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The ERP omitted stimulus response to "no-stim" events and its implications for fast-rate event-related fMRI designs

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Abstract

A major difficulty in fast-rate event-related fMRI experiments is the extensive overlap from adjacent trials in the stimulus sequence. One approach to address this problem is to include "no-stim" or "null" events as a trial type. These are randomized as if they were true stimulus events but no stimulus actually occurs. Assuming that no response is elicited by the null events, their time-locked average reflects only the averaged overlap. Thus, contrasting the averages for the other trial types versus the null-event average subtracts out the overlap, enabling the extraction of the response functions for these other trial types. ERP studies, however, have indicated that an endogenous brain response, the omitted stimulus response (OSR), can be evoked by a missing event in a stream of regularly occurring stimuli. To the extent that this response is elicited by null events in an event-related fMRI experiment, the null-event subtraction or contrast would falsely introduce the inverse of the OSR into the averaged responses to the other trial types. Using high-density ERP recordings, we investigated the effect of different percentages of omitted stimuli (11, 22, and 33%) on the auditory OSR at stimulus rates of one event per second or one event per 2 s. Significant OSRs were found for each percentage in the 1-s condition as well as in the 11% 2-s condition. The responses consisted of an early posterior negative wave (180–280 ms) followed by a larger anterior positive wave. These results have important implications for fast-rate fMRI designs, while also providing new data on the brain's response to omitted stimuli.

Keywords: Event-related potentials; Functional MRI; Functional imaging; Response overlap; Null events; Omitted stimuli

Introduction

In fast-rate event-related fMRI experiments with stimulus onset asynchronies (SOAs, the time between the onsets of two successive stimuli) of less than around 10–12 s, there is substantial signal overlap from responses to adjacent trials in the stimulus sequence. This overlap is due to the sluggishness of the blood oxygenation level-dependent (BOLD) contrast response, which peaks ~5–6 s after the triggering event and lasts 10–12 s or more (Blamire et al., 1992; Buckner et al., 1996). Limiting SOAs to be more than 12 s, however, greatly constrains the experimental paradigms that can be employed and the number of trials that can be obtained in a reasonable scanning session period. In addition, it is difficult to directly compare neuroimaging results from studies using such long SOAs to previous behavioral and ERP results from studies that typically use much shorter SOAs.

The development of certain approaches for overlap removal, however, has made it possible to perform event-related fMRI at much faster rates of stimulus presentation. As originally described with ERPs (Woldorff, 1993), if the neurophysiological responses from adjacent stimuli in a sequence overlap but the stimulus types are presented in randomized order, this overlap will be, on average, about the same for the different stimulus types; thus, in a contrast between the responses to two event types this overlap will subtract out, enabling the extraction of the event-related *differential* response activity between the event types. Even

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with the very severe overlap that can be incurred with event-related fMRI, this approach has been found to work well at stimulus rates of one per 2 s (Buckner et al., 1998; Dale and Buckner, 1997) or even as fast as one event per 500 ms (Burock et al., 1998).

A useful extension to the randomization approach is the use of so-called “no-stim” events, which are points in time in the trial sequence that are randomized just as if they were a real stimulus events, but during which no stimulus actually occurs (Buckner et al., 1998; Burock et al., 1998). Because their occurrence is randomized in the sequence, on average they also contain the same overlap from adjacent trials as any other trial type. Assuming that the no-stim event does not evoke a response itself, its average therefore only reflects the summated response overlap from adjacent trials. Thus, a contrast between the no-stim average and the average for the other trial types will subtract out the overlap, revealing the full hemodynamic response functions to these other trial types. This overlap subtraction method makes it therefore possible to assess the time courses of the BOLD signal to individual trial types, rather than just the differential activity between two stimulus types.

A critical assumption in this approach, however, is that the no-stim trials do indeed not elicit any systematic brain response. However, human electroencephalographic (EEG) and magnetoencephalographic (MEG) studies have described an endogenous event-related brain response, termed the omitted stimulus response (OSR), that is evoked by the absence of an expected stimulus in a regular sequence of events (e.g., visual, Barlow, 1969; somatosensory, Klinke et al., 1968; auditory, Sutton et al., 1967). If this brain response were consistently elicited by no-stim events in an event-related fMRI experiment, the final averages of the relevant event types would be contaminated with the *inverse* (i.e., the *negative*) of the hemodynamic equivalent of the OSR after using the no-stim subtraction approach.

In the auditory domain the OSR has been reported as consisting of a broad positive wave with a peak latency of 380–520 ms and an amplitude of about 6–12 μV when the omitted stimuli were task relevant (e.g., Hamon et al., 1989; Simson et al., 1976; Stapleton et al., 1987; Tarkka and Stokic, 1998). Even when subjects are engaged in a different task and do not pay attention to the omissions, an OSR is still produced, although the onset and peak of the response are delayed and its amplitude is significantly reduced (Decker and Weber, 1976). Hamon et al. (1989) report a frontocentral preponderance of the OSR, although more posterior distributions have been shown (Simson et al., 1976). In some OSR experiments, an earlier-latency negative wave peaking at about 200 ms and preceding the later positivity has also been found (Karamüsel and Bullock, 2000; Klinke et al., 1986). Comparing studies of the OSR in the visual modality to the results mentioned above reveals that similar OSRs are also elicited in visual paradigms (Bullock et al., 1994; Rogers et al., 1992). However, some differences in latency and distribution of the components have also been shown (Simson et al., 1976).

In most of the omitted stimulus experiments that have been reported, the percentage of missing stimuli has been set to around 10% of the total amount of stimuli. This proportion seems apt to generate the OSR because the omissions violate a strong expectancy of the regularly occurring tone. In contrast, larger omission percentages would lead to sequences with open periods (i.e., those with no stimuli occurring) of various lengths, which tend to make the presentation sequence just seem temporally jittered; intuitively, they would therefore seem less likely to produce OSRs. Accordingly, in some previous fast-rate event-related fMRI studies using no-stim trials, the proportion of no-stims has been set at 25% or more, perhaps in part to mitigate the likelihood of such responses (e.g., Buckner et al., 1998; Burock et al., 1998; Konishi et al., 2000; Koutstaal et al., 2001; Vandenberghe et al., 2001; Wagner et al., 1998). However, it remains unclear if this percentage is really appropriate to avoid any systematic responses to the null event or, for that matter, just what an appropriate minimum percentage might be. Furthermore, it is also not known what effect the SOA might have, although intuitively one might expect these effects to be larger at shorter SOAs because of the greater likelihood of the percept of a violation of a regular temporal pattern.

The present experiment uses high-density ERP recordings (i.e., recordings from a high number of scalp sites) to investigate the influence of percentage of omitted stimuli and the overall stimulus rate on eliciting an OSR in the EEG. Rates of presentation of auditory stimuli were either one per second or one per 2 s. The latter SOA corresponds to the rates used in most fast-rate event-related fMRI experiments, whereas the former rate has typically been used in the omitted stimulus experiments. Including the 1-s SOA condition therefore makes comparisons to previous literature possible and also allows us to investigate the implications for future fMRI paradigms that will make use of very rapid stimulus presentation. We hypothesized that smaller percentages of omitted stimuli and shorter SOAs would increase the OSR amplitude as well as its likelihood of being elicited. In contrast to most OSR experiments, we had the omitted stimulus be irrelevant to the subject’s task, just as no-stims are meant to be irrelevant in a fast-rate event-related fMRI experiment.

Materials and methods

Subjects

Eighteen subjects (7 men, 11 women) with a mean age of 23 years participated in the experiment. All gave their written informed consent for taking part in the experiment. Subjects either were paid or received university class credits for their participation. Four of these subjects were excluded from the analysis because more than half of their trials were rejected because of physiological artifacts such as eye blinks, eye movements, or muscle activity.

Stimuli and task

Series of auditory tone pips were delivered binaurally via headphones to the subjects, with 11% of a deviant (oddball) pitch (1480 Hz) in a train of standard tones (pitch of 1400 Hz). Both tone types had a duration of 50 ms, including a 15-ms rise and fall period. The standard and target tone pips were randomly intermixed with no-stim events (omitted stimuli), which were of different percentages in different runs. To best approximate typical fMRI experiments, the presented stimuli were attended, with the task to detect the occasional oddball tones. Thus, the omitted stimuli in the stream of auditory stimuli were irrelevant to the subject's task, just as null events would be in a fMRI experiment. In different runs, three different percentages of omitted stimuli/null events (11, 22, and 33%) and two different SOAs (1 and 2 s, constant within a run) were used, resulting in six run conditions. The absolute numbers of omitted stimuli were 81, 90, and 108 for the different percentages, respectively. Because we expected the OSR to be smaller with increasing percentage of omitted stimuli the number of trials was slightly increased for the conditions of 22 and 33%. The amplitude of the standard and target stimuli was set at 60 db SL (i.e., 60 db above individual sensation-level threshold, which was determined at the beginning of the session for each subject).

The stimuli within each condition were first-order counterbalanced—that is, each stimulus type was preceded and followed by each other type equally often. This corresponds directly to the randomization procedure important for fast-rate event-related fMRI experiments. The first-order counterbalancing was performed for each subject individually. The trials were divided into single runs that lasted between 2.5 and 3.0 min each. At the beginning of each run a 100-ms auditory warning signal was delivered, and the same signal marked the end of the run. The order of the runs was randomized between subjects.

Subjects were instructed to sit still and to keep their eyes fixated on a marked point in front of them while they performed the auditory target detection task. They indicated the occurrence of the deviant target tones by pressing a button with their right hand. Reaction times and accuracy of the responses to the targets were recorded for all the runs. The subjects were naive regarding the purpose of the experiment and the occurrence of omitted stimuli.

ERP recordings

The EEG was recorded from 64 electrodes in an elastic cap (Electro-Cap International, Inc., Eaton, OH) and referenced to the right mastoid during recording. Electrode impedances were maintained below 2 kΩ for the mastoids, below 10 kΩ for the facial electrodes, and below 5 kΩ for all the remaining electrodes. Horizontal eye movements were monitored by two electrodes at the outer canthi of the eyes, and vertical eye movements and eye blinks were detected by two electrodes placed below the orbital ridge of each eye. During recording, eye movements were additionally monitored by using a video zoom lens camera. The EEG recording acquisition system was Neuroscan SynAmps (Neuroscan, El Paso, TX). The 64 channels were recorded with a bandpass filter of 0.05 to 100 Hz and a gain of 500. The raw signal was continuously digitized with a sampling rate of 500 Hz. Recordings took place in an electrically shielded, sound-attenuated chamber. The experiment was conducted in dim light.

Data analysis

Artifact rejection was performed off-line by discarding epochs of the EEG that were contaminated by eye movements, eye blinks, excessive muscle-related potentials, drifts, or amplifier blocking. Averages were calculated for the different stimulus types from 1000 ms before to 1200 ms after stimulus onset. ERPs for the OSRs were obtained by averaging of the EEG epochs time-locked to the point in time that a stimulus would have occurred had it not been omitted. The averages were digitally low-pass filtered to reduce frequencies at and above 60 Hz. After averaging all channels were re-referenced to the algebraic average of the two mastoid electrodes. The ERP averages for the individual subjects were grand averaged across subjects, and statistical analyses across subjects were performed of the mean amplitude across various latency windows, relative to a 100-ms prestimulus baseline. Separately for the omitted-stimulus ERP in each condition, one-sided t tests against zero were calculated to assess the presence of the OSR in the different conditions. Additionally, responses were evaluated with two-way repeated-measures analyses of variance (ANOVA) with the factors percentage of omitted stimuli (11, 22, and 33%) and rate of presentation (one event/1 s, one event/2 s). Significance levels were adjusted with the Greenhouser–Geisser correction when appropriate. However, the original degrees of freedom are reported for each analysis.

Mean values for each subject's reaction times (RT) for correct detections of targets, hit rate (HR), and false alarm rate (FA) were computed separately for the different conditions. Only behavioral responses that occurred within 1000 ms of target presentation were counted as correct target detections. Two-way ANOVAs were performed on these behavioral measures, with the factors of omitted-stimulus percentage and presentation rate.

Table 1
Behavioral data: reaction times for correct detections (RT for hits), hit rates (HR), and the ratio of false alarms (FA) for the six experimental conditions

Condition	RT for hits (ms)	HR (% possible hits)	FA (% standards)
11%, 1 s	508	83.1	0.7
11%, 2 s	595	83.5	1.8
22%, 1 s	549	80.9	1.1
22%, 2 s	592	78.1	1.3
33%, 1 s	558	78.6	1.2
33%, 2 s	604	79.3	2.3

Results

Behavioral data

As Table 1 shows, subjects performed faster in conditions with shorter SOAs (ANOVA on RT, main effect of SOA, $F(1,13) = 76.1$, $P < 0.001$). The ANOVA on hit rates revealed a main effect for percentage of omitted stimuli ($F(2,26) = 5.471$, $P < 0.05$) with a higher detection rate for targets in conditions with lower percentages of omitted stimuli. Performing an ANOVA on false alarm rates did not yield any significant main effects or interactions.

ERPs to standard and target stimuli

The auditory evoked responses to the standards were composed of a scalp-negative, frontocentrally maximal, N1 wave at ~100 ms and a scalp-positive, centrally maximal P2 wave at ~200 ms, as typically found for auditory stimuli. As expected, the target tones elicited—in addition to these earlier auditory sensory evoked responses—a strong late-positive wave (P3b) in each of the conditions, largest over parietocentral scalp. The distribution of voltages for the P3b to targets is shown in Fig. 1.

ERPs to the omitted stimuli

We first confirmed that artifact rejection did not distort the original counterbalanced distribution of the different stimulus types in the various conditions. Table 2 shows the percentage of preceding stimulus types for the omitted stimuli after artifact rejection in each condition. The results indicate that the originál counterbalancing was preserved even after the rejection of trials contaminated by artifacts.

Fig. 2 shows superimposed averaged waveforms for standard tones and omitted stimuli in the six conditions at a midline frontal (Channel 3) and midline parietal (Channel 37) electrode site. These electrodes approximately correspond to the standard locations FCz and Pz of the International 10–20 System. While the typical auditory N1 and P2 exogenous components seen for the standards are absent for the omitted stimuli, the effects of an omitted stimulus can easily be observed in some of the conditions, manifested most prominently in the positive deflection starting around 350 ms after expected stimulus onset. This late positive wave appeared to be maximal over electrode site 3 (FCz). A small negative deflection preceding the positive wave can also be seen over the more posterior electrode site 37 (Pz) in the earlier time interval of 180–280 ms after expected stimulus onset.

Late positive OSR

Fig. 3 shows the scalp voltage topographies for the late-positive OSR in the six different conditions. Note that the response distributions look comparable for all the conditions in which an observable OSR was elicited, namely in all the 1-s SOA conditions and in the 11% omitted, 2-s SOA condition. These positive potentials appeared most prominently around frontocentral midline electrodes. In contrast, the corresponding topographic maps for the time-locked averages to the omissions in the remaining two 2-s SOA conditions (i.e., those with 22 and 33% omissions) did not reveal any systematic distribution, consistent with their lack of significant activity.

To statistically assess the presence of significant OSRs, we calculated one-sided *t* tests against zero on the mean amplitudes. We performed these analyses across the whole window from 300 to 700 ms, as well as for multiple consecutive 100-ms intervals. The longer time interval was included because of the relevance of this work with respect to fMRI studies where the temporal resolution is much lower than in electrophysiological techniques. Because the temporal resolution of fMRI lies rather in the range of seconds than in milliseconds a broad extended response with a lower amplitude might contribute as much to a fMRI signal as a well-defined shorter response with a higher amplitude.

The *t* test against zero for the whole analysis window revealed the same pattern as observed in the analyses for the individual 100-ms intervals: over the whole time 300- to 700-ms interval the waveforms were significantly different from zero in each of the conditions with the 1-s SOA and in the 11% omitted stimuli, 2-s SOA condition ($t(13) > 3.79$, $P < 0.0011$ in each of the cases), whereas they did not reach

Table 2
Percentage of preceding stimulus type for omitted stimuli after artifact rejection

Condition	Omitted	Standards	Targets
11%, 1 s	11.3	76.6	11.1
11%, 2 s	10.6	77.5	10.9
22%, 1 s	22.4	67.6	10.0
22%, 2 s	20.8	67.0	12.2
33%, 1 s	34.6	55.4	10.0
33%, 2 s	30.7	57.9	11.4

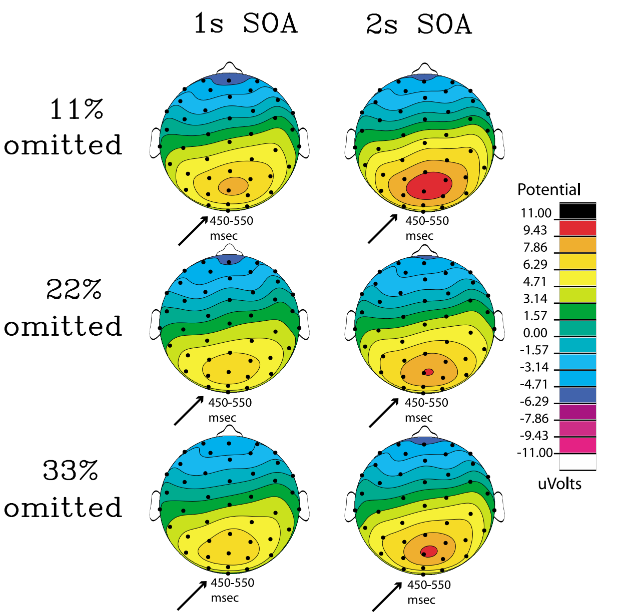


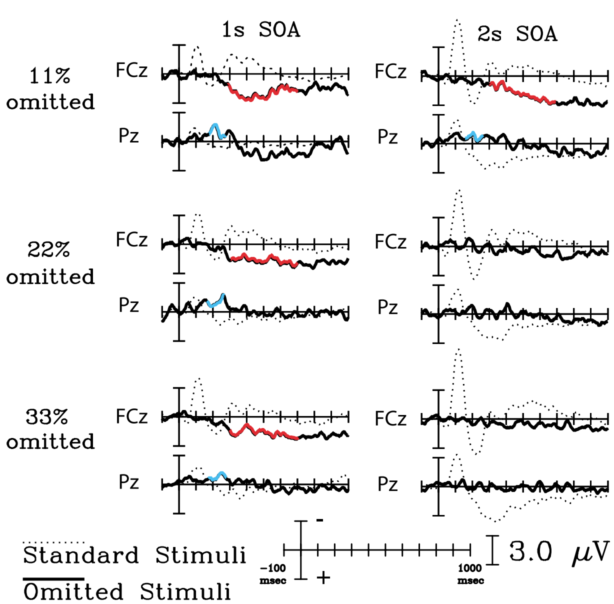
Fig. 1. Topographic plots of the P300 elicited by the targets for each of the conditions in the time window from 450 to 550 ms. The maximum and minimum of the plot scale is ±11.0 μV. The arrows point toward the parietal maximum of the P3b.

significance for the two remaining percentages of the 2-s SOA condition (22% omitted stimuli, $t(13) = 1.41$, $P = 0.09$; 33% omitted stimuli, $t(13) = 1.35$, $P = 0.10$).

A repeated-measures ANOVA with the factors percentage of omitted stimuli and SOA across the whole time interval yielded a significant main effect of SOA ($F(1,13) = 10.99$, $P = 0.0056$) with responses in the 1-s SOA condition being larger than those in the 2-s SOA. The main effect of percentage of omitted stimuli and the interaction between percentage of omitted stimuli and SOA did not reach significance in this global analysis ($F(2,26) = 2.52$, $P = 0.1288$; and $F(2,26) = 2.51$, $P = 0.1067$, respectively). Dividing the analysis time into consecutive 100-ms intervals yielded the main effect of SOA for the first three windows (300–400, 400–500, and 500–600 ms; F value between 6.61 and 17.3, P value between 0.023 and 0.0011), with the activity being larger for the 1-s condition than for the 2-s one. In addition, for several of these windows a significant interaction between percentage of omitted stimuli and SOA was observed (500–600 ms, $F(2,26) = 4.01$, $P = 0.032$; 600–700 ms, $F(2,26) = 7.18$, $P = 0.0034$). Analyzing individual 100-ms time windows for only the 1-s SOA condition (in which an OSR was elicited in each case) a main effect of percentage of omitted stimuli was found for 400–500 ms with smaller percentages yielding larger OSRs ($F(2,26) = 3.90$, $P = 0.06$). The mean amplitudes for the collapsed time windows are shown in Fig. 4.

Early negative OSR

The topographic maps for the average voltages of this early negative OSR in the different conditions are shown in



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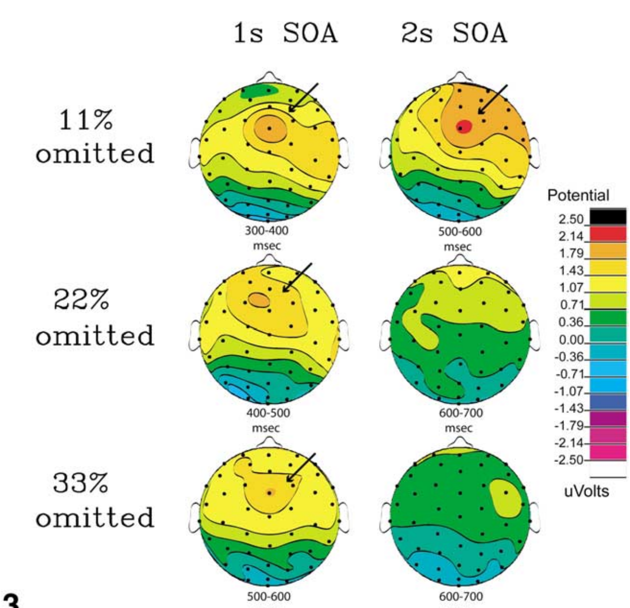

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Fig. 2. Grand average waveforms to standards (dotted line) and omitted stimuli (solid line) at electrode locations FCz and Pz. The time window from -100 to 1000 ms is shown. Significant omitted stimulus response (OSR) activity is marked in color (early parietal negativity, blue; late anterior positivity, red).

Fig. 3. Topographic plots of the late anterior positivity of the omitted stimulus response. Time windows were chosen to achieve an optimal representation of the response in the different conditions. Because of different time courses of the response these intervals differed across the conditions. The scaling for the topographic maps is set to be the same across the different conditions (±2.5 μV). The arrows point toward the frontocentral focus of the significant OSR responses.

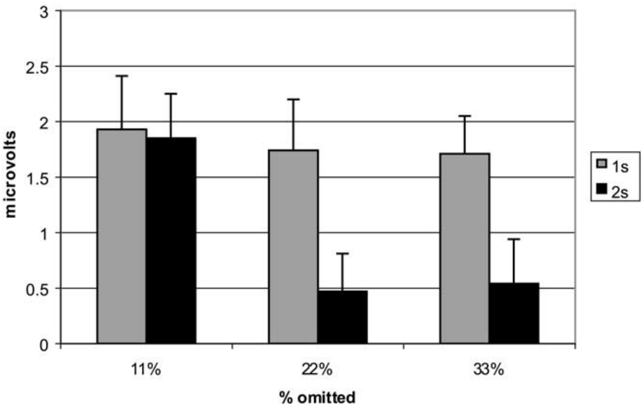

Fig. 4. Magnitudes of the late anterior OSR positivity at electrode Cz. Displayed are the mean amplitudes in microvolts (±SE) across the collapsed time windows from 300 to 700 ms.

Fig. 5. This early negative wave to the omitted stimuli was largest over parietal scalp and was statistically assessed at Electrode 37 (Pz). One-sided t tests for mean amplitudes in the interval from 180 to 280 ms after expected stimulus onset time yielded significant results for each of the 1-s SOA conditions (11%, $t(13) = -2.18$, $P = 0.02$; 22%, $t(13) = -3.23$, $P = 0.0033$; 33%, $t(13) = -1.92$, $P = 0.038$). For the SOA of 2 s the only significant negative-wave response was again for the 11% omitted stimuli condition ($t(13) = -2.26$, $P = 0.02$), while responses for the 22 and 33% percentages at 2-s SOAs were not significantly different from zero ($t(13) = -0.85$, $P = 0.21$; and $t(13) = 0.14$, $P = 0.44$, respectively).

The ANOVA for this time interval revealed a main effect for SOA ($F(1,13) = 6.16$, $P = 0.028$) where the mean negative amplitude for the 1-s condition was -1.0 μV while it only reached -0.31 μV in the 2-s SOA condition.

Discussion

In this study, we investigated the electrophysiological responses to different percentages of task-irrelevant omitted stimuli in a regular sequence of tone pips delivered at two different SOAs. This was assessed by time-locked signal averaging of the EEG to the expected onset of the stimuli.

Discussion of the OSR

Statistical comparison of mean amplitudes of the OSR against zero revealed significant activity in all percentages (11, 22, and 33%) at the faster rate (one per second), as well as in the 11% omitted, 2-s SOA condition. In each of these comparisons an early negative component in the time window from 180 to 280 ms after stimulus onset was observed, followed by a larger, longer-latency, positive wave with a broader time course. These components of the OSR have previously been reported in the literature (e.g., negative component, Simson et al., 1976; Karamüsel and Bullock, 2000; Klinke et al., 1968; positive component, e.g., Decker and Weber, 1976; Hamon et al., 1989; Karamüsel and Bullock, 2000; Tarkka and Stokic, 1998; Simson et al., 1976). The data therefore suggest that an endogenous response to an omitted stimulus is present even if the percentage of omitted stimuli is as high as 33%, at least at a constant SOA of 1 s. However, when the SOA is increased to 2 s the OSR is only elicited for fairly low percentages of omitted stimuli (11%). These results seem to confirm our hypothesis that smaller percentages of omitted stimuli and a faster rate of presentation would increase the OSR.

One could argue that some of these results, especially in those conditions with higher percentages of omitted stimuli, could have derived from a biased artifact rejection procedure. More specifically, it might have been the case that subjects were more likely to move or to blink during the silent period of a row of consecutive stimulus omissions (which will occur more often at higher omitted-stimulus percentages) than during single omitted stimuli following a standard or target. In addition, it might have been the case that omitted stimulus trials preceded by other omitted stimulus trials would have been less likely to elicit an OSR than would isolated omitted trials. Thus, if these had been rejected in a disproportionately high rate, the average OSR in these conditions might have been artifactually inflated. However, this possibility is ruled out by the fact that even after artifact rejection the averages of omitted stimuli were

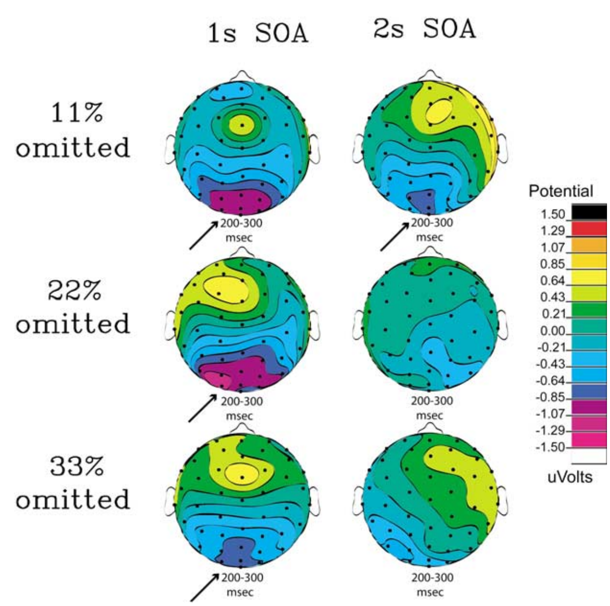

Fig. 5. Topographic plots of the early parietal negativity of the omitted stimulus response. Average voltages for the time interval between 180 and 280 ms. The scaling of the voltages is constant for the different conditions (±1.5 μV). The arrows point toward the maximum of the negative component in the conditions with significant OSR.

still composed of the same proportion of different stimuli types comparable to the original counterbalanced design.

The amplitudes of the OSR in the present study were generally smaller than most of those described in the literature. For example, Simson et al. (1976) reported a negative deflection with a peak voltage of 7.5 μV and a subsequent positive wave peaking at 12 μV while the most prominent responses in our experiment barely reached 3 μV. However, most of the experiments reported in the literature involved an *active detection* of the omissions. In those designs subjects were explicitly informed about the stimulus omissions and the omissions were the task-relevant targets that the subjects were asked to detect. In contrast, as in a typical fMRI experiment that has no-stim events embedded to facilitate overlap removal, in our experiment subjects were engaged in a different task (the detection of the deviant-pitch target stimuli) and were not explicitly informed about the significance either of the regular pattern of tones or of the stimulus omissions. When comparing responses in an active condition (e.g., counting of omissions) versus a non-active condition (e.g., reading a book) a significant reduction in amplitude has previously been observed for the OSR (Decker and Weber, 1976; Joutsiniemi and Hari, 1989; Raij et al., 1997).

Thus, the larger amplitudes in previously reported studies in which the omitted stimulus was the task-relevant stimulus (i.e., the "target") can be accounted for by the fact that the brain response in those conditions was likely to be confounded by the addition of target-related activity, including the large-amplitude late positivity known as the P3b. Similar to the positive component of the OSR, the P3b is generated by a violation of expectancy and consists of a long-latency potential peaking between 250 and 500 ms (e.g., Sutton et al., 1965). However, a key characteristic of the P3b is that it is elicited after an active detection of a relevant target. Because our task involved the detection of an infrequent target *other* than the omission itself, we are able to directly contrast the voltage distribution of the target-related P3b to the pure positive component of the OSR (i.e., that is not confounded by a target effect). A comparison of Figs. 1 and 3 clearly demonstrates that the distribution of the P3b shows the typical posterior–parietal focus for this component, while the positive component of the OSR is maximal over more frontocentral electrode sites. The large difference implies that the OSR is probably not a low-amplitude version of the P3b but rather that these components reflect two distinct neural processes.

However, another late-positive wave, the P3a, is elicited for task irrelevant intermittent stimuli that are surprising or novel (Squires et al., 1975). The P3a has a more frontocentral distribution and is of smaller amplitude and shorter latency than the P3b (Friedman et al., 2001). This component is interpreted as a signature of involuntary attentional reorienting to unexpected irregularities in the stimulus environment (Schröger et al., 2000). Given these characteristics, the P3a and the positive part of the omitted stimulus response might be more likely to reflect a common process. However, direct experimental comparisons would be necessary to completely answer this question.

Considering the late-positive component, we found the most distinct responses in the 11%, 1-s SOA condition, whereas the response in the corresponding slow-rate condition appears to have a more smeared out pattern in time and a broader scalp distribution. In the timing literature the scalar property of interval timing is a well-studied phenomenon, namely that the standard deviation of the interval being timed grows proportionally to the mean of the interval (Gibbon, 1977; Matell and Meck, 2000). A broader latency in the 2-s SOA conditions thus could be attributed to a variation in time estimation that would lead to a greater temporal variability in the OSR and consequently to a lower amplitude and later peak in the averaged signal (Ruchkin and Sutton, 1978).

We also found higher mean voltages of the positive wave for the lower than for the higher percentage of omitted stimuli in the 1-s SOA condition (400–500 ms), and in the 2-s SOA condition we only found a significant OSR at the smallest omission percentage (11%). The most probable explanation for this percentage effect here is that at smaller omission percentages the omissions are more likely to be perceived as a violation of a regular temporal pattern, whereas at large percentages (with more omissions in succession and long breaks between a few stimuli) the percept might tend more toward being that the stimulus presentation is just temporally jittered.

Discussion of the implications for fast-rate event-related fMRI designs

The percentage of omitted stimuli used for overlap removal in fast-rate fMRI designs has been set to values from 25% to 33% (e.g., Buckner et al., 1998; Burock et al., 1998; Konishi et al., 2000; Koutstaal et al., 2001; Vandenberghe et al., 2001; Wagner et al., 1998). According to our data, these values seem to be well suited to not evoke a response for SOAs of 2 s or more. However, lowering the percentage of null events to gain more trials in the conditions of interest or to reduce the total scanner session time holds a substantial risk of introducing the inverse of the no-stimulus response in the data. Thus, at the constant SOA of 2 s that is often used in fast-rate fMRI studies we would not recommend using no-stim percentages that are less than 22%. For experiments with shorter constant SOAs, it seems to be the case that even in designs with one-third omitted stimuli significant brain activity might be evoked by the no-stimulus events.

One possible solution to avoid the OSR to the no-stimulus events would therefore be to increase the number of omitted stimuli to a fairly high value, such as 50%. With such a high percentage of randomly interspersed omitted stimuli it is harder for the system to perceive a regular rhythm and to generate a precisely timed expectation about the next stimulus occurrence. However, this approach would have the disadvantage of resulting in longer run times and/or a fewer number of trials. Both parameters are critical in event-related fMRI, especially since recording time is restricted and expensive, as well as tiring for subjects.

An alternative manipulation that we would propose to fully attenuate the OSR even at shorter SOAs would be to jitter the SOA of all event types, *including the no-stims*, in a range around a mean value. The lack of precise rhythm would increase the uncertainty of the expected stimulus occurrence that would presumably lead to a severe reduction in the OSR. McCarthy and Donchin (1976) showed that temporal uncertainty reduces the P300 amplitude at central electrode sites in an auditory paradigm. More directly related, evidence for the elimination of the OSR by jittering the SOA has been shown by Bullock et al. (1994) in a visual OSR paradigm and by Karamüsel and Bullock (2000) using auditory stimulation. Thus, it seems likely that temporally jittering the stimulus presentation would be beneficial to avoid a systematic response to no-stims in fast-rate event-related fMRI paradigms. This approach might have the advantage of allowing for a relatively low percentage of no-stims and/or enabling the use of very short SOAs without eliciting an OSR. In addition, besides the possible elimination of the OSR, the jittering of the stimulus occurrence relative to a constant TR (MR scan repetition time) has been shown to have the additional advantage of providing a higher effective sampling of the hemodynamic response (Josephs et al., 1997). Behavioral results in our laboratory indicate that jittering eliminates the percept of the omitted stimulus, and our preliminary electrophysiological results also suggest that the OSR brain response to the missing stimuli is eliminated as well. However, whether jittering the SOAs would fully abolish the OSR to no-stim events, and how wide the SOA jitter would need to be, remains to be tested experimentally.

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