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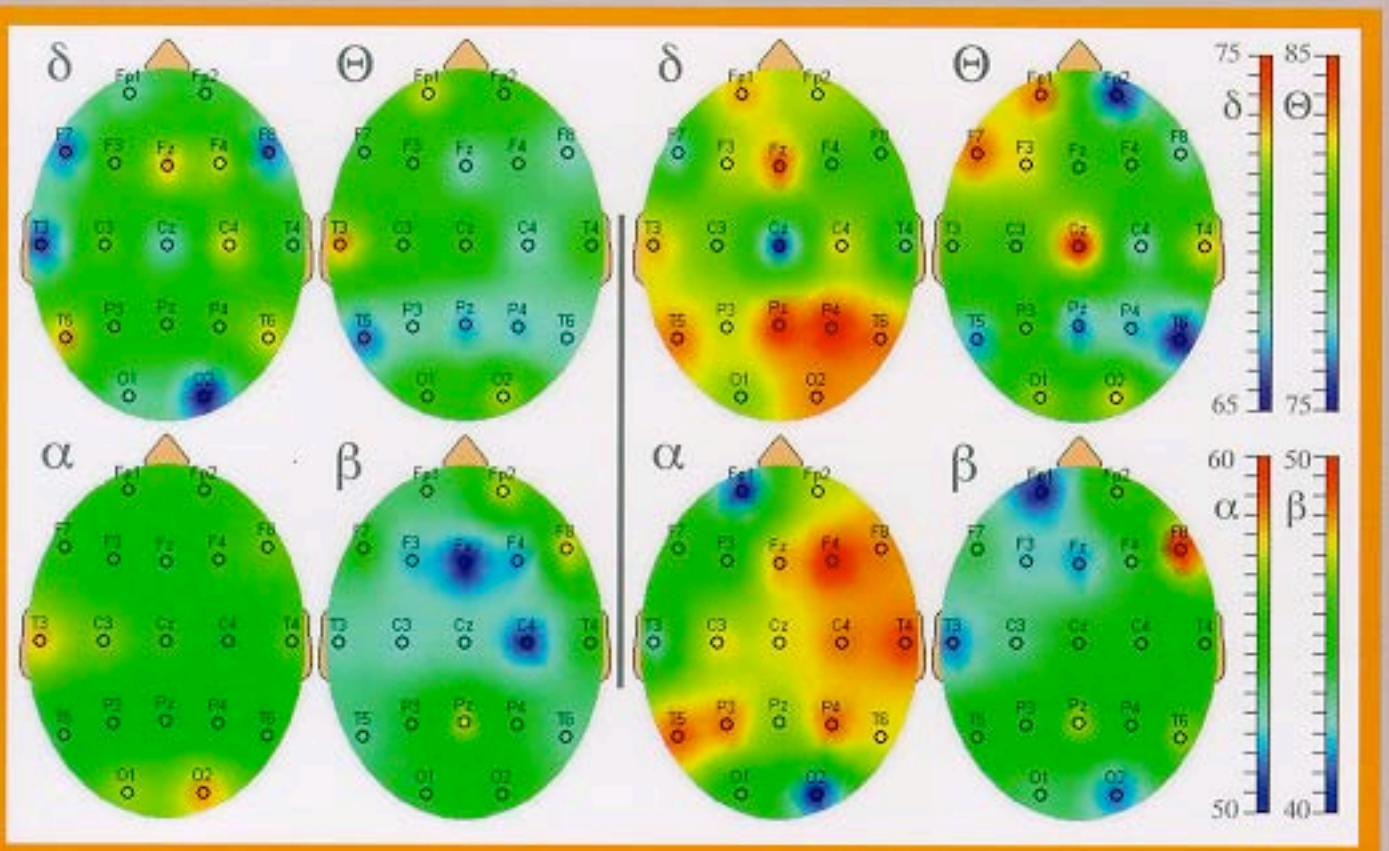

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Identification of Diagnostic Evoked Response Potential Segments in Alzheimer's Disease

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Evoked response potentials (ERPs) to brief flashes of light were analyzed for constituent features that could be used to distinguish individuals with Alzheimer's disease (AD, $n = 15$) from matched control subjects ($n = 17$). Statistical k nearest-neighbor methods distinguished AD from control with a maximum sensitivity of 29% and false alarm rate of 12%. The comparable sensitivity/false-alarm values for a statistical projection pursuit method and an extended projection pursuit method, which selectively identify discriminative features for classification, were 75%/18% and 100%/6%, respectively. The results demonstrate that combinations of selected ERP time segments across different electrodes contain signal features that discriminate AD from control subjects with high sensitivity and specificity.

Key Words: **Alzheimer's disease, EEG; evoked response potentials; projection pursuit.**

INTRODUCTION

A number of quantitative EEG measures have been used in attempts to identify physiological correlates of the cognitive changes found in early stage Alzheimer's disease (AD). Using multiple linear regression analysis, Claus *et al.* (7) established that a slowing of spectral EEG predicts the rate of subsequent cognitive and functional decline in patients with AD. EEG coherence is thought to be a measure of regional cortical synchronization and possibly the functional status of intracortical communication (33). Wada *et al.* reported that patients with AD had significantly lower intra- (49) and interhemispheric coherence (50) than controls in the alpha and beta frequency bands. Other workers showed that AD patients, particularly those with severe cognitive impairments (17), have reduced alpha band coherence in temporo-parieto-occipital areas (32). Further evidence linking coherence to the evolution of AD comes from results suggesting that patients homozygous for the Apo-E epsilon4 allele, a predisposing condition for sporadic Alzheimer's, have particularly reduced bilateral coherence in select cortical fields.

EEG complexity (correlation dimension) is another measure reported to discriminate AD from other age-related disorders of cognition. Recent work with this method found that the dynamics of brain state development differed in mild AD patients from that measured in mild cognitive impairment or subjective memory complaint individuals (51). Still other EEG indices are reported to discriminate AD from normal controls (6, 16, 40–42) or other types of dementia (45, 11), as well as to differentiate subgroups among AD patients (26, 33).

Taken together the above findings constitute impressive evidence that early stage AD is associated with a particular set of EEG characteristics. There is also reason to suspect that these characteristics may be sufficiently pronounced to be useful in diagnosis. Since early diagnosis and intervention may alter the outcome of the disease (48, 14), the development of practicable and efficacious test regimens is of increasing importance. In a review of objective diagnosis in AD, Hegerl and Moller (21) concluded that EEG has comparable diagnostic sensitivity and higher specificity than SPECT and other routine structural brain imaging (cCT, MRI). For monitoring changes of brain function by serial sampling (e.g., during therapy with antidementia drugs), the authors found EEG to be the best available method. However, there a number of well recognized problems in using quantitative EEG as a diagnostic aid for neurological and psychiatric disorders (27–30, 22, 3, 5).

The present study tested if an approach developed for radar and sonar signal processing (2, 8, 31, 20, 39) would be useful for identifying EEG correlates of AD. The evolved method uses projection pursuit algorithms to search for differentially diagnostic segments within the time locked signals, with correlated co-occurrences of segments used as composite features in classification. Because time-locked signals are required, evoked

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response potentials (ERPs) to photic driving were used in the studies instead of free running EEG. The results indicate that application of iterative projection pursuit to ERPs can be used to recognize AD with a high degree of accuracy.

METHODS

Patient Population

All data were collected at the University of California, Irvine, Medical School. Fifteen patients with AD were admitted to the study. All were outpatients, unhospitalized and unmedicated, meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV) criteria for dementia of the Alzheimer's type and National Institute of Neurological and Communicative Disorders (10) and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD. Average age was 76.2 ± 5.7 years. The severity of illness was limited to mild or moderate, based on a screening Global Deterioration Scale (GDS) rating of 3, 4, or 5 and a screening Mini-Mental State Examination (MMSE) score between 16 and 28, inclusive (22.0 ± 3.2, mean plus standard deviation).

Normal Controls

Seventeen normal subjects matched for age, gender, and education level were recruited from the community. Each subject was interviewed by a research psychiatrist using DSM-IV and MMSE to rule out AD and other psychiatric diagnoses.

Exclusion Criteria

Any subject with a history or current evidence of any of the following medical conditions were excluded from the study: (i) severe or unstable disease other than AD, (ii) medical or psychiatric disorders that might complicate the assessment of dementia, (iii) a disability that may prevent the subject from completing all study requirements (e.g., blindness, deafness, language difficulty), and (iv) recent intake of an investigational drug, drug known to cause major organ system toxicity, any CNS-active medication, or any recreational drug. Prior drug or alcohol use was not screened. All subjects' vision was checked.

Apparatus

The testing system consisted of an electrode cap (Physiometrix), amplifier system (Nihon-Kohden), and PC-based analysis/display device, along with a bright strobe light (1.28 J per flash). ERPs were collected from 19 sites on the skull through scalp electrodes embedded in a tight-fitting meshwork cap. (For sites of electrode placement, see Fig. 4.) The leads were connected to an amplifier system including a set of 19 amplifiers, digitizing of the amplifier outputs, and interface to PC. The amplifiers had 12-bit resolution, 24-bit DSP preprocessing, and EEG/ERP sample rates of 256 Hz. Each of the 19 channels exhibited frequency response 0.1 Hz to 5 KHz; risk current <10 μA; sensitivity 0.05 μV; input impedance >800 Me; noise $< 2\mu$V p-p 0.5 to 30 Hz; CMMR >90 db, 60 Hz, output to PC serial port. Captured signals were stored real-time in the PC and the raw unprocessed signals were available for analysis by the algorithms as described below.

Procedures

Subjects were acclimated to the apparatus for 5 min during which time the quality of each of the 19 leads was checked; acceptable electrode impedance level was 10 Kohm. Once normal voltage EEG was recorded from all sites, stimuli (visual light flashes) were presented at 60 per minute (1 Hz) for a session of 5 min in duration, and continuous ERPs were collected.

Analyses

For each subject, ERPs were averaged into 1-s voltage series for each electrode channel, and binned in 5-ms time segments, so that there was a sequence of 200 voltage values for each channel. These voltage vectors for all electrodes were conflated to make a single vector for each subject consisting of $200 \times 19 = 3800$ elements.

k-nearest-neighbor analysis. For each subject, the k nearest neighbors among the remaining subjects (15 Alzheimer's and 17 controls, minus the subject currently being analyzed) were found using Mahalanobis distance measures, for $k = 1,3,5$. In each case, the category (Alzheimer's or control) that was in the majority of nearest neighbors was chosen as the deduced diagnosis of the subject being tested. A deduced Alzheimer's diagnosis of an actual Alzheimer's patient was classed as a true positive; a deduced Alzheimer's diagnosis of an actual control subject was a false positive; a deduced control diagnosis that was correct was a true negative; and a deduced control that was not correct was a false negative.

Projection pursuit. Subsets of the data were randomly generated, in which all but a few voltage values were removed. For purposes of projection pursuit methods, these subsets are equivalent to subspace projections of the 3800-dimensional vector that corresponds to the total recorded evoked response, as just described. In each subspace, k nearest neighbor (for $k = 1,3,5$) was performed against all remaining subjects as above (24). Votes for Alzheimer's versus control were tallied across all sampled subspaces, and the resulting majority classification reported for each of the three values of k used.

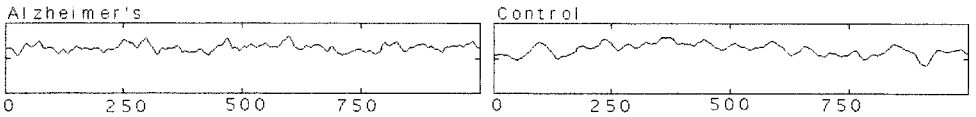

FIG. 1. Representative evoked responses from an Alzheimer's (left) and matched control subject (right). Shown are 1 s of averaged data (positivity up) for a single electrode site (C4). The light cue occurs at the left edge of each waveform; time marks appear at 250, 500, and 750 ms after the cue (see text).

Extended projection pursuit. An initial series of subspace projections were generated randomly as above, *k* nearest neighbor was performed, and votes scored as above. Based on these findings, the most predictive subspaces were selected and the process performed again; this iterative compilation of subspaces continued until all subspaces chosen were more predictive than a preselected threshold amount (71%), and the resulting majority classification was reported as above.

Cluster analysis. Euclidean distances were computed among the subjects using (a) all 3800 features for each subject and (b) only the 100 features in the final subset arrived at via extended projection pursuit. Single-linkage cluster analysis (12) was applied with the results plotted as dendrograms in which the height of each bar indicates the average distances between all elements included under that bar.

RESULTS

Figure 1 shows a representative example of averaged evoked potentials from an Alzheimer's subject (left) and a matched control (right) in response to light flashes repeated at 1-s intervals (see Methods). Shown are complete 1000-ms (1 s) averaged evoked responses for a single electrode (standard electrode site C4, located just to the right of center on the scalp); time tick marks are at 250, 500, and 750 ms.

Discrimination of AD from Control

Single vectors (3800 elements) were constructed for each subject. Jackknife analyses were run in which all the subject records but one were used as matching data, and the remaining subject was tested to see which category (Alzheimer's or control) that subject would be placed in, based on which of the matching data were its nearest neighbors. For comparative purposes, as described, each record was run for each of three classification algorithms (*k* nearest neighbor, projection pursuit, extended projection pursuit) with three parameter settings. Receiver operating characteristic (ROC) plots were made for all of these tests.

Figure 2 shows the results. Sensitivity [true positives/(true positives + false negatives)] is plotted on the *Y* axis against the false positive rate (1-specificity) on the *X* axis. For *k* nearest neighbor, with 1, 3, and 5 neighbors chosen, sensitivity does not exceed 25% with a false positive rate of 12%. Projection pursuit methods with three parameter settings achieved a best rate of 75% sensitivity with a 29% false positive rate.

The extended projection pursuit method, via iterative identification of differently predictive regions within the ERPs (as shown in Table 1), attained sensitivity of 100% with a false positive rate of 6.1% (these figures were the same for *k* of 1, 3, and 5). All Alzheimer's subjects were correctly classified, and one control subject was misclassified as Alzheimer's.

Quantitative Classification

Single vectors (3800 elements) were constructed for each individual. Metric distances were then used to measure the relative similarity of the responses of different participants in the study. Figure 3 shows dendrograms indicating pairwise Euclidean distances among the waveforms with complete feature sets (left) and with reduced feature sets identified by extended projection pursuit (right). Subjects are identified as Alzheimer's (A) or control (C). The height of a crossbar indicates the average distances among records under the crossbar. Distances among high-dimensional objects cannot be fully illustrated with dendrograms. In part this is due to the nontransitive nature of neighbor relations: for instance, it is possible for A1's nearest neighbor to be A4, but for A4's nearest neighbor to be some other vector; the dendrogram does not describe both such relationships. The left-hand dendrogram records that subjects A1 and A4 are very similar, as are A11 and C18. It can be seen on the left that the similarity measures are not substantially larger among members of a single diagnostic category (Alzheimer's or control) than they are between members of different categories. The right-hand panel of Fig. 3 shows the pairwise distances among only those components of the waveforms identified by the extended projection pursuit method as already described. The distances among members within diagnostic categories are significantly lower than the distances of members between categories; i.e., the within-category similarity is lower than the between-category similarity in this subspace.

As described above (see Fig. 2), a single control subject was incorrectly classified as Alzheimer's; that subject, C23, has nearest neighbors in the reduced space that are Alzheimer's subjects (A4 and A7). Subject C29 also appears to have Alzheimer's subjects as nearest neighbors, but actually has nearest neighbors that are controls. In this instance, C29's nearest neighbor is

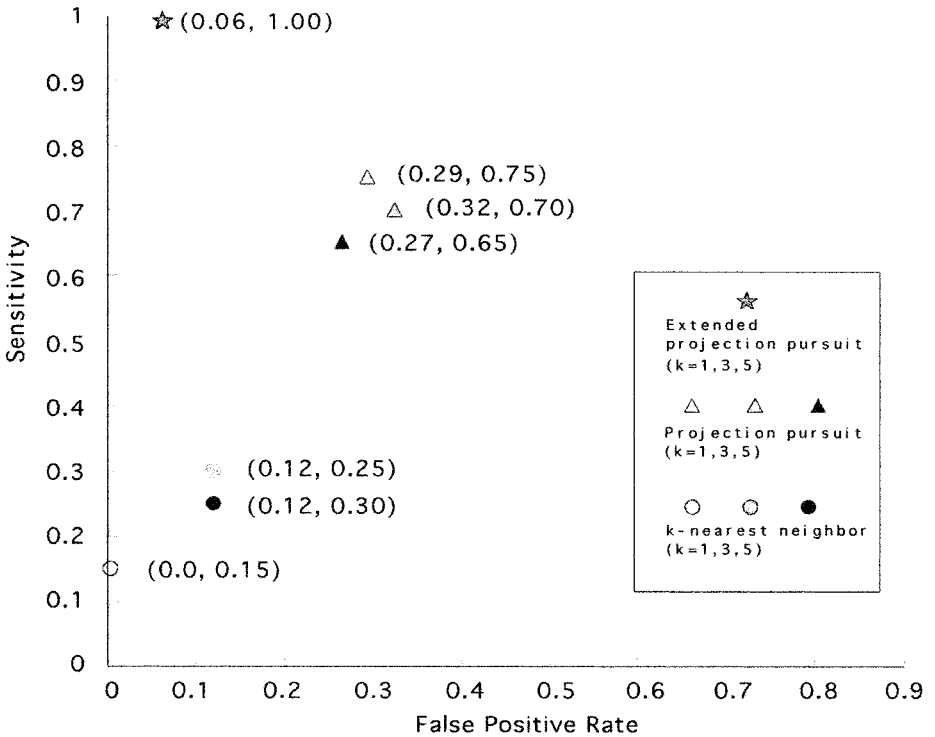

FIG. 2. Receiver operating characteristic for three analysis techniques (*k* nearest neighbor, projection pursuit, extended projection pursuit) for each of three parameters ($k = 1, 3, 5$). See text.

C-16, but since A-7's nearest neighbor is C-29, the latter subjects are adjacent in this diagram. This is an instance of the nontransitivity of nearest neighbors, as discussed above.

Temporal Location of Predictive Features in the ERP

Each 5-ms time segment was scored for its predictiveness, calculated as the number of times a segment is used in a correct prediction divided by the number of times the segment is used in all tests. (Thus the measures of predictiveness range from 0 to 100). Table 1 shows the most predictive time intervals identified in the averaged records of a single electrode, with their relative predictiveness. (The electrode selected for this table, C4, is typical of the predictiveness of other electrodes). Segments with highest (>90%) predictiveness were found at latencies of 250–300 and 350–400 ms following the light flash and at latencies of 850–900 and 900–950 ms following the light flash. Subsequent analysis showed that these predictive components were not present in initial trials for a subject but instead developed during repetitive testing.

Spatial and Frequency Location of Predictive Features in the ERP

Figure 4 shows the relative power in each of four frequency bands (delta, theta, alpha, beta) for averages

TABLE 1

Predictive ERP Time Segments (in ms)

	0–99	100–199	200–299	300–399	400–499	500–599	600–699	700–799	800–899	900–999
96–100			+	+						+
91–95			+						+	+
86–90	+	+					+	+	+	
81–85	+						+	+		
76–80	+	+	+					+		+
71–75	+	+	+	+		+			+	+

Note. Occurrence of predictive time segments identified by extended projection pursuit for a single electrode (C4), together with their relative predictiveness (see text). Each column indicates a period of 100 ms; each row is the predictiveness (defined above) of identified segments occurring within each 100-ms period.

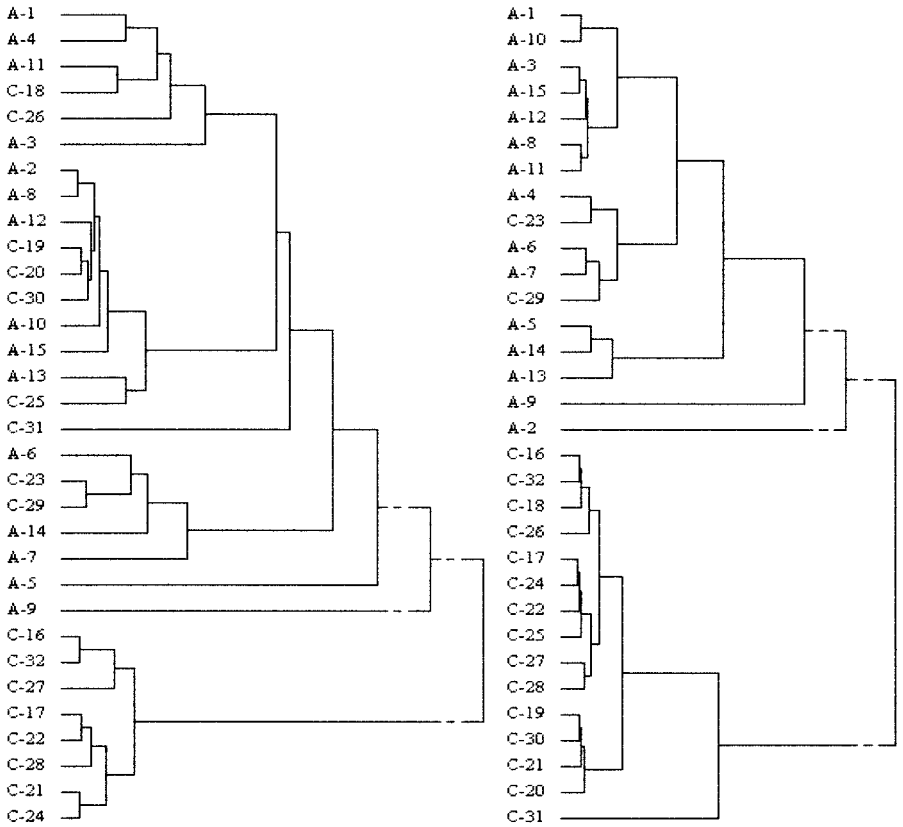

FIG. 3. Dendrograms generated by a single-linkage clustering algorithm (see Methods). Shown are Euclidean distances among evoked response records with all features (left) and reduced feature set (right).

of Alzheimer's and matched controls, plotted across the 19 electrodes of the headset apparatus. The left half of the figure shows the four plots for Alzheimer's subjects; those for controls are on the right. For each plot, the head is shown from the top, with the head facing toward the top of the page.

The figure shows the log of the average relative spectral and spatial distribution of power within groups (Alzheimer's, control) and between groups. Power in the delta frequency band was greater in Alzheimer's subjects than in controls; much of the added power was in the central and parietal regions. Alzheimer's subjects also showed a slight decrease in power in the alpha band, and alpha activity measures shifted to more anterior electrode sites; a similar shift occurred in the beta band. Consistent with these findings, Huang *et al.* (23) found a shift in computed sources of alpha and beta activity in an anterior direction, as well as increased power in delta.

DISCUSSION

Projection pursuit is a computational method that is coming into wide use for isolating similarity-based clusters in high-dimensional data sets. Extended or iterative pursuit is a variant in which dimensions are dropped and the remaining dimensional set searched for more sharply defined clusters. The method can uncover otherwise obscured groupings and has the further advantage of isolating defining variables (24). It is also computationally simple. The present study is a first attempt to apply projection pursuit to the problem of identifying electroencephalographic correlates of Alzheimer's disease.

Temporally segmented (5-ms bins) averaged evoked responses to photic stimuli from 19 recording sites were used to generate a high dimensional vector for each of 15 AD patients (diagnosed by conventional methods) and 17 matched controls. Extended iterative projection pursuit, but not *k* nearest neighbor analysis or projection pursuit alone, successfully distinguished between the two groups. In a round-robin procedure in which each subject was classified as being in one or the other group, the method exhibited high sensitivity (1.00) with a low false positive rate (0.06) under a range of parameter settings. Examination of the initial classification space showed that Euclidean distances among members within a diagnostic category (Alzheimer's or control) were not reliably smaller than distances between members of different categories; thus nearest-neighbor classification could not reliably classify subjects in their correct categories. However, the

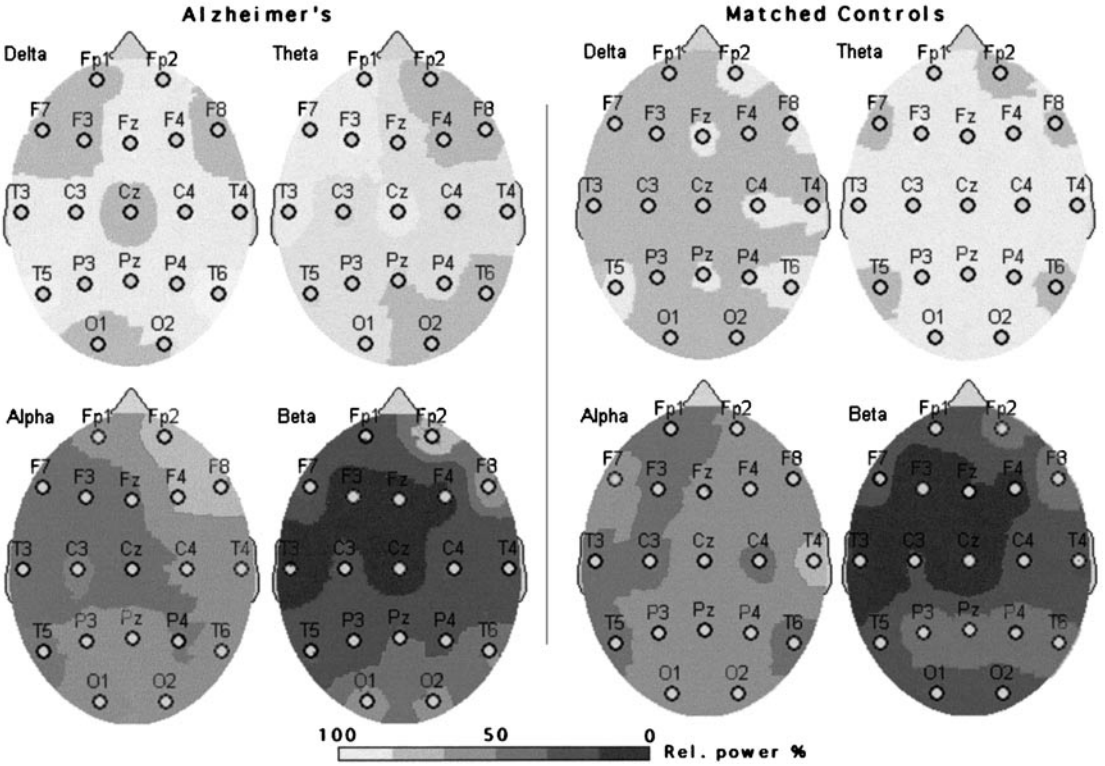

FIG. 4. Relative power distribution across four frequency bands (delta, theta, alpha, beta) and 19 electrodes, in averaged evoked response records of Alzheimer's (left) and control subjects (right). Scale bar shows log of relative percentage power across all records.

distances among members of a diagnostic category were consistently smaller than the distances between members of different categories in the classification space composed of the reduced discriminative feature sets identified with extended projection pursuit. Not surprisingly then, nearest-neighbor classification in the reduced space led to groupings with good sensitivity and specificity.

Examination of the reduced set of dimensions provided information about which spatio-temporal components of the ERP contributed significantly to distinguishing between the two groups. Key dimensions were identified by asking how often they predicted a correct "diagnosis" (AD or non-AD). The most predictive events occurred between 200 and 400 ms and from 800 to 1000 ms. Previous studies have established that at least one well studied wave (P300) occurring in the former time bin changes with normal aging. Reduced amplitudes and delayed peaks relative to young adult values are reported to be already present by age 50 (cf., 4, 25, 15). P300 waves triggered by novel stimuli are greatly reduced in early stage AD patients relative to matched controls (9, 19). Changes in late potentials are also reported to occur by late middle age, although there is disagreement in the literature about the direction and size of these (15, 25, 37). And, as with P300, late components of the ERP (800–1500 ms) are significantly altered in AD relative to controls (44). It seems likely that the present detection of early AD-related disturbances in the ERP reflects these described changes.

Most studies directed at identifying ERP correlates of Alzheimer's use stimulus paradigms that emphasize a particular aspect of cognitive processing (working memory, novelty detection). Based on the results from such studies, the effects recorded in the present experiment would probably be significantly changed with more complex cues. In accord with this, examination of the temporal segments showed that the most predictive events developed with repeated testing, an observation that suggests that simple forms of learning (e.g., habituation) contributed to the observed AD vs control differences.

Frontal and parietal recordings provided the greatest discrimination between AD and control. There is a substantial literature pointing to frontal dysfunction as a component of Alzheimer's and that this can be detected with ERPs. The frontal P300 response is described by several investigators as having greater than normal latency in AD (13, 38) and ERP data have been used to support the hypothesis that fronto-parietal changes contribute to the working memory problems that characterize the disease (35).

In summary, the present results establish that extended pursuit projection identifies correlates of AD in ERPs elicited by simple visual stimuli. The most dis-

tinctive features occurred within two temporal segments and arose from fronto-parietal recording sites. There is prior evidence indicating that correlates of mild AD are found within these spatio-temporal coordinates. Although there was evidence that simple learning contributed to the observed differentiation of the AD group, the unstructured stimuli used in the study have the disadvantage of not activating cognitive activities thought to be impaired by AD. Between-group differences could be enhanced, and probably markedly so, with paradigms that engage attention to novelty or working memory (e.g., 9, 18, 35). On the other hand, unstructured cues have the important advantages of test simplicity and applicability across patient populations. Regarding the latter, the same procedures used in the present study are being applied essentially without modification to subjects with any of several neuropsychiatric disorders. If the extended projection pursuit techniques are successful in discriminating these groups from each other, then it should be possible to classify a subject within a space containing collections of clusters rather than forcing a choice between positive or negative for a given disease class.

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