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Review

P300 Energy Loss in Aging and Alzheimer's Disease

J. Wesson Ashford[a,e,*], Kerry L. Coburn[b], Terrence L. Rose[c] and Peter J. Bayley[d,e]
[a]*War Related Illness and Injury Study Center, VA Palo Alto Health Care System, Palo Alto, CA, USA*
[b]*Department of Psychiatry and Behavioral Sciences, Mercer University School of Medicine, GA, USA*
[c]*Multivariate Measurement Technology Corporation, Sherman, CT, USA*
[d]*VA Palo Alto Health Care System, Palo Alto, CA, USA*
[e]*Department of Psychiatry and Behavioral Sciences, Stanford University, Palo Alto, CA, USA*

Abstract. The amplitude of the event-related potential P300 component is sensitive to aging and Alzheimer's disease (AD). Using a standard 20-electrode configuration, the P300 was measured during an "oddball" task in 14 young normal individuals (YN: 21–41 years), 11 elderly normal individuals (EN: 61–80 years), and 23 probable AD patients (AD: 63–93 years; NINCDS-ADRDA criteria). P300 latencies and amplitudes were measured at PZ. Additionally, algorithmic calculations were made from spline plots across the 11 central electrodes for P300 peak voltage latency and total field energy. The measured versus calculated latencies were in general agreement. Furthermore, the measured P300 voltage amplitude was closely related to the calculated total field energy. P300 voltage latency was significantly prolonged in the elderly, but not more so in AD patients (average latency [ms $\pm$ SD]; YN, 315 ± 21; EN, 364 ± 48 and AD, 361 ± 56). P300 amplitude showed the expected pattern of change from young to elderly to AD (average voltage [uV $\pm$ SD]; YN, 13 ± 5.1; EN, 8.3 ± 2.8; and AD, 4.9 ± 3.3). Summing the squares of each wave (an indication of power: $P = V^2 R$) showed the expected change with age more strongly than the P300 amplitude (average $\pm$ SD; YN, $44{,}397 \pm 32{,}386$; EN, $9{,}996 \pm 7{,}018$; and AD, $3{,}347 \pm 2{,}971$). Mini-Mental State Exam scores showed no relationship to P300 latency and minimal relationship to amplitude. Results suggest that the P300 is not obliterated in early AD, but is barely discernable in late AD. The approaches to calculating the P300 described here are potentially useful for measuring specific neural systems affected by aging and AD.

Keywords: Aging, Alzheimer's disease, dementia, event-related potentials, P300, P3a, P3b

INTRODUCTION

The P300 event-related potential (ERP) component represents an electrophysiological response of the brain to a stimulus which is unexpected or "surprising". This component is characterized by a positive voltage wave, occurring about 300 msecs after the stimulus onset in young individuals, and somewhat independent of stimulus modality or detail. The P300 phenomenon is widely studied due to the probability that it reflects an information processing cascade in which both attentional and memory processes are engaged [1–3]. Furthermore, the P300 has a particular relevance to Alzheimer's disease (AD) due to the profound memory impairments which occur early in the course of the disease and form the most prominent hallmark of this disorder [4].

The characteristics of the P300 are usually considered in terms of amplitude and latency. Using these indices, numerous studies have shown that P300 latency increases with age (1.0 to 2.0 msec/year; [5, 6]). In addition, studies suggest that the P300 latency is further increased in dementia [7–10] and is delayed in proportion to the severity of the dementia. P300 amplitude decreases with age and often becomes so small in

*Correspondence to: J. Wesson Ashford M.D., Ph.D., VA Palo Alto Health Care System, 3801 Miranda Avenue, Mailcode 151Y, Palo Alto, CA 94304-1290, USA. Tel.: +650 852 3287; Fax: +650 852 3297; E-mail: ashford@stanford.edu.

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elderly demented patients that it is difficult to measure [11]. However, it is recognized that task demands and other methodological factors can blur the distinction between the P300 changes in normal aging, mild dementia [12], and severe dementia [13, 14].

There is considerable controversy over the utility of the P300 as a diagnostic tool for AD. Some studies advocate the use of P300 as a reliable marker for AD [15]. A P300 abnormality is observed in demented patients in proportion to the degree of dementia [13, 14]. However, similar abnormalities are also observed in age matched controls [13, 14]. Further, P300 changes are found to be non-specific with regard to the etiology of dementia [16] or even diverse cognitive changes, as in schizophrenia [17]. For example, in schizophrenia (dementia praecox, clearly a form of impairment of cognitive functioning), the P300 amplitude is decreased without a change in latency [17, 18]. Because of the variability and uncertainty of P300 measurements in demented patients, a clear relationship between the P300 and dementia severity is not always apparent [13, 14]. In view of these inconsistent findings, it is now generally accepted that the most robust difference between AD and control groups is a reduction in P300 amplitude in the AD group, while latency is a less robust measure (for review see [11]).

One potential difficulty in measuring the P300 in AD patients is the change in waves that occur temporally before the P300, which may interfere with the P300 generation and delay its activity independently of any pathology directly impacting the P300 [19]. When resolving this issue, topographic specificity may be a key factor to consider [20]. Topographic specificity of the P300 can be divided into two components: the P3a and the P3b. These components are observed in healthy controls using various experimental designs which evoke ERPs which vary in scalp topography. To illustrate these differences, three different task designs can be considered; a "standard 3-item discrimination design", a "novelty design", and a "no-go design". Using a "standard 3-item discrimination design" (e.g., [21]) subjects press a button whenever an infrequent target (small circle) is detected in a series of standard stimuli (larger circle). Infrequently presented distracter patterns (checkerboard) are also presented. The checkerboard elicits the P3a component which has a frontal/central maximum, whereas the small circle elicits a P3b component with a bilateral parietal maximum. Peak latency is shorter over the frontal (P3a) and longer over the parietal electrode sites (P3b). The so-called "novelty P300" design produces a different pattern of results and is found when perceptually novel unexpected distracters (e.g., dog bark, color forms, etc.) occur in a series of more expected stimuli (e.g., tones, letters of the alphabet, etc.). Under these conditions, a frontal/central P300 is elicited with a relatively short peak latency that habituates rapidly [22, 23]. This potential is interpreted as reflecting frontal lobe activity related to the hippocampus [24, 25]. It is observed across modalities [26, 27] and populations ([28–31]. Consistent with the novelty interpretation, novelty P300 decreases in amplitude with repeated stimulus presentations suggesting that it may be more directly related to the orienting response than the P3b [23, 32–34]. Finally, an oddball design can be used in which an infrequent distracter is similar to the target and makes the discrimination between distracter and target more difficult. Under these conditions the distracter elicits the so called "No-Go" P300. Under these conditions, subjects do not respond to the infrequent distracter and only respond to the targets [35, 36]. The P300 from this type of distracter has maximum amplitude over central/parietal areas [37, 38]. The topographic distribution is somewhat more central than the parietal P300 from the target stimulus. The "no-go" P300 has been linked to response inhibition mechanisms, although this hypothesis is debated [39–42].

The P3a, novelty P300, and no-go P300 pattern of results reviewed here are suggested to be variants of the same ERP (see [1] for review). The P3a is considered to be related to focused attention and working memory and is elicited around the vertex as a reflection of some orienting response and subsequent medial frontal inhibitory neural processes involving dopaminergic modulation. In contrast, the P3b is considered to be related to updating of the neural representation of a stimulus, memory operation, and subsequent inhibitory processes following the target and is elicited in parietal regions bilaterally and is mainly generated by temporal-parietal cortex involving noradrenergic modulation.

When selecting a task capable of discriminating between the P300 generated by AD patients and controls, discrimination will obviously depend on the magnitude of the latency and the amplitude in each group. Amplitude has been suggested to be modulated by global level of arousal, such that the higher the arousal level, the higher the P300 (both P3a and P3b). When task conditions are relatively undemanding (such as when using an easy discrimination as with the standard oddball stimuli), P3b amplitude following

target presentation is suggested to be an index of attentional resources. Under these conditions, the amplitude of P3b is relatively large, and the peak latency is relatively short. In contrast, when demands for attentional resources increase, the P3b amplitude is smaller and the peak latency is longer due to the extra processing of intervening non-target events which engage attention [43]. The P300 can therefore be manipulated in terms of its latency and amplitude. At issue is whether the P3a or P3b component of the P300 produces a better discrimination of age-related and AD-related changes. One suggestion which is supported by empirical data [14] is that an oddball task with a simple discrimination shows the best discrimination between normal elderly and AD patients. One advantage of this task is that it is relatively easy and makes minimal demands on attentional resources. A second advantage is that an easy task would produce higher performance in the AD group, which in turn would produce more EEG epochs to be used for the averaging procedure.

The present study examined the effects of AD on P300 with regard to age, behavioral performance, and dementia severity as measured by the Mini-Mental State Exam (MMSE) [44] using a standard auditory oddball design. In order to determine the topographic distribution of the P300 impairment, recordings were made from 20 scalp leads. The P3b component of the P300 relates to underlying memory performance and has a posterior parietal distribution, which corresponds to the well-known posterior-temporal/inferior parietal distribution of Alzheimer pathology (particularly neurofibrillary changes and decrease of blood flow and metabolism). Therefore, a measure was developed for assessing the amplitude of the P300 in a relevant topographic distribution. Accordingly, this study used potentials from 11 electrodes at posterior locations anterior to the occipital leads for calculating "total field energy". The hypothesis was that global field energy measurements would account for a larger proportion of the age-related and dementia-related changes associated with the P300 than the conventional latency and amplitude measurements.

MATERIALS AND METHODS

Subjects

Older subjects were recruited from the patient population presenting with memory problems and dementia symptoms to the Southern Illinois University Regional Alzheimer Disease Assistance Center in Springfield, IL, and from a normal elderly population volunteering through the Center for Dementia Research (between 1987 and 1990). Of 47 serial patients meeting DSM-III-R criteria for dementia, 23 were further diagnosed as probable AD (mean age $\pm$ SD = 74.7 $\pm$ 7.7 years; mean symptom duration $\pm$ SD = 4 $\pm$ 3 years; mean MMSE score $\pm$ SD = 16.6 $\pm$ 7.3) [27] on the basis of NINCDS-ADRDA criteria [45] and included in the study. Eight of the 47 patients were diagnosed as unlikely AD (mean age $\pm$ SD = 71 $\pm$ 11 years; mean symptom duration $\pm$ SD = 5 $\pm$ 6 years; mean MMSE score $\pm$ SD = 25.6 $\pm$ 4.2) and were excluded from the study. The remaining 16 of the 47 patients met criteria for possible AD and were excluded from this report due to diagnostic uncertainties. Eleven elderly normal (EN) controls (mean age $\pm$ SD = 69.3 $\pm$ 6.3 years; mean MMSE score $\pm$ SD = 28.8 $\pm$ 1.7, note all >27 except one with MMSE = 24), spouses of dementia patients, had medical histories free from psychiatric and neurologic illnesses and showed no evidence of dementia. Thirteen young normal (YN) controls were medical staff or wives (mean age $\pm$ SD = 28.3 $\pm$ 6.2 years, range: 21 to 41 years). All subjects were free from medications having notable effects on the cholinergic system, including nonprescription antihistamines, for at least 2 weeks prior to recording (note that these recordings occurred prior to the availability of cholinesterase inhibitor medications for the treatment of dementia). Visual Evoked Potential (VEP) recordings from patients and global field power (GFP) analyses were performed blind to clinical diagnosis. Previous studies of these patients had found a selective flash P2 delay in the mandibular-referenced voltage records of the probable AD group [19] and that the GFP peak corresponding to the late P2 component of the flash VEP is delayed in the probable AD group but not in the demented unlikely AD group [46].

Auditory oddball recording

EEG recordings were made using 20 active scalp electrodes of the International 10–20 System (plus Fpz as inactive ground) referenced to linked mandibles. (This recording reference allowed comparison to a large normative database for clinical purposes.) Individual low-noise tin electrodes were applied with collodion, all electrode locations were recorded and confirmed to be within 3 mm of their target positions, and all impedances were kept below 1.6 kOhm. Additional electro-oculogram, electrocardiogram, and submental electromyogram electrodes were used for

artifact monitoring. The recording instrument was a Bio-logic Brain Atlas III with a parallel Grass model 6 electroencephalograph (EEG) for artifact monitoring.

Auditory oddball task and ERP analysis

In a darkened room, subjects were instructed to count rare tones in an auditory oddball task. Performance on the auditory oddball task was recorded as the percentage of target items identified as oddball tones. Data were recorded between 0 and 512 msecs after the stimulus onset. To achieve an unbiased estimate of P300 latency and GFP, potentials were referenced to a virtual average reference [46]. Re-referenced bins were then subtracted (rare-frequent) and 3-point smoothed 40 times to achieve an effective low-pass filter. Topographic display with a spline program [47] indicated that young individuals had relatively less positivity during the P300 epoch over the frontal or anterior temporal electrodes compared to posterior regions (Fig. 1A). Therefore, the estimated potentials at the 11 central electrodes (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, T3, T4; International 10–20 System) based on the spline program (Fig. 1), were squared (preserving sign) transforming potential (voltage) into an index of power (assuming constant resistance at all electrodes: $P = V^2 R$, units related to watts). The power indices from all 11 electrodes were added (if positive, thus

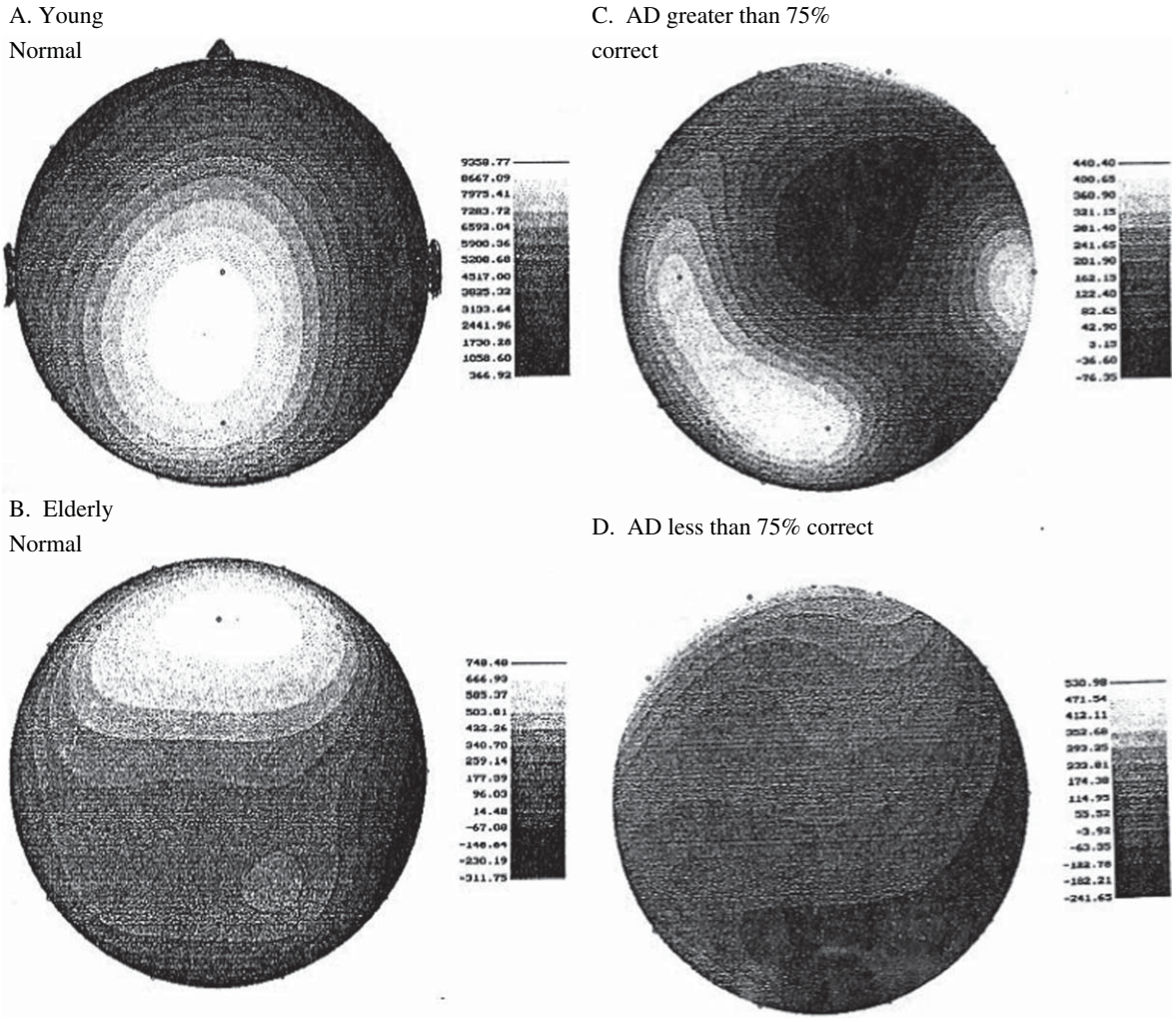

Fig. 1. Topographic distribution of P300 total field energy made from averaging of repeated stimulus presentations in an auditory oddball task in; (A) young normal adults ($n = 14$), (B) elderly normal adults ($n = 11$), (C) patients diagnosed with probably Alzheimer's disease ($n = 10$) who scored >75% on the oddball task, and (D) patients diagnosed with probably Alzheimer's disease ($n = 13$) who scored <75% on the oddball task. Spline plot data was measured across 11 central electrodes.

removing negative voltages), to give an index of field power. The maximum value in the 290 to 490 msec range was designated as the P300 peak power latency. The latencies at 15% of the estimated P300 peak power amplitude, before and after the peak were found (rising and falling) and the power values from these points were summed (essentially integrating the area under the curve produced by the P300 wave), yielding an index of P300 total field energy (units related to watt-hours, but not absolute given uncertainties in tissue factors including skull and scalp). For the oddball paradigm, there were 20% rare tones, and the task was run until 50 artifact-free rare-tone trials were recorded, providing 50 rare, target tone responses and approximately 200 frequent tone responses. The responses were averaged to visualize specific ERPs.

Analysis

There was considerable variability in all aspects of the P300 component, including latency, amplitude, sharpness of focus, total energy, scalp location of peak energy, and general topography. The purpose of this study was to evaluate the relationship between P300 peak voltage latency, amplitude, peak power latency, and P300 total field energy with respect to age and dementia diagnosis, including auditory-oddball task performance and the MMSE index of dementia severity. Statistical tests included one-way analysis of variance (ANOVA). Significant effects were further characterized using follow-up t-tests. Two-tailed levels of 0.05 were used in all tests.

RESULTS

Task performance

YNs and ENs had close to perfect performance on the auditory oddball task. Of 23 probable AD patients, there were 10 mild to moderately demented individuals (mean MMSE $\pm$ SD = 22.1 $\pm$ 3.6, range = 18–28) who scored >75% correct on the task. There were 13 probable AD patients (mean MMSE $\pm$ SD = 12.4 $\pm$ 6.5, range 1–23), who scored less than 75% correct on the task. A score of less than 75% suggests that the individual with these scores may not have been adequately attending to the oddball task. Consequently, subjects were grouped according to whether they scored above or below 75% correct on the oddball task. A t-test for groups with unequal variances showed the MMSE scores of the two AD groups were significantly different ($t(18) = 4.55, p < 0.0005$). However, initial analyses revealed that none of the observed mean differences between the two AD groups on the P300 parameters were statistically significant. For this reason the two AD groups were combined for most subsequent analyses.

P300 Measurements

Latency

Two measures of P300 latency were examined. Peak voltage latency reflects the traditional measure of latency used in prior studies. Means ($\pm$SD) for the three groups on this measure were 315 ± 21 ms in the YN group, 364 ± 48 ms in the EN group, and 361 ± 56 ms in the AD group. A one-way ANOVA indicated a significant main effect of group ($F(2,44) = 4.67, p < 0.05$). The two elderly groups (EN and AD) did not differ reliably from each other but the young participants had shorter latencies than the elderly normal participants ($t(32) < 1$, ns, and $t(22) = -3.33, p < 0.005$, respectively) (Fig. 2A).

The calculated measure, peak power latency, was also examined. Mean scores ($\pm$SD) on this measure were 331 ± 38 ms in YN, 371 ± 41 ms in EN, and 378 ± 69 ms in the AD group. Thus, this measure of latency of the peak of the field power was prolonged in the elderly (Fig. 2B), but not further prolonged in the AD group. An ANOVA revealed a marginally significant main effect of group ($F(2,44) = 2.99, p = 0.06$).

Amplitude and energy measures

The peak voltage amplitude measure showed effects of both age and dementia. Young participants displayed the greatest amplitude (13.0 + 5.1 uV) followed by those in the EN group (8.3 + 2.8 uV), and then the AD participants (4.9 + 3.3 uV). A significant effect of group was revealed in the ANOVA ($F(2,44) = 18.96$, $p < 0.0001$), and post-hoc tests showed the mean difference between the YN and EN groups to be significant ($t(22) = 2.73$, $p < 0.05$) (Fig. 2C), as well as that between the EN and AD groups ($t(32) = 2.92, p < 0.01$). This order is the expected pattern of deterioration from young to elderly to dementia.

Rather than examining only the amount of peak energy, the total field energy (summing the squares of each wave across its duration and expanse) variable reflects the total amount of energy of the P300 waveform, again showing the expected amplitude pattern even more strongly. As with peak ampli-

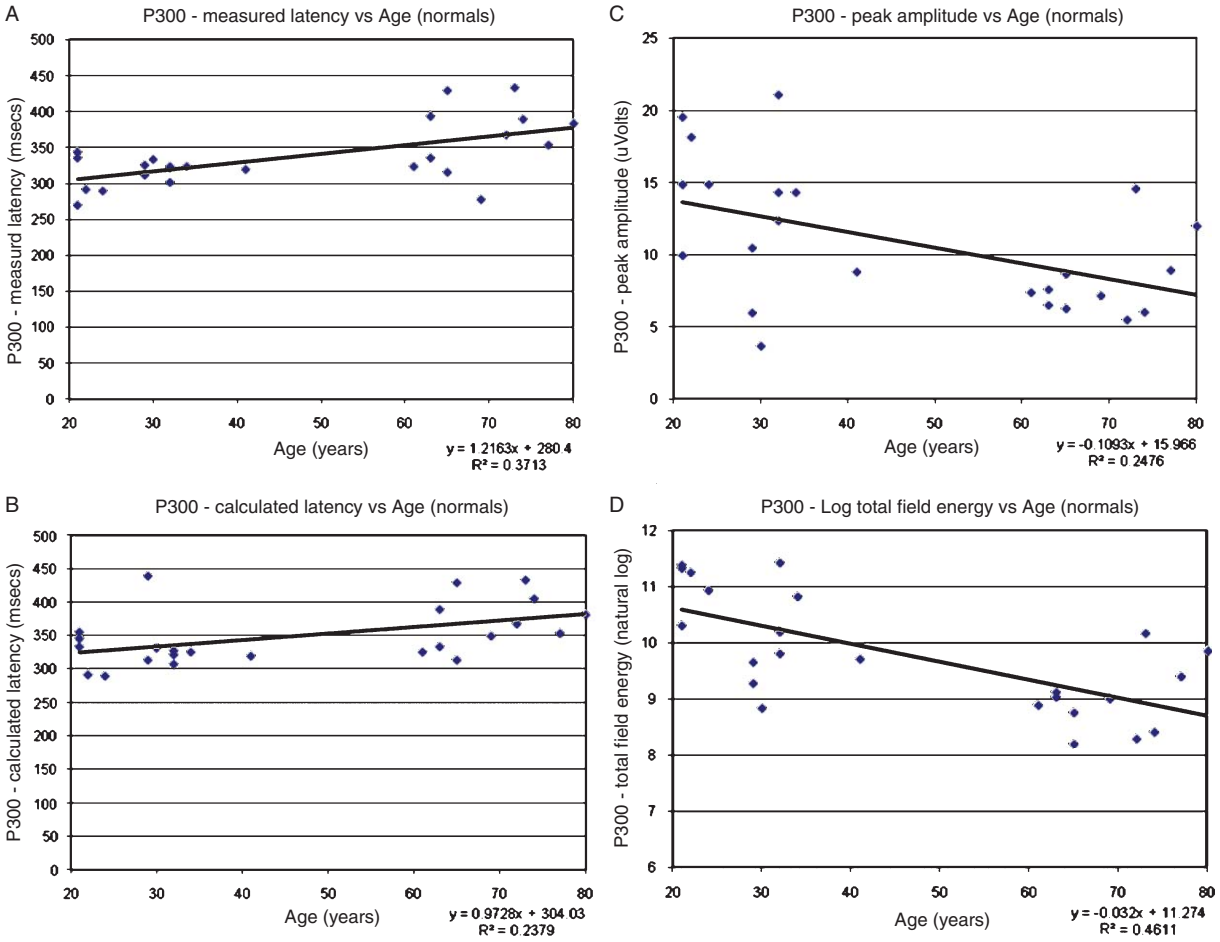

Fig. 2. P300 waveform as a function of age in young normal adults ($n = 14$) and elderly normal adults ($n = 11$); (A) P300 measured latency, (B) P300 calculated latency, (C) P300 peak amplitude, (D) Log total field energy.

tude, mean scores (±SD) on this measure were greatest for the YN group (44,397 + 32,286) followed by the EN group (9,996 + 7,018) and, finally, the AD group (3,347 + 2,971) (Fig. 2D). For AD patients with MMSE scores >20, mean total field energy (±SD) was 3,223 ± 3,357; with MMSE scores 10–20, 3,719 ± 3,259; and with MMS < 10, power = 2,327 ± 1,210, indicating that the P300 is not obliterated early in AD, but is barely discernable in late AD (Fig. 1).

Unlike the peak amplitude measure, variances on total field energy revealed large departures from homogeneity of variance across groups, and a graph of this variable against age showed the relationship to be nonlinear. The ratio of the largest to smallest variance was 118, a very large value. Therefore, in order to more adequately equate the variances across groups and transform the scores to ones more linearly related to age, a natural logarithmic transform was applied to the original scores, (a transformation supported by the Gompertz Law of Aging). This transformation reduced the ratio of largest to smallest variance to 4.0 and provided a more linear relationship to age. Mean values (±SD) on the transformed scores were 10.4 + 0.88, 9.0 + 0.62, and 7.6 + 1.24 for the YN, EN and AD groups, respectively.

An ANOVA of the log transformed total field energy scores revealed a highly significant main effect of group ($F(2,44) = 31.91$. $p < 0.0001$). A t-test contrasting the YN and EN groups was highly significant ($t(22 = 4.34$, $p < 0.0005$), as was the contrast between the EN and AD groups ($t(32) = 3.67$, $p < 0.001$). Thus, both age and dementia were associated with reductions in total field energy.

DISCUSSION

The results from this study replicate the numerous studies that have shown that the latency of the P300 phenomenon increases with age. Our results also show a corresponding decrease in P300 amplitude with increasing age, especially when calculated using spline interpolations and deriving total field energy. While the spline plots appear to show that the P300 peak shifts forward with age, an analysis of energy amplitudes across the scalp shows that this effect was in fact due to a decline in energy in posterior regions relative to anterior regions. Presumably the latency reflects the time course of activity responsible for recognizing the improbability of the stimulus, while the amplitude represents the size of the ascending volley of neuronal activity and the capacity of neuronal systems to respond to that volley. Thus, the P300 latency prolongation with aging indicates that P300-related processing slows with age, while the energy decrease associated with the P300, about 75% from the young to the elderly in this sample, is associated with a decline in the posterior cortex more than the frontal cortex (comparing spline plots and field potentials). The shift in latency from normal elderly to dementia is not apparent in our data, although the P300 in the AD group was generated with significantly less energy relative to the normal elderly group. The finding of no shift in latency in the AD group relative to controls is at variance with many other studies which have used an auditory oddball task (for review, see [11]). This may be due to the fact that unlike our study, participants in most of the previous studies were required to perform an overt motor response, thus allowing averaging of the EEG epochs relative to correct performance. Furthermore, the requirement for making an overt motor response might better probe some attentional processes associated with the selection of the motor response and sensorimotor integration. The topography of the small potentials seen in several probable AD patients indicates severe disruption of the physiological mechanisms generating the P300. However, since the rare tones still elicited more energy than the common tones in the 300 to 500 msec range, some residual P300 activity seems to be present, even in the severely demented AD patients.

This study further shows that the latency of the P300 peak field power increases with age, just as has been extensively reported for voltage peak latencies in many prior studies [4, 8–10, 25]. Furthermore, the amplitude of the total field energy decreased with age, by as much as 75%, and is consistent with prior reports of a decrease of P300 peak voltage amplitude with age. The P300 total field energy decreased further in the AD group even in mildly demented individuals. Further, in several of these demented individuals, the P300 activity is so small that measurement of the latency, field potentials, and total field energy becomes uncertain. A substantial difference between normal elderly and the mildly demented AD patients is present even though the patients could perform the oddball task with substantially correct performance, so the difference in the P300 parameters between these groups was not specifically related to task performance. Furthermore, without removing patients with unclear P300 events [9], neither task performance nor severity of dementia corresponded to a robust difference in P300 amplitude or latency compared to normal elderly subjects.

The major decline in P300 total field energy in the elderly seems to be located posteriorly, though there is also evidence for a loss of frontal activity with aging and age-associated memory impairment [6]. While others have suggested that the P300 vector moves forward with age [12], the data from the present sample indicate that the apparent shift is actually due to a selective loss of energy over the posterior temporal-parietal regions (Fig. 1A,B). In the more mildly demented patients (MMSE >20 and/or >75% correct on the auditory oddball task), the distribution of the P300 energy seems to reflect a loss of energy centrally, represented as a black hole (Fig. 1C) and essentially no P300 in the more impaired patients (Fig. 1D). This finding is consistent with the observation of large reductions of P300 amplitude in the parietal region for AD patients [48]. The topographical distribution found in the present study is similar to that seen in patients with hippocampal damage [25]. This pattern of loss is consistent with the pathological data which indicate that AD-related neurofibrillary changes occur in the entorhinal cortex and hippocampus very early in the course of the disease, and soon extend to the posterior-temporal and inferior parietal regions [49]. This pattern is reflected in AD patients by reduced blood flow and metabolism in the posterior temporal and parietal regions [50]. Thus, the pattern of loss of P300 energy over the posterior cortical regions is consistent with the distribution of neuronal disturbance seen in the brains of AD patients.

The P300 generation likely occurs in a sequence of at least two steps. First, a brain region or dedicated distributed system sensitive to "unexpected occurrences" must determine that an unusual event has occurred [6]. The temporo-parietal junction appears to be impor-

tant in such detections [27]. There is also evidence that the prefrontal cortex plays a role [51], likely as an attention system to guide processing in cortical regions more involved in the processing of incoming sensory information [52]. The initiating system must in turn activate the neurons responsible for synchronizing and generating the P300 component. That activation likely involves a signal through critical ascending brain systems, such as the cholinergic nucleus basalis of Meynert [53], the noradrenergic system projecting rostrally from the locus coeruleus [54], or the serotonergic raphe neurons [55]. All three systems project to the hippocampus and diffusely to the cortex and are affected by age and AD pathology. Which system is involved in the generation of any given P300 event may depend on internal sets or task demands. However, as discussed above, these neural systems whose activity appears to involve generating the P300 are associated with the slowing and amplitude reduction shown in this study to be associated with aging and AD.

An important issue is exactly which brain regions generate the actual P300 component observed on the scalp. Cortically projecting axons cause potential changes in a substantial proportion of radially oriented dendrites of cortical pyramidal neurons, leading to the voltage changes observed on the scalp [56]. The location of the major field generators has been suggested to be temporal lobe structures, possibly including the hippocampus [57, 58], or frontal and temporo-parietal structures [51]. Alternatively, multiple brain structures may be activated diffusely [52, 59–61]. The loss of P300 over a particular large cortical region may suggest either that the medial temporal lobe structures are not suitably activated to generate a scalp voltage or that cortical generators in diffuse areas are dysfunctional.

Simultaneous activation of numerous brain structures, which the P300 may be reflecting, would support concurrent activation of diffusely spread neural networks [52, 62] and parallel distributed processing [63]. Synchronous activation would provide a mechanism for permitting long-term potentiation-type memory mechanisms, which is the specific type of memory function that is most disrupted by AD [4]. The loss of P300 energy across a specific scalp region would suggest that the neuronal ensembles responsible for generating that energy were dysfunctional and have a reduced capacity to store new information. The basis for that dysfunction could lie at any of the steps leading to the generation of the P300, including both loss of cortically projecting brainstem neurons (cholinergic, noradrenergic, or serotonergic) or loss of the synapses involved in generating the dendritic dipoles, in the medial temporal lobe or neocortex [64–67]. Accordingly, a large amount of P300 energy loss occurs across the posterior scalp in normal elderly, and the dementia associated with AD appears to develop after that loss progresses beyond a critical threshold.

It should be noted that the current study used a measure of global field power (GFP) which was based on squaring the output of up to 11 electrodes showing positive P300. This method is different from the standard index in which GFP is calculated by squaring the output of all electrodes, regardless of whether they are positive or negative. In the standard calculation, both positive and negative polarities assume positive values according to the view that the activity of generators are indifferently associated with positive or negative scalp voltages. The assumption is that the underlying pattern of cortical sources can generate both positive and negative components of the voltage at scalp level as a function of their orientation with respect to the scalp surface. However, there is no ideal electrode montage for computing GFP, and virtually all ERP studies use limited electrode montages centered on Pz or Cz. The current findings based on a subset of 11 electrodes suggest that the modified GFP analysis may be more sensitive to the effects of age and AD than the standard array. However, this conclusion awaits further investigation using broader samples with regard to both the aging and dementia severity spectra.

One of the major difficulties in the AD field is the distinction of normal aging from AD. Our data suggest that most of the P300 energy loss occurs during the course of aging, while the scalp distribution of P300 energy loss in early dementia associated with AD is different from normal aging. However, an important issue in the AD field that has recently emerged is the association of the APOE genotype with the risk of developing AD [68]. More specifically, the association between the APOE genotype and early reductions in CSF Aβ and Aβ levels in fronto-corical regions is potentially related to the P300 changes [69, 70]. Our data suggest a need to study the P300 waveform in relation to APOE genotype and to investigate the involvement of attention mechanisms. Recent evidence indicates that P300 voltages are significantly decreased in amplitude and increased in latency in individuals with a family history of AD [71] and for ApoE-ε4 carriers compared to non-carriers [72].

The P300 is an electrophysiological phenomenon that is relevant to the study of dementia and AD. For example, longitudinal monitoring of P300 could reveal

pathology-specific changes. Future understanding of AD and its progression may be gained by studying P300 effects using higher density electrode arrays and other brain imaging techniques across the spectrum of normal aging and AD with regard to specific genetic factors, particularly APOE genotype.

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