant increase in the BOLD response after targets was observed in only one site (the supramarginal gyrus). Subject no. 3; $P < 0.0001$ uncorrected.

of intractable epileptic patients, and as such their target sites in the brain are strictly chosen on a purely clinical basis. Thus there are many cerebral regions that are inaccessible to depth electrodes, not just from a technical, but also from an ethical point of view.

Event-related functional MRI has been repeatedly used in recent years in the investigation of oddball task, seemingly replacing the "old-fashioned" invasive electrophysiological approach with its excellent temporal but poor spatial resolution. Despite a considerable methodological heterogeneity of published studies, rather concordant findings have been independently described (Ardekani et al., 2002; Brázdil et al., 2003b; Clark et al., 2000; Kiehl et al., 2001; Kirino et al., 2000; Linden et al., 1999; McCarthy et al., 1997; Menon et al., 1997; Mulert et al., 2004; Opitz et al., 1999; Stevens et al., 2000; Strange and Dolan, 2001; Yoshiura et al., 1999). The efMRI results obtained in the present study correspond with the results of above-listed papers. A congruently significant increase of post-target BOLD response was consistently observed in multiple brain regions. Group data efMRI analysis again revealed significant activation mainly, within both-sided parietal and frontal lobe cortex (including ACC), with overall right-sided predominance. Similarly, more extensive activation in the right hemisphere was independently observed in several previous studies. This finding may reflect a preferential involvement of a neural system for directed attention in a completed task (Ardekani et al., 2002; Brázdil et al., 2003b; Clark et al., 2000; Kirino et al., 2000; McCarthy et al., 1997; Mulert et al., 2004; Stevens et al., 2000; Yoshiura et al., 1999). In accordance with previous observations, a significant BOLD response was also proven in our subjects within the subcortical grey matter, again with a slight right-sided predominance (putamen and thalamus). However, a significant activation within the supplementary motor area, which was repeatedly described by different authors (Linden et al., 1999; Mulert et al., 2004; Yoshiura et al., 1999) but did not appear in our results (see Table 2), could actually be "hidden" in a huge cluster of activation with its center in ACC (BA 32). The extension and anatomical localization of this conspicuous ACC activation corresponded very well with previously published results. No activation within the posterior cingulate gyrus or in the mesiotemporal areas was observed in our group data. When evaluating mesiotemporal structures in individual data, the same negative findings were obtained. In reviewing previously published efMRI studies on auditory oddball task, we only rarely found a description of any activation in the mesiotemporal region (Clark et al., 2000; Kiehl et al., 2001; Yoshiura et al., 1999). In addition, these rare observations were fairly heterogeneous and demonstrated a very limited activation, just within the extrahippocampal

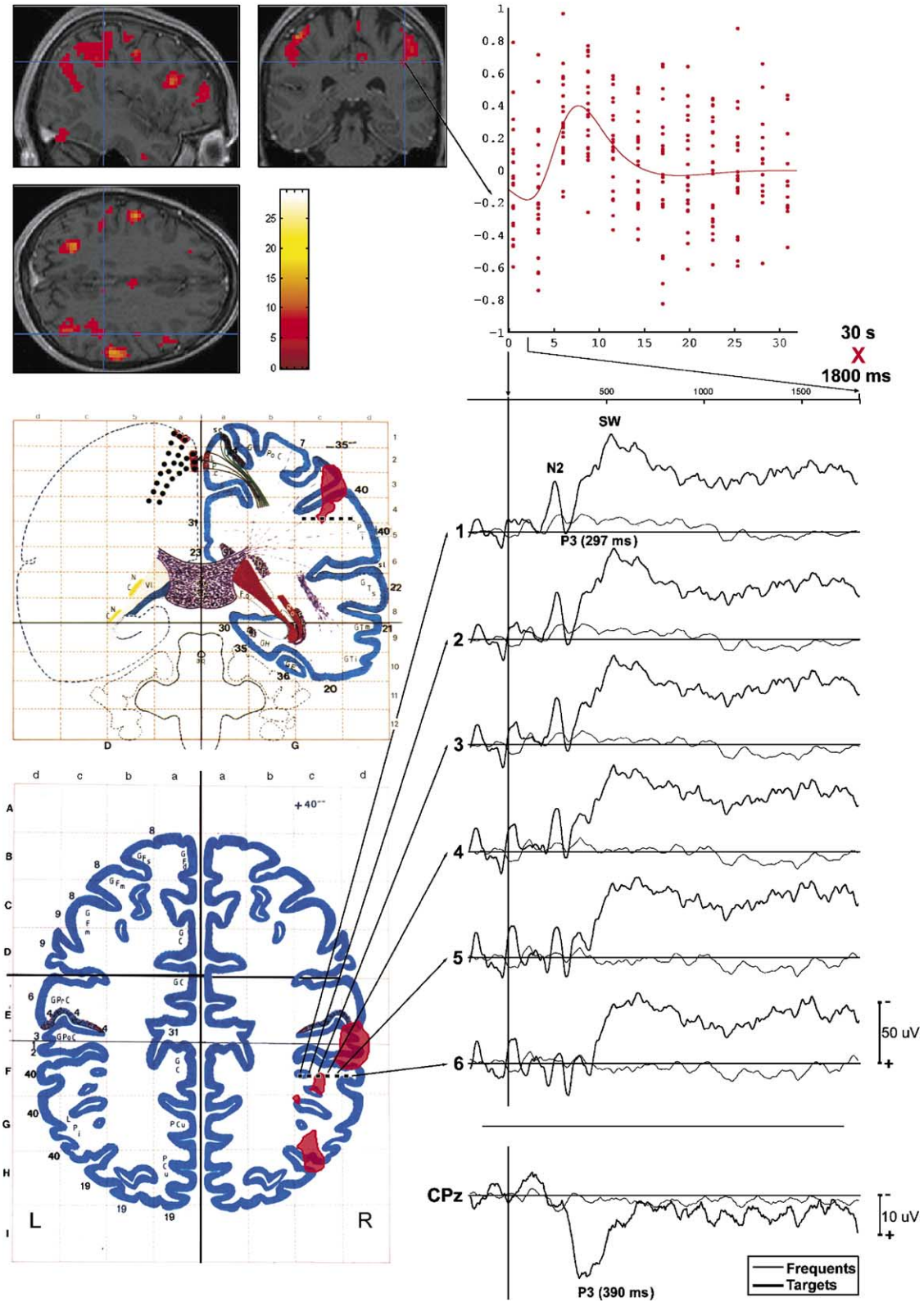

Fig. 3. Concordant findings of significant hemodynamic response and local source of P3-like activity within the right-sided inferior parietal lobule (subject no. 2; $P < 0.0001$ uncorrected). In the upper part of the figure, significant post-target fMRI activations are demonstrated on anatomical images with a typical fitted response within the inferior parietal lobule (on the right). ERP recordings (revealing steep voltage gradients of P3s) from adjacent six contacts of the depth electrode passing through the brain sites with fMRI activations (see left-positioned schematic picture with electrode contacts and identical red clusters of activation within BA 40) are given in bottom slices. Notice substantial time differences between the hemodynamic and electrophysiological responses.

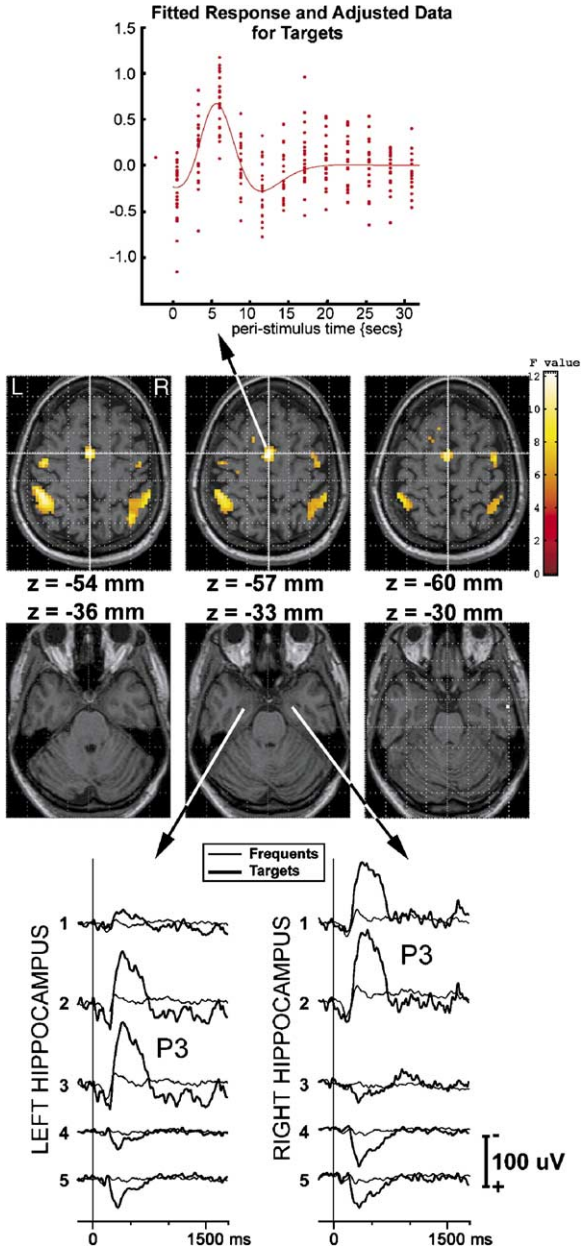

Fig. 4. Apparently absent hemodynamic response in the sites of proven P3 generators (in both-sided hippocampi; bottom slices). In the upper part of the figure, a significant BOLD response after target is given from the same subject within anterior cingulate cortex (see fitted response above) and both-sided inferior parietal lobule. Subject no. 4, significance level was increased to $P < 0.001$ uncorrected.

areas (either the parahippocampal gyrus or the amygdalar complex). Most authors apparently did not observe any significant activation within the mesiotemporal areas; nor did we. Nearly identical efMRI findings in previous studies on healthy volunteers (including our study using identical methodology; Brázdil et al., 2003b) and the present study with patients suffering from intractable epilepsy are noteworthy.

In contrast to the described absence of any significant efMRI activation within the mesiotemporal regions, the obvious local sources of P3 potential were revealed in the same subjects' electrophysiological recordings within the hippocampus, amygdala, fusiform, and parahippocampal gyrus. In general, our electrophysiological findings of the multiple P3 generators and their precise localization did not differ substantially from previously published data (Baudena et al., 1995; Brázdil et al., 1999; Halgren et al., 1995a,b, 1998; Kiss et al., 1989; McCarthy, 1992; McCarthy et al., 1989; Puce et al., 1989, 1991; Seeck et al., 1995). In addition to the most frequent findings of P3 local sources within the mesiotemporal regions, other P3 generators were also revealed throughout the frontal, parietal, and temporal lobes. Even if some degree of concordance between our efMRI and electrophysiological findings was clearly observed in terms of depicted neural activity, in many areas cerebral activation was evidently detectable only with EEG, and not with the fMRI method. In addition to the mesiotemporal areas, apparent discrepancies were observed within ACC. For example, the efMRI results did not reveal any significant activation within the rostral parts of ACC, where P3 generators were repeatedly observed. By changing the probability of target presentation in their recent efMRI oddball study, Horovitz et al. (2002) revealed no correlation of hemodynamic changes within the anterior cingulate cortex with scalp P3 amplitude. However, fMRI signal changes in supramarginal gyri, thalamus, insula, and medial frontal gyrus correlated very well with the amplitude of scalp P3. These findings may reflect either a limited contribution of the cingulate P3 to the scalp P3 recordings in terms of its amplitude (which is extremely unlikely), different response properties of ACC (which is rather questionable), or possibly an incomplete recording of underlying brain activity by fMRI method. In addition to neuronal populations, which activation results in massive hemodynamic changes, other neuronal groups might be able to produce P3 potential but not sufficient changes in the perfusion within corresponding anatomical sites.

Our significantly different findings of the two methods in some brain areas can hardly be explained just by that they were recorded in two separate sessions. Even if the sessions substantially differed in the experimental environment, Mulert et al. (2004) recently found no significant differences in latency nor in the amplitude of scalp P3 potential recorded inside and outside the scanner. Another difference between the two sessions was the level of background noise, which can result in the subjects' different levels of arousal. However, the increase in arousal that is presumable in the environment with MR noise would probably not result in the decrease of activation within mesiotemporal regions or rostral parts of the cingulate. A familiarity with the task in the second session is also unlikely to produce opposite results. In ERP as well as fMRI research of oddball task, a good reproducibility of both P3 potential and efMRI measurements was proven (Kiehl and Liddle, 2003). In addition, no differences in localizations or in other physical parameters of intracerebral P3 potentials were observed in the present study or in our previous intracerebral ERP research with a single-session target presentation.

Taking into the consideration all of the above-mentioned facts, it can be concluded that some portion of neural activity evoked by deviant (target) stimuli might be detectable only with EEG and not observed using contemporary efMRI methodology. The discrepancies may be caused by basic differences between the mechanisms of ERPs and BOLD fMRI signal generation, which have yet to be fully described. We can only speculate that fMRI methods may not reflect blood oxygenation changes caused by the brief synaptic activity associated with P3 per se, but rather the sustained activity of a neuronal system triggered by the target event (McCarthy et al., 1997). The targets could then evoke a more

sustained activation in the prefrontal and parietal cortex than that evoked in the hippocampus. Another plausible hypothesis explaining inability of efMRI technique to identify all brain areas involved in the target detection is its use of a "subtraction strategy". This strategy subtracts the pattern of brain activation evoked by the "baseline" task from that evoked by an "active" task formally identical in all respects except that it is hypothesized to demand one additional cognitive process of interest. If areas tend to be engaged even if they have only a very slight probability of being needed, then it is likely that many of the essential areas in the "active" task will also be engaged in the "baseline" task, even though they are not essential. The subtraction may not reveal such areas and thus may greatly underestimate the extent of the brain involved in a given cognitive process (Halgren et al., 1995b). In accordance with the described hypothesis, some activation within the hippocampi was also revealed in the oddball task after frequent stimuli (Kukleta et al., 2003). Finally, it is likely that efMRI can reflect only the activation of large neuronal groups with massive alterations of their postsynaptic potentials, while in some brain areas P3 potential may be produced by spatially very limited neuronal population, the activation of which is not strong enough to produce significant hemodynamic changes. It is unlikely that the effect of fMRI susceptibility artefacts could explain differences exclusively in areas prone to them, such as anteroventral parts of the temporal lobes (hippocampi), but not in the other parts of the brain, including ACC.

To summarize our findings, although event-related fMRI provides excellent spatial resolution, methodological limitations may decrease its sensitivity in detecting target stimulus-evoked activity in certain brain areas. Event-related fMRI may thus complement, rather than replace, intracranial ERPs in investigations of the spatial distribution of cortical and subcortical activation during oddball tasks.

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