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Temporal Progression of the Cortical Potential Distribution for the AEP P300 Component in Mild Traumatic Brain Injury

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Abstract

An objective scoring system has been developed to quantify degrees of auditory evoked potential (AEP) abnormalities in patients suffering from mild traumatic brain injury (mTBI). In this study the AEP P300 responses for 20 patients with scores in the abnormal range were compared to the responses in 20 age and gender equivalent controls. The cortical imaging technique (CIT) was used to calculate the evolution of potential changes on the surface of the brain during a 50-millisecond epoch containing the AEP P300 response for both groups of subjects. AEP P300 condition recordings were obtained from 20 EEG and 2 EOG artifact channels. Previously published CIT results showed anterior and posterior peaks, implying multiple sources, for the P300 component. This study suggests that the anterior sources are significantly attenuated in the patient group and this anterior P300 attenuation appeared relatively more focal than that seen with scalp topographical maps alone and that the effects of the injury appear to be selective at the anterior sites.

Introduction

This study compares the auditory P300 evoked responses of a group of subjects who have suffered mild traumatic brain injuries (mTBI), with those of a group of age and gender matched normal controls. Analyses were conducted using the cortical imaging technique (CIT), a mathematical procedure for constructing activity as it theoretically would appear on the cortical surface. The goal is to detect subtle differences in the evoked response that are not apparent from the scalp recordings, and may suggest the intracerebral site of injury.

A growing body of radiological, neuropsychological, electrophysiological, neuropathological and experimental evidence indicates that mild brain injury may occur in the absence of direct impact to the head, and in cases where there is no loss of consciousness [Binder, 1986; Evans, 1992a,b]. MRI, CT, routine EEG and conventional evoked potential (EP) recordings are often unremarkable in these cases, yet the patients may have sequelae that affect professional functioning and activities of daily living for months or years.

Sequelae of mild traumatic brain injury (TBI) have been thoroughly reviewed [Evans, 1992c]. The most common of these are headaches, dizziness, blurred vision (or other visual disturbances), memory impairment, attention/concentration difficulties, increased reaction and information processing times, and personality changes including increased irritability, anxiety and depression.

Ford and Khalil [1996a,b] have developed an objective scoring system for AEP, VEP and EEG findings from patients with suspected mTBI. In these studies, significant group differences were found between patients and controls, a relatively objective scoring system was developed, and the patterns were used to identify about 60% of the patients, with no false positives. The following analysis is limited to the auditory P300 response.

The auditory P300 component is one of the most investigated of all the cognition-driven evoked responses. It is a prominent, posterior vertex positive component, peaking at approximately 300-350 ms post-stimulus in response to randomly presented "oddball" stimuli that are **counted** or otherwise **identified by the subject**.

The generator sources of the auditory P300 component have been suggested in the hippocampus [Halgren et al., 1980; Wood et al, 1984; Neshige & Luders, 1992] and, possibly, with neocortical localization with deep frontal and thalamic contributions [Yingling & Hosobuchi, 1984; Wood et al., 1984; Neshige & Luders, 1992]. Recent work [Pilgreen, 1995; Gevins & Cutillo, 1995] expand on these earlier studies.

In this study we compared the auditory P300 responses of two groups - a patient group identified by the scoring system referred to above with a normal group of age and gender matched controls. The comparison was performed as follows: the potential field for each subject was approximated at the cortical surface using the cortical imaging technique [Sidman, 1991] for a 50 msec epoch extending from 25 msec prior to the latency of the maximum voltage at Pz (the P300 latency) to 25 msec after the maximum. The average normal response and the average abnormal response on the cortical

surface were calculated and compared using t-scores. The average normal response during the N2a/P300/N3 endogenous complex of responses to the rare "oddball" auditory stimulus has been discussed and analyzed in [Ford, Sidman & Ramsey, 1993].

Mathematical Analysis-The Cortical Imaging Technique (CIT)

The mathematical method that was used to perform the analyses reported here is the cortical imaging technique [Sidman, 1991]. Briefly, this method is a way of simulating the potential field on the cortical surface, presumably closer to the actual generators of the scalp-recorded field.

Subjects and Measuring Procedure

Twenty normal subjects and twenty mTBI patients (as identified in [Ford and Khalil, 1996a]) were included in this study. Twenty channels of EEG and two channels of EOG activity were recorded with a NeuroScience Brain Imager, Series III (for amplification and on-line filtering) and a NeuroScan, Inc. software based system using two Dell 433/L PCs (for stimulus presentation, A-to-D conversion, data recording and off-line baseline correction, filtering, artifact minimization, averaging and group statistics).

Electrode sites were the twenty standard International 10-20 system placements (FP1/2, F3/4, F7/8, T3/4, C3/4, T5/6, P3/4, O1/2, Fz, Cz, Pz and Oz), with a linked ear reference. Vertical and horizontal eyeball and eyelid movements (VEOG and HEOG) were also recorded for possible artifact rejection. The recording protocol for all subjects included both resting and P300 auditory.

In the AEP P300 recording, 165 total responses were recorded to the frequent tone (1kHz, 95dB, 50ms duration, binaural) and to the "oddball" or rare tone (2kHz, 95dB, 50ms duration, binaural). There was a variable inter stimulus interval of 1.9-2.1 secs. The probability of an "oddball" or rare tone occurrence was 20%, and the same sequence of frequent and rare stimuli was presented to all subjects. The subjects were instructed to count the rare tone silently to themselves, and their answers were recorded at the end of the session.

The low pass filter was set at 100Hz, high pass filter set at 1.05Hz, with the 60Hz notch filter activated. Sweeps were automatically rejected for artifact if the voltage in either VEOG or HEOG channels exceeded $\pm$100 μv. Analog to digital processing was performed at 320 Hz yielding 256 points and an EP epoch from -100ms to 700ms (3.125ms resolution) for all EP recordings.

Results

All of the mTBI patients (20) and all but one of the normal controls (19) exhibited a well defined AEP P300 component, as identified by a distinct voltage maximum primarily at Pz. The standard deviation of the latencies was 25 ms. In each case scalp (Figure 1) and cortical surface (Figure 2) potential maps were constructed for the epoch extending from 25 ms (one standard deviation) prior to the latency of the peak to 25 ms after the peak. The time point t_0 is the latency of the AEP P300 , different for each individual, and pairs of consecutive time points are 3.125 ms apart. The evoked responses were aligned at time point t_0 for each group of subjects to obtain the average normal response and average patient response for 50 ms (see [Ford, Sidman & Ramsey, 1993]), on the scalp (Figure 1) and cortical surface (Figure 2). The SURFER® software was used throughout for making the graphical displays. The right-most column of pictures for each figure compares the two sequences of pictures by plotting the t-scores (degrees of freedom = 37) at each of the 20 scalp sites, for Figure 1, and for 160 cortical surface sites, for Figure 2.

Ford et al.,1993 [Ford, Sidman & Ramsey, 1993], contains a similar analysis for the entire ~250 ms epoch containing the N2a/P300/N3 complex of responses for normal subjects.

T-score differences between groups show significant attenuation in the patient group at time points leading into and including the P300 component peak, but not afterward. The differences were significant at the anterior source only.

Conclusions

Scalp topography of the auditory P300 component typically shows the peak amplitude at posterior vertex area sites, with no strong indication of more than one generator site. In previous studies with CIT, using 28 channel data [Ford, Sidman & Ramsey, 1993], we have demonstrated that there are several apparent sources in normals, including an anterior one and symmetric, bilaterally homologous, centro-parietal sources. In another previous study, we found that individuals with histories and symptoms consistent with mild TBI showed attenuation of the scalp-recorded auditory (and visual) P300 component, with significant differences spread widely across all anterior sites. The primary purpose of the present study was to analyze the P300 recordings from the mild TBI cases using CIT to determine whether CIT was more sensitive in identifying group differences.

The results of the P300 scalp recordings from both groups showed the expected P300 peak in the area of Pz, with no anterior source indicated. Statistical differences between groups were negligible. CIT analyses of the recordings in both groups showed two clear sources - including one from Fz and the surrounding area. When compared statistically, the differences between groups were significant at the anterior - but not posterior -source. These results indicate that whatever injury is present in these cases differentially affects the anterior source contributing to the generation of the P300 component, while the posterior source remains unaffected.

Although it is not possible to determine the exact mechanism nor locus of injury, based upon the analysis of 20-channel scalp-recorded EP data, the results are not inconsistent with other reports of abnormal findings involving anterior or subcortical regions. (Parenthetically, the availability of 128- and 256-channel recordings may make the elucidation of the mechanism involved possible.) The purpose of the study was to determine whether CIT analyses provided additional information beyond that obtained from scalp recordings, and the results suggest a focal effect at the anterior midline area, thus suggesting subcortical involvement, since the differences from adjacent areas over frontal cortex were not significant.

In summary, the P300 has been shown to have significant amplitude attenuation and/or latency increases in association with a host of clinical disorders and conditions, including schizophrenia, dementia, alcoholism, brain injury, and some instances of learning disability, to name a few. The typical scalp recorded P300 waveform shows amplitude attenuation and/or latency increases across diagnostic groupings, and is thus concluded to be a nonspecific indicator of dysfunction. However, further analyses using analytical techniques such as CIT may ultimately show differential effects on the generator sources for the P300 component among groups, thereby yielding information that is valuable in understanding the underlying processes involved.

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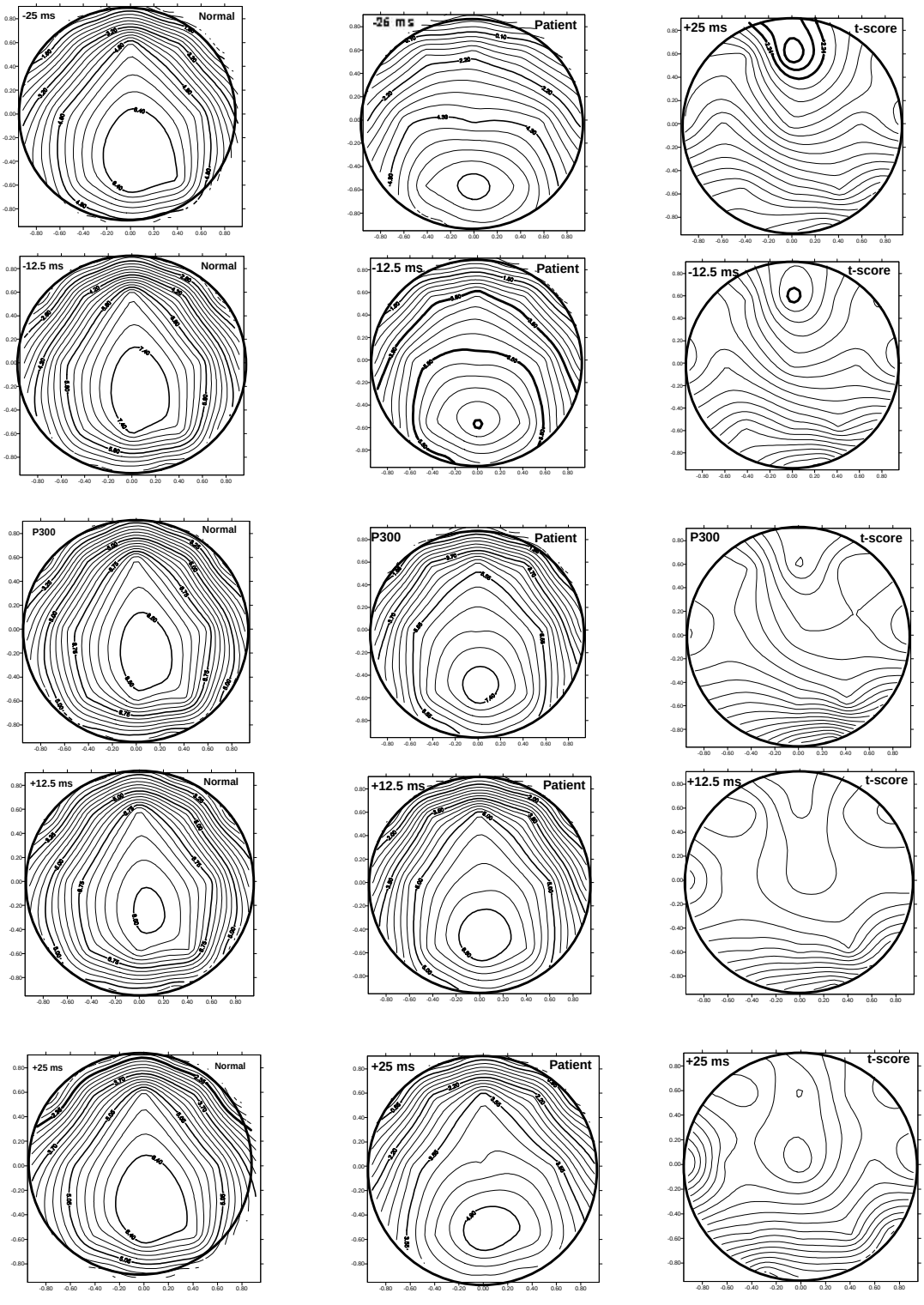
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Patient
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Normal
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Normal
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A
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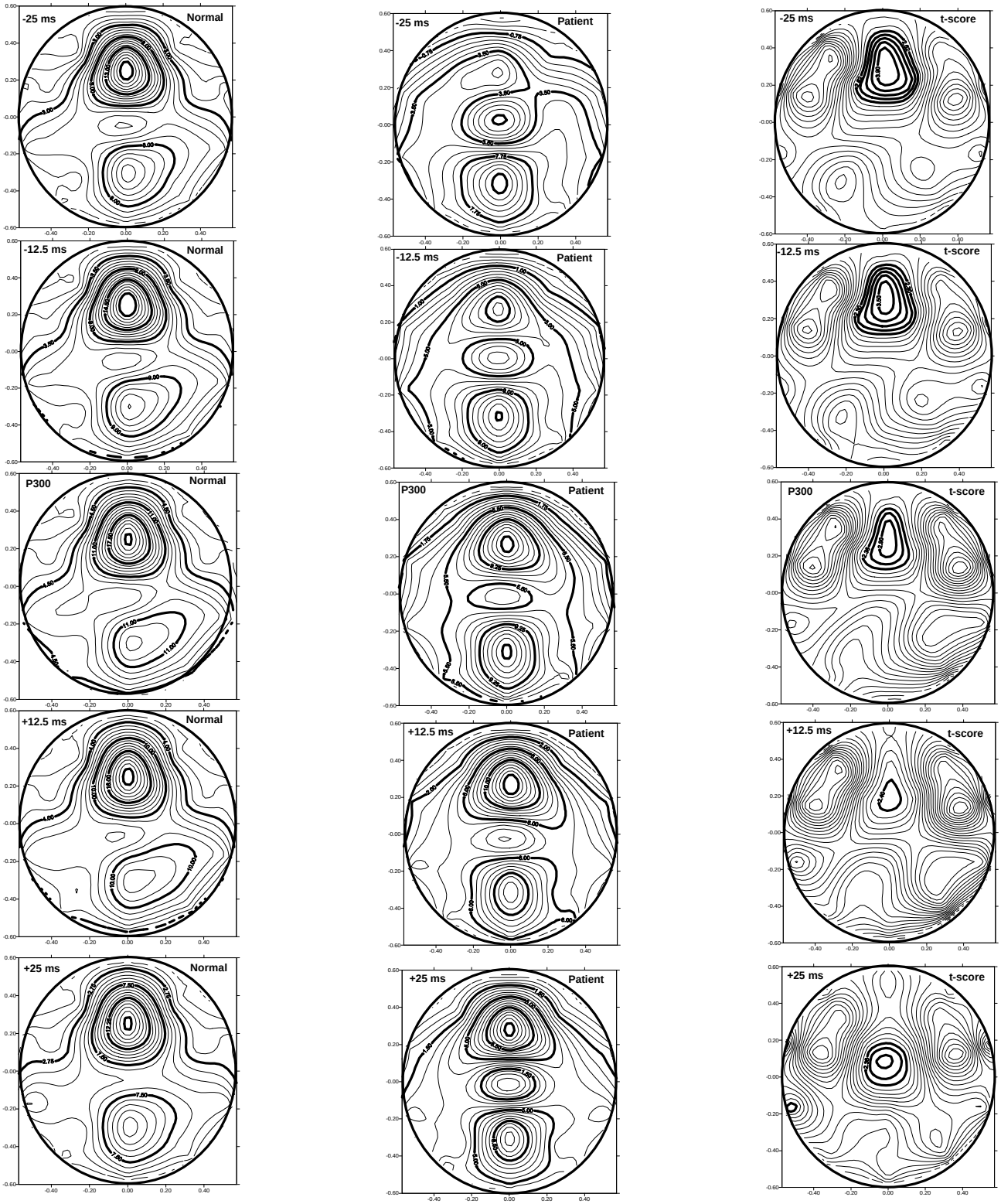
C

FIGURE 1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t-score
-12.5 ms
t-score
P300
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t-score
A
B
C

FIGURE 2

Figure Legends

Figure 1 - 1a) Scalp-recorded voltages for the average normal subject at latencies ranging from 25 ms. prior to P300 to 25 ms. after P300. Values are in microvolts. **1b)** Scalp-recorded voltages for the average mTBI subject at the same relative latencies as in 1a). **1c)** t-score comparison of the scalp contour plots in 1a) and 1b). Regions where the scalp-recorded voltages for the average patient are significantly attenuated ($p < .02$) in comparison with the average normal subject are highlighted with **bold contours.** These pictures each represent an overhead view of the scalp, modeled as a sphere of radius 1.0, in which the top- center is the nasion.

Figure 2 - 2a) Voltages on the cortical surface (as computed by **CIT**) for the average normal subject at latencies ranging from 25 ms prior to P300 to 25 ms after P300. Values are in microvolts. **2b)** Voltages on the cortical surface for the average mTBI subject at the same relative latencies as in 2a). **2c)** t-score comparisons of the cortical surface contour plots in 2a) and 2b). Regions where the cortical surface voltages for the average patient are significantly attenuated ($p < .02$) in comparison with the average normal subject are highlighted with **bold contours.** These pictures each represent an overhead view of the cortical surface, modeled as a sphere of radius 0.6, in which the top-center lies under the nasion.