On the neural generators of the P300: evidence from temporal lobectomy patients

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The P300 is the most widely studied cognitive component of the event-related brain potential (ERP). Thus, when Halgren et al. (1980) found potentials in anterior medial temporal lobe (MTL) structures that behaved like the scalp-recorded P300, this was of great interest to ERP researchers. Identification of the brain structures responsible for generating the P300 will contribute to a clearer understanding of the still unresolved issue of its functional significance (Donchin and Coles 1988; Verleger 1988; Johnson 1993). As subsequent studies confirmed Halgren et al.'s initial findings (Squires et al. 1983; Wood et al. 1984; Halgren et al. 1986; Meador et al. 1987; McCarthy et al. 1989; Puce et al. 1989; Paller et al. 1992), experiments were undertaken to determine whether this intracranial MTL activity was responsible for generating all or part of the scalp-recorded P300. The results of these experiments are reviewed here.

Most of the studies of humans using indwelling intracranial electrodes have been conducted in patients with intractable epileptic seizures. These studies, which have relied primarily on the oddball paradigm to elicit ERP activity, have consistently found P300-like potentials in MTL structures, including the hippocampus and amygdala. While Halgren’s group localized the intracranial P300-like activity to the anterior portion of the MTL, Wood and his colleagues have placed its locus in more posterior regions. Although the reasons for the differences between these laboratories remain unresolved, the relatively unambiguous unit data reported by Halgren et al. (1986) provide additional evidence in favor of local generation of P300-like potentials within the anterior MTL.

The strategy used by those testing the MTL generator hypothesis (i.e. that the scalp P300 is generated exclusively or primarily by MTL structures) has been to look for asymmetrical P300 activity in patients who have undergone unilateral temporal lobectomy (TL) surgery. Such operations typically involve the removal of the areas cited specifically by Halgren and co-workers (1980) as generating P300-like activity: the amygdala, pes, uncus, and the anterior portion of the hippocampal complex.

The assumption is that, if the scalp P300 were generated either exclusively or primarily by MTL structures, then removal of 1 of these 2 symmetric neural generators should significantly alter its scalp distribution and/or reduce its amplitude.

In contrast, the idea that unilateral removal of 1 of 2 neural sources should produce clear, if not dramatic, changes in the behavior of P300 has received relatively little attention from investigators wanting to test the MTL generator hypothesis. This
is surprising since the main characteristic that distinguishes the P300 from other components of the ERP is its behavior (i.e., its response to experimental variables). For example, it is well established that P300 amplitude is inversely related to stimulus probability and directly related to stimulus and task complexity (see Johnson 1986, 1988a for reviews). Similarly, P300 latency increases in response to increases in stimulus complexity and to decreases in stimulus discriminability. It is reasonable to expect, therefore, that removal or alteration of any structure contributing to the activity of the scalp-recorded P300 should produce clear alterations in the relation between cognitive variables and P300 amplitude and latency. Thus, the MTL generator hypothesis can also be evaluated by assessing the degree of ‘behavioral’ independence or dependence of P300 on a particular anatomical location, since the extent of that brain region’s contribution to the scalp P300 could be determined.

Another frequently overlooked method for assessing the impact of brain lesions on P300 activity involves the evaluation of variations in P300 scalp distribution. It has been known for some time that P300 scalp distribution varies as a function of the subjects’ task (Johnson 1986, 1988a). Thus, since it is possible that any particular brain structure may contribute to P300 activity in one task but not another, it is also important to determine whether particular lesions interfere with the normal distributional shifts in patients’ P300 activity.

**Methods**

Seven patients with a left temporal lobectomy (LTL), 7 with a right temporal lobectomy (RTL), and 7 normal adults, matched on the basis on age and education, were tested. In order to evaluate specifically the contribution of MTL potentials to scalp ERP activity, the patients were selected carefully to eliminate any cases with bilateral or extratemporal foci, the presence of any other lesions or tumors, right hemisphere speech, or any history of psychiatric illness. All subjects were right handed. Other relevant patient data are presented in Table 1. The stringency of the exclusion criteria is evidenced by the fact that 6 of the 7 patients in each group were entirely seizure free following the surgery, while the remaining two cases have had no more than 1 seizure per year. This fact strongly suggests that the extent of the diseased tissue was confined to MTL structures that were removed during the TL surgery. The TL surgery consisted of removal of the medial and lateral aspects of the anterior temporal lobe (averaging 4.3 cm from the tip for the LTLs and 7.1 cm for the RTLs), with complete removal of the pes, uncus and amygdala and partial removal of the hippocampal gyrus (1.5–2.5 cm).

To test both the MTL generator hypothesis and to study further their neuropsychological deficits, the patients were tested in 5 paradigms in 2 experimental sessions. The first session included an auditory oddball paradigm with 5 levels of stimulus probability (.10/.90, .30/.70, .50/.50) and a visual oddball paradigm at 2 levels of probability (.30/.70). For both stimulus modalities, the oddball paradigm was run twice, once with instructions to count the .10, .30 and .50 stimuli and once with instructions to make a rapid button press (RT) after every stimulus. Next, a feedback paradigm, using the same tones as those in the oddball paradigm and .50/.50 stimulus probabilities, was performed. In the second session, the patients were tested in 1) a spatial categorization paradigm in which the outlines of left and right hands were presented in two or more different orientations in different series; 2) a visual discrimination paradigm in which degraded and undegraded stimuli were presented; and 3) a study-test recognition memory paradigm. Throughout the second session, the stimulus category probabilities were always .50/.50 and the subjects made a choice RT response after every stimulus.

**Oddball paradigm**

The first test of the MTL hypothesis was designed to duplicate the conditions used by Halgren et al. (1980) to elicit P300-like potentials in the anterior MTL. Thus, TL patients and controls were presented with an auditory oddball paradigm with instructions to count the low-probability (.10) stimuli (Johnson and Fedio 1986; Johnson 1988b). As shown in Fig. 1, there was no evidence of any left–right
TABLE I
NEUROPSYCHOLOGICAL DATA
(Range, mean, and standard deviation in parentheses)

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Left temporals</th>
<th>Right temporals</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Sex</td>
<td>3M, 4F</td>
<td>2M, 5F</td>
<td>5M, 2F</td>
</tr>
<tr>
<td>Age (years)</td>
<td>28–56</td>
<td>25–46</td>
<td>29–50</td>
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<tr>
<td></td>
<td>42 (10.9)</td>
<td>35 (7.8)</td>
<td>39 (7.7)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>12–16</td>
<td>10–16</td>
<td>9–16</td>
</tr>
<tr>
<td></td>
<td>13.7 (1.7)</td>
<td>12.3 (1.8)</td>
<td>12.1 (2.3)</td>
</tr>
<tr>
<td>Pre-operative data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, onset (years)</td>
<td>–</td>
<td>8 mo–21</td>
<td>3–21</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>7 (7.9)</td>
<td>12 (8.3)</td>
</tr>
<tr>
<td>WAIS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIQ</td>
<td>–</td>
<td>92 (13.7)</td>
<td>107 (5.8)</td>
</tr>
<tr>
<td>PIQ</td>
<td>–</td>
<td>86 (10.2)</td>
<td>98 (9.5)</td>
</tr>
<tr>
<td>FSIQ</td>
<td>–</td>
<td>88 (11.4)</td>
<td>103 (7.2)</td>
</tr>
<tr>
<td>Post-operative data</td>
<td></td>
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<td>119 (10.2)</td>
<td>94 (6.1)</td>
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</tr>
<tr>
<td>FSIQ</td>
<td>115 (9.3)</td>
<td>94 (10.0)</td>
<td>106 (7.2)</td>
</tr>
</tbody>
</table>

Hemispheric asymmetry in P300 (peak latency of 350 msec) scalp distribution that varied as a function of the side of surgery. When the waveforms from the two hemispheres are superimposed, all 3 groups showed either no asymmetries, or perhaps slightly larger P300s elicited over the right hemisphere (Fig. 1B). Moreover, there were no statistically significant differences in overall P300 amplitude or latency between the patients and controls.

Nevertheless, there were clear group differences since the LTL patients showed apparently reduced P300 and slow wave amplitudes and increased amplitudes for all negative components. However, both a principal components and a baseline-to-peak analysis indicated that these amplitude changes were due to the addition of an overlapping frontal maximal negative slow wave that spanned virtually the entire ERP waveform (70–900 msec) in the LTL patients. This negativity was present to a greater extent in some patients than in others (see Fig. 1 of Johnson 1988b), with two LTL patients showing substantially greater amounts of this negativity than the others. In the subjects whose waveforms contained this negativity, there was an increase in the amplitude of negative components (i.e. N1: peak latency of 110 msec; N2: peak latency of 250 msec) and a proportionate decrease in the amplitude of positive components (i.e. P2: peak latency about 200 msec; P300, post-P300 slow wave: 450–700 msec). This negativity was also apparent in the waveforms of the RTL patients, although it was more restricted to the frontal-central scalp.

This finding of an absence of any surgically-related asymmetries or of any reduction in overall
P300 amplitude has been replicated in TL patients (McCarthy and Wood 1987; Stapleton et al. 1987). In addition, Paller et al. (1988) found no changes in the P300-like activity of monkeys who had undergone bilateral TL surgery. Still other reports have described a general lack of alterations in the scalp-recorded P300 activity in patients whose temporal lobe function has been impaired by the presence of tumors (Rugg et al. 1991a) or damaged by encephalitis (Onofri et al. 1991; Potter et al. in press).

It is still possible that removal of these MTL structures might reduce scalp P300 amplitude or introduce asymmetries at more lateral electrode sites. Indeed, while replicating the results of the above studies at the electrode sites in Fig. 1, McCarthy and Wood (1987) reported small asymmetries in P300 activity at some far-lateral electrode sites (T5 and T6). Their results suggest that MTL generator activity may indeed reach limited areas of the overlying scalp. However, the meaning of their results is not clear since there are few published reports about the behavior of P300 at these particular sites and thus there are virtually no data to indicate what (or how) cognitive variables influence P300 activity at these far-lateral sites. That is, virtually all our knowledge about the behavior of the P300 is derived from recordings made at midline or near-midline lateral electrodes (e.g. F3, C3, P3, O1, F4, C4, P4, O2), where...
no significant changes in P300 have been observed in patients with any kind of damage to their MTL structures.

In most studies using intracranial electrodes or testing the MTL generator hypothesis, only the P300s elicited by relatively rare stimuli were quantified. While this is sufficient to evaluate the amplitude and topography of P300, it does not address the behavior of P300. Yet, if P300 were generated solely or primarily in bilateral MTL areas, "behavioral" asymmetries in P300 activity could reasonably be expected for two reasons. First, it is likely that there is at least some functional asymmetry between the anterior MTL areas in the 2 hemispheres so it is reasonable to expect asymmetries in the behavior of the P300s generated in each hemisphere (in addition to or in conjunction with the topographic asymmetries reported by Stapleton et al. 1987). Second, since more brain tissue typically is excised from the right than from the left hemisphere, asymmetrical changes in the behavior of P300 would be expected even in the unlikely event that these bilateral MTL areas are functionally symmetrical. Overall then, if the MTL played a prominent role in P300 generation, it would be reasonable to expect differential alterations in the response of P300 to experimental variables depending on the side of the surgery. More generally, any time one or more P300 generators is removed there should be clear changes in the behavior of P300. Thus, by quantifying only the responses to the rare stimuli, fundamental changes in P300 activity might have been missed in some tests of the MTL generator hypothesis. For example, the graded relation between P300 amplitude and stimulus probability may have been altered in some fundamental way.

Five levels of stimulus probability were used so that any alterations in the patients' response could be assessed. As shown in Fig. 2, the usual graded inverse relation between P300 amplitude and stimulus probability obtained in all 3 groups. Moreover, larger P300s were elicited in the RT condition compared to the count condition in all groups. In the count condition, all subjects also showed the well-documented 'target' effect, in which counted stimuli (.10, .30, .50) elicit disproportionately larger P300s than the uncounted stimuli. Thus, in

Fig. 2. See following page for figure legend.
Fig. 2. A) Grand-averaged ERPs elicited in the control subjects at the 3 midline electrodes superimposed at all 5 levels of stimulus probability in the count and reaction time tasks for the oddball paradigm. B) Same waveforms for the LTL patients. C) Same waveforms for the RTL patients.
the RT condition, when all stimuli were treated equally, the relation between P300 amplitude and stimulus probability was clearer and more regular. The waveforms for the LTL patients also clearly show that the long-lasting negative slow wave is directly related to stimulus probability and that overlap of this activity on the other ERP components produced a consistent pattern of amplitude alterations for the affected components (i.e. N1, P2, N2, P300, post-P300 slow wave). These data indicate that the behavior of the P300 activity in both patient groups matched that of the controls in all of the cognitive aspects invoked by this paradigm (i.e. subjective probability, target effects, task effects). Thus, the absence of any changes in the behavior of P300, in addition to the absence of changes in overall amplitude or topography, is further evidence against the idea that the MTL is the major, or even a minor, contributor to the scalp-recorded P300 in the oddball paradigm.

Effect of stimulus modality
Consistent with the generally accepted idea of P300 as a modality-dependent component, subsequent studies with intracranial electrodes showed that visual and auditory P300-like potentials were elicited in the same MTL areas (Squires et al. 1983; McCarthy et al. 1989). Hence, in a second test of the MTL hypothesis, auditory and visual P300 activity was compared in TL patients (Johnson 1989a). As with the auditory stimuli, there were no significant surgically-related alterations in either the hemispheric symmetry or amount of overall P300 activity evident in the patients' responses to visual stimuli (Fig. 3). However, the ERPs of the RTL patients did show clear differences over frontal scalp where there was a prominent negative slow wave that spanned the interval 200–700 msec. This activity was restricted topographically such that P300 activity was not significantly altered at central and parietal sites in the RTL patients. These data also reveal that the long-lasting negative wave that was present in the LTL patients' responses to auditory stimuli was not present in their responses to the visual stimuli. Consequently, in this modality, their ERPs were essentially the same as those of the controls, with the exception of increased amounts of P2 activity (250–350 msec).

Taken together, the data indicate that, at least in one modality, each TL group showed P300 activity that closely approximated that of the control group. In the other modality, each TL group had a temporally overlapping modality-specific slow wave that appeared to affect the amplitude of a number of ERP components, including the P300. Thus, for both auditory and visual stimuli, at least one TL group showed normal P300 activity. Since the intracranial MTL recordings show that auditory

![VISUAL STIMULI (P= .30)](image)

Fig. 3. Grand-averaged ERPs elicited in the controls (solid lines), LTL patients (dashed lines), and RTL patients (dotted lines) at all 9 electrode sites in response to the infrequent (.30) visual stimuli in the oddball paradigm.
and visual P300-like potentials arise from the same locations in both hemispheres, the pattern of scalp P300 results observed here is inconsistent with the idea that the MTL makes any substantial contribution to the scalp P300. While the nature of these modality-specific frontal negative slow waves remains elusive, they may prove to be of some diagnostic utility.

An unexpected finding from this study was that the P300s elicited by the auditory and visual stimuli had different scalp distributions due to the presence of larger visual P300s over frontal scalp. To determine if these differences were significant, an extensive analysis of the scalp topographies of these potentials was performed by comparing normalized auditory and visual P300 amplitudes in a series of topographic profile comparisons (Johnson, 1989a). Since the topographies remained significant even after normalization (see McCarthy and Wood 1985), there was unambiguous evidence that different patterns of neural generators were activated for the P300s elicited in each modality. The existence of modality-specific P300 activity was replicated (Johnson 1989b) and thus these data add to similar topographic differences reported between auditory and somatosensory stimuli (Barrett et al. 1987; Johnson et al. 1991; Miltner et al. 1991).

**Evidence for information-specific P300 generators**

The unexpected finding of modality-specific P300 activity led to an investigation of the P300 scalp distributions associated with the other experimental variables: stimulus probability and subject task. Based on a review of P300 results, it had suggested previously that task and probability effects on P300 amplitude should each be due to different neural generators (Johnson 1986, 1988a). Since the patients and controls had performed the oddball paradigm under different task instructions (count, RT), with different stimulus probabilities (.30/.70) it was possible to determine whether the P300 activity associated with the task and probability variables had their own distinct patterns of generator activity. Using a subtraction procedure similar to that used in PET studies of brain activation, statistical tests on normalized P300 amplitudes revealed the presence of significantly different scalp distributions as a function of stimulus modality, event probability, and subject task for both the P300 and slow wave components (Johnson 1989a). These results, therefore, indicated that the scalp-recorded P300 represents the summation of a number of simultaneously active neural generators that are each related to specific cognitive processes.

Corroborative evidence for the presence of different generators for probability and task-related processing was also obtained in the same paradigm by Pritchard (1989). Moreover, Ruchkin et al. (1990) showed that the P300 activity elicited by each of 3 different types of stimulus information was associated with different scalp distributions. Taken together, the results of these 3 studies and others (see Johnson 1993 for a review) confirm the predictions made by the triarchic model that P300 amplitude represents the summation of activity from multiple neural generators (Johnson 1986, 1988a).

**Feedback paradigm**

Since the early studies using intracranial electrodes relied exclusively on the oddball paradigm to elicit a P300, the final 'amplitude' task in the first session was a feedback paradigm (Johnson and Fedio 1987). This paradigm was selected because it had been shown that, unlike the Pz maximal potentials obtained in the oddball paradigm, feedback stimuli elicit P300s that are maximal at Cz when the stimulus series depends entirely on the subjects' task performance (Johnson and Donchin 1978; Stuss and Picton 1978; Campbell et al. 1979). Such task-related variations in P300 scalp distribution were found even when the same subjects were tested in both an oddball and a feedback paradigm (Johnson and Donchin 1978). Since such scalp distribution differences indicate the presence of different patterns of generator activity, the feedback paradigm was intended to provide another, independent test of the effects of the TL surgery on the scalp-recorded P300. To maximize the comparability between the oddball and feedback data, the same tones were used in both paradigms and the correct and incorrect feedback stimuli were presented equally often. Thus, the main difference between these two paradigms was the subjects' task.

Subjects were instructed to estimate the passage
of 1 sec following a light flash and indicate their estimate with a button press. Estimates within a critical interval, or ‘window’ around 1 sec were followed 300 msec later by a tone indicating a correct estimate. Estimates that were outside of the window either because they were too short or too long were followed by the other tone, indicating an incorrect estimate. The probabilities of correct and incorrect feedback tones were maintained at .50 by increasing and decreasing the duration of the correct window after the incorrect and correct estimates, respectively (see Johnson and Fedio 1987 for further details).

As shown in Fig. 4a, all 3 groups showed the previously documented Cz maximal P300s, with lesser amounts of activity being elicited at Pz and Fz. To better illustrate the magnitude of this change in P300 scalp distribution, the P300 elicited at Pz by the counted .50 tones in the oddball paradigm is superimposed here (also compare the data from Figs 1 and 2). Note that, in addition to the change in scalp distribution, the amplitudes of the P300s elicited at all electrode sites in the feedback task were considerably larger than those elicited in the oddball paradigm as reported previously (Johnson and Donchin 1978). The topographic differences between the P300s elicited by the auditory stimuli elicited in these two tasks indicates that a different pattern of neural generator activity was present during performance in these two tasks. These data also clearly refute the often used statement that a stimulus must be rare to elicit a large P300. When the .50 stimuli delivered feedback information, they elicited P300s that were larger than those elicited by the .10 stimuli that were counted.

These data also showed that the frontal maximal negative slow wave activity in the LTL patients was modality specific and not task specific since this activity was again in evidence when the same auditory stimuli were used in this paradigm. In addition to reduced P300 amplitudes, there was a reduction in the positive slow wave that followed P300 (500–1000 msec) and an increase in N1 amplitude. Nevertheless, the amplitudes of the RTs
P300s were the same as those of the controls and there were again no surgically-related asymmetries in the P300s elicited in either patient group in this task (Fig. 4b). In fact, all 3 groups showed the same asymmetrical P300 activity with larger P300s being elicited over the left hemisphere at frontal and central sites. This pattern of hemispheric asymmetry is also in marked contrast to that observed in the oddball paradigm. Thus, in the feedback paradigm, when a different mix of cognitive processes was required to perform the task, there was a different mix of generators contributing to the scalp P300 activity than was activated in the oddball paradigm. Nevertheless, the LTL and RTL patients’ P300 activity still varied in all the same ways as it did in their controls.

The finding of large task-related differences in P300 scalp distribution in the same subjects provides further evidence that there are multiple P300 generators and that different combinations of these generators contribute to the P300 activity elicited in different tasks. The fact that the feedback P300 generators also remained unaffected by the TL surgery indicates that none of them resides in anterior MTL structures. The cognitive nature of different generator patterns across tasks is indicated by the fact that the same stimuli and stimulus conditions were used in both paradigms.

Visual discrimination paradigm

Although the oddball paradigm provides a useful method for eliciting P300 activity, additional information about the patients’ processing deficits and the nature of P300 can be gained from paradigms that provide functional information about different brain structures. For example, if altered P300 activity could be found in tasks that were sensitive to the patients’ particular deficits, this could provide information on the locations of some P300 generators. Thus, since it is known that RTL, but not LTL, patients suffer from impaired visual perception under conditions that reduce the normal redundancy of complex stimuli (Meier and French 1965; Milner 1975), a visual discrimination task was included in the second session. It was expected that RTL patients would have greater difficulty categorizing degraded stimuli, which would be evidenced behaviorally and by smaller and later P300s (perhaps with different scalp distributions) than would be elicited in the LTL patients or controls (cf., Johnson and Donchin 1978).

Discriminability was varied by adding ‘noise’ letters to verbal stimuli. The high-quality stimuli were the words ‘L E F T’ and ‘R I T E’ and the low-quality stimuli were ‘XLXEXFXTX’ and ‘XRXXFXTX’. The stimuli were equally probable and, 10% of the time, ‘catch’ trials were given on which the stimuli were misspelled (i.e. ‘L F E T’, ‘R T I E’, ‘XLXFXTX’, ‘XRXTXIE’). Subjects were instructed to make fast and accurate button presses with the compatible thumb and to withhold their response when they detected the catch stimuli.

Both the ERP and behavioral data clearly showed that stimulus quality was successfully manipulated (Scheffers et al. 1991). P300 amplitude and response accuracy decreased while P300 peak latency and RT increased when stimulus quality was reduced in all 3 groups. However, the expected group differences in P300 amplitude and latency did not obtain, although the RTL patients did make significantly more errors, particularly on the catch trials, which suggests that they did not process the stimuli as thoroughly and accurately as the subjects in the other two groups. Finally, as in the oddball and feedback paradigms, neither patient group showed any evidence of any surgically-related asymmetries or loss of overall P300 amplitude.

These results extended the evidence against the idea that the MTL makes any substantial contribution to the scalp P300 in a visual discrimination paradigm. Furthermore, the demonstration that the patients’ P300 latencies increased and P300 amplitudes decreased in response to the degraded stimuli extends the range of normal responsiveness of the patients’ P300 activity.

Recognition memory paradigm

The fact that LTL, but not RTL, patients show verbal memory deficits (both recognition and recall) has been well-documented (e.g. Smith 1989). In an attempt to learn more about the nature of the LTL patients’ verbal memory deficits, a recognition memory paradigm was included in the second session.

In order to explain that it is possible to recognize
a person without being able to remember where or when that person was seen previously, a number of investigators have proposed that recognition memory consists of two distinct processes (e.g. Atkinson and Juola, 1973; Mandler 1980). These dual process theories distinguish between the feeling of familiarity and a retrieval process which is based on a memory search for item-specific information. Whereas familiarity effects are considered to be maximal after a single presentation, the magnitude of retrieval effects increases with repetition. Thus, recognition in the TL patients was evaluated in a repeated study-test paradigm since it permits the assessment of both of familiarity and retrieval contributions to recognition (Johnson 1990). That is, familiarity effects can be seen in the differences between the ERP activity elicited by the old and new words while the retrieval effects can be seen in any changes that occur over tests.

The patients were presented with a list of 40, 4-letter words to memorize (study series), displayed consecutively on a CRT screen at a rate of 1 every 2.5 sec. After a 2-min delay, the ‘old’ words were presented again in a randomly mixed list with an equal number of ‘new’ words (test series). The patients’ task was to categorize each word as being either old or new and press the appropriate button as quickly as possible. The study-test combination was repeated 4 times using the same old words and non-repeating lists of new words on each test (cf. Johnson et al. 1985 for further details). It should be noted that, due to lower numbers of correct trials, losses from eye artifacts, and the requirement that averages with sufficient numbers of trials be available for all stimulus types for all tests, data from this paradigm were available from only 5 LTL patients.

The memory paradigm was preceded by a control condition consisting of a random .50/.50 series of the words ‘noun’ and ‘neon’ to which the subjects were to press 1 of 2 buttons as quickly as possible. By using an orthographic discrimination, this series was intended to determine the basic P300 response to word stimuli that were presented under the identical conditions but which required only minimal contact with memory. These control stimuli elicited P300 activity (peak latency 500–600 msec) in all groups with the same scalp distribution and characteristics as obtained in the visual oddball paradigm (Fig. 5).

While the number of correctly recognized items increased over tests in all 3 groups, in accord with previous findings, the LTL patients had significantly worse performance than the RTL patients or controls (Fig. 6). In addition, the LTL patients’

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**ORTHOGRAFIC CONTROL SERIES**

![Graph](image)

*Fig. 5. Grand-averaged ERPs elicited in the controls (solid lines), LTL patients (dashed lines), and RTL patients (dotted lines) at all 11 electrode sites in the orthographic control series for the recognition memory paradigm. For this comparison, the data from the ‘noun’ and ‘neon’ trials were averaged together.*
performance was further reduced, relative to the other groups, when the number of their false alarm responses was subtracted from the number of correctly recognized old (target) words. In parallel with the increases in number of correct responses, the RTs of all 3 groups decreased over tests.

The old words presented during the test series elicited a complex pattern of ERP activity (Fig. 7a). At the Pz electrode site, P300 amplitude (peak latency 500–600 msec) in all 3 groups increased over tests in a manner that approximated the concomitant increases in the number of correctly recognized old words. Parietal P300s were asymmetrical, being largest over the left hemisphere. In addition, large P300s over elicited over frontal scalp (even larger than at Pz at test 1), but the small variations in P300 amplitude at these sites did not covary with test repetition. Frontal P300s were also asymmetrical, with larger potentials being found at F4 than at Fz or F3. The activity at Cz appeared to be a linear summation of the activity at Pz and Fz. Thus, while behavior of the P300 activity at Pz

was consistent with the hypothesized retrieval processes in dual process models, the meaning of the memory-related frontal P300 activity remains unclear.

There were some group differences in P300 activity, most notably the fact that larger P300s were elicited in both patient groups over parietal scalp. These differences were not significant, most likely due to the reduced number of LTL subjects (5) in these comparisons. Frontal P300 activity was the same in controls and LTLs, while the RTL patients showed the same frontal negative slow wave activity that characterized their responses to visual stimuli in the previous paradigms. However, as in all of the previous paradigms, there were no significant asymmetries in the patients' ERP waveforms that were related to the side of surgery nor, as noted, was there any reduction in overall P300 amplitude during recognition in either TL group.

The large amount of frontal P300 activity in this paradigm was completely unlike that seen in any of the other paradigms described above despite the fact that these were the same subjects. For example, during the orthographic control series, P300s were smaller over frontal scalp but larger over parietal scalp compared to the P300s elicited by the old words in test 1. By test 4, however, increased amounts of P300 activity over parietal scalp meant that the P300s elicited by the old words were larger over both frontal and parietal scalp than those elicited in the control series. Thus, the data suggest that the frontal P300s were related to recognition memory operations and that they had different neural generators than those responsible for the parietal P300 activity.

P300 amplitudes at Pz also increased over tests in response to the new words (Fig. 7b), a finding that replicates those reported previously for this paradigm (Johnson et al. 1985). These P300 amplitude increases covaried with the number of correctly classified new words and decreases in RT over tests. Thus, even though they had not been seen before, the ERP and behavioral changes associated with the new words paralleled those seen for the repeated old words. Moreover, as for the old words, the 'retrieval' effects were restricted to parietal scalp as P300 amplitudes over frontal scalp were again constant over tests. These data suggest
Fig. 7. A) Grand-averaged ERPs elicited at the midline electrode sites by the 'old' words in the 3 subject groups during the recognition memory paradigm. B) Grand-averaged ERPs elicited at the midline electrode sites by the 'new' words in the 3 subject groups during the recognition memory paradigm. The waveforms elicited during the 4 test repetitions are superimposed in both panels.
that even when retrieval operations are conducted for items not in memory, this process is manifested in the parietal P300. Johnson et al. (1985) suggested that this parietal P300 activity reflects the strength or discriminability of the memory trace, although it cannot be a direct representation of memory trace strength since the P300 elicited by the new words also increased over tests. Consistent with a strength explanation, the P300 amplitude increments were accompanied by RT and P300 latency decreases over tests.

The results from this paradigm revealed the first evidence of surgically-related changes in P300 activity in the paradigms reported here. However, the alterations were manifested as a change in the behavior of P300 rather than in changes in symmetry or lost overall amplitude. A comparison of the P300s elicited by the old and new words reveals that larger P300s were elicited by the old words, as reported previously (Johnson et al. 1985). The old–new amplitude difference did not increase across tests, a characteristic that has led to its being associated with the posited familiarity processes (e.g. Smith and Halgren 1989; Rugg et al. 1991b). The old–new amplitude difference also had its own distinctive scalp distribution as it was roughly equal at Fz, Cz, and Fz, despite the differences in absolute amplitude across these same sites. This same distribution can be seen in previous studies of the old–new effect (e.g. Rugg et al. 1991b). Replicating Smith and Halgren (1989), the old words elicited larger P300s than did the new words in the controls and RTL patients but not in the LTL patients, due to their larger than normal responses to the new words. In contrast, Rugg et al. (1991b) reported significantly reduced old–new effects in both LTL and RTL patients in a continuous recognition memory paradigm, suggesting that there may be some differences between the recognition memory operations used in study–test and continuous recognition paradigms.

ERP activity was also recorded during the acquisition (study) phase of the experiment and it is evident that P300 activity elicited during this stage was considerably different from that seen during retrieval (Fig. 8). For example, there was another distinct P300 scalp distribution present during the study series; P300s were greater at Cz than at either

Fig. 8. Grand-averaged ERPs elicited at the midline electrode sites by the 'old' words in the 3 subject groups during the acquisition (study) series in the recognition memory paradigm. The waveforms elicited during the 4 study repetitions are superimposed.
Pz or Fz in the undistorted waveforms of the controls and LTLs. Moreover, P300 amplitude did not covary in a predictable way with test repetition at any recording site. Also striking was the fact that the LTL patients’ P300s were smaller than those of the controls during acquisition, despite their having the larger potentials during retrieval. Compared to the other groups, this relative decrease suggests that their deficits in recognition and recall may also result from deficient processing during acquisition.

Overall, the P300 data from this paradigm appear to indicate the presence of 2, and possibly 3, distinct memory-related processes that were operating in parallel during long-term recognition memory and another set during acquisition. The relation between the recognition performance and the amplitude and latency of the parietal P300 is consistent with an effortful retrieval process while the P300 amplitude differences between the old and new words is consistent with a familiarity process. These two contributions to recognition were characterized by P300 activity with different scalp distributions, a finding that indicates that the underlying pattern of neural activity associated with each process is different. Taken together, the results from the 3 studies of TL patients implicate the anterior MTL in the generation of old/new effects but not in the generation of the strength aspect of recognition memory. Moreover, the fact that both these effects were seen in the P300s elicited by the old words suggests that both the old/new and strength processes operated in parallel (cf. Mandler 1980). Finally, there was evidence for a third parallel recognition memory process in frontal areas since the P300 activity there did not covary with test repetition.

In this conceptualization, the fact that LTL patients were able to increase their number of correctly classified old and new words over tests is consistent with their having intact strength effects (as evidenced by their increasing P300 amplitudes at Pz). The overall lower level of recognition performance in the LTL patients could be due to their lack of old/new effects (no old/new P300 amplitude difference). However, it should be noted that, at least in a continuous recognition paradigm, Rugg et al. (1991b) failed to find any relation between old–new effects and recognition performance in either their RTL or LTL patients. Finally, the parietal-central aspects of the P300 scalp distribution during acquisition may be similar to that seen during retrieval, but without the addition of the frontal or old–new effects. These data support those from other studies suggesting that long-term memory is a collection of different processes that depend on different brain structures (Tulving 1987; Squire and Zola-Morgan 1988).

Summary

Across all 4 paradigms used here, the only clear evidence to suggest that anterior MTL structures are involved in generating the scalp-recorded P300 came from the recognition memory paradigm when altered P300 activity was associated with behavioral changes. The absence of the old–new word effects on P300 amplitude in the LTL patients is consistent with the well-documented results of behavioral studies showing a selective deficit in verbal memory in LTL patients. Thus, it appears that the only clear instance in which MTL function affected the activity of the scalp P300 occurred in a paradigm that required cognitive functions that have been demonstrated previously to be dependent on MTL brain structures. In the paradigms in which there were no significant changes in P300 activity, there were no significant differences in the patients’ cognitive performance. The other clear group differences in ERP activity consisted of the differential presence of modality-specific slow waves in the two groups that spanned virtually the entire averaging epoch and overlapped all other ERP components. These findings, then, reinforce the notion that measurable changes in P300 activity should be accompanied by measurable changes in some cognitive activity.

Taken together, the data reviewed here present a reasonably consistent picture in which the P300-like activity found in anterior MTL structures does not appear to make a meaningful contribution to the scalp-recorded P300 in any paradigms that do not directly invoke certain verbal memory processes in long-term recognition memory paradigms. Thus, while nearly all intracranial recordings have
been made in the context of the oddball paradigm, to date there have been no reports of either reduced overall amplitudes or surgically-related hemispheric asymmetries in P300s elicited in this paradigm in ‘clean’ patients who have undergone unilateral TL surgery. These results apply to the P300 activity recorded at the midline and most of the lateral and far-lateral electrode sites, the same sites that have formed the basis of virtually the entire P300 literature. Moreover, such findings have been replicated in patients with unilateral or bilateral temporal lobe damage due to tumors or other diseases. Whereas there is some evidence that TL patients can show small asymmetries at far lateral electrode sites, the meaning of such asymmetries remains to be clarified. Nevertheless, such results can be interpreted as further evidence of the presence of multiple P300 generators.

One could argue that these attempts to test the MTL generator hypothesis on groups with different types of damage to their temporal lobe structures are limited by a lack of power. This is a frequent problem with studies of neurological patients which, by necessity, can only involve limited numbers. However, as reviewed above, convergent evidence from various laboratories have demonstrated significantly altered P300 activity in memory paradigms, to the exclusion of all other paradigms, despite testing limited numbers of patients.

Because of the surgery, a number of investigators have questioned whether the resulting skull defect might induce changes in current flow that could affect the scalp field distribution of ERP components. Presumably, any such changes would be opposite in the two patient groups given the unilateral nature of this defect. However, this does not appear to be a factor since no asymmetries have been reported for any ERP component in any report published to date that can be attributed to a skull defect. Hence, given the absence of any demonstrated ERP alterations related to the skull defect, it would appear safe to ignore this facet of these patients.

It is quite likely that altered scalp potentials may be found in studies of epilepsy patients based on less carefully selected groups of patients than those described here, particularly since epilepsy frequently involves brain areas outside of the anteromTL. For example, if patients continue to have frequent seizures and stay on high levels of antiepileptic drugs even after TL surgery, this is a clear indication that the initial brain pathology was not limited to anterior MTL structures. In such cases, the nature and extent of the additional pathology makes it difficult, if not impossible, to make meaningful statements about the neural generators of any ERP component. The same could be true in studies of pre-surgical epilepsy patients, and therefore great care must be taken in interpreting the results of studies based on heterogeneous patient groups. In such studies, it is even more important that investigators demonstrate that altered cognitive functioning co-occurs with alterations in P300 amplitude or latency. To date, no such connection has yet been made outside of recognition memory paradigms in these patients.

Implications
The results from the controls and patients in the studies described above highlight the sensitivity of P300 scalp distribution to the specific combinations of cognitive processes that are invoked both within and across paradigms. The fact that all these data were obtained from the same patients and controls in two experimental sessions is further support for the assertion that these scalp differences represent real changes in the underlying configuration of P300 generators. Taken together, the data from all these different paradigms indicate that P300 is a highly variable composite of the activity arising from a number of independent generators. These data therefore confirm the predictions of the triarchic model of P300 amplitude (Johnson 1986, 1988a). An important implication of these results is that P300 amplitude should be measured at as many scalp locations as possible since the information obtained from any given site will not necessarily be redundant with that measured at adjacent sites.

The conclusion that P300 is the summation of the activity of multiple, independent neural generators, each related to different cognitive variables, is also consistent with what is known about the types of information conveyed by even simple stimuli, such as those used in the oddball paradigm. For example, target stimuli in an oddball
paradigm are processed for a variety of types of information including 1) global probability, 2) sequential probability and, 3) the target effect. Each of these variables has been shown to have its own influence on P300 amplitude. While it could be hypothesized that each of these types of information is processed simultaneously in the same brain region, this is not consistent with the P300 scalp topography analyses described above showing that the target and global probability effects arise from different patterns of brain activity (Johnson 1989a; Pritchard 1989).

In this conceptualization, it is easy to understand why the activity of MTL generators might not contribute to the scalp-recorded P300 and why other investigators have found indications of additional generators of P300-like activity. For example, Yingling and Hosobuchi (1984) reported a negative wave in the thalamus of one patient that was coincident with the scalp P300 and not consistent with a MTL generator and Knight (1989; Yamaguchi and Knight 1991) has found evidence that lesions in frontal and temporal-parietal areas affect P300 amplitude. Also, McCarthy and Wood (1987) reported a possible candidate P300 generator in the frontal lobe that is active in an oddball task using auditory, visual and somatosensory stimuli. Finally, Smith et al. (1990) found evidence of local generation of P300-like potentials in frontal and parietal lobes, in addition to the MTL, and suggested that activity from the inferior parietal lobule was responsible for the majority of the scalp-recorded P300 activity in an auditory oddball task.

These investigators, however, interpret their results very differently from the position advocated here. That is, they appear to consider the different putative P300 generators as acting in concert within a fixed network, with the activity of the entire network being required to produce a P300. The implied dependence among the different components of this network can be deduced from the fact that none of these investigators has attempted to ascertain whether the individual P300 generators are all associated with the same or different cognitive processes. Thus, it has not been determined, for example, if the frontal P300 generator is responsible for the stimulus probability effect while the parietal P300 generator is responsible for the target effect.

In contrast, it has been argued that the variability in P300 scalp distribution has important implications for how and where it is generated and thus for its functional significance (Johnson 1993). The specificity of P300 scalp distribution to the type of information being processed, as documented above, suggests that P300 activity is generated in a large number of “specific-purpose cortical processors.” These processors appear to have 3 general properties: 1) each is responsible for processing a particular type of stimulus or task information; 2) each has a similar neurophysiological basis; and 3) each is bound to a particular anatomical location. These “specific-purpose cortical processors” constitute a system of parallel processors, distributed throughout the cerebral cortex, that are activated simultaneously as part of a temporary neural network that arises in order to perform, in parallel, all the cognitive processes required to evaluate all aspects of the stimulus and task information. These characteristics allow the processors to be combined in an essentially infinite number of patterns to form a powerful and extremely fluid computational network. In this scheme, P300 amplitude and latency provide measures of the extent and timing of processor activation, respectively, while P300 topography provides an indication of which processors are activated during task performance. Functionally, the nature and apparent ubiquity of these processors suggests that they may represent a form of memory access with activation of any given processor dependent on which stored memories are required for task performance. This conceptualization is similar to modular systems proposed as a basis for a variety of cognitive processes (e.g. Mesulam 1990; Damasio and Tranel 1992; Moscovitch 1992).

Conclusions

Based on convergent results from a number of different approaches, it seems clear that the P300-like activity found in anterior MTL structures does not make any meaningful contribution to the scalp-recorded P300s elicited in tasks that do not involve some rather specific recognition memory processes. Nevertheless, the reports of intracranial
P300-like activity, beginning with the seminal report by Halgren et al. (1980), have done much to provoke efforts to locate the neural sources of ERP components, and the P300 in particular. The ensuing research has refuted the old notion that the P300 is a monolithic component with a relatively invariant pattern of scalp activity. In its place is an evolving view in which the P300 represents a summation of the activity of many independent, simultaneously active neural generators that form a temporary network for analyzing incoming information. Future hypotheses about the functional significance of P300 must reflect these and future results that are likely to come from increased efforts to characterize the apparently quite numerous variations in P300 scalp distribution.

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Notes

1. These data were for the auditory oddball paradigm. There were minor differences in the composition of the patient samples across paradigms due to problems of obtaining sufficient trials for every patient in every paradigm after error trials and trials with eye movement artifacts were removed. Nevertheless, these data are representative of all paradigms.

2. In the oddball data reported here, asymmetries were found in the auditory N1 such that the largest potentials were recorded on the side of the surgery, although the Group x Hemisphere interaction did not attain significance. However, the pattern of N1 asymmetries observed in the LTL patients was almost the same as that in the controls.

References


