

Responses of Human Auditory Association Cortex to the Omission of an Expected Acoustic Event

H. C. Hughes,* T. M. Darcey,† H. I. Barkan,‡ P. D. Williamson,† D. W. Roberts,§ and C. H. Aslin*

*Program in Cognitive Neuroscience, Dartmouth College and Medical School; *Department of Psychological and Brain Sciences and †Thayer School of Engineering, Dartmouth College, Hanover, New Hampshire 03755; and ‡Section of Neurology and §Section of Neurosurgery, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire 03756*

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Unexpected auditory events initiate a complex set of event-related potentials (ERPs) that vary in their latency and anatomical localization. Such “mismatch” responses include active responses to the omission of an expected event or the omission of elements in expected stimulus composites. Here we describe intracranial recordings of middle-latency ERPs elicited by the omission of an auditory event. We first presented a sequence of tones at regular temporal intervals and the tone was omitted 20% of the time. In a second condition, we presented a sequence of tone pairs and the second tone of the pair was omitted 20% of the time. These two conditions are complementary in that the single tone conformed to the expectancy in one condition, but violated the expectancy in the other. All patients demonstrated localized cortical responses to missing tones that were topographically similar to the responses evoked by actual tones. Responses to both actual and omitted tones were observed bilaterally in the vicinity of the temporal-parietal junction, where we also obtained midlatency ERPs to a variety of other auditory stimuli. Responses that appeared to be selective for the nonoccurrence of expected tones were also observed in a number of subjects. We interpret these effects in terms of processes associated with the comparison of sensory inputs to the contents of a short-term auditory memory. Such a system could automatically detect deviant auditory events, and provide input to higher-level, task-dependent cognitive processes. © 2001 Academic Press

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INTRODUCTION

The efficient classification and processing of the continuous stream of stimuli our sensory systems routinely encounter requires neural processes which can

rapidly evaluate the potential significance of individual events. Behaviorally important events often differ from the sensory background in some way and are therefore correlated with change of one sort or another. As a result, even the most primitive sensory systems are very adept at detecting changes in complex spatio-temporal patterns of input. Lateral inhibition is a ubiquitous form of synaptic circuitry that acts to accentuate spatial differences in activity that occur across an array of neurons. Recurrent feedback inhibition appears to perform a similar role in identifying temporal contours and transients. Such “transient” neurons are found at early levels of most sensory pathways and are associated with efficient detection of stimulus onsets and offsets (Tolhurst, 1975; Burbeck and Luce, 1982).

However, detection of change within a sequence of temporally discrete events is presumably a more complex process. First, detecting changes in discrete events requires spanning the temporal interval between the events. The neural systems involved must create a neural representation of the event that can be retained for some interval of time—that is to say, a rapid and flexible form of sensory memory. If the change is manifest as a deviation from a recently established pattern, the relative probabilities of different events must also be incorporated in these stored representations. That is, the system must be able to use the recent past to generate estimates of the relative probabilities of future events. We shall refer to this process of estimating probabilities as the generation of an expectancy. The evaluation of a current event in the context of the recent past could then proceed using mechanisms that were sensitive to a difference between the stored representation of recent events with the neural representation of the present event. What form might these neural representations take?

A first principle of sensory physiology is that discriminable stimuli evoke different spatiotemporal patterns of activity within the corresponding afferent pathway. If different events evoke different patterns of neural activity, then the retrieval of the sensory mem-

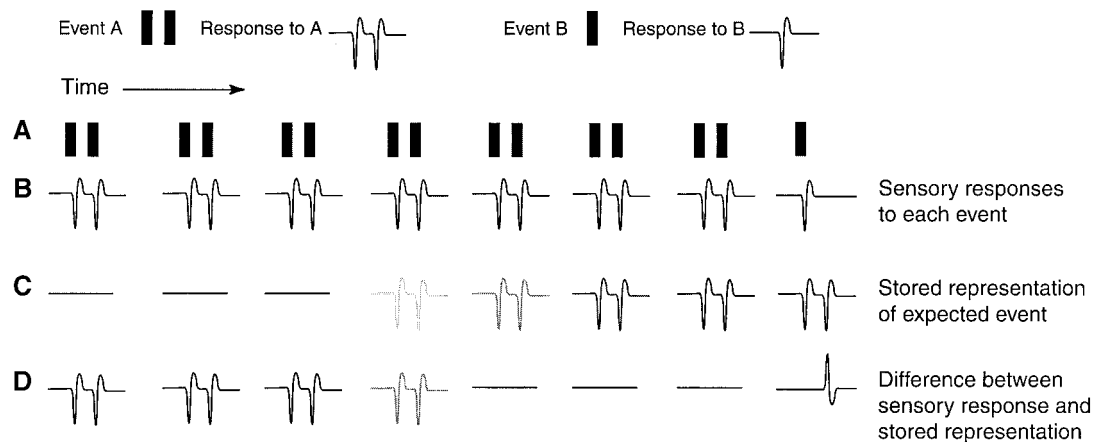


FIG. 1. Hypothetical responses that one would expect to observe at some stage in a system that holds a stored representation of expected or high probability events and detects the occurrence of unexpected or low probability events. In the present study, the high probability event was a pair of tones ($P = 0.8$) and the low probability event was a single tone ($P = 0.2$). Row A represents the stimulus sequence. Row B consists of obligatory sensory responses that follow the stimulus (referred to as veridical responses in this paper). Row C consists of responses based on a memory trace of the expected stimulus. This memory must develop over the course of several repeated presentations, and that process is schematized by the gradual darkening of the hypothetical responses. Row D consists of responses that are selective to the occurrence of an unexpected stimulus. Since this difference depends on that state of the memory trace schematized in Row C, transitions in the mismatch responses are also indicated by gray level.

ory for an expected event might be accomplished by reactivating a pattern of activity that is similar to the pattern evoked by the event itself. If recent events created the expectancy for a particular stimulus, the contents of this "sensory memory" might contain a pattern similar to that produced by the expected event. The occurrence of the next event might not only evoke activity that corresponds to the current event, but might also invoke the stored pattern associated with the expected event. A comparison between these two responses (via subtraction, for instance) could then be used to determine whether the current event was expected or was "different." According to this view, the detection of change or a violation of expectancy occurs when there is a mismatch between the representations of the current event and the stored representation of the expected event (see Fig. 1). Similar ideas have been discussed and incorporated in models of auditory change detection published by Näätänen (1992), Schröger (1997), and others.

A great deal of evidence suggests that operations not unlike those hypothesized above occur in human neocortex. For instance, the mismatch negativity (MMN) is a difference potential (expected response–deviant response) that has many of these expected characteristics. The MMN is triggered by a stimulus event that violates the prevailing pattern of inputs. Usually, the deviant event is in the auditory modality. The auditory MMN appears about 100–150 ms after stimulus onset and peaks between 200 and 250 ms (e.g., Näätänen, 1992). The MMN clearly depends on a short-lived sensory memory, which appears to last about 6 s (Mäntysalo and Näätänen, 1987). The MMN is triggered by

virtually any auditory event that deviates from the prevailing pattern, and appears to reflect preattentive, task-independent processes (e.g., Näätänen, 1992). Dipole analyses (Scherg *et al.*, 1989), intracranial recordings (Kropotov *et al.*, 1995; Halgren *et al.*, 1995a,b), and MEG studies (Hari *et al.*, 1992) suggest that the MMN consists of two distinguishable components—a "preconscious" sensory-specific component originating in the auditory cortices and a later component originating in the frontal lobes (Näätänen and Michie, 1979; Näätänen, 1992).

As suggested by Näätänen (1992), many manifestations of the MMN could depend on decreases in the responsiveness of the afferent elements that follow repeated presentations of the same stimulus. However, reports of mismatch responses to the partial or total omission of an expected event cannot be explained in these terms (e.g., Nordby *et al.*, 1994; Winkler *et al.*, 1996; Raij *et al.*, 1997). An active response to an omitted stimulus appears to require endogenous sources, such as the retrieval of a stored representation of the expected event (see Fig. 1; also see Näätänen, 1992; Schröger, 1997). The results of such an analysis could then initiate a sequence of events related to orienting and the allocation of attentional resources. The electrophysiological correlate of these later effects is called the P300, which is a task-dependent, supramodal complex of responses that begins at least 300 ms after the occurrence of a novel or unexpected event (e.g., Polich *et al.*, 1995).

In this paper, we describe middle-latency (80–150 ms) MMN-like intracranial field potentials that appear to reflect two components of the auditory processes

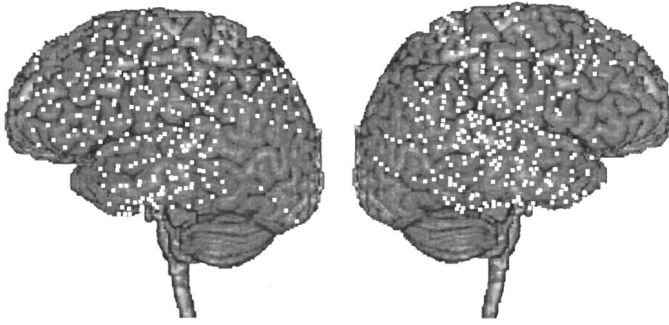


FIG. 2. Composite showing 584 neocortical subdural recording sites in the 10 patients studied. The individual electrodes were localized following implant using CT coregistered and fused with MRI (Darcey *et al.*, 1996). Additional depth and interhemispheric electrodes used in several patients are not shown. Although statistically reliable responses were obtained in many of these sites, the extrema of the responses as determined by analysis of the potential distributions was confined to the areas indicated in Fig. 10.

schematically illustrated in Fig. 1. First, we identify cortical sites that respond to both the occurrence of an acoustic event as well as the omission of an expected acoustic event (a partial omission procedure). Second, we identify cortical sites that do not respond to auditory stimuli, but generate robust responses to the omission of an acoustic event that was expected. We hypothesize that the first class of responses reflects the activation of a sensory memory trace for the expected event by the unexpected (non)event. We further hypothesize that the second type of response (selective responses to the mismatch) reflects the results of a comparison between the activated memory and the representation of the deviant event. These findings provide a compelling example of purely endogenous activity in intermediate stages of sensory processing.

MATERIALS AND METHODS

Patient Population

The experiments were performed at the bedside in epileptic patients implanted with intracranial electrodes as part of their diagnostic workup for chronic seizures that are not adequately controlled by medications. The purpose of electrode implantation is to record spontaneous seizures for localization of the epileptic focus when this cannot be done by non-invasive methods. In some cases critical functional areas that might overlap the seizure focus were mapped by delivering electrical currents through the electrodes. Based on the outcomes of these procedures, treatment by surgical resection may then be performed.

This report is based on 10 patients (9 male, 1 female; average age 36 years, range 25–52; average full-scale IQ = 93, range 76–112) and a grand total of 584 neocortical recording sites (276 left hemisphere, 308 right hemisphere). As illustrated in Fig. 2, our recordings

included an extensive sampling of sites within the temporal, parietal, and frontal lobes. Although many patients also had electrodes implanted in medial temporal structures including the hippocampus, those results are not discussed in the present paper. Four of the patients had bilateral cortical implants. In two patients, the initial implants were clinically inconclusive, and these patients underwent a second implant procedure. Both of these patients were tested following each of their implants. Seven of the 10 patients were implanted with at least one 4×8 subdural grid assembly (1 cm on center contact spacing), which made it possible for us to construct isopotential contour plots of the recorded responses.

Five of the 10 patients had MRI lesions and the remaining 5 had normal MRIs. These lesions included one case each of the following: right temporal encephalomalacia, right temporal gliotic scar, right occipital porencephalic cyst, left sensorimotor cavernous angioma, and left insular cortical dysplasia. All but the last were pathologically confirmed from resected tissue. Two patients had previous standard temporal lobe resections (which include the anterior temporal lobe and hippocampus) and a third patient had a previously resected cavernous hemangioma in the posterior temporal lobe. The intracranial diagnosis determined the following foci for seizures: 2 frontal, 1 parietal, 5 temporal, 1 occipital, and 1 multifocal. Of the 10 patients, 8 eventually had resections. The effects in this report did not depend on any of the known differences between patients—including the presence or absence of a lesion, the site of seizure origin, or the integrity of the anterior and mesial temporal lobe. None of the patients had any obvious auditory or language dysfunctions.

Recording Methods

The recordings were carried out over a 7- to 10-day period while the patients were under constant video/EEG monitoring. The EEG monitoring equipment is capable of digitizing up to 128 channels at 200 Hz with an analog bandpass of 0.3 to 70 Hz. Our recordings made use of this system without interrupting clinical monitoring. For each experimental procedure (described below), referential EEG recordings (linked mastoid reference) were captured to disk files and average ERP waveforms were obtained off-line using conventional signal averaging methods. The electrode locations were localized after implant using CT coregistered and fused with MRI (Darcey *et al.*, 1996). The exact electrode configuration in each patient was determined entirely by clinical criteria (the suspected location of the seizure focus). However, it was frequently necessary to sample the temporal neocortex in at least one hemisphere, which allowed us to obtain the data presented here. Our institutional human subject internal review board has approved all the experimen-

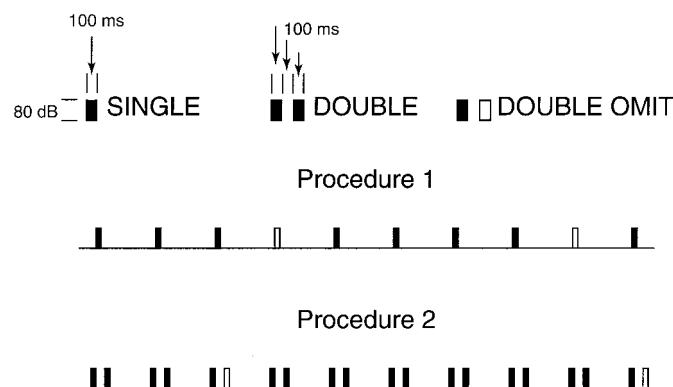


FIG. 3. Illustration of the two tone sequences and stimulus nomenclature used in this study. Note that the SINGLE and DOUBLE OMIT conditions are identical except for their relative probability in the two sequences.

tal protocols used in this report, and patients were fully briefed concerning the details of the experiments before being asked to sign an informed consent.

Stimuli and Experimental Procedures

These experiments employed two complementary procedures, which are schematically illustrated in Fig. 3. In the first (Procedure 1), we presented a sequence of 1000 Hz tones (100 ms duration, 80 dB) at fixed temporal intervals (1200 ms inter-stimulus-interval [ISI]). The oddball in this case was the omission of the tone, and this occurred randomly with a probability of 0.2. In the second (Procedure 2), we used a tone pair (100 ms duration, separated by 100 ms (100 ms ISI)) as the frequent stimulus ($P = 0.8$) and a single tone (100 ms duration) as the oddball. Thus, in Procedure 1, listeners expected a single tone to occur at regular temporal intervals, and that expectancy was occasionally violated by presenting no tone at all. In Procedure 2, listeners expected a tone pair, and that expectancy was violated by the presentation of a single tone. The paradigms are complementary because the same stimulus that conformed to the expectancy in Procedure 1 violated the expectancy in Procedure 2. Taken together, the two procedures produced four different stimulus conditions. To simplify discussion of the results, we shall refer to the single tone in Procedure 1 as the SINGLE condition, and the omitted tone in Procedure 1 as the SINGLE OMIT condition. The frequent double-tone condition in Procedure 2 is referred to as the DOUBLE condition, whereas the infrequent single tone presentation in Procedure 2 is called the DOUBLE OMIT condition. Each of these four conditions was presented for a minimum of 50 trials.

Signal Extraction and Statistical Analyses

We first computed the time-locked average and variance for each electrode derivation as a function of time

and each of the four stimulus conditions. We then screened the recordings from each electrode derivation both visually and quantitatively for auditory responses and responses to omitted tones. These procedures yielded concordant results, although the quantitative technique tended to detect auditory and omit effects at more electrode sites. Subsequent potential distribution analysis made it clear that these additional detections were frequently the result of volume conduction to multiple electrode contacts.

To perform a quantitative analysis we began by defining three temporal intervals. The first interval consisted of the 200 ms epoch prior to stimulus onset. We refer to this interval as the BASELINE. The second interval corresponded to the 200 ms epoch following onset of the first tone. This is the time interval in which the initial responses in the SINGLE, DOUBLE, or DOUBLE OMIT conditions were expected, and is called INTERVAL1. The third interval corresponded to 200–500 ms following the onset of the first tone. This corresponded to the expected time of responses to the second tone in the DOUBLE condition (i.e., the 300 ms following the onset of the second tone) and is referred to as INTERVAL2. These temporal intervals and their relationships to the various stimulus conditions are illustrated in Fig. 4. In the following we refer to various types of “responsiveness” detectable at electrode sites. In doing so we wish to emphasize that this terminology does not imply that the recording of a response at a particular derivation indicates that the source of this response directly underlies that electrode. We are well aware that in this situation one is always measuring field potentials that arise via volume conduction from

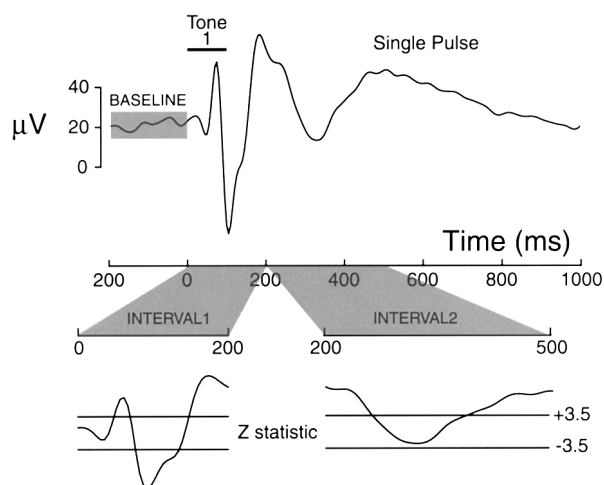


FIG. 4. Quantitative method for detecting auditory responsiveness by statistical comparison to baseline in the time interval following each stimulus. INTERVAL1 is the 200 ms following the first 100 ms duration tone at time 0, while INTERVAL2 is the 300 ms following the second (present or missing) tone at time 200 ms. This example shows auditory responsiveness in both intervals for the SINGLE condition (a single 100 ms tone with $P = 0.8$).

cortical source(s) that may be near or far from a particular recording electrode and that issues of source localization would depend on distributional analyses. Indeed, the topographic findings that we present in this report indicate that volume conduction plays a major role in the apparent dispersion of sites at which we find "responsiveness" to actual and omitted tones.

Evaluation of Auditory Responsiveness

After computing the mean and variance for each channel as a separate function of time and stimulus condition, we computed the grand mean and variance for the BASELINE interval. Next, the mean and variance associated with each time sample through INTERVAL1 and INTERVAL2 were compared to this BASELINE mean and variance using the z statistic (corrected for unequal n and unequal variances). We then found the peak of the resulting z score waveform in both INTERVAL1 and INTERVAL2. Z scores greater than ± 3.5 were considered significant deviations from baseline.

Significant deviations within INTERVAL1 were taken as evidence of a response to the first tone in the SINGLE, DOUBLE, and DOUBLE OMIT conditions, and also permitted us to evaluate possible responses during the SINGLE OMIT condition. Similarly, significant deviations within INTERVAL2 were taken as evidence for a response to the second tone in the DOUBLE condition or a response to the omission of the second tone in the DOUBLE OMIT condition. An illustration of this procedure is provided in Fig. 4.

Evaluation of DOUBLE OMIT Responses

A preliminary examination of the recordings obtained in the SINGLE, DOUBLE, and DOUBLE OMIT conditions indicated that a variety of sites demonstrated an incremental response in INTERVAL2 to the omission of the second tone in the DOUBLE OMIT condition. This response was typically as large or larger than the response seen in INTERVAL2 to the actual second tone in the DOUBLE condition. The DOUBLE OMIT response was quantified by doing a point-by-point statistical comparison (again corrected for unequal n and unequal variances) between the SINGLE and DOUBLE OMIT as well as between the SINGLE and DOUBLE responses. The statistical confirmation procedure is illustrated in Fig. 5A. An electrode was identified as having a significant response to the omission of the second tone in the DOUBLE OMIT condition if (1) there were significant auditory responses in INTERVAL1 for the SINGLE, DOUBLE, and DOUBLE OMIT conditions, and (2) there were significant differences between the SINGLE and DOUBLE OMIT, as well as the SINGLE and DOUBLE conditions in INTERVAL2. Fig. 5A shows an example of an electrode meeting these criteria.

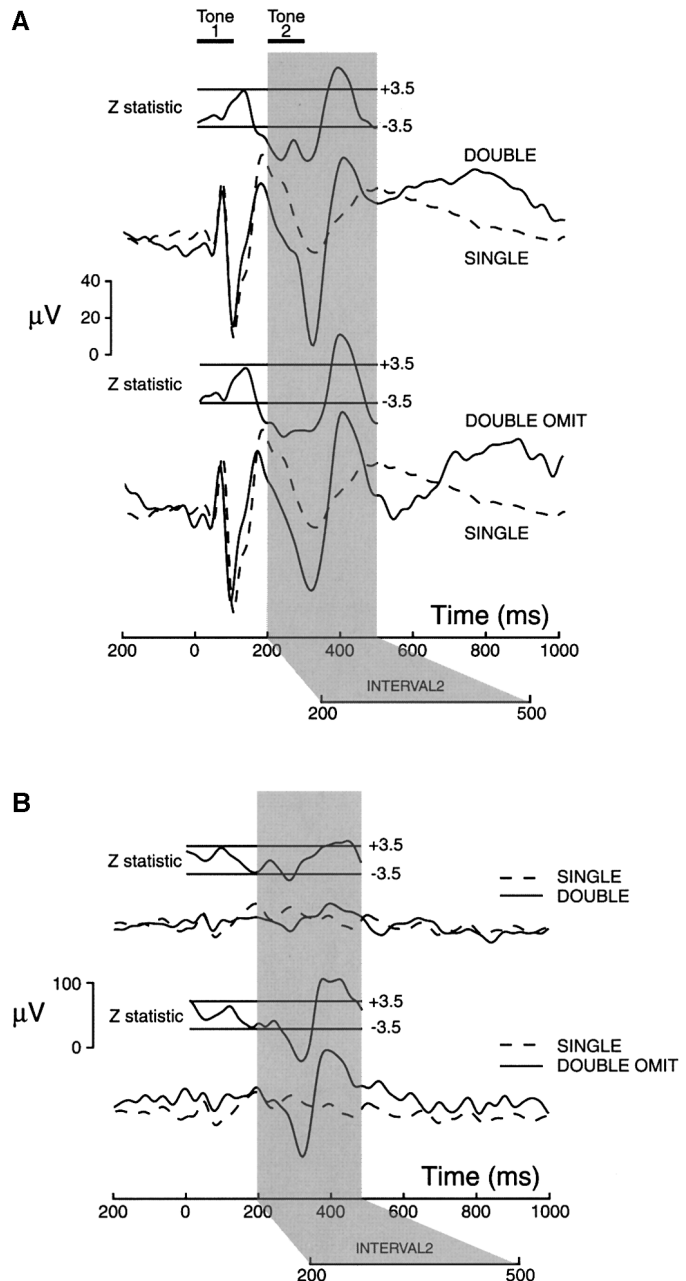


FIG. 5. Quantitative statistical method for detecting omit and selective omit responses, showing examples of each type of omit response. (A) An omit response was detected if there was auditory responsiveness (Fig. 4) to the SINGLE, DOUBLE, and DOUBLE OMIT stimulus conditions in INTERVAL1, and a statistically significant incremental response in INTERVAL2 for the DOUBLE and DOUBLE OMIT conditions relative to the SINGLE condition. (B) A selective omit response was detected if there was no auditory responsiveness and only a response in INTERVAL2 for the DOUBLE OMIT condition.

Evaluation of Selective Responses to Stimulus Omission

Preliminary informal examination also revealed cortical sites that seemed to respond selectively to the

omission of an expected tone. A response that is selective to stimulus omission could reflect the output of the hypothesized comparison process schematized in Fig. 1. A truly selective response to stimulus omission would *not* display a significant response in INTERVAL1 for any stimulus condition (i.e., SINGLE, DOUBLE, or DOUBLE OMIT), but would display a significant response in INTERVAL2 for the DOUBLE OMIT condition only. Figure 5B illustrates our statistical confirmation procedure in an electrode that exhibits a selective response to stimulus omission.

Evaluation of Veridical Auditory Responses

In the present context, we define a veridical response as one that follows the time course of the physical stimulus and is not sensitive to stimulus omissions. The present analysis is capable of detecting veridical responses in each of the three relevant conditions (SINGLE, DOUBLE, and DOUBLE OMIT). Thus, for instance, a cortical site producing a veridical response would generate similar responses in the SINGLE and the DOUBLE OMIT conditions and would display significant deviations in both INTERVAL1 and INTERVAL2 in the DOUBLE condition. As described more fully in the Results, we failed to detect these responses, but assume they must exist somewhere within the auditory pathways.

RESULTS

Responses to a variety of auditory stimuli were obtained from the temporal-parietal junction in all 10 patients. This region was sampled unilaterally in six patients and bilaterally in four patients. Two patients with bilateral implants also had subsequent unilateral grid implants to achieve greater precision in localizing the focus of their seizures.

In each patient, we also found clear cortical responses to the expected missing tones in addition to responses to the actual tones. This effect was observed in both hemispheres and was obtained bilaterally in patients with bilateral implants. These responses typically included a focus in the vicinity of the posterior temporal-parietal junction. Contour mapping in patients with grid implants revealed very consistent topography within subjects, but a high degree of topographic variability between subjects.

We also observed responses that appeared to be selective for the nonoccurrence of the expected tones. Neither type of omit response appeared to be task dependent. In general we focused on the SINGLE, DOUBLE, and DOUBLE OMIT conditions, since the SINGLE OMIT condition tended to produce responses that were dispersed in time due to the lack of a time reference.

Response Timing

Sites in the vicinity of the temporal-parietal junction were typically responsive to the tone stimuli, with initial deflections to the first tone as early as 50 ms from tone onset, but generally peaking at 90–150 ms. Typical early and middle latency responses for the SINGLE condition are shown for a variety of patients and electrode sites in Fig. 6. These sites were also typically responsive to a second expected tone (DOUBLE condition) and to an omitted second tone (DOUBLE OMIT condition). Figure 7 provides examples of responses from a variety of patients and electrode sites in the DOUBLE and DOUBLE OMIT conditions. Note that all the sites shown in Fig. 7 also had significant responses in the SINGLE condition. Significant responses were also recorded from electrodes located at some distance from the temporal-parietal junction (e.g., patients L.P., M.B., P.A., and A.W. in Figs. 6 and 7). In one instance (patient A.W., see Fig. 11) we were able to identify 2 distinct areas of auditory responsiveness: one in the temporal-parietal junction and another in the superior aspect of the prefrontal gyrus. These areas both demonstrated robust, but asynchronous omit responses, with the frontal response beginning some 40 ms earlier than the temporal-parietal.

Figure 8 summarizes the timing of responses in the different conditions across subjects. Although there was considerable latency variation across subjects, there were clear responses in INTERVAL1 for all three conditions, followed by distinct responses in INTERVAL2 for the DOUBLE and DOUBLE OMIT conditions. In the aggregate, the response to the first tone peaks at approximately 100 ms for all three conditions, whereas the response to the actual or omitted second tone peaks at approximately 300 ms (or 100 ms following the second tone).

Responses to Omitted Tones

We consistently found midlatency cortical responses to missing and actual tones at electrodes that met the criteria for auditory responsiveness described under Materials and Methods. We should note that these same electrodes also exhibited ERPs to a variety of auditory stimuli, including tones, chirps, and spoken words. Again, omit responses were defined by the presence of a significant difference in INTERVAL2 (the time interval following the scheduled time of the second tone) between the SINGLE and DOUBLE OMIT, as well as the SINGLE and DOUBLE conditions. These responses were manifested as positive or negative waves and were typically as large or larger than that seen in INTERVAL2 to the actual second tone in the DOUBLE condition. Figure 9 shows two examples meeting our criteria for an omit response in which the responses to the DOUBLE OMIT and DOUBLE conditions are comparable in INTERVAL2, while Fig. 12

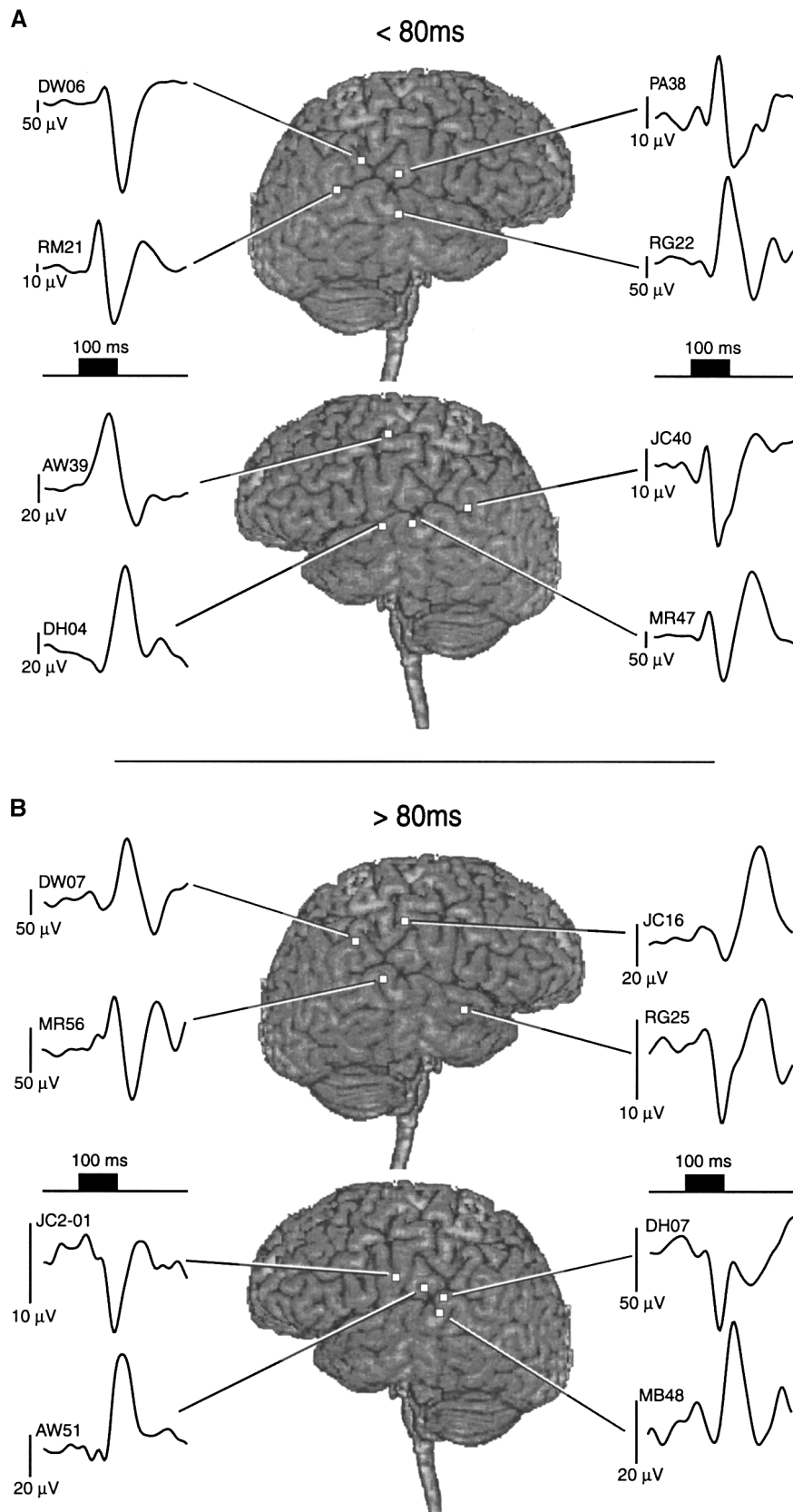


FIG. 6. Representative examples of early (<80 ms) and midlatency (>80 ms) auditory responses to frequent single tones (SINGLE condition). All these recordings passed the test described in Fig. 4 for auditory responsiveness. These and all waveforms in subsequent figures are plotted positive up.

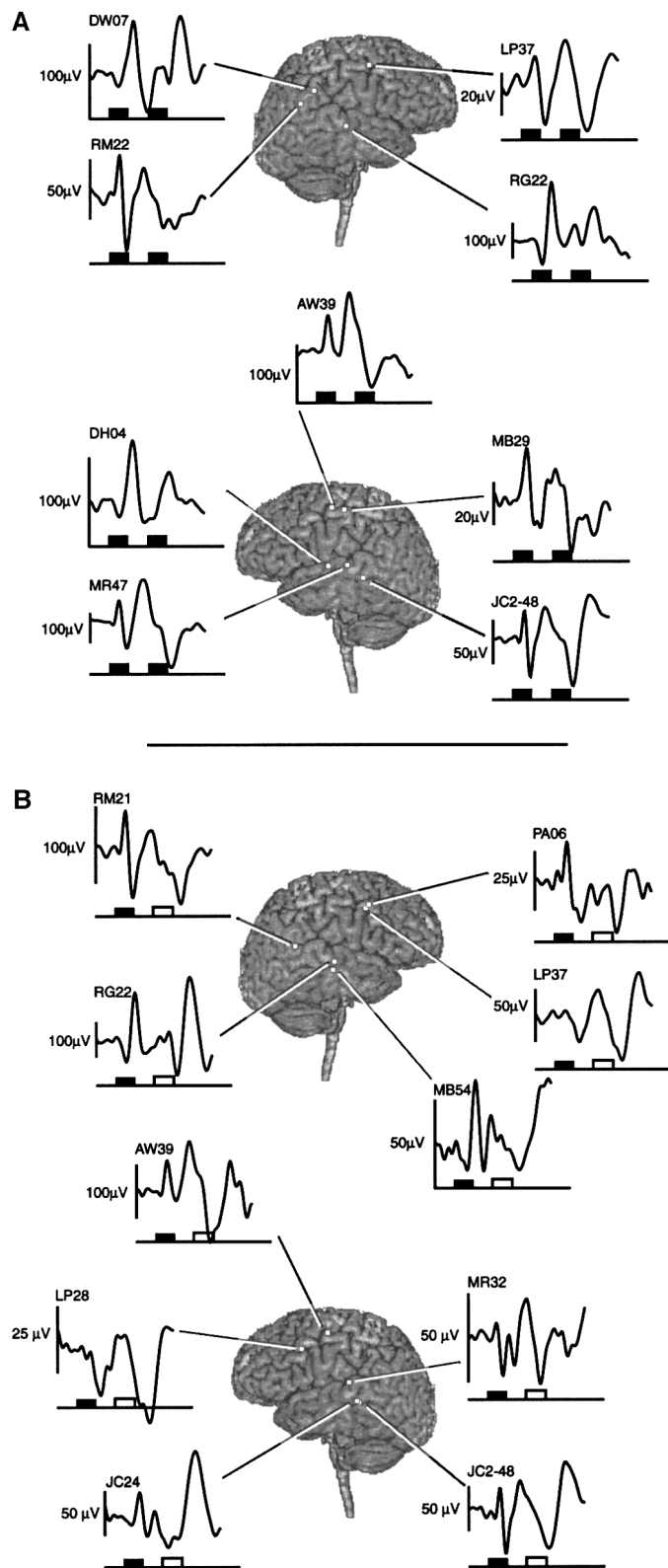


FIG. 7. Representative examples of auditory responses to (A) frequent tone pairs (DOUBLE condition) and (B) single tones when tone pairs are expected (DOUBLE OMIT condition).

(Channel 21) shows an example with an even larger response to the omitted second tone (DOUBLE OMIT condition) than to the actual second tone (DOUBLE condition). Figures 9 and 12 also illustrate the topography of these responses. As expected, the timing and topography of the responses for the SINGLE, DOUBLE, and DOUBLE OMIT conditions were very similar during INTERVAL1. The responses in the SINGLE and DOUBLE conditions differed substantially during INTERVAL2 and during this time the responses from the DOUBLE OMIT condition were similar to the DOUBLE condition even though the DOUBLE OMIT and SINGLE conditions presented physically identical stimuli.

The topographic similarities during INTERVAL2 for the DOUBLE and DOUBLE OMIT conditions suggests that similar source configurations are active in response to actual and missing tones. Although there was considerable intersubject variability in terms of focality, polarity, field orientation, and the locations of the extrema, the response topographies were relatively simple and the highest gradients were typically found in the immediate vicinity of the temporal-parietal junction. Figure 10 shows the locations of field extrema in those patients with electrode grids overlying the Sylvian fissure and/or the temporal lobes. In general, our topographic findings are indicative of superficial source generators in or near the posterior Sylvian fissure—tissue generally considered to be a component of auditory association cortex. However, responses were also obtained from electrodes in the parietal and frontal lobes, and in Pt A.W. (see Fig. 11) we obtained evidence for an additional generator in the superior aspect of the precentral gyrus that is clearly independent of the classically known auditory areas. In fact, stimulation of this site produced movements of the face, so this appears to be a case of an auditory field within the M1 face area. We should note that this patient had multiple cavernous angiomas in the sensorimotor area, so that this finding may be an instance of anatomical reorganization.

The omit effect was obtained near the temporal-parietal junction of both hemispheres, and there was no apparent relationship to handedness or speech dominance. The four patients with bilateral temporal-parietal implants (two 1×8 subdural strips in each hemisphere) all showed the omit effect simultaneously in both hemispheres.

Selective Responses to Omitted Tones

In half (5/10) the patients, we observed responses that appeared to be selective for the omitted second tone, i.e., there was little or no response to first or second tones, but a clear response during INTERVAL2 in the DOUBLE OMIT condition. Hence, there was no auditory responsiveness per se, but there was a re-

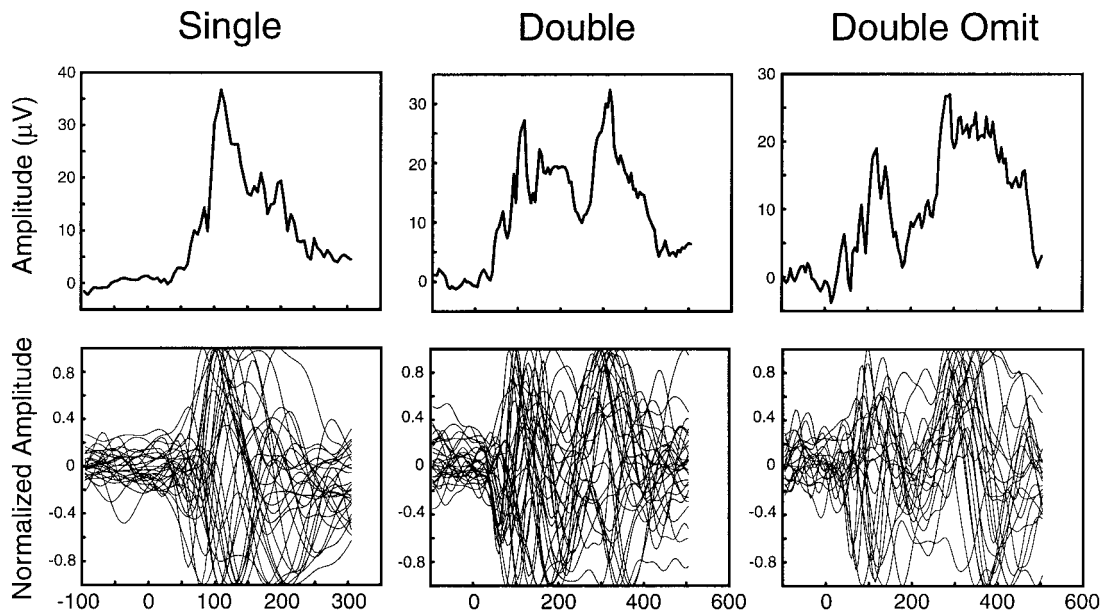


FIG. 8. Illustration of response timing for the SINGLE, DOUBLE, and DOUBLE OMIT conditions. The lower panels show normalized waveforms obtained from each subject in the vicinity of the temporal-parietal junction, while the upper panels show the absolute median waveforms calculated from the individual subjects. Although there was considerable variation in latency across subjects, there were clear responses in INTERVAL1 for all three conditions, followed by distinct responses in INTERVAL2 for the DOUBLE and DOUBLE OMIT conditions.

sponse to the omission of the tone. This is illustrated in Figs. 12 and 13, which show both types of omission response in two patients. These selective responses were observed to have foci that were spatially distinct from the omit responses. Their latency also varied across patients. These selective omission responses preceded the omit responses in some cases and followed it in others.

Veridical Responses

Surprisingly, we failed to find electrodes demonstrating veridical responses, i.e., obligatory responses only to actual tones and not to omitted tones.

Task Dependence

In four patients we compared the responses in both IGNORE (patient given no instructions other than to passively listen to the tones, called PASSIVE ATTEND by some authors) and COUNT (patient asked to silently count omitted tones and report the total afterwards) conditions. The intent of this difference in instructions was to evaluate whether active attention was a necessary condition for observing these effects. We found that attending to and/or counting the tones was clearly not necessary for the recording of either omit or selective omit responses, and had no systematic effect on the amplitude of either type of response in the middle latency range. This is illustrated in Fig. 14. Although it is not the focus of this paper, we did find

significant task dependent P3-like effects at longer latencies in the temporal lobe, hippocampus, and superior frontal lobe. Figure 14 provides what might be an example of a weak P3 in the temporal lobe (indicated by the asterisk).

DISCUSSION

Using a variant of the auditory oddball paradigm, we have recorded and characterized intracranial field potentials that are evoked by the omission of tones. Auditory responses were consistently recorded from cortex in the vicinity of the temporal-parietal junction, although similar responses were occasionally obtained from more remote sites, most commonly in the dorso-lateral aspect of frontal lobe.

Tone pairs produced two distinct responses that followed each tone by approximately 100 ms. Comparisons between the response to a single tone when tone pairs were expected (DOUBLE OMIT condition) and responses elicited by an identical tone when a single tone was expected (SINGLE condition) revealed that the field potentials were highly sensitive to context: a clear, incremental cortical response occurred about 120 ms following the omission of the second tone. This response was found in every patient, and it closely approximated the timing and topography of the response elicited when the second tone was actually presented (DOUBLE condition).

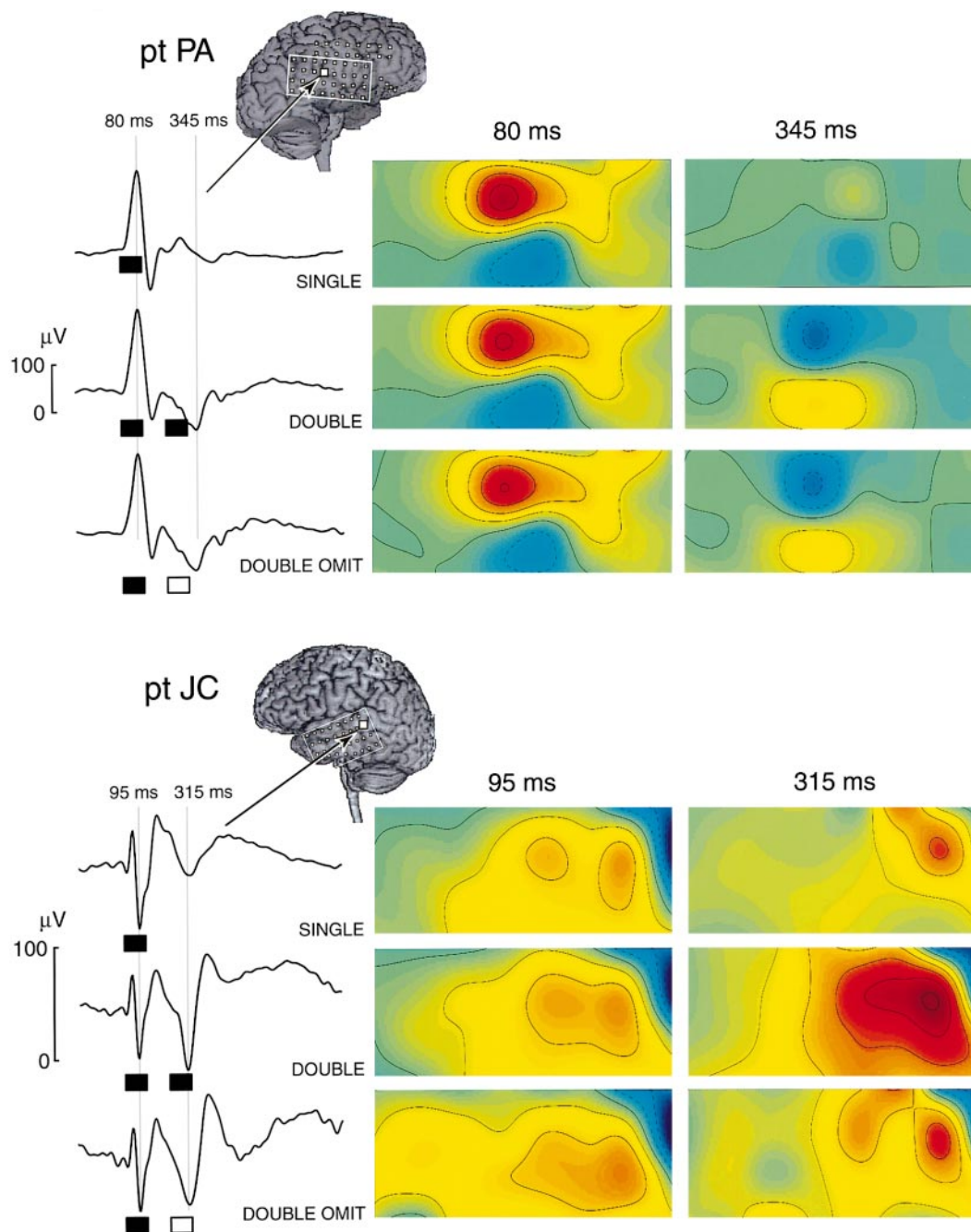


FIG. 9. Two examples of omit responses from patients with 4 x 8 subdural grid implants, including waveforms from a selected electrode in the vicinity of the temporal-parietal junction and isopotential contour maps at the indicated times in INTERVAL1 and INTERVAL2. For these and all subsequent contour plots, the contour interval is 20 μ V, negative values are indicated by dashed contour lines, red areas are positive and blue areas are negative.

In half the patients, we were also able to identify cortical sites that only reacted to the non-occurrence of expected tones. By definition, these selective omit responses were recorded at sites that demonstrated little or no response to the actual tones and therefore exhibited topographic features and timing that distin-

guished them from the omit responses produced at sites that were also responsive to the auditory stimuli. Surprisingly, we only found the aforementioned two types of omit response and were unable to record responses that seemed to merely follow the physical stimuli (veridical responses).

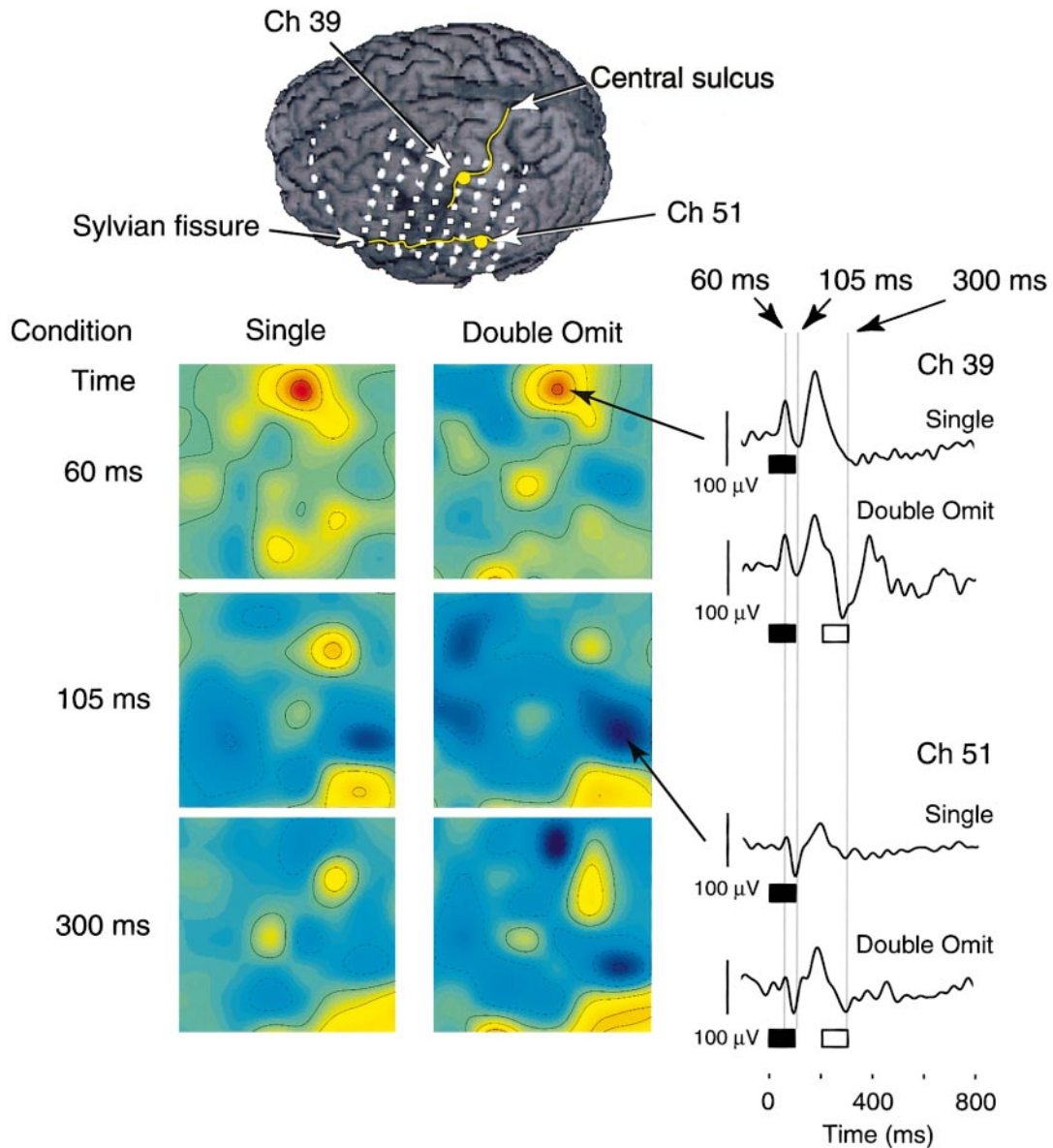


FIG. 11. Omit responses from a patient with an 8×8 subdural grid implant showing two foci of activity: one near the temporal–parietal junction (channel 51) and another in the sensorimotor cortex (channel 39).

Source Considerations

We have not yet performed a formal quantitative source analysis of these intracranial field data, so the following inferences are primarily qualitative, although they are based on the biophysics of source and field behavior (e.g., Vaughan, 1974; Darcey, 1979). The most consistent topographic feature of these data (Figs. 9–13) is the finding of field extrema and maximum voltage gradients for both the auditory and auditory omit responses in the vicinity of the temporal–parietal junction. The high degree of intrasubject stability in topography (shape and extrema locations) is indicative of a stable generator configuration, while the high degree of intersubject variability in topography reflects

the fact that different sulci and/or gyri are engaged in each individual. We found fields with primarily tangential (Figs. 9 and 11) or radial (Figs. 12 and 13) orientations, which are reflective of generators located within cortical sulci and gyri, respectively (Vaughan, 1974).

Given a homogenous sphere approximation to the volume-conducting brain tissue under the electrode grid (which is embedded in a nonconducting silastic sheet), one can estimate the maximum depth of an equivalent single dipole source for the auditory and auditory omit responses from the spatial characteristics of their recorded voltage extrema (Darcey, 1979). In the present data, the extrema are no more than 2 cm

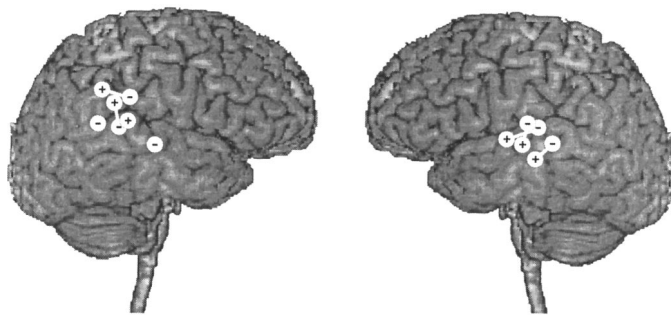


FIG. 10. Schematic summary of topographic extrema (derived from 8 cases in which at least one 4x8 subdural electrode was recorded from) found in the vicinity of the temporal-parietal junction for the frequent single tone (SINGLE) condition at approximately 100 ms following the onset of the tone in INTERVAL1. Linked + and - symbols indicate the locations of paired maxima and minima (that covary together over time, i.e., tangential distributions), while isolated + or - symbols indicate the locations of an unpaired maxima or minima (i.e., radial distributions). For each patient, these extrema locations were consistently the same for all 3 conditions in INTERVAL1, and for the DOUBLE and DOUBLE OMIT conditions in INTERVAL2.

apart in the fields with tangential orientations (Figs. 9 and 11). Similarly, the half-amplitude half-widths of fields with radial orientations (Figs. 12 and 13) are not greater than 2 cm. Based on these figures, we estimate that 1.3 cm is the *maximum* depth of the equivalent single dipole source for the radial fields, and 0.9 cm is the *maximum* depth for the tangential fields. We take this as a conservative upper limit of the source depth, since an extended best-fit (radial cap) dipole layer would always be more superficial than a single best-fit dipole (Vaughan, 1974; Darcey, 1979). Thus, both the auditory and auditory omit field potentials are compatible with at least one superficial generator in or near the posterior end of the Sylvian fissure.

Since these are very conservative estimates, we think it is unlikely that any of these potentials originated from the primary auditory cortex (A1) which typically lies deeper within the Sylvian fissure than our maximum source depth estimations and should consistently produce a field with a tangential orientation. The conclusion that these potentials do not originate from A1 is also compatible with our observation that electrical stimulation (systematic mapping with brief electrical currents is a standard clinical procedure performed in all of our grid patients) of sites in the vicinity of the posterior temporal-parietal junction never elicited auditory hallucinations that are reportedly induced by stimulation of A1. In fact, the only effects that were observed when the aforementioned temporal-parietal sites were stimulated electrically were disruptions of speech comprehension when the stimulation was applied to language dominant hemisphere (i.e., Wernicke's Area). The above considerations suggest that these responses originate from cor-

tical fields within classically defined auditory association cortex (which typically overlaps Wernicke's Area in the dominant hemisphere).

The evidence for a second generator process was strongest in those 5 of 10 patients in whom the selective omit response could be seen in isolation. In those cases, the sharp extrema suggest that the generator of this response was quite superficial (estimated at no more than 0.5 cm from the surface using the same logic outlined above), and tended to lie inferior (e.g., Fig. 12; 340 vs 400 ms) or anterior/inferior (e.g., Fig. 13; 380 ms) to the focus of the auditory activity. Interestingly, the dipole source analysis of grand averaged scalp data reported by Scherg *et al.* (1989) suggested that the MMN was composed of two distinct but partially overlapping neural generators, including a tangential generator in the bank of the Sylvian fissure and a radial generator located at a more anterior site in the lateral temporal lobe. That analysis is confirmed and extended by the present results.

Although we expect to find additional generators beyond those we attribute to temporal-parietal area and the anterior temporal lobe, we think it is premature to discuss generator considerations for sensorimotor field data such as we show in Fig. 11, since we have insufficient cases to know if this is a general finding and not an isolated instance of reorganization.

Theoretical Significance: Monitoring for Change

Along with many others (e.g., Näätänen, 1992; Schröger, 1997; Knight, 1996; Alain *et al.*, 1998; Koch and Poggio, 1999), we have cast these effects within a specific conceptual framework that emphasizes the need for sensory systems to rapidly classify a given stimulus as being either the "same" or "different" with respect to the prevailing stream of stimulus events. In keeping with this reasoning, we suggested that such a system might have three component operations (see Fig. 1). First, it must possess a rapidly formed and highly plastic form of memory that constitutes the neural representation of the "frequent" events. An efficient monitoring system designed to detect change must also accurately represent the current stimulus, regardless of whether it is "same" or "different," "prevalent" or "infrequent." Deviant stimuli could then be detected via a comparison between the representations of the current stimulus and the memory trace for the stimulus that has been prevalent in the recent past.

The present findings appear to provide evidence for two of the three component processes. What we have called auditory omit responses are really auditory responses whose topography in space and time resemble the response to the expected double tone stimulus more than the response to the presented single tone stimulus. Such responses fit the requirements of a stored

neural representation of the prevailing stimulus—a cortical model of what will happen next. We hypothesize that this system operates in the following way. A stored representation is created by the repetitive presentation of the same stimulus. Once formed, this stored representation is evoked (or to use a familiar term from memory research—retrieved) by the next event. When a single tone is embedded in a sequence of tone pairs, the single tone evokes the representation of the tone pair that was expected, producing what we have called an auditory omit response.

We further hypothesize that the responses we have called selective omit responses represent the output of the change detection process itself—the mismatch (difference) between the sensory response to the current event and the stored representation of the expected event.

Our patients can readily count the number of unexpected events, so they clearly discriminate between the single and double tones irrespective of the context in which they are presented. That discrimination implies that their auditory systems produced veridical representations of the actual stimulus events that were context-independent. It is therefore puzzling that we did not record veridical sensory responses (responses that follow the stimulus rather than the context). The failure to observe such responses is not attributable to the poor resolution of the recordings, because the recordings readily distinguish between SINGLE and DOUBLE auditory pulses.

It is possible that the auditory omit responses contain a mixture of veridical sensory responses and purely endogenous, context-dependent responses that summate to produce the appearance of an omit response in conjunction with auditory activity. However, we feel the interpretation of three distinct processes is the more plausible explanation, since it is consistent with the isolated responses that were specific to stimulus omissions that were observed in one-half of this group of patients. Thus we think the most likely explanation is that veridical responses occur somewhere within the auditory pathways, but that they occur outside the region we have been able to sample in the present series of patients.

Relationship to Previous Findings

The presentation of a novel auditory stimulus or one that deviates in some way from the prevailing sequence produces a negative potential in scalp recordings called the Mismatch Negativity (MMN). It is usually illustrated as a difference wave (ERP to deviant stimulus – ERP to standard). The MMN is regarded as an electrical manifestation of automatic, preattentive, task-independent processes associated with the processing of novel or infrequent events (e.g., Näätänen, 1992). In other studies (not reported here) using para-

digms that are known to produce an MMN, we have frequently observed differences in the intracranial ERPs evoked by infrequent and frequent stimuli. These differences appear around 100 ms—the same latency range as the MMN. While we cannot be sure without performing simultaneous intracranial and surface recordings, it appears that the present findings and the MMN are closely related phenomena. Whereas previous studies have shown that the omission of one component of a compound stimulus produces an MMN-like response (Nordby *et al.*, 1994; Raji *et al.*, 1997), we are unaware of any previous reports of an MMN-like response evoked by the complete omission of an auditory event.

Source analyses of scalp recordings of the MMN suggested the neural generator lies in the region of the Sylvian fissure (Scherg *et al.*, 1989), a suggestion supported by recent fMRI results (Opitz *et al.*, 1999) and intracranial recordings (Kropotov *et al.*, 1995; Halgren *et al.*, 1995a,b). The present results are consistent with those suggestions, but also indicate that the topography of these responses demonstrates a high degree of variability between individuals. Inverse dipole modeling of source localization based on grand average scalp recordings (Scherg *et al.*, 1989) have raised the possibility that the generator of the MMN may be spatially or temporally distinct from the generator(s) of the auditory responses. The present data are pertinent to this issue, because they suggest that one type of omission response (the one that occurs at acoustically sensitive sites) can have a topography that is very similar to the auditory responses recorded at those same sites (patients P.A. and J.C., Fig. 9; patient R.G., Fig. 13). At the same time, selective omit responses (those that are not accompanied by a well-defined auditory response) display a topography that differs from the auditory response—that is how we found them. The impression one gets from the present data is that, while these effects are observed in all individuals, the cortical generators might not be in homologous areas in every individual. These change detecting processes may therefore be a cortical function that is localizable, but whose exact location demonstrates fairly substantial individual differences.

The present observations expand upon a growing body of evidence suggesting that cortical tissue in the general vicinity of the temporal–parietal junction has the ability to rapidly form a template or cortical model of high-probability events, and it can store those events for a period of several seconds (Winkler *et al.*, 1996). The presentation of the next stimulus evokes this stored template, and the neural response to the current stimulus is compared with the stored representation. When these two representations differ, a mismatch response occurs, and this response is transmitted to a

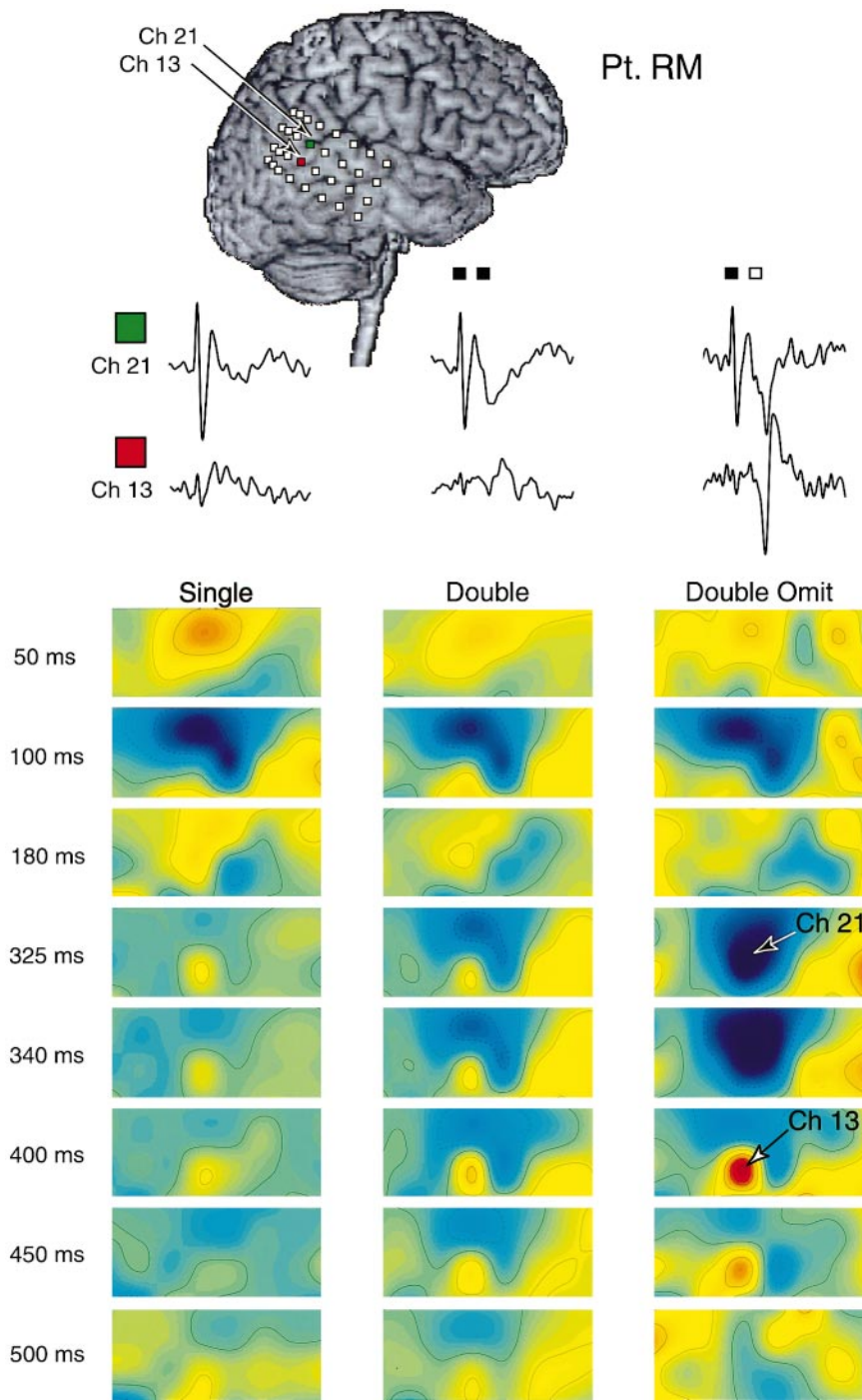


FIG. 12. Example of omit (channel 21) and selective omit (channel 13) responses occurring in the same patient, including waveforms and isopotential contour maps at the indicated times spanning INTERVAL1 and INTERVAL2, with the omit response peaking at approximately 340 ms and the selective omit response peaking at approximately 400 ms.

distributed neural system that includes the hippocampus in addition to cortical areas within the parietal, temporal, and frontal lobes.

One of the intriguing features of the present findings is that responses to stimulus omissions provide us with

an unmasked view of the stored template for an expected event because they are elicited in silence. We feel the temporal precision revealed in the present recordings is one of their most notable traits, and this precision may correspond in important ways to a vari-

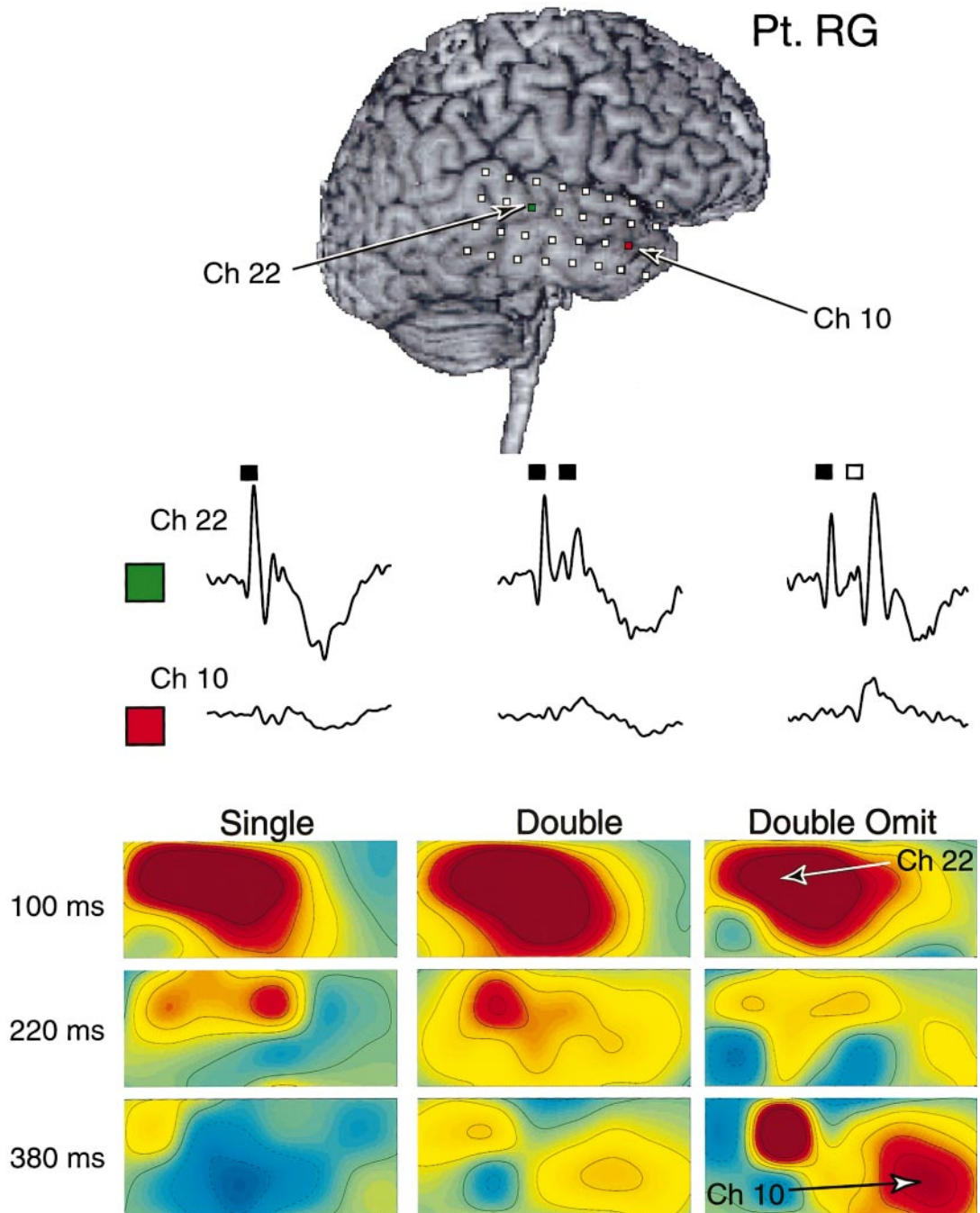


FIG. 13. Example of omit (channel 22) and selective omit (channel 10) responses occurring in the same patient, including waveforms and isotemporal contour maps at the indicated times from INTERVAL1 and INTERVAL2, with both types of response peaking at approximately 380 ms.

ety of perceptual skills that emphasize the timing of events. Recent theoretical efforts have tried to develop notions as to what types of processes might underlie and control the dynamic properties of expectancies and attention over time (Large and Jones, 1999). The goal of this work is to model the results of psychophysical studies of perception of rhythmic patterns and to ac-

count for the fact that specific types of perturbations are perceived as variations in a pattern rather than a change in the actual rhythm. The present findings suggest that intracranial recordings provide a potentially unique opportunity to help identify the neural substrates that control the dynamics of expectancies over time.

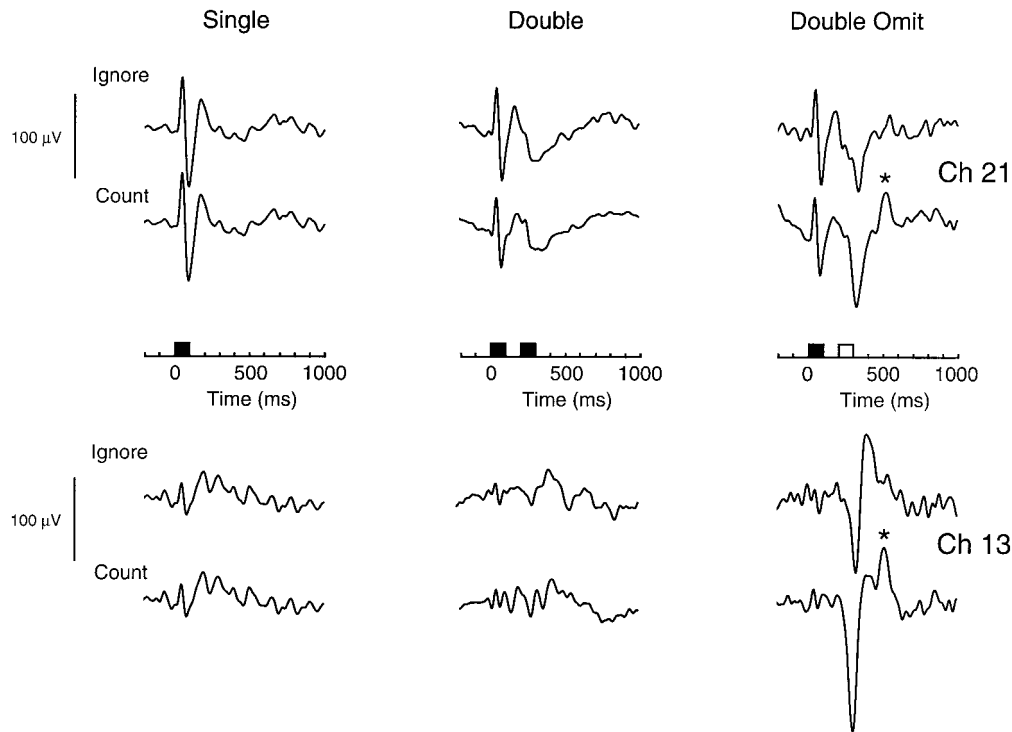


FIG. 14. Comparison of omit (channel 21) and selective omit (channel 13) responses under ignore and count conditions, illustrating the lack of clear task dependence in these responses. The electrode locations are shown in Fig. 12.

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