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Alzheimer's Disease: The Relationship between P300 Latency and PET Scan Ratios

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Alzheimer's Disease: The Relationship between P300 Latency and PET Scan Ratios

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Alzheimer's Dementia: The Relationship Between P300 Latency Measures and PET Scan Ratios

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Running head: P300 LATENCY AND PET RATIOS IN ALZHEIMER'S

Abstract

The P300 component of the auditory EEG event-related potential (ERP) and Positron Emission Tomography (PET) were investigated in individuals considered to be early cases of probable Alzheimer's type dementia (PAD) and a control group of similar age. Two questions were investigated: (a) The degree to which P300 latency was sensitive to neurocognitive changes in very early stages of PAD; and (b) The relationship between P300 latency and specific areas of reduced neural functions as reflected in PET scans. A significant difference was found between PAD and normal subjects in P300 latencies, with those in the patient group having longer P300 latencies than the control group. The P300 latencies were significantly correlated with cortical, but not subcortical, metabolic rates. The highest correlation was between P300 latency and pareital PET scores, with other significant correlations with P300 latency in the following order: frontal, temporal and parahippocampal. These data indicate that P300 latency is an index of the integrity of association cortex and, as such, is sensitive to the very early stages of Alzheimer's dementia.

Dementia of the Alzheimer's type (DAT) is diagnosed in at least one-half of all cases of dementia [19] but nevertheless remains a difficult diagnosis to make with confidence. This category of dementia is characterized by atrophy of the cerebral cortex and dilation of cerebral ventricles. This change in the cerebral anatomy, though often more marked, is not necessarily different than that of normal aging. Senile plaques and neurofibrillary tangles, which are believed to be partially responsible for the dementing process, are found in both demented and non-demented persons, although usually in different quantities. The nucleus basalis appears to be responsible for diffuse cholinergic projection to the cerebral cortex. Significant cell loss has been reported [8] in the nucleus basalis possibly acccounting for the cholinergice deficit found in Alzheiemr's patients. The dependence upon behavioral signs for the clinical diagnosis of DAT in the living patient often causes confusion between the various dementias, as well as between dementia and various other conditions which have overlapping behavioral features, such as depression. Both anatomical and neurobehavioral differences are obviously least distinct in very mild, early stages of DAT when diagnoses are usually sought. There is, thus, a need for more precise and objective

means of diagnosing Alzheimer's dementia in the elderly. The latency of the P300 component of the auditory event-related potential (ERP) has shown promise as a means of evaluating cognitive functioning.

Marsh and Thompson [23] were perhaps the first to report increases with normal adult aging in P300 latency measurements using auditory discriminative tasks. An increase in latency was seen for normal elderly individuals. A continuous linear or exponential increase in P300 latency with adult aging has been demonstrated by a number of investigators [5 ,17, 38].

The latency of the P300 increases further in most cases of persons with a neurological disease which results in dementia, whereas persons with functional disorders or neurological disease without cognitive impairment rarely exhibit an increase in P300 latency. [4, 17, 38]. Thus P300 latency measurements may prove to be an important tool in the differential diagnosis between demented and non-demented patients.

One possible cause for the occurrence of a P300 outside the normal range for some demented patients and not for others could be the sensitivity of the P300 latency to cortical neural activity within specific regions of the brain. That is, regardless of the global level of dementia, certain specific neural tissue must be

dysfunctional for P300 latency to become abnormally long. The neural substrates for abnormal P300 latencies are not known, that is, it is not as yet known whether or not the abnormally prolonged latencies seen in dementia are associated with functional deficits in specific brain systems, structures, or regions.

With recent advances in Positron Emission Tomography (PET), it is now possible to measure the metabolic activity of specific brain regions in living, active patients. The earliest and most specific changes occurring in diseases of the brain have been shown to be reflected in disturbances of underlying biochemical processes [32].

PET scans have recently been found to be characteristically abnormal in cases of Alzheimer's disease. Kuhl et al. [20] found that 2-deoxy-2-fluror-D-glucose (FDG) scans in Alzheimer's type dementia revealed abnormal metabolic patterns suggestive of neuronal degeneration which was most severe in the cortex. The average decrease in zonal metabolism was 47% in parietal and dorsolateral occipital cortex, and 28% in caudate and thalamus. There is a significant positive correlation between cortical glucose use measured by the PET and the Full Scale IQ, Verbal IQ and Performance IQ scores on the Wechsler Adult Intelligence Scale in both normal and

demented patients [7]. It has been found that cerebral glucose utilization is most dramatically reduced in the posterior pareital cortex of DAT patients [15]. Cerebral blood flow was also found to be markedly reduced in the pareital and temporal regions for these patients [16].

This study investigated the relationship between PET scan and P300 latency measures in individuals considered to be early, mild cases of probable Alzheimer's type dementia (PAD) in order to determine the relationship of P300 latency increase to specific regional changes in brain metabolism. It was hypothesized that: (a) P300 latency is a reflection of brain integrity which will be manifested in PET indices of metabolic rate. (b) P300 latency will reflect most strongly neocortex and/or archecortex metabolic rate and less metabolic activity of subcortical regions. (c) P300 latency will be relatively longer in patients with reduced parietal and/or temporal metabolic rate.

Method

Subject Evaluation

A very large group of possible subjects was recruited from the community via letters sent to area physicians, neurologists and psychiatrists asking for referrals of normal controls and persons with early signs of memory and intellect problems. The research program was also

announced in local newspapers, trade journals and on radio and television interviews.

Each potential subject was given an initial assessment to determine if s/he met standardized intake criteria of early dementia and to exclude those not meeting these criteria or alternatively, consider them for the control group. An interviewer gathered information regarding educational and occupational background, and medical or neurological history. Part of this information was obtained from a second source who knew the subject well. A brief standardized test of cognitive and functional abilities, the Mini-Mental state (MMS; Appendix F) [13], was completed. The significant other of the patient was asked to rate the patient (on a 7 point scale) in daily functions of remembering, problem solving, clinical signs, and home activities using the Dementia Scale [2] with inclusion criterion being a score of equal to or less than 10. The Zung Self Rating Depression Test was also given with a score of less than 60 excluding the patient from this study. A score between 2 and 6 on the partial Hachinski Ischemic Scale (Appendix G) was taken as a sign of possible dementia, a score of 7 or greater suggested possible multiple infarct dementia and excluded the patient.

Following the initial assessment, a more thorough dementia evaluation was completed to establish a preliminary diagnosis. A full medical, psychiatric and social history was obtained. Further tests included complete neuropsychological and neurolinguistic evaluations. The degree of memory impairment was assessed, cognitive status was fully evaluated and the presence of aphasic or apraxic signs noted. In order to be included in the study each patient earned scores as follows: WAIS Digit Span (forward and backward) with a score equal to or less than 8, the Word Generation Test (less than 12 in 1 minute), and Rey's Visual Scanning Tests [36] (less than 18 words in one minute, i.e. the 25th percentile).

The final stage of subject evaluation involved a series of medical laboratory tests to rule out sources of cognitive impairment other than DAT. Medical tests included: chest x-ray, electrocardiogram, urinalysis, erythrocyte sedimentation rate, full screening blood panel, B12, folate, and thyroid function tests. Tests to assess organic brain syndrome included EEG, MRI and CT Scans.

The control group consisted of 17 individuals 52-71 years of age who agreed to participate as volunteers. All

individuals in the control group earned a Mini-mental State score of 28-30 and fell within the normal range on a battery of neuropsychological tests.

The patient group consisted of 32 individuals 56-76 years of age with a score on the Mini-mental state between 20-27. Their scores on the neuropsychological battery fell below the normal range, and they exhibited behavioral symptoms congruent with a diagnosis of mild dementia. Patients were divided into two subgroups according to Clinical Diagnostic Ratings (CDR; see Appendix E) [19] of 0.5 and 1.0. This constitutes possible and probable DAT, respectively. The CDR utilzes information gathered through interviews to determine the stage of dementia a patient has reached. Six categories of functioning are assessed including: memory, orientation, judgment/problem solving, community affairs, home/hobbies and personal care.

P300 Recording

For P300 recording, EEG electrodes were fixed with electrolyte paste at the Fz, Cz, Pz sites on the patient's head (International 10-20 Electrode System). Ear clips were used for reference and ground. Subjects were seated in an electrically shielded, sound attenuating room for EEG recording, and headphones placed over the patient's

ears. An attendant was in the recording room with the subject at all times.

An "auditory oddball" stimulus paradigm was utilized with frequent tones (250 Hz, 70db SPL, 60 msec duration) occurring on 80% of the trials and target tones (450 Hz, 84db SPL, 60 msec duration) occurring on 20% of the trials. One tone was heard every 1.5 seconds until a total of 32 artifact free responses to the target tone were recorded. Responses spoiled by muscle or eye movement artifact were rejected automatically by the averaging computer according to an amplitude threshold adjusted for each individual subject. Each subject was asked to listen to the tones as they were presented and instructed to count silently the louder, higher pitch tone (target tone), and ignore the softer, lower pitch tone. The attendant informed the subject that periodically the tones would be stopped and a count asked for from the subject. Following these instructions, a short trial segment was presented in order to determine that the subject understood the instructions and was able to discriminate between the two tones and do the task. In the event that the subject was unable to keep an internal count, s/he was instructed to lift her/his index finger at the sound of the target tone. If necessary, this skill was shaped during practice trials by the attendant,

indicating to the subject when to lift a finger. When it was determined that the subject was prepared for the task, two runs were completed with a short break in between runs. For this study, six patients were unable to keep an internal count, and the shaping technique was utilized. Each of these six patients had an initial CDR of 1.0 and a P300 Z-score which exceeded 2 SD beyond the mean.

For each recording locus, event-related potentials were amplified (Gain = 14,000, Bandpass = .1 - 50 Hz), digitized (250 samples/sec) and separately averaged for the frequent and target stimuli. Average ERPs spanned 1000 msec, including a 100 msec prestimulus epoch.

Average responses were stored on computer disks and plotted on an X-Y plotter immediately following a run. For each electrode derivation, plots include the ERP to the frequent and target stimulus, and the difference between these potentials for reasons explained below.

P300 latencies were measured at PZ, CZ, and FZ sites. The P300 component was identified as the first positive peak after 250 msec. Where a single peak does not appear, but rather a flat-top or multiple peak waveform, a midwave measurement was made. Scalp topography and difference waveforms (i.e. target minus frequent) were used as aids in identifying the P300 wave.

Since P300 latency in this paradigm increases progressively with normal aging [5], z-score deviation from the age/P300 latency function adjusted for this effect on the basis of a larger normative group. The P300 latency measures at Cz were expressed in Z-scores in reference to the age/P300 latency regression function derived from a very large group (N= 71, 57 < 40 years of age) of normal, elderly individuals previously recorded using the same task and recording procedures.

PET Scan

Each patient and control underwent a glucose utilization Positron Emission Tomography (PET) scan which involved the injection of F-18 labeled 2-deoxy-2-fluror-D-glucose (FDG). An extension of Sokoloff's DG model for measuring local cerebral metabolic rate of glucose in autoradiography, which included the dephosphorylation reaction, was applied to this PET study.

For comparison between groups and individuals, PET FDG values were expressed as ratios of different brain areas in order to adjust for variability in absolute metabolic measure between individuals. Cortical and subcortical PET FDG values were expressed as ratios with cerebellar values, a structure found to be relatively stable in mild to moderate DAT. Studies have found that

such ratios are less variable in demonstrating regional differences in metabolic rate [27].

Results

The groups admitted for study were not significantly different in age compared either between normals and possible Alzheimer's dementia (PAD) or between the 3 CDR groups (CDR 0, 0.5 and 1.0).

Figure 1 gives an example of the actual ERPs recorded from two PAD patients and controls. The shaded areas demonstrates the P300 component obvious in the difference between the response to the frequent and the rare stimuli. It can be seen that the P300 for the PAD patients are significantly longer than for the control.

Insert Figure 1 about here

Figure 2 presents the P300 latency z-scores for the normal control and two PAD groups. It can be seen that while all the normal patients fell below +1.5 SD of the normative group, 27 of 32 PAD patients exceeded norms by more than +2 SD. Remarkably, despite relatively mild PAD in the two patient groups, P300 latencies were grossly abnormal in a large number of cases.

Insert Figure 2 about here

There was a significant difference in P300 latency z-scores between the combined PAD group and the control group ($p < 0.0005$) and between the three CDR groups compared separately ($p< 0.0005$). The mean P300 measure for those with a CDR of 0 (normals) is significantly lower than those with a CDR rating of either .5 or 1.0 ($p< 0.003$) (see Table 1).

Insert Table 1 about here

There is, however, no significant difference in P300 latency z-score between those with a CDR of 0.5 and those with a CDR of 1.0 (see Table 1).

A significant correlation was found between MMS and P300 z-scores ($r= -0.59$, $p < 0.0005$) for the three groups combined. As P300 latencies become longer, there is a decline in MMS scores. However, again within the patient groups, the P300 latency/MMS correlation was not significant ($r= -0.21$, n.s.).

There was a significant negative correlation between P300 latency and cortical PET FDG ratios in the combined control and PAD groups. Specifically, there was a significant correlation demonstrated between P300 z-scores and Parietal/Cerebellum ($p < 0.001$); and Frontal/Cerebellum ($p < 0.001$); Temporal/Cerebellum ($p < 0.003$); and Para-hippocampal/Cerebellum ($p < 0.004$) FDG

ratios (see Figure 3). Thus, decrease in relative cortical metabolic rate for these structures was associated with a long P300 latency. There was no significant correlation with P300 latency for Caudate Thalamus/Cerebellum ratios or for the global measure of FDG uptake ratios (see Figure 3). This correlation was

Insert Figure 3 about here

essentially carried by the pareital/cerebellum ratio. The frontal, temporal and parahippocampal ratios contributed only 0.12 combined.

When P300 and PET measures were compared within only the PAD patients there was a significant correlation ($p < 0.006$) for the Frontal/Cerebellum FDG ratio. There was no significant correlation for any of the other FDG ratios. (see Figure 4). There were no significant PET/P300 latency correlations when compared only within the control group (see Figure 4).

Insert Figure 4 about here

Discussion

These data demonstrate a number of important points about P300 latency in Alzheimer's type dementia. First, the data indicate that the P300 latency is sensitive to very early, mild forms of DAT. In this

sample of carefully diagnosed and screened, but marginally demented PAD subjects, 85% showed prolonged P300 latency at clinically detectable levels (i.e. > +1.5 SD). Although P300 does not discriminate within the PAD group (between CDR 0.5 and CDR 1.0), there is a significant difference in the P300 latencies even between the control and the 0.5 CDR group (i.e. those with only "possible" Alzheimer's dementia). Sensitivity of P300 to mild dementia was also seen in the significant correlation between P300 latency and MMS over a moderate range of MMS scores (i.e. >20) and P300 latencies. These data are thus consistent with the results of studies by Lai [21], and Brown, Marsh and LaRue [5].

Recent literature [31, 33] has brought into question the clinical usefulness of the P300 latency in the diagnosis of dementia. It was suggested that the P300 is only able to accurately detect major cognitive deficits, and would produce too many false negatives for persons with early, mild forms of dementia and too many false positive among "non-demented" psychotic individuals. Pfefferbaum et al. [31] used a more difficult paradigm with two infrequent stimuli and a wider standard deviation range, a standard error of regression being amost twice that of Goodin et al. [17], in the normative aging data than other studies. They found 20 to 30 percent of their

schizophrenic patients had P300 latencies which fell more than 2 SD above the mean while fewer that one/half of the P300 latencies of the demented group fell two or more SD beyond the mean for their age. In the Brown et al. [4] study there were no false positives meaning that no non-demented person was classified as demented using the P300 latency. They did find though that 7 of 26 demented patients were misclassified as non-demented using a cutoff of 2 SD beyond the mean for the patient's age. Polich et al. [33] reported that 31 percent of the demented patients fell 2SD beyond the age regression line and 54 percent fell beyond 1 SD of the regression line. The present data at least indicate that the P300 is sensitive to cognitive deficit associated with early, mild probable Alzheimer's disease. The P300 latencies of the patients were in many cases more than four standard deviations different from the latencies of non-demented subjects of similar age.

The dramatic differences between groups in this study may be due to the very careful screening of both patients and controls. Most other studies of this problem have used mixed groups of dementias less well diagnosed and screened [31, 33]. It is possible that DAT differs from other types of dementias in having relatively direct effects on P300 latency. Thus in a relatively pure DAT group the association between P300 latency and dementing

illness is stronger than found in studies including a less homogeneous group.

A second major finding of this study is the relationship between P300 latency and cortical metabolic activity. From this study it can be observed that the P300 latency is a reflection of brain functional integrity as revealed in PET measures. Significant negative correlations were found between P300 latency and PET measures of metabolic rate. As the metabolic rate of the brain decreases, the P300 latency becomes longer.

P300 latency appears to reflect primarily cortical metabolic activity. The correlations between the PET ratios and the P300 are significant for neocortical structure (i.e. parietal, temporal, and frontal) and archecortical (parahippocampus) structures of the brain. However, P300 does not appear to be related to relative subcortical metabolic rate, as manifested in PET measures from the caudate/thalamus. Nor is P300 latency associated with global measures of whole brain metabolic activity.

From these data, it appears that the P300 latency is specifically sensitive to a decline in the metabolic rate of posterior brain regions, especially the pareital and temporal areas. These data correspond with the recent studies of Foster et al. [15] and Frachowiak et al. [16] of Alzheimer's patients which suggest that the pareital

and temporal areas show the earliest decline in metabolic rate with onset of the disease. Since a decline in metabolic activity in these areas are suggestive of early, mild Alzheimer's dementia, it can be suggested that the P300 shows promise in being useful for the diagnosis of early Alzheimer's dementia.

P300 latency reflects the time required to complete demands of a task. The more difficult the task, the greater the time needed for completion. The P300 latency has been shown to be related to the processes associated with stimulus evaluation independent of reaction time [11, 27, 35]. This suggests that P300 latency is likely to be dependent upon the neural systems of the posterior pareital cortex which are involved in the perception, analysis and discrimination of stimulus information. This would be consistent with the PET/P300 latency correlations of this study.

Much of the discussion regarding the cognitive significance of the P300 has focused on the relationship between P300 and memory functions. P300 amplitude has also been found to correlate with new learning [22]. P300 amplitude was larger for learned items than new items but smallest for overlearned items, whereas P300 latency was longest for new items and shortest during overlearning. The authors suggest that new items may results in a

mismatch and updating of working memory or schema [10]. Memory span size nearly doubles between the ages of 5 and 12 years [34]. Miller [24] suggested that the size increase stems from a change in the number of memory "slots" available to store information. It has been hypothesized [6, 34] that this developmental increase in memory capacity results in improvement in speed of mental operation processing. A relationship between memory performance as measured by the Digit Span task and P300 amplitude has been found [18, 35], with better memory performance correlated with P300 amplitude.

The P300 latency prolongation may reflect deficits in the immediate memory of older patients, especially those with a dementing disease. Several studies [4, 17, 25, 38, 39] have found increased P300 latencies associated with cognitive dysfunction for both young and old subject populations. Ford et al. [14] suggested that the elderly are slower at deciding what information was relevant causing an increased P300 latency especially as the amount of information needed to be remembered increased. Pritchard [35] reports that several studies found that P300 latency increased in a linear fashion with an increase in memory load.

The decrease in memory functioning is suggestive of lowered metabolic activity in both temporal and

parahippocampal areas, thus we would expect to see a negative correlation between the P300 latency and metabolic activity of these areas. As the P300 latency increases, the metabolic activity observed in the pareital, temporal and parahippocampal areas decreases, important areas for the maintenance of an immediate memory trace and consolidation to longer term memory.

There has been and continues to be controversy regarding the neural generators of the P300. Depth electrode studies have suggested [1, 26, 37] that the P300 may be generated from the medial temporal lobe. But these studies have concluded that there are most likely multiple generators rather than a unitary source. It is probable that several generators may contribute to a unitary psychological function. Many neural generators may need to be activated to carry out a unitary psychological process [12]. Although depth electrodes P3s and scalp-P3s are not identical, Altafullah et al. suggests [1] that there is enough resemblance to make hypotheses regarding the generators.

In investigating the PET scans of Alzheimer's patients, we are not able to trace the neural generators of the P300, but rather to demonstrate the brain systems whose integrity is necessary for the invoking of an early P300

suggesting the ability of the brain to rapidly and efficiently complete mental processing.

In summary, a decline in cortical metabolic activity with the onset of Alzheimer's dementia, which initially appears most markedly in the pareital area of the brain, is a likely source of prolonged P300 latency found in DAT patients. Thus, prolonged P300 latency appears to be a sensitive index of diminished metabolic activity, particularly in cortical association areas. Clinical utility of P300 latency measures may thus lie not in its ability to detect dementia in every case or to differentiate dementias of different etiologies, but as a relatively direct measure of the integrity of cortical association areas.

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Table 1

Mans and Significance Levels

CDR	AGE	MMS	P3(Z)	P3(LAT)
0.0	63.94	29.59 ab	0.0929 ab	334.7059 ab
0.5	65.89	25.00 c	3.1056	421.9445
1.0	68.43	22.71	3.3800	436.7857

a. Control different from all PAD patients ($p < 0.0005$)

b. Control different from CDR 0.5, $p < 0.0005$.

c. CDR 0.5 different from CDR 1.0, $p < 0.0005$.

Figure Captions

Figure 1

Sample ERP traces from normal controls (CDR=0.0), possible dementia (CDR=0.5) and probable dementia (CDR=1.0). Responses to the target and non-target tones are superimposed with the area of the P300 wave elicited by the target tone shaded. Recordings are from midline pareital (Pz), central (Cz) and frontal (Fz) leads referenced to an earlobe. Recording epoch is one second, with tone onset at 100 msec. Note that both PAD patients show longer P3 latencies than those of normal controls. For the traces illustrated in the right hand column (CDR=1.0) there appears to be a clear P3a (orienting response) and P3b (processing response), the latter is the wave of interest.

Figure 2

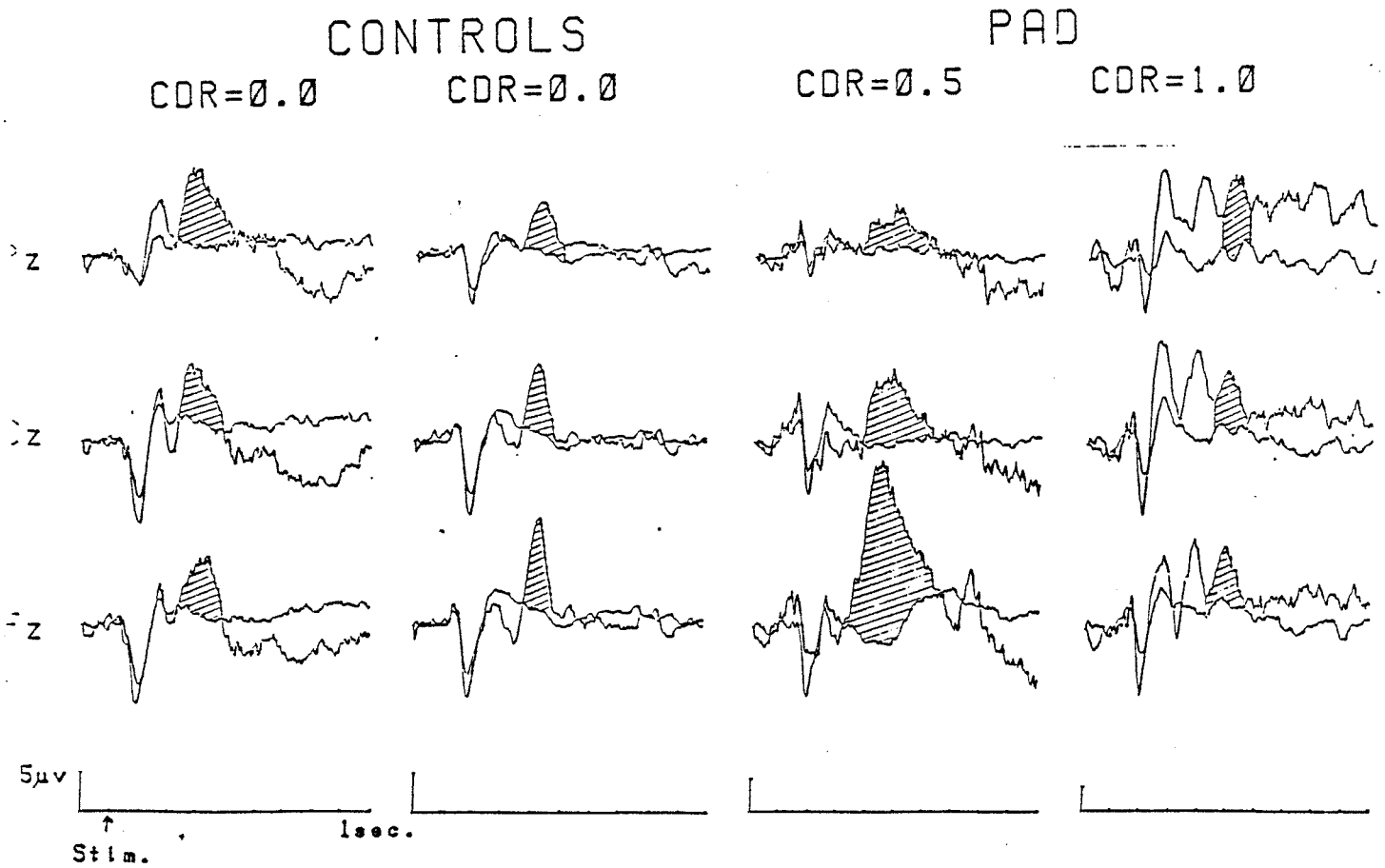
P3 latency data converted to Z-scores for all subjects. From the left, columns are normal controls (CDR=0.0), possible dementia (CDR=0.5), and probable dementia (CDR=1.0). The dashed line represents the maximum Z-score value (1.8) for the normal controls of this study. Only five of the 35 patients fall within the range of normal subjects.

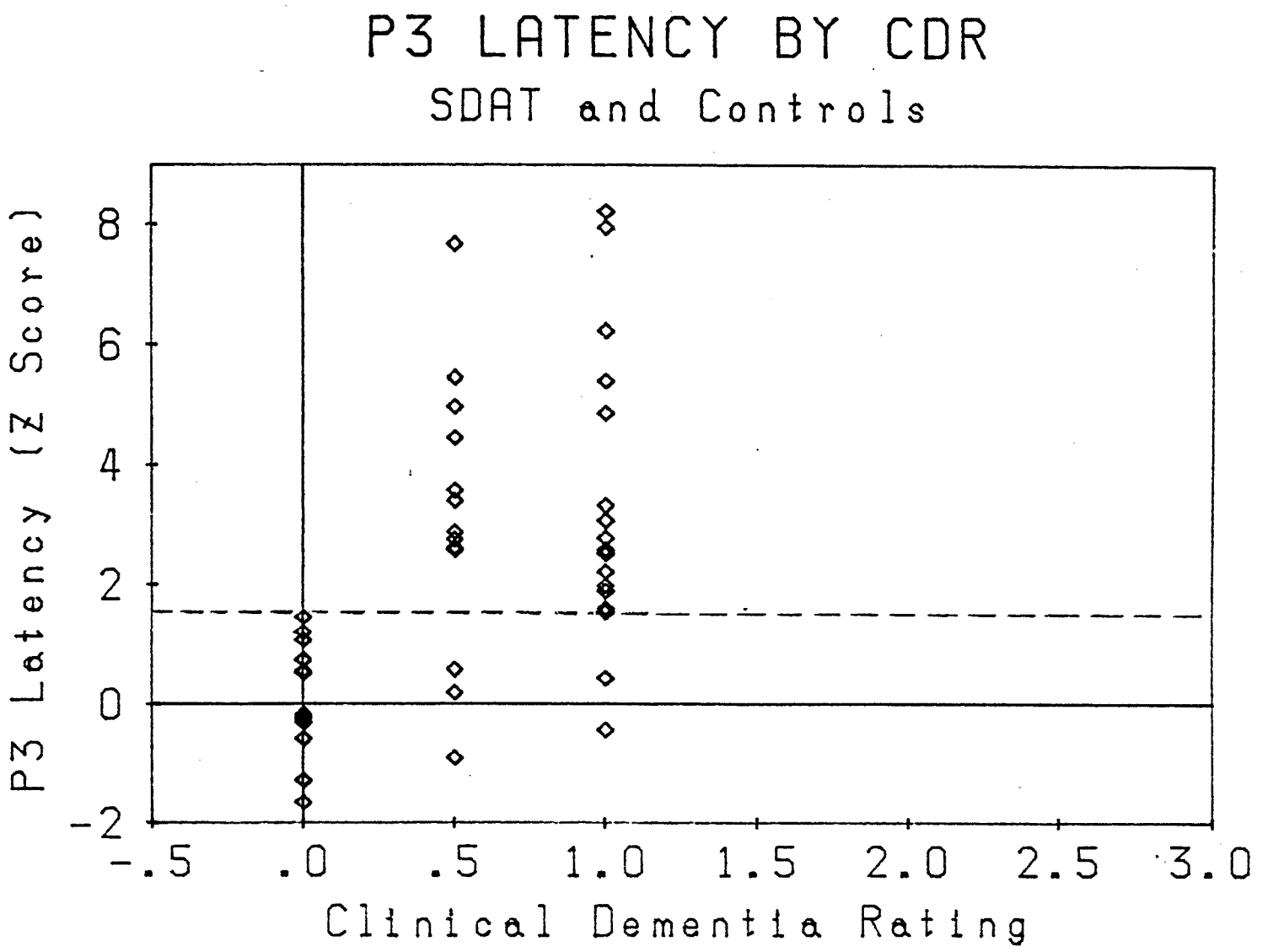
Figure 3

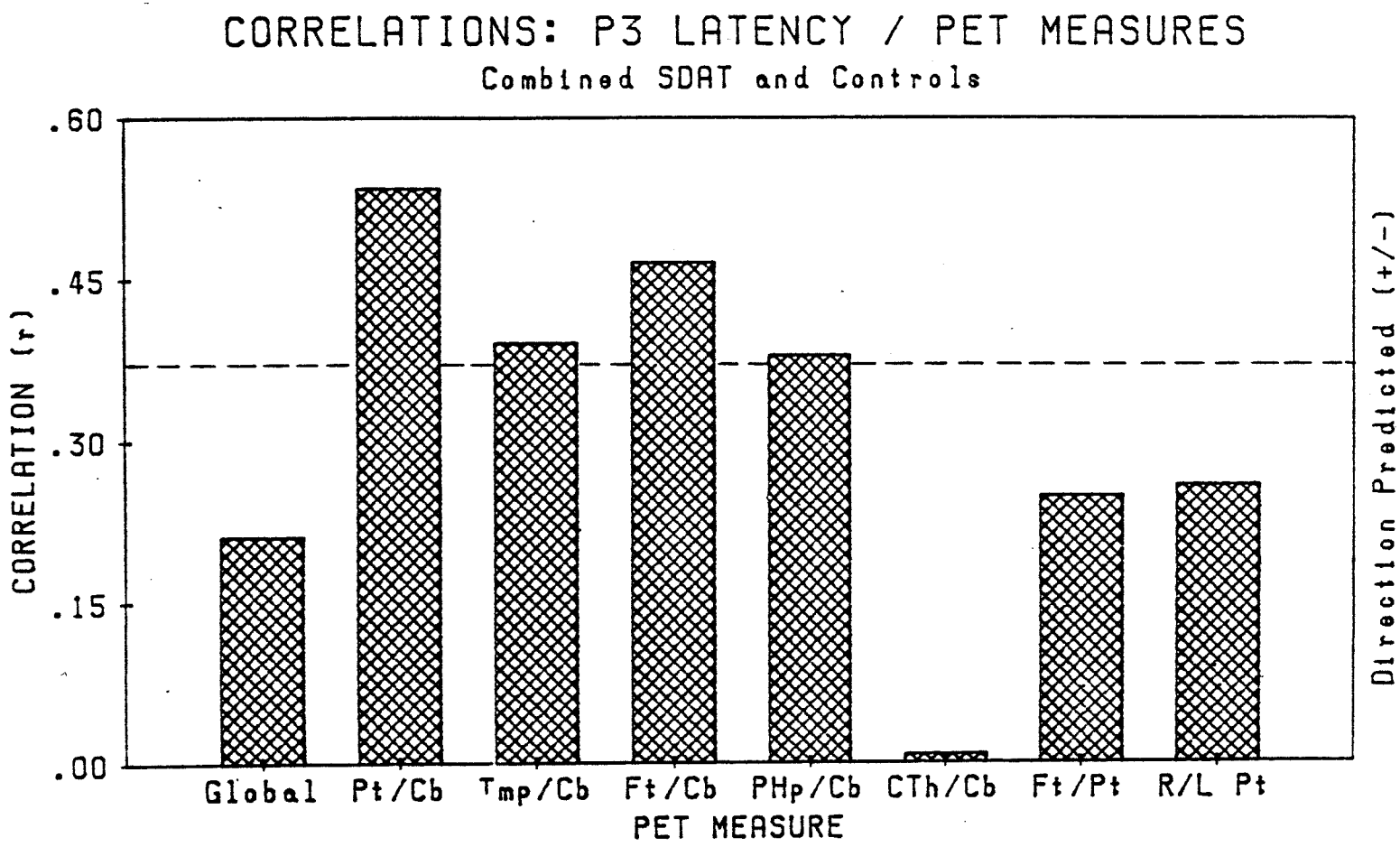
Correlation of P3 latency (in Z-scores) with PET measures. From left to right, bars represent correlations with the following PET measures: global metabolic rate; parietal metabolic rate divided by cerebellar metabolic rate (Pt/Cb); temporal divided by cerebellar (Tmp/CB); frontal divided by cerebellar (FT/Cb); parahippocampal divided by cerebellar (PHp/Cb); caudate-thalamus divided by cerebellum (Cth/Cb); and frontal divided by parietal (Ft/Pt). All correlations are positive when in the predicted direction (all negative except for the last column, Ft/Pt. The dashed line represents the two-tailed $P< 0.5$ level, adjusted for multiple comparisons.

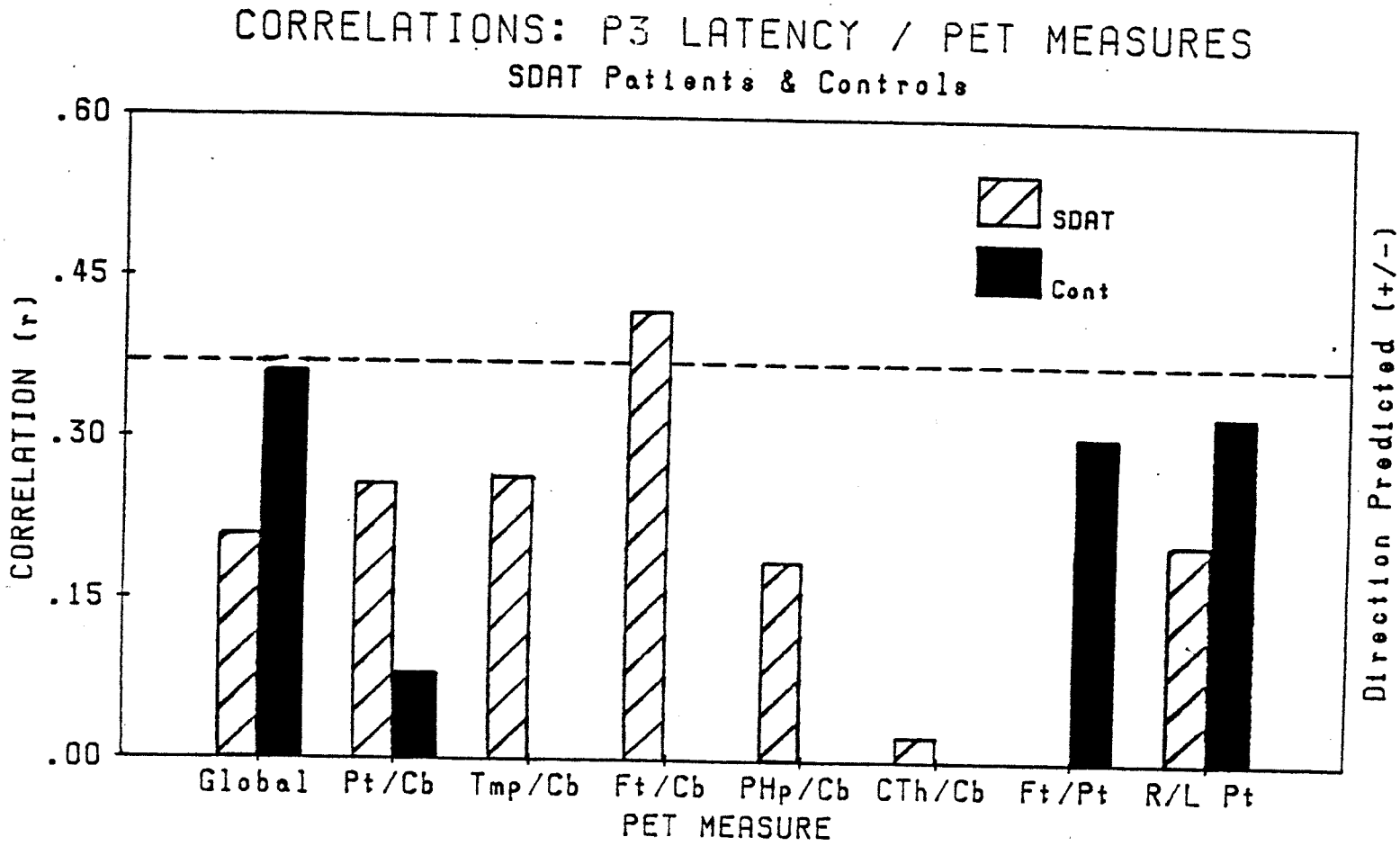
Figure 4

Correlation of P300 latency (in Z-scores) with PET measures for patient and control group separated. The dashed bars represent the patient group. The solid bars represent the control group. From left to right bars represent correlations with the following PET measures: global metabolic rate for patient and control; parietal metabolic rate divided by cerebellar metabolic rate (Pt/Cb); temporal metabolic rate divided by cerebellar (Tmp/Cb); frontal metabolic rate divided by cerebellar (Ft/Cb); parahippocampal metabolic rate divided by cerebellar (PHp/Cb) caudate-thalamus divided by cerebellum (CTh/Cb); frontal metabolic rate divided by parietal (Ft/Pt) and right perietal metabolic rate divided by left parietal (R/L Pt). The dashed line represents the two-tailed $P< 0.5$ level, adjusted for multiple comparisons. The correlation of the frontal metabolic rate for the patient group is the only PET measure that is significant when the groups are separated.


CONTROLS
PAD
CDR=Ø.Ø
CDR=Ø.Ø
CDR=Ø.5
CDR=1.Ø
Z
Z
Z
5µv
1sec.
Stim.


P3 LATENCY BY CDR
SDAT and Controls
P3 Latency (Z Score)
8
6
4
2
0
-2
-.5
.0
.5
1.0
1.5
2.0
2.5
3.0
Clinical Dementia Rating


CORRELATIONS: P3 LATENCY / PET MEASURES
Combined SDAT and Controls
.60
.45
.30
.15
.00
CORRELATION (r)
Direction Predicted (+/-)
Global
Pt/Cb
Tmp/Cb
Ft/Cb
PHp/Cb
CTh/Cb
Ft/Pt
R/L Pt
PET MEASURE


CORRELATIONS: P3 LATENCY / PET MEASURES
SDAT Patients & Controls
.60
.45
.30
.15
.00
CORRELATION (r)
SDAT
Cont
Direction Predicted (+/-)
Global
Pt/Cb
Tmp/Cb
Ft/Cb
PHp/Cb
CTh/Cb
Ft/Pt
R/L Pt
PET MEASURE

Alzheimer's Dementia: The Relationship Between P300 Latency and PET Scan Ratios

The relationship between P300 latency and PET scan measures of focal cortical and subcortical metabolic activity was investigated in individuals considered to be early cases of probable Alzheimer's type dementia (PAD). The latency of the P300 component of auditory event-related EEG potentials (ERP) has been suggested to reflect stimulus evaluation time, which increases significantly in most cases of neurological disease resulting in dementia. The Positron Emission Tomography (PET) provides a spatially discrete, quantitative, noninvasive measurements of the rate of physiological activity of the living human brain.

The PAD patient group consisted of individuals 56-76 years of age who scored below the normal range on the neuropsychological battery and exhibited behavioral symptoms congruent with a diagnosis of mild dementia (MMS 20-27). Non-Alzheimer types of dementia were ruled out by extensive medical evaluation. The control group consisted of individuals 52-71 years of age who fell within the normal range on a battery of neuropsychological tests (MMS 28-30).

An "auditory oddball" paradigm was utilized for P300 measurement, (frequent tones 80%, target tones, 20%). Each subject was instructed to count the target tone to

her/himself. P300 latencies were expressed in z-scores in reference to the age/P300 regression line from a large population of normal elderly to control for age variations.

Each patient and control underwent a glucose utilization PET scan using F-18 labeled 2-deoxy-2-fluror-D-glucose (FDG). PET values from different brain areas were reconstructed from multiple scans in the horizontal plane. Areas tested were expressed as ratios of cerebellar metabolic rate, a relatively stable structure in progressive degenerative dementia, to control for individual differences.

A significant difference was found between PAD and normal subjects in P300 latency, with those in the patient group having longer P300 latencies than the control group ($p < 0.0005$). The P300 latencies were significantly correlated with cortical, but not subcortical, metabolic rates. The highest correlation was between P300 latency and parietal PET scores, with significant correlations also for frontal, temporal and parahippocampal areas. Results suggest that P300 latency is a sensitive measure of the functional decline in cortical association areas associated with early stages of Alzheimer's disease.

Alzheimer's Disease, P300 Component of Event-Related Potentials, and Positron Emission Tomography in Diagnosis and Research in Aging.

With the increase of life expectancy within the last century, we have had to confront new difficulties that accompany older age. One of these problems is one we have termed Dementia, a nonspecific clinical syndrome with an organic etiology characterized by the deterioration in intellectual, cognitive and psychological functioning. The diagnosis of dementia is based on a cluster of psychological as well as behavioral symptoms rather than on a causative factor. Often the specific causative factor is not confirmed until post-mortem.

The criteria, according to DSM III, utilized to diagnose dementia include: (a) loss of intellectual ability resulting in social or occupational impairment; (b) memory impairment; (c) impairment in abstract thinking, judgment or higher cortical functioning or personality change; (d) retention of clear consciousness and (3) documented or presumed evidence of a specific organic cause. Various disorders producing dementia

include: Alzheimer's disease, Pick's disease, Creutzfeld-Jacob disease and Multi-infarct, as well as disorders in which dementia is a significant, but not primary symptom; Parkinson's and Huntington disease. There are also numerous metabolic and toxic states producing permanent or reversible dementia.

Alzheimer's Type Dementia

Alzheimer's Disease was first diagnosed in 1907 by Alois Alzheimer. It is now the most common cause of adult-onset dementia and is diagnosed in at least 50-55% of all cases of dementia (Tomlinson, Blessed & Roth, 1970; Kuhl, Metter, Reige & Hawkins, 1985). Approximately 10-15% (Price, Whitehouse, Struble, 1985) of persons over the age of 65 years will become at least mildly demented with 50-60% of those suffering from Alzheimer's Disease.

Physicians describe at least two forms of Alzheimer's (Lezak, 1983; Barnes, 1987), one having an early onset around the age of 50, and the other having an onset much later. Local or personal preference seems to dictate whether dementia of the Alzheimer's type is considered a presenile dementia (called Alzheimer's disease) or a senile dementia (called senile dementia of the Alzheimer's type). Significant differences in rate of cognitive decline have been found (Lezak, 1983; Loring & Larsen, 1985) between those patients with an early and

those with a late onset of Alzheimer's dementia. Those who have an early onset of Alzheimer's dementia are found (Loring & Larsen, 1985) to decline more rapidly and be more impaired than those with a later onset. Since identical patholologic changes and clinical features are found in both early and late onset dementia (Cummings and Benson, 1983), this does not necessarily designate two separate dementing diseases and thus this present discussion will use the terminology Alzheimer's Disease regardless of the age of the patient at onset.

Clinical Features

There are several observable clinical features that accompany the onset of Alzheimer's Disease including loss of memory, and disorders of language, praxis and perception (Price et al., 1985), with the earliest signs denoting Alzheimer's disease being a deficit in recent memory, depression and irritability (Lezak, 1976). Reisberg (1985) suggests seven phases in Alzheimer's with the first three phases, which include forgetfulness and early confusional states, indistinguishable from normal aging. The onset of diagnosable PAD occurs at stage four with deficit in areas of knowledge of current and recent events, memory of personal history, concentration and ability to travel, handle finances etc.

McKhann, Drachman, Folstein, Katzman, Price, and Stadlan (1981) outline the criteria necessary for the diagnosis of probable, possible and definite Alzheimer's disease. These criteria include: dementia established by a clinical exam and documented by Mini-Mental Test, and Blessed Dementia Scale; deficits in two or more areas of cognition; no disturbance of consciousness; onset between 40 and 90 years of age. A diagnosis of probable Alzheimer's disease is made if there is a typical insidious onset of dementia that is progressive and no other systemic or brain disease can account for the memory and other cognitive deficits. This diagnosis is supported by: impaired activities of daily living; family history of similar disorders; and laboratory results such as CT scan. A diagnosis of possible Alzheimer's disease may be made depending on the clinical course. Definite Alzheimer's Disease is not diagnosed until postmortem by autopsy.

Cerebral Structure and Neurochemistry

Alzheimer's Disease is characterized by atrophy of the cerebral cortex and dilation of cerebral ventricles. "There is evidence that cognitive deficits in Alzheimer's, especially memory, are related to a disorder of cortical cholinergic innervation associated with selective degeneration of cholinergic neurons whose cell bodies lie

in the basal forebrain." (Kuhl et al. 1985, p 419). In the past it was believed that patients with Alzheimer's show a selective degeneration of cholinergic neurons (Davis, 1979; Whitehouse, Price, Clark, Coyle, & Delong, 1982). Foster, Chase, Mansi, Brooks, Fedio, Patronas, Di Chiro, (1984) brought this theory of selective degeneration of acetylcholine-releasing neurons into question, suggesting that this does not necessarily occur throughout the cerebral hemispheres from forebrain nuclei except in very the elderly.

In a study of 17 drug-free Alzheimer's patients and 15 normal subjects, Greenwald, Edasery, Mohs, Shah, Trigos and Davis (1985) found no significant differences in red blood cell choline, plasma choline or the ratio between the two. In a similar study Kanof, Greenwald, Mohs and Davis (1985) compared choline uptake into the red blood cells finding no difference in any kinetic parameters of red cell choline uptake between the Alzheimer's patients and controls. They did find a strong correlation between k_d and V_{max} values (calculated from Lineweaver-Burke plots and expressed in units of nanomoles choline per gram protein) for red blood cell choline uptake for the normal groups but not the patients. The authors suggest that this may be due to a selective vulnerability of central

cholinergic neurons in patients with Alzheimer's disease resulting in an altered choline metabolism.

Price et al (1985) state that reductions in presynaptic markers for cholinergic neurotransmission are currently the most consistent neurochemical observation in Alzheimer's Disease. Dysfunction and death to cells in the areas of medial septum, diagonal band of Broca, and basal forebrain cholinergic system may be partially responsible for the reduction of cholinergic markers.

The difficulty in diagnosing dementia is that the change in the cerebral anatomy is not necessarily different than that of normal aging. For some demented patients, a CT scan shows no cerebral atrophy (Duara, Grady, Haxby, Sundaram, Cutler, Heston, Moore, Schlageter, Larson & Rapoport, 1986). Others may show little or no change. Senile plaques and neurofibrillary tangles, which are believed to be partially responsible for the dementing process, are observable only at autopsy and are found in both demented and non-demented persons, although usually in different quantities in various regions. The distribution of amyloid plaques and neurofibrillary tangles in Alzheimer's appears to be more specific to the hippocampus, amygdala and cerebral cortex regions of the brain (Price et al, 1985; Barnes, 1987). However, this overlapping with normal brain aging, along with the

dependence upon behavioral signs for the clinical diagnosis of dementia in the living patient, often causes confusion between the various dementias, as well as between dementia and various other conditions which have similar behavioral features. This is especially true with elderly, depressed patients.

Recent studies (St George-Hyslop, Tanzi, Polinsky, Haines, Nee, Watkins, Myers, Feldman, Pollen, Drachman, Growdon, Bruni, Foncin, Salmon, Frommelt, Amaducci, Sorbi, Placentini, Stewart, Hobbs, Conneally & Gusella, 1987; Tanzi, Gusella, Watkins, Bruni, St. George-Hyslop, Van Keuren, Patterson, Pagan, Kurnit & Neve, 1987) have found a familial and chromosomal pattern in Alzheimer's patients suggestive of a genetic link. This research suggests that Alzheimer's, which has an early onset, may be caused by an inherited abnormal gene which is located in the same vicinity as chromosome 21. According to Tanzi et al. (1987) the highest level of expression of the beta protein gene was found in the association cortex, which may be related to some of the clinical symptoms observed with Alzheimer's. They hypothesize that this protein might be the basis of the inherited form of Alzheimer's. In addition research has shown (Sjögren, Sjögren, & Lundgren, 1952) increased morbidity risk for family members of early onset Alzheimer's patients.

Changes in cerebral structure found in Down's Syndrome are identical to that of Alzheimer's Disease (Crapper, Dalton, Skopitz, Eng, Scott, Hachinski, 1975) which are believed to be a consequence of the same chromosomal defect as found in Down's patients. This defect is presented on the chromosome 21 (Reisberg, 1981). Price, Whitehouse, Struble, Coyle, Clark, DeLong, Cork and Hedreen (1982) compared changes in the cholinergic system of both persons with Alzheimer's Disease and older persons with Down's syndrome and found support for a cholinergic abnormality resulting from selective destruction of neurons in the nucleus basalis of Meynert. They also found a link between the selective lesion in the nucleus basalis of Meynert and the cortical cholinergic deficiency which may be responsible for the formation of neuritic plaques. It has been stated (Reisberg, 1981) that 100% of person with Down's syndrome who live into middle life will develop a clinical and pathological condition identical to Alzheimer's Disease. The incidence of Down's syndrome is higher in families of individuals with Alzheimer's disease.

Neuropsychological Evaluation

Clinical neuropsychology presents one non-invasive technique for the evaluation and diagnosis of dementia in the elderly, as well as the differentiation from

depression or other psychiatric, treatable conditions. Albert (1984) categorizes mental functions into five basic areas: attention, language, memory, visuospatial ability and conceptualization. Numerous standardized test have been developed for the assessment of these areas for both impaired and non-impaired. Research suggests (Lezak, 1983) that patient's with Alzheimer's Disease retain functions that are familiar and overlearned longer (i.e. scores on WAIS subtests Information, Vocabulary, many Comprehension and Similarities items, and Digits Forward are highest) than unfamiliar, abstract, and speed-dependent tasks (i.e. WAIS Block Design, Digit Symbol and Digits Backward are often the lowest scores obtained). Immediate span and short-term memory tend to be spared (Lezak, 1983), whereas subtle language deficits can appear very early in the disease.

Persons with delirium or clinical depression will exhibit attentional deficits whereas individuals in the early stages of a dementing disorder can often perform simple attentional tasks within the normal range (Albert, 1984). This area can be assessed by using Digit Span forward, a simple and easily administered test of attention.

Albert (1984) suggests that a comprehensive aphasia examination be administered to assess the degree

of impairment in comprehension, repetition, reading, writing and naming abilities. The Boston Naming Test (Kaplan, Goodglass & Weintraub, 1978), The Multiple Choice Naming Test (Huff, Corkin & Growdon, 1983), and The Category Fluency Test have been utilized (Huff & Corkin, 1984) to assess the presence of aphasia in Alzheimer's patients. While there do not appear to be consistent deficits in naming ability with either depression or delirium, persons with early Alzheimer's Disease will show disturbances in naming. They will often make circumlocutory errors or errors of association.

Memory loss is characteristic of early Alzheimer's Disease, but can also be seen in individuals with clinical depression. In contrast to the person with dementia, the depressed person tends to recall as much or sometimes more following a delay, whereas the demented patient will show a dramatic loss of information following a delay. Thus memory assessment should include both immediate and delayed memory tests according to Albert (1984).

Visuospatial skills can be assessed with a simple copying task. Deficits in visuospatial tasks will also be seen with the Alzheimer's patient. These patients will show the decline in visuospatial skills seen with normal aging such as slowing in ability to complete the tasks, but may also demonstrate perseverative tendencies such as

repeating an earlier drawing. According to Albert (1984) the "average mildly to moderately impaired Alzheimer patient can generally perform simple visuospatial tasks quite well" (p. 316), but there is a subgroup whose copying performance is grossly distorted and they often complain of "not seeing right". Albert stated that with this subgroup, the perceptual abilities are almost always more severely effected than their memory performance.

Proverb interpretation, Similarities, card sorting, maze learning and list generation are tests suggested (Albert, 1984) for the assessment of conceptualization. The Alzheimer's patient will demonstrate significant impairment in conceptualization of abstract information. They tend to be much more concrete that those with normal aging deficits.

Feher, Largen, Barr and Smith (1984) found Alzheimer's patients to fall significantly below the normal on a wide range of neuropsychological tests including scores on the WAIS Verbal, Performance and Full Scale IQ, Buschke Selective Reminding Test, Dementia Rating Scale, Seashore Rhythm Test, Digit Cancellation Test, Hidden Words Test and the Wechsler Memory Scale Visual Reproduction subtest.

Storandt, Botwinick, Danziger, Berg and Hughes (1984) were able to correctly classify patients with mild Alzheimer's Disease from normal, healthy older adults

utilizing a battery of tests which included: Wechsler Memory Scale, Word Fluency Test, Boston Naming Test, Entertainment Questionnaire, Visual Retention Test, Wechsler Adult Intelligence Scale, Trailmaking A and a Depression scale. From this list of tests given they found that with a short battery which included only WMS subtests logical memory and mental control in addition to Trailmaking A and Word Fluency 98% of the subjects were correctly classified.

Pseudodementia

Depressive pseudodementia is the term often used for patients who appear to have suffered a loss of cognitive functioning, but who in reality are experiencing moderate to severe depression. This condition is reversible if treated, and thus the importance of a correct differential diagnoses is apparent. Depressive symptoms which mimic dementia include: apathy, psychomotor retardation impaired memory and judgment, orientation and intellectual functions such as comprehension, calculation and general knowledge. Thus a common source of error in the diagnosis of dementia is in those suffering from depression or transient confusional states. Wells (1979) lists the following distinctions between dementia and depressive pseudodementia: in pseudodementia the person exhibits short duration of symptoms, rapid progression of the

difficulty, previous psychiatric dysfunctions, pervasive affective changes, vociferous and detailed complaints of cognitive impairment, "don't know" rather than the near-miss answers, variability of performance, well-preserved attention span and concentration.

There is controversy regarding the use of the terminology, depressive pseudodementia. Post (1975) considers the category to be unimportant, stating that a differential diagnosis can be made between depression and dementia. Shraberg (1978) regards the category to be merely a myth. Reifler, Larson and Hanley (1982) found the concept to be of very little use.

The misdiagnosis of dementia, however, has serious consequences. The treatment of the patient may be terminated upon the diagnosis of most types of dementia since they are progressive and non-reversible. The patient may be placed in a nursing care facility and negative attitudes within and toward the patient may develop. Families may withhold necessary emotional support.

Thus, there is a need for more precise and objective means of diagnosing dementia in the elderly. The P300 component of auditory event-related potentials (ERP) has shown promise for making a significant contribution to the evaluation of cognitive functioning.

P300 Component

The P300 (also referred to as P3) is the third positive wave in the ERP which peaks at approximately 300 msec following the onset of a task-relevant, rare stimulus. The P300 is termed an "endogenous" component of ERP's because it is reliant upon an internal evaluation process of the stimulus by the subject. Pritchard (1981) suggests that the P300 is the actual phenomenon of interest rather than being used merely as a measure for drawing inferences regarding a different phenomenon of interest. Therefore the question to be asked is what correlates with P300. In fact there are many variables which correlate with the presence or absence of P300 such as: stimulus probability; classification of stimuli (signal or nonsignal); and task relevance. Depending on the instruction given to the subject, the stimulus will serve in one of these various functions. Thus, the same stimulus may or may not result in a P300. Based on this differentiation, Pritchard suggests that the P300 is "invoked" rather than "evoked". The variations of the experimental context result in an internal change as the subject evaluates the stimulus.

Two conditions are required to elicit a P300 wave: (a) a low probability stimulus, and (b) a discriminative task given to the subject. Typically an "auditory

oddball" paradigm is used to elicit a P300. Regularly occurring auditory stimuli of a given pitch are occasionally and randomly replaced with ones of a different pitch and/or intensity. The infrequently occurring stimuli are made task-relevant by having the subject count them. Averaged evoked EEG responses elicited by the counted, infrequent stimulus manifest a large positive wave (P300) which is not apparent in the response to its frequent stimulus. P300 disappears in the response to rare stimuli if the subject ignores them.

Donchin (1981) states that P300 latency is not an orienting response. He found that orienting responses habituate. Once the stimulus is not longer novel, the response does not occur. P300 does not habituate, nor does it disappear while the person is involved in the stimulus task. He suggests that the P300 is involved with the process of memory modification or learning, and the process manifested by P300 is association with the updating of our schema.

P300 Amplitude

Past research (Pritchard, 1981) has demonstrated that P300 amplitude and latency systematically correlate with a number of specific cognitive manipulations. Sutton, Braren, Zubin and John (1965) were the first to suggest a relationship between P300 amplitude and uncertainty

resolution (information delivery). P300s were invoked when the stimulus supplied the subject with information (Pritchard, 1981). But it was soon discovered that uncertainty resolution did not offer enough explanation of the phenomenon of P300 amplitude.

In his review of the P300, Pritchard (1981) found P300 amplitude to decrease as the subject's confidence in his/her own perceptions decreased. P300 amplitude is larger following signals than nonsignals which indicates the involvement of an interaction between incoming information and memory. Increased memory capacity and functioning, which occurs with normal development, is significantly correlated with P300 amplitude. Also, there is evidence that P300 amplitude invoked by task relevant stimuli is a function of the actual use of the information by the subject. As subjects master a trail-and-error concept-formation task, P300 amplitude decreases. Furthermore, P300 amplitude can, under some conditions, be predicted by the subject's expectancy regarding signal presentation. P300 amplitude does appear to index perceptual limited-capacity processing, meaning that when a P300 component is observed, the subject was conscious of the stimulus that preceded the component by roughly 300 msec. Polich (1986) found in studying students with no neurological or

psychological disorder that the amplitude of the P300 was affected by how conscientiously the subject is involved in the task, i.e. attention. P300 amplitude is sensitive to perceptual load (Donchin, 1981). If perceptual demand for other concurrent tasks increases, P300 amplitude in the original task decreases.

P300 Latency

Duncan-Johnson and Donchin (1979) and Duncan-Johnson (1981) suggested that the P300 latency is a useful index of the duration of stimulus-evaluation processes independent of the time necessary for stimulus selection and response execution. Stimulus-evaluation processes are defined as "the subset of cognitive operations involved in the encoding, identification and categorization of a stimulus" (p. 209). Duncan-Johnson and Donchin (1979) recorded ERPs and response times (RT) from 12 male subjects using a warned, choice RT task. The subjects were presented with a series of visual stimuli that fell into one of three categories; match, mismatch or star. The probability of the various stimuli appearing changed over the course of the series. Conditional probability was found to be the principal determinant of P300 and RT. The lower the probability, the later the P300 and the slower and less accurate the response. It was concluded that P300 can be used as a measure of stimulus evaluation

time in tasks with relatively low processing levels. Duncan-Johnson (1981) concluded that P300 is not merely another measure of response time, like a motor reaction time, but is in fact free from response-related factors. This hypothesis has found support from many studies (Squires, Donchin, Squires & Grossberg, 1977; Donchin, Ritter & McCallum, 1978; Ford, Hink, Roth, Pfefferbaum, & Kopell, 1979).

Picton, Stuss, Champagne and Nelson (1984) found no change in reaction time with age. They suggest that the P300 component is initiated in young adults at approximately the same time as a motor response, although the P300 compenent is independent of response time. With aging the P300 process occurs later than reaction time. They suggest that there are two parallel processes occurring in the brain, one generating the reaction time the other a cognitive event which is manifested in the P300 latency.

Fitzgerald and Picton (1983) found that increasing the difficulty for detecting target stimuli prolonged the latency of the P300. They conducted a series of three experiments in which the target stimuli were varied in degree of detection difficulty on 19 subjects ages 17 to 37 years. The frequency of occurrence and number of target stimuli were varied. Subjects were instructed to count

or press a button upon hearing the target stimulus. Fitzgerald and Picton found that the P300 component was significantly smaller in amplitude and prolonged in latency for the more difficult target compared with the easily detected stimulus. This result occurred in all three experimental conditions. They postulated that the amount and type of updating that occurs in the final stage of stimulus discrimination is indexed by the P300 component.

Hillyard, Squires, Bauer and Lindsay (1971) found the P300 amplitude to increase as the confidence of the subject regarding correct signal detection increased. Paul and Sutton (1972) were able to confirm this hypothesis adding the relationship between the P300 compenent and response bias to the confidence explanation.

Fourteen subjects ranging in age from 19 to 31 years were studied by Brookhuis, Mulder, Mulder and Gloerich (1983), using a visual task which increased in the amount of information that needed to be remembered. They found that there was an overall main effect for the processing load. The P300 latencies were affected by the time needed to make either a positive or negative decision but not by response time. P300 latencies increased as a function of processing load or increased task difficulty. Ford, Roth and Kopell (1976) and McCarthy and Donchin (1981) also

found support for the increase in P300 latency as task difficulty increased.

Ford, Pfefferbaum, Tinklenberg and Kopell (1982) studied the P300s and response times of 10 elderly (mean age 79 years) and 10 young (mean age 23 years) female subjects each receiving a series of visual memory retrieval tasks. Subjects were instructed to press a button with the index finger of one hand if the probe was a positive and press the other button with the index finger of their other hand if the probe was negative. The stimuli were numbers constructed with unconnected dots. Some stimuli were degraded by adding random dots making the identification more difficult. They found that P300 latency was longer for the elderly subjects than for the young as reported by others (i.e., Ford et al; 1979; Pfefferbaum et al; 1980a). The also found that increasing the difficulty of the memory set from 2 to 4 prolonged the P300 latency for the young subjects but not for the elderly. This finding supports that of Pfefferbaum et al. (1980). Ford et al. suggest that operations designed to make the decisions more difficult (e.g, increasing memory load) do not affect P300 latency but those designed to make the discrimination more difficult (degrading) do affect P300 latency.

McCarthy and Donchin (1981) manipulated the stimulus difficulty by visually presenting the word "right" or "left" surrounded by either the # sign or other random letters. In addition the word "different" or "same" appeared on the screen indicating which hand the subject was to use in responding. They found that the P300 latency was affected only the presence of noise (the words surrounded by random letters) but not the incompatible response instructions (different, meaning if the stimulus word was "right" respond with your left hand). McCarthy and Donchin suggest that their data indicate that the P300 can serve as a dependent variable for studying human information processing.

Polich (1986) studied 12 normal subjects between the ages of 18 and 24 years using variations in frequency and intensity of the target tone to determine the effect upon P300 latency. He found that P300 latency was not significantly affected by variable of attention but was stable, varying little as a function of the task when the subject was engaged in a discrimination paradigm of some type. A decrease in P300 latency was found when subjects were asked to ignore the stimuli. Polich commented that even when given instructions to ignore, there appeared a P300 which he suggests may be an indication that some

information processing occurs even when told to ignore the stimulus.

P300 Generators

Much discussion has occurred regarding the location of the neural generator(s) of the P300. Depth electrode implantation has offered general information of possible areas where P300 generators may lie. Altafullah, Halgren Stapleton and Crandall (1986) studied responses from electrodes implanted in the hippocampus, parahippocampal gyrus and amygdala of 16 patients with partial complex epilepsy in order to lateralize seizure activity. They found support for local generation of the P300. Although the Medial Temporal Lobe (MTL)-P3 is not identical to the scalp-P3, they appear to be very similar. They suggest that MTL may generate a significant portion of the scalp-P3 with the late posterior and lateral P300 reflecting more MTL activity than the earlier fronto-midline P300 in simple tasks. They found that the scalp-P3 was about twice as large as expected suggesting that the MTL is not the sole source of activity resulting in a scalp-P3. This theory has found support by other investigators (Smith, Stapleton & Halgren, 1986; Halgren et al, 1980, 1985a; Squires et al, 1983 and Wood et al, 1984). Smith, Stapleton and Halgren (1986) found that MTL-P3 changes during recognition memory tasks were small or absent to

non-repeated words and large to word repetitions. They suggest that MTL-P3 might indicate the completion of MTL involvement in memory search and retrieval operations.

According to Okada, Kaufman and Williams (1983), an endogenous potential (200-630 msec) appears at the scalp when a subject is involved in tasks requiring judgment about a stimulus. Intracranial recordings have found increased single unit firing in or near the hippocampal formation and amygdala while subjects were engaged in task-relevant activities. In their study of 3 young adults using magnetic and electrical recordings, Okada et al. suggest that their data strongly support the hippocampal formation as the location of the major source or sources of P300 for at least the right hemisphere.

These studies suggest the possibility of multiple generators of the P300 component. It has been discussed in light of this indication (Fabiani, Gratton, Karis & Donchin, in press) that multiple generators does not mean multiple psychological processes are also involved. Many neural generators may be involved in order to activate and carry out a unitary psychological process in diverse brain regions.

P300 and Memory

Howard and Polich (1985) studied 24 children (5-14 years) and 24 adults (20-40 years) using the Digit

Span subtest of the Wechsler Adult Intelligence Scale (WAIS). They found that as memory span increased, P300 latency decreased for the children relative to the adults. They suggested that perhaps fewer resources are utilized for encoding and item-identification processes when the memory capacity is more developed, thus the shorter P300 latency.

Polich (1986) observed the ERPs of 100 undergraduates (mean age 20.4 years). He found P300 amplitude and latency to be negatively correlated implying a systematic relationship with the association the greatest at the parietal/central scalp locations. His data support Donchin's (1981) theoretical interpretation of the P300 as relating "incoming sensory information to memory updating processes" (Polich, 1986; p. 239) as well as neuropsychological observations that the parietal lobe engages in such activities.

Mäntysalo and Gaillard (1986) studied ERPs of 9 normal male subjects while completing a syllable learning task. P300 latency was found to be longest for new syllables and shortest during overlearning. They suggest that the P300 invoked during the test phase when new syllables were being introduced, could be associated with the updating of working memory. They indicate that this updating may occur by a match/mismatch function, a prolonged cognitive

process manifested in a long latency P300. P300 amplitude was found to be largest for learned items but smallest for overlearned items during a word recall task. These data suggest that the evaluation of unlearned items takes longer resulting in longer P300 latencies, than the evaluation of just learned items which elicit larger P300 amplitudes.

Donchin (1981) proposes that the P300 is involved in the process of memory modification or learning. Responses that are to be remembered may possibly be those processes manifested by the P300. He presented subjects with a series of words displayed one at a time with half of the words appearing dimmer on the screen. The subject was told to memorize the dim words. The subject is then tested with all words appearing at the same intensity. He found large differences between the ERPs elicited by the words that were dim during the training phase, and those that were bright during the training phase. These differences were not attributable to the intensity of the words because all words were the same intensity during the testing phase, rather the P300 differences are due to the subject attempting to identify the words that were to be remembered.

P300 and Normal Aging

Changes have been found (Courchesne, 1977; Courchesne, Ganz & Norcia, 1981) in the P300 that correlate with cognitive development in children. P300 latency decreases from the ages of 5 to puberty, then stabilizes and then increased with age. Marsh and Thompson (1972) were perhaps the first to report age differences in P300 latency measurements using auditory discriminative tasks. An increase in latency was seen for normal elderly individuals. This was substantiated later by other investigators (i.e, Brent, Smith, Michalewski & Thompson, 1977; Ford, Roth, Johns, Hopkins & Kopell, 1979)

Pfefferbaum, Ford, Roth & Kopell, (1980a; 1980b) found similar results with P300 and normal aging from data collected from 8 elderly (74-90 years) and 12 young (20-29 years) healthy, normal women. The subjects were given visual memory retrieval tasks and P300 recorded. They found that the elderly subjects differed significantly from the younger subjects in three major areas: (a) P300 amplitude at Pz was smaller for the elderly; (b) P300 latency and response time were slower for the elderly group; and (c) the relationship between P300 and response time was altered, less tightly coupled. There was a significant difference, not age related, in P300 latency between the young and elderly groups, although there was

no significant difference in P300 latency-reaction time correlations. These results were substantiated (Pfefferbaum, Ford, Wenegrat, Roth & Kopell, 1984) with a larger number of subjects and utilizing computerized measures of P300 latency and single as well as averaged trials. In addition to the findings that P300 latency increases with age, they also found that scalp topography of the P300 changes with age. P300s in young subjects have a parietal distribution. With age, the P300 becomes more frontally distributed.

Goodin, Squires, Henderson and Starr (1978) found that P300 significantly increases with age in a linear fashion at a rate of 1.2 msec per year. Syndulko, Hansch, Cohen, Pearce, Goldberg, Montan, Tourtellotte, and Potvin (1982) found latencies to increase .7 at Fz, 1.0 at Cz and 1.1 msec per year at Pz. Pfefferbaum, Wenegrat, Ford, Roth, and Kopell (1984) found an increase of 1.0-1.5 msec per year in P300 latency. Brown, Marsh, and LaRue (1983) further found that a exponentially accelerating curve described the P300 latency/age interaction more precisely than merely a straight line. They studied 49 normal subjects (15-80 years) using a modified version of the "auditory oddball" paradigm. They suggested that the slope for the regression line was different for persons under 45 years of age than for those over 45 years. They

found that the P300/age correlation for subject under 45 years was not significant, whereas for those over 45 years of age, the P300/age correlation was highly significant and yielded a linear slope of 3.14 msec/year. They suggest that P300 latency is a positively accelerating function of age.

Picton, Stuss, Champagne and Nelson (1984) found no evidence of a curvilinearity in the regression line of P300 latency for normal aging in their study of 72 subjects ages 20-79 years. They suggest that in addition to the linear age effect on P300 latency there may also be other variables related to subject selection which affects P300 latency and may bring out a curvilinearity in the age regression.

P300 and Dementia

The latency of the P300 increases beyond the effects of age, in most cases, for persons with a neurological disease which results in dementia, whereas persons with functional disorders or neurological disease without cognitive impairment rarely exhibit an increase in P300 latencies (Goodin et al. 1978; Squires, Chippendale, Wrege, Goodin, & Starr, 1980; Brown, Marsh & LaRue, 1982).

Brown, March and LaRue (1982) studied 24 elderly (50-81 years) normal subjects and an inpatient group of 25

individuals (65-88 years) who had been admitted to the hospital for treatment. The patient group consisted of individuals diagnosed with Alzheimer's Disease (10), multi-infarct (5), dementia associated with Parkinson's Disease (3), and depression with no dementia (7). Utilizing the P300 latencies from an auditory oddball paradigm, to diagnose the subjects, they found that no psychiatric cases were classified as demented (i.e. these did not fall outside 2 SD of the age/P300 regression line). Whereas three non-demented patients were classified as demented with the MMS, there were no false positives using P300 latency. False negative (failing to detect the presence of dementia) occurred in 7 of 17 patients using the P300 latency. It was suggested that the P300 and the MMS could be used in conjunction for the most accurate differential diagnosis of patients as demented or non-demented (i.e. depressed).

Syndulko et al. (1982) replicated the findings of Goodin et al. (1978) focusing more specifically upon elderly patients with the diagnosis of moderate progressive dementia. Their findings suggest that not only is the P300 latency useful to discriminate functional from any dementing disorder, but specifically from primary dementing disorders.

In contrast to these studies, Pfefferbaum, Wenegrat, Ford, Roth and Kopell (1984b) concluded that the P300 latency is not sensitive enough for clinical diagnoses. They studied three inpatient groups, one consisted of patients who demonstrated clinical evidence of cognitive impairment and two groups who met criteria for schizophrenia and major depression (Research Diagnostic Criteria, Spitzer & Endicott, 1978). They found that although there were differences in P300 latency and amplitude in the three groups, they were not large enough nor specific enough for clinical differentiation. The demented group had significantly prolonged P300 latencies, but less than 50% fell 2 SD outside the predicted age related score. Twenty to thirty percent of the schizophrenic patients had P3 latencies more than 2 SD longer than the mean for their age.

Lai (1984) suggested that these conclusions may be a result of the fact that the schizophrenic subjects were chronic patients medicated on neuroleptics. It is quite likely that some of these patients were also in fact organically impaired.

P3a

A moderate number of false negative diagnoses for dementia using P300 may be accounted for by the confounding occurrence of "P3a". Squires, Squires, &

Hillyard, (1975) differentiated an early P300 wave (P3a) from a later occurring P300 wave (P3b). The P3a peaked between 220-280 msec in young normals and had a frontal scalp distribution when these subjects were asked to ignore the stimuli. When asked to count the rare stimuli, the P3b occurred at 310-380 msec with a parietal scalp distribution. P3a was not found in all cases of active attention, while at other times it could be seen superimposed upon a P3b component. Thus, P3a appears to occur in both active and passive conditions, although it may be obscured in the active condition by the P3b. P3a may be an index of a basic sensory mechanism which registers any change in background stimulus and thus can be interpreted as an orienting response. Ford, Roth et al, (1976) confirmed the existence of P3a.

In the case of patient testing, it is likely that a P3a would occur without a P3b in those persons who are unable to understand or retain the instructional set. However, failure to recognized the wave as P3a may lead to the conclusion that the P300 (P3b) was within normal limits, and that the person was not demented. Thus it may be that the early P300 wave found in some clearly demented patients was in fact a P3a. Thus measurement of P3a rather than P3b would result in false negatives for dementia.

Lai et al. (1985) have demonstrated that the P3a confounded the measurement of P300 (P3b), and subsequent diagnosis, in two ways; (a) in some cases P3a preceded P3b as an inflection of a fairly distinct wave or (b) P3a was the only P300 wave elicited to the infrequent stimulus. This often occurred in severely demented patient. Lai et al. (1985) added a third surprising tone which was non-task-relevant to the typical "auditory oddball" paradigm in order to elicit P3a in isolation. Also the stimulus differentiation was made more difficult by eliminating the intensity differences between target and frequent tones. This was thought to increase P3b latencies in elderly patients. Thus P3a and P3b would be more distant.

Lai et al. (1985) found the expected decreasing amplitude from posterior to anterior for P3b, and an increasing amplitude from posterior to anterior with the P3a. P3b was found to be significantly different in latency between the normal and patient groups, but P3a measurements were not different. For patients with Mini-Mental State scores greater than 26 and less than or equal to 26, P3b was again significantly different while P3a was not.

Contrary to earlier suggestive evidence (Brown et al, 1982), Lai et al, (1985) found that P300 latency did not appear to discriminate Primary Degenerative Dementia from

Multi-infarct or Parkinson Dementia. Polich et al. (1986) also found no statistical difference between different diagnoses of dementia and P300 latencies. It appears from these studies that at least for group averages the dementing illnesses produce similar effects on P300 latency and amplitude across etiologies. The many factors which contribute to a variety of dementing illnesses apparently have some relatively common factor which serves to increase the P300 latency independent of age related changes. Thus P300 latency measurements may prove to be an important tool in the differential diagnosis between demented and non-demented patients, but thus far does not provide information regarding various possible etiologies of dementia.

One possible cause for the occurrence of a P300 outside the normal range for some demented persons and not for others could be the sensitivity of the P300 latency to cortical integrity within specific brain regions or systems. That is, regardless of the global level of dementia, certain specific neural tissue must be dysfunctional for P300 latency to become abnormally long. Thus, different anatomical progressions or different stages of various dementing processes may or may not impinge on neural systems influencing P300 latency.

Positron Emission Tomography

With the new advances of the Positron Emission Tomography (PET), it is now possible to measure the metabolic activity of specific brain regions in living, active patients. The earliest and most specific changes occurring in various diseases of the brain are reflected in disturbances of underlying biochemical processes and thus are apt to be detectable by PET scanning.

Three major components are required in order to obtain quantitative ratios of biochemical activity using the PET scanner: injectable compounds labeled with radioisotopes, the positron tomograph, and tracer kinetic mathematical models.

Radionuclides such as Fluorine-18 can be used to label biological substrates or analogues such as glucose or water and then be injected into the blood stream of the subject. This short-lived radioisotope then circulates and otherwise interacts in a normal physiological manner. In the case of Fluorine-18 labeled glucose the radioisotope is thus taken up into active neural tissue. The greater the activity level of specific tissue, the greater the uptake of the radioisotope. The isotope Flurodeoxyglucose is a very unstable form of fluorine with as half-life of approximately 17 minutes. It is quickly transported to the brain since glucose is the only source of energy

utilized by the brain. Trapped with active neural cells, the unstable isotope releases an unequal number of electrons and protons resulting in collisions which form the very energetic gamma rays.

The tomograph is an array of radiation detectors placed circumferentially around the head of the patient. These detectors record the emission of gamma rays from the tissue distribution of positron activity within neural tissue which has taken on the radioisotope by normal physiological activity. The data collected are then processed by a computer to form a tomographic brain image. Images can be constructed for multiple 2-dimensional planes, comprising in all a 3-dimensional image of brain physiological activity. Thus PET provides a spatially discrete, quantitative, noninvasive measurements of the rate of physiological activity of the living human brain in three-dimensional perspective.

Tracer kinetic models represent mathematical descriptions of biochemical reaction sequences. Each segment of the sequence is a compartment, and differential equations describe the movement of the natural labeled compounds between the compartments. Measurements are made of the flux between compartments which are then used to determine the rate at which the reaction sequence proceeds. These reaction rate calculations form the

numerical basis of the digital brain image created by positron emission tomography.

Due to the short half-lives of the positron-emitting isotopes, it is possible to perform multiple studies in a single setting to observe the effects of changes in spontaneous or stimulus-induced alterations on regional brain distributions of different biochemical processes.

PET and Normal Aging

The study of cerebral blood flow (CBF) and cerebral metabolism in normal aging as well as dementia has yielded contradictory results. Some researchers (Kety, 1956; Navitomi, Meyer, Sakai, Yamaguchi, & Shaw, 1979) suggest that CBF and cerebral metabolism decrease with age. Others (Butler, Dastar, & Perlin, 1965; Fujishima, & Omae, 1980) report no change. De Leon and his associates (De Leon, Ferris, George, Christman, Fowler, Gentes, Reisberg, Gee, Emmerich, Yonekura, Brodie, Kricheff and Wolf, 1983) studied PET scans of 15 young normal subjects (mean age 26.1), 22 elderly normal subjects (mean age 66.6), and 24 mild to severe Alzheimer's patients (mean age 73.4). Their results failed to demonstrated any significant difference in glucose metabolism due to normal aging although there was a trend toward decreased metabolism within the older normal group.

PET and Dementia

All diseases of the brain result from or produce focal or diffuse biochemical changes, reflective of functional brain disturbance. PET images display functional processes, often demonstrating larger, earlier and more distributed lesions than those found in anatomically oriented techniques (CT or MRI scans). Significant correlations exist between the PET measures of glucose use and the measures of cognitive functioning in demented patients (de Leon et al. 1983). The cognitive deficits of Alzheimer patients may have focal as well as a generalized decrease in cerebral glucose metabolism (Foster, Chase, Fedio, Nicholas, Patronas, Brooks, & Di Chiro, 1983).

The PET scan has been found to be more consistently related to cognitive decline than the CT scan (de Leon, George, Ferris, Rosenbloom, Christman, Gentes, Reisberg, Kricheff & Wolf, 1983). In their study of 19 subjects (60-85), with 8 Alzheimer's patients and 11 normal subjects, de Leon et al. (1983) found all mean regional glucose use values to be significantly lower for the Alzheimer's patients. However, no differences were found with the regional CT scan data between the two groups. Interestingly though, they found a correlation between structural attenuation and mental status in the region of the temporal lobes for the CT scan. There was also a

correlation between thalamic CT attenuation and global reduction in brain metabolic activity. They suggest that the anatomic and metabolic changes may reflect impairment of thalamic functions although this is speculative at this point. Similar results were found by Duara, Grady, Haxby, Sundaram, Cutler, Heston, Moore, Schlageter, Larson and Rapoport (1986). They found no atrophy with the CT scan but reduced cerebral metabolism for 21 patients with a clinical diagnosis of Alzheimer's Disease.

De Leon et al. (1983) found that they were able to correctly classify the Alzheimer's patients with accuracy greater that 80% utilizing the reduced glucose metabolic rate noted for the PET scan. They found consistent correlations between measures of glucose utilization and degree of cognitive impairment.

Kuhl, Metter, Riege and Hawkins (1985) found that 2-deoxy-2-fluror-D-glucose (FDG) scan is a sensitive indicator of local brain dysfunction in Multi-infarct dementia (MID). In MID, multiple lesions from focal ischemia caused an abnormal cerebral metabolic pattern. FDG scans revealed scattered metabolic defects in cortex, caudate, thalamus, white matter and cerebellum.

Patients with Huntington's disease were found (Kuhl et al, 1985) to have markedly depressed glucose utilization (20%) in the caudate and putamen regardless of duration of

the disease or the presence or absence of caudate atrophy. They suggest that decreased metabolism appears to be a "process that occurs prior to bulk loss of striatal tissue" (p. 421).

In Alzheimer's type dementia, the FDG PET scan revealed (Kuhl et al., 1985) abnormal metabolic patterns which reflected neuronal degeneration most severe in the cortex. The average decrease in zonal metabolism was 47% in parietal and dorsolateral occipital cortex, and 28% in caudate and thalamus. Friedland, Budinger, Koss and Ober (1985) found a glucose metabolic decrease of 27% in the temporal-parietal cortex of an Alzheimer group. Chase, Fedio, Foster, Brooks, Di Chiro and Mansi (1984) found a significant positive correlation between cortical glucose use measured by the PET and the Full Scale IQ, Verbal IQ and Performance IQ scores on the Wechsler Adult Intelligence Scale in both normal and demented patients. The VIQ correlated more closely with cortical metabolism in the left cerebral hemisphere while PIQ correlated with cerebral metabolism of the right hemisphere.

Greater impairment in cortical glucose metabolism was found in another study (Koss, Friedland, Ober & Jagust, 1985) specifically for the right hemisphere in patients with early Alzheimer's disease. They studied 18 patients who met the DSM-III criteria for primary degenerative

dementia finding that the decline in metabolism was related to age of disease onset. Thus they suggest once again that Alzheimer's Dementia has two distinct populations. From their research they define a unique subset of patients under 65 years with a decrease in right hemisphere metabolic activity.

Foster, Chase, Mansi, Brooks, Fedio, Patronas and Di Chiro (1984) found a 10-49% decrease in glucose utilization within the Alzheimer's group when compared with the control group. They observed that the posterior parieto-temporal areas were the most affected, whereas the frontal cortex and sensorimotor cortex were least affected. They postulated that as the disease progressed the frontal lobe would also become subject to deterioration. These finding support those of Friedland, Budinger, Ganz, Yano, Mathis, Koss, Ober, Heusmann and Derenzo (1983) who also found cortical degeneration to be most marked in the posterior temporal and parietal regions in Alzheimer's patients.

Frackowiak, Pozzilli, Legg, DuBoulay, Marshall, Lenzi and Jones (1981) found a decline in cerebral blood flow and cerebral oxygen utilization which was correlated with severity of dementia. They found the parietal area to be most affected with a 29-33% fall in cerebral blood flow. There was a similar decline in the temporal area

also. Bilateral metabolism decrease was found (Friedland, Budinger, Brant-Zawadzki & Jagust, 1984) in temporal-parietal cortex, and more markedly in the right hemisphere in their study of two Alzheimer's patients.

PET, P300 and Dementia

Given the new technological advances of the PET scan and the P300 latency measures, this study will investigate the relationship between these two techniques in individuals considered to be early, mild cases of Alzheimer's type dementia. Based upon past research, the use of both P300 latency and PET scan measures could assist greatly in the diagnosis of Alzheimer's Disease, perhaps even in its very early stages. One would expect to find decrease metabolism in the parietal, temporal and parahippocampal areas as well as a prolonged P300 latency. In combination, these two methods could greatly reduce the incidence of misdiagnosis. Furthermore in studying the relationship between the PET Scan and P300 latency, more understanding of the possible neural systems influencing the P300 may be gained. It is possible that the integrity of the parietal, temporal and parahippocampal systems is necessary in order to invoke a age-normal P300 latency. Thus as these system begin to decrease in their rate of glucose metabolism, the processes necessary for a normal P300 become less efficient. Perhaps fewer resources are

available for the encoding and processing of information, resulting in a prolonged P300 latency. Thus, a better understanding of the relationship between P300 and PET may enlighten us regarding the false negative that occur with the use of the P300 in diagnosis dementia. It is possible that, as long as the parietal and temporal systems are fairly well intact, the stimulus evaluation time is not decreased and normal P300 latency is seen even though the person may have signs of a dementing illness. Thus, it is hypothesized that: (a) the P300 latency is a reflection of brain integrity which will be manifest in PET indices of metabolic rate. (b) P300 latency will reflect cortical versus subcortical metabolic rate. (c) P300 latency will be specifically longer in those patients with reduced parietal and/or temporal metabolic rate.

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List of Appendices

Appendix A

List of Journals for Submission of Profession Article

Science

Neurpsychologia

Electroencephalography and Clinical Neuropsychology

August 12, 1987

Richard Gorsuch, Ph.D.
Graduate School of Psychology
Fuller Theological Seminary
135 N. Oakland
Pasadena, CA 90811

Dear Dr. Gorsuch,

I am writing to request that the requirement of a signed letter of submission of my article to an appropriate journal be waived. Due to my involvement in a collaborative research grant, I must have any article approved and edited by several other members of the project including Dr. David Kuhl of the University of Michigan and Dr. Walter Reige of UCLA. At this time, Dr. Kuhl has not given his permission for any publication submissions. There are two articles in process at this time and will be submitted as soon as possible.

Sincerely,

Glena L N Schubarth
Glena Lynne Needham Schubarth

Waiver approved:

Warren S. Brown
Warren S. Brown, Ph.D.
Chair

Richard Gorsuch
Richard Gorsuch, Ph.D.
Director of Research

Appendix B

Table 2

Correlations of PET and P300 Latency Measures for PAD Group Only

	P300 Z-score	P300 Raw Score
Global	-0.2093	-0.2194
	p = 0.125	p = 0.114
Parietal/ Cerebellum	-0.2569	-0.1778
	p = 0.078	p = 0.165
Temporal/ Cerebellum	-0.2640	-0.2350
	p = 0.072	p = 0.098
Parahip/ Cerebellum	-0.1863	-0.2271
	p = 0.154	p = 0.106
Frontal/ Cerebellum	-0.4193 *	-0.3771
	p = 0.008	p = 0.017
CaudThal/ Cerebellum	-0.0230	-0.0518
	p = 0.450	p = 0.389
Frontal/ Parietal	-0.1237	-0.1913
	p = 0.250	p = 0.147
Right Par/ Left Par	0.2071	0.2077
	p = 0.128	p = 0.127

* $p < 0.0012$

Table 3

Correlations of PET and P300 Latency Measures for Control Group Only

	P300 Z-score	P300 Raw Score
Global	-0.3762	-0.4844
	p = 0.068	p = 0.024
Parietal/ Cerebellum	-0.0811	0.0748
	p = 0.378	p = 0.388
Temporal/ Cerebellum	0.3797	0.3144
	p = 0.066	p = 0.110
Parahip/ Cerebellum	0.2366	0.2874
	p = 0.180	p = 0.132
Frontal/ Cerebellum	0.0526	0.1885
	p = 0.421	p = 0.234
CaudThal/ Cerebellum	0.2330	0.1693
	p = 0.184	p = 0.258
Frontal/ Parietal	0.3055	0.2792
	p = 0.117	p = 0.139
Right Par/ Left Par	0.3257	0.3849
	p = 0.101	p = 0.064

* $p < 0.0012$

Table 4

Correlations for PET and P300 Latency Measures for PAD and Control Groups Combined

	P300 Z-score	P300 Raw Score
Global	-0.2112	-0.2232
	p = 0.073	p = 0.062
Parietal/ Cerebellum	-0.5336 *	-0.4962 *
	p = 0.001	p = 0.001
Temporal/ Cerebellum	-0.3915 *	-0.3946 *
	p = 0.003	p = 0.003
Parahip/ Cerebellum	-0.3803 *	-0.4068 *
	p = 0.004	p = 0.002
Frontal/ Cerebellum	-0.4662 *	-0.4330 *
	p = 0.001	p = 0.001
CaudThal/ Cerebellum	-0.0078	-0.0351
	p = 0.479	p = 0.405
Frontal/ Parietal	0.2500	0.2219
	p = 0.042	p = 0.063
Right Par/ Left Par	0.2604	0.2623
	p = 0.035	p = 0.034

* $p < 0.0012$

Figure Captions

Figure 5:

This scatterplot displays the regression line for the correlation of P300 Z-scores and the parietal/cerebellum ratio. "A" represents each patient data point. "C" represents each control data point.

Figure 6:

This scatterplot shows the correlation of the P300 Z-scores and the temporal/cerebellum correlation. "A" indicates patient. "C" indicates control.

Figure 7:

This figure displays the P300 z-score and frontal/cerebellum ratio correlation and regression line. "A" represents the patient, and "C" represents the control.

Figure 8:

This scatterplot shows the correlation between P300 z-scores and the parahippocampus/cerebellum ratio. The "A" indicates a patient data point, the "C" a control.

Figure 9:

This figure shows the P300 z-score and global measure correlation and regression line. "A" indicates a patient data point, "C" a control.

Figure 10:

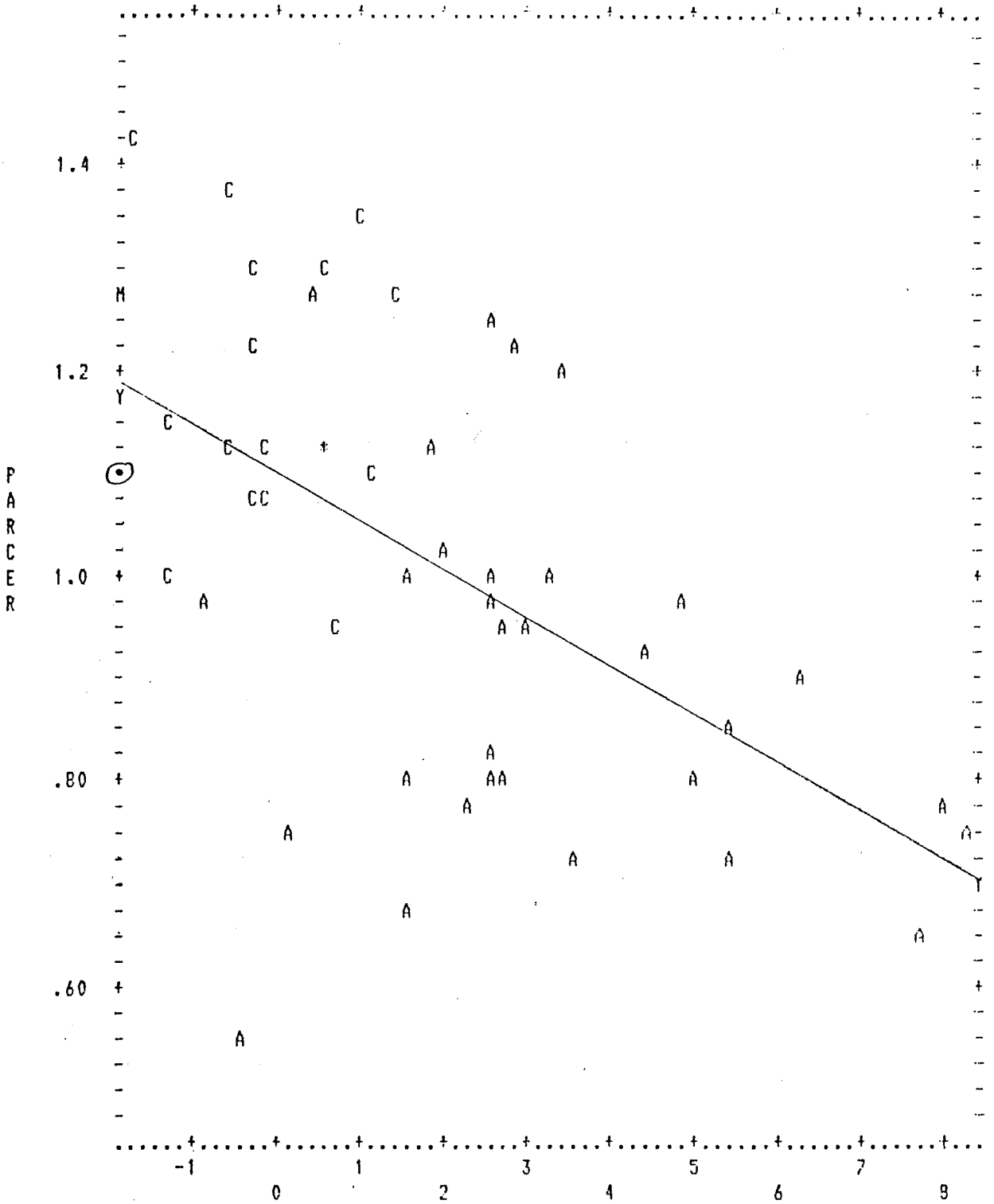
This shows the correlation for P300 z-scores and the frontal/parietal ratio. Patients are indicated by "A", controls by "C".

Figure 11:

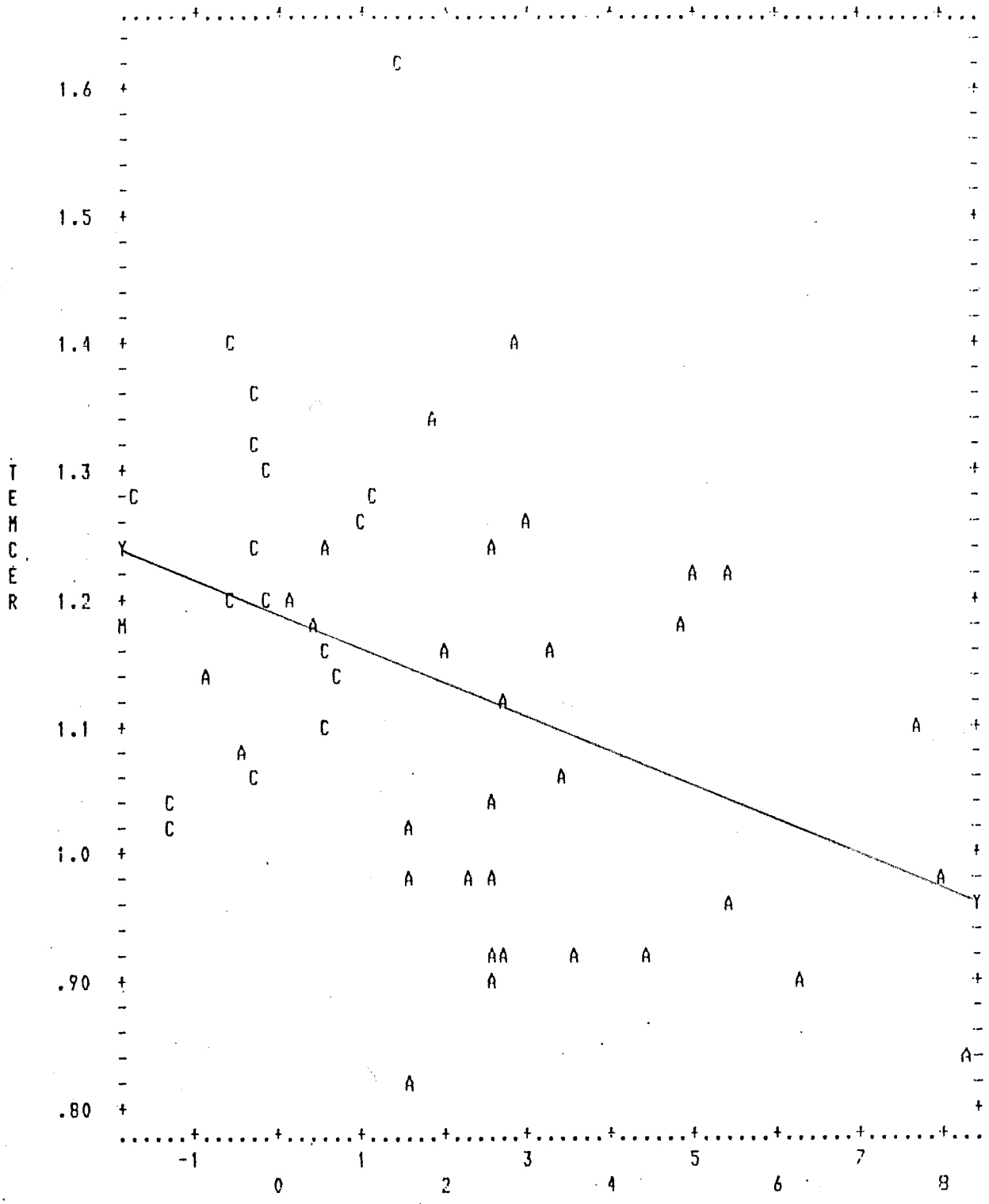
The scatterplot shows the P300 z-score and right/left parietal ratio correlation with patients desinatedby "A" and controls by "C".

Figure 12:

Thei figure shows the correlation between the P300 z-scores and the caudate thalamus/cerebellum ratio. Patients are repsented with an "A", controls with a "C".



N = 49
R =-.5336
P < .0016



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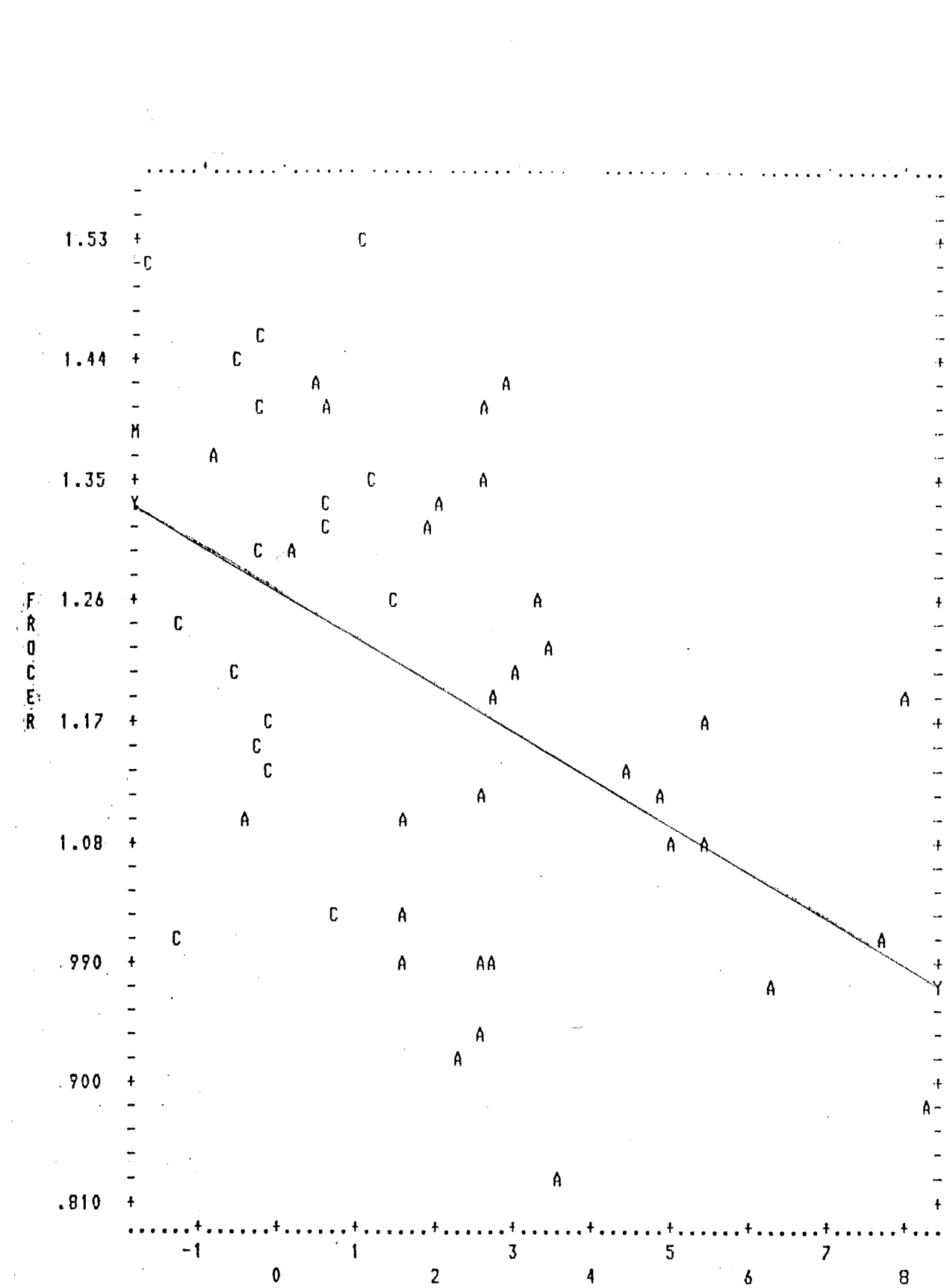
P = .0050



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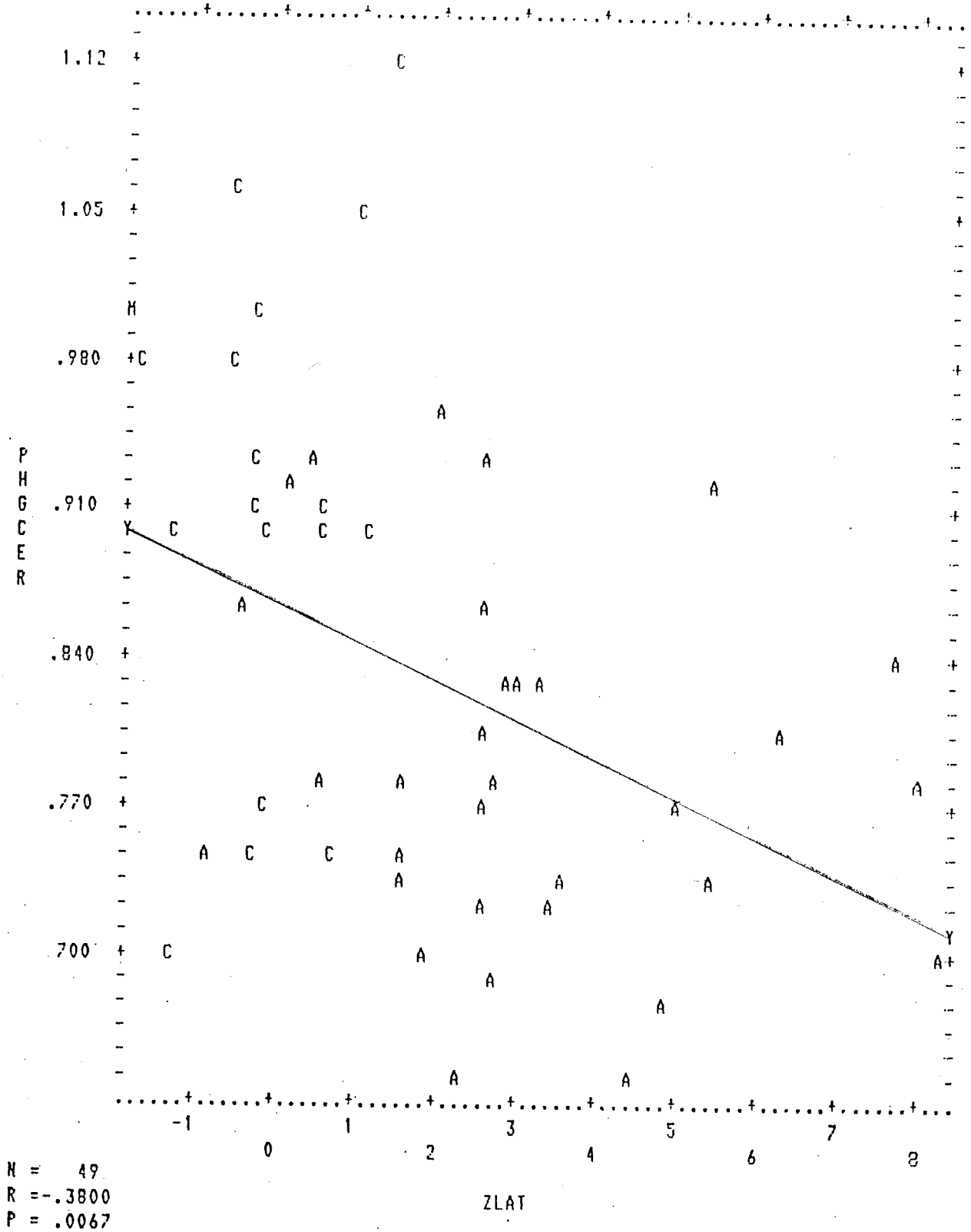

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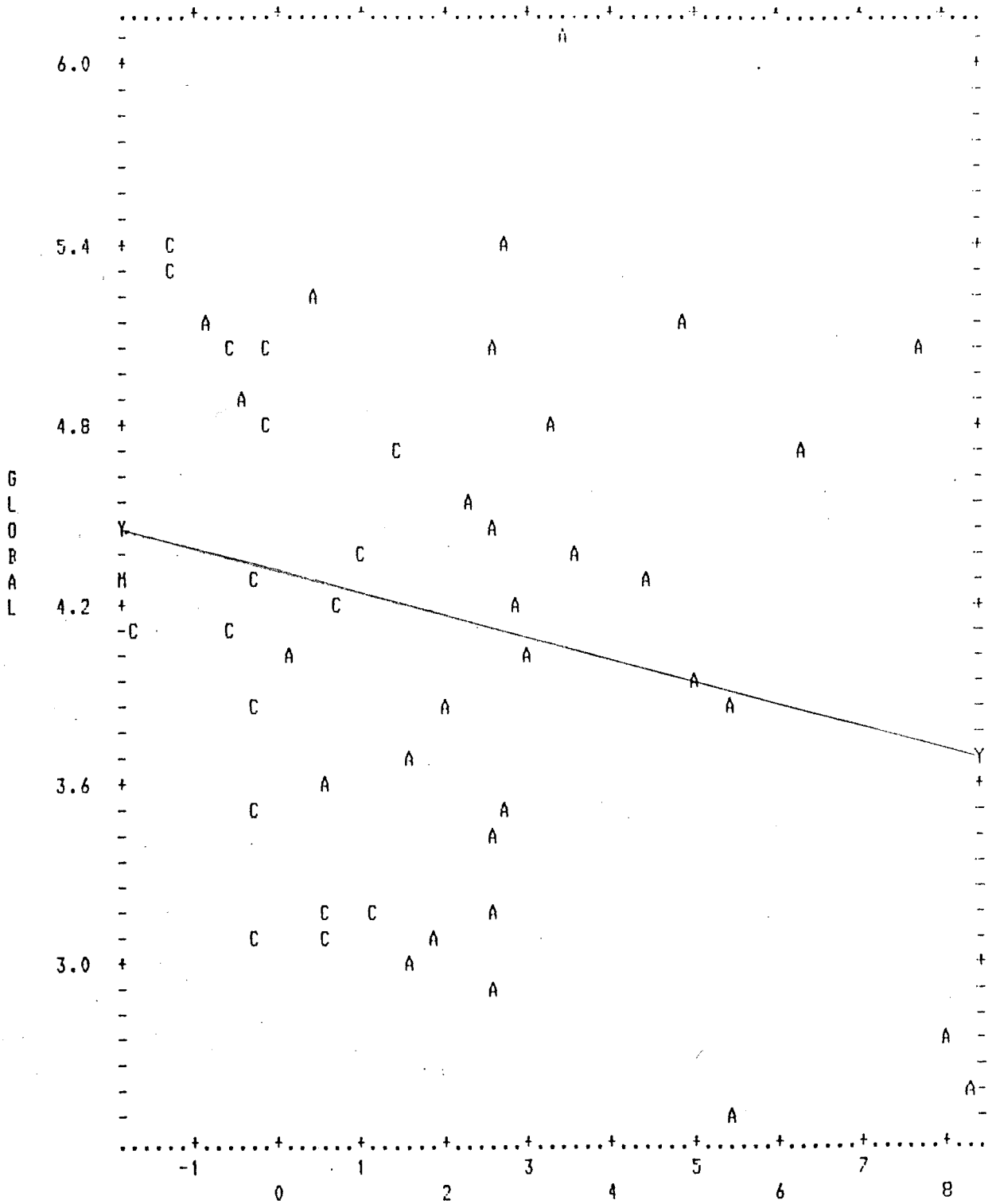

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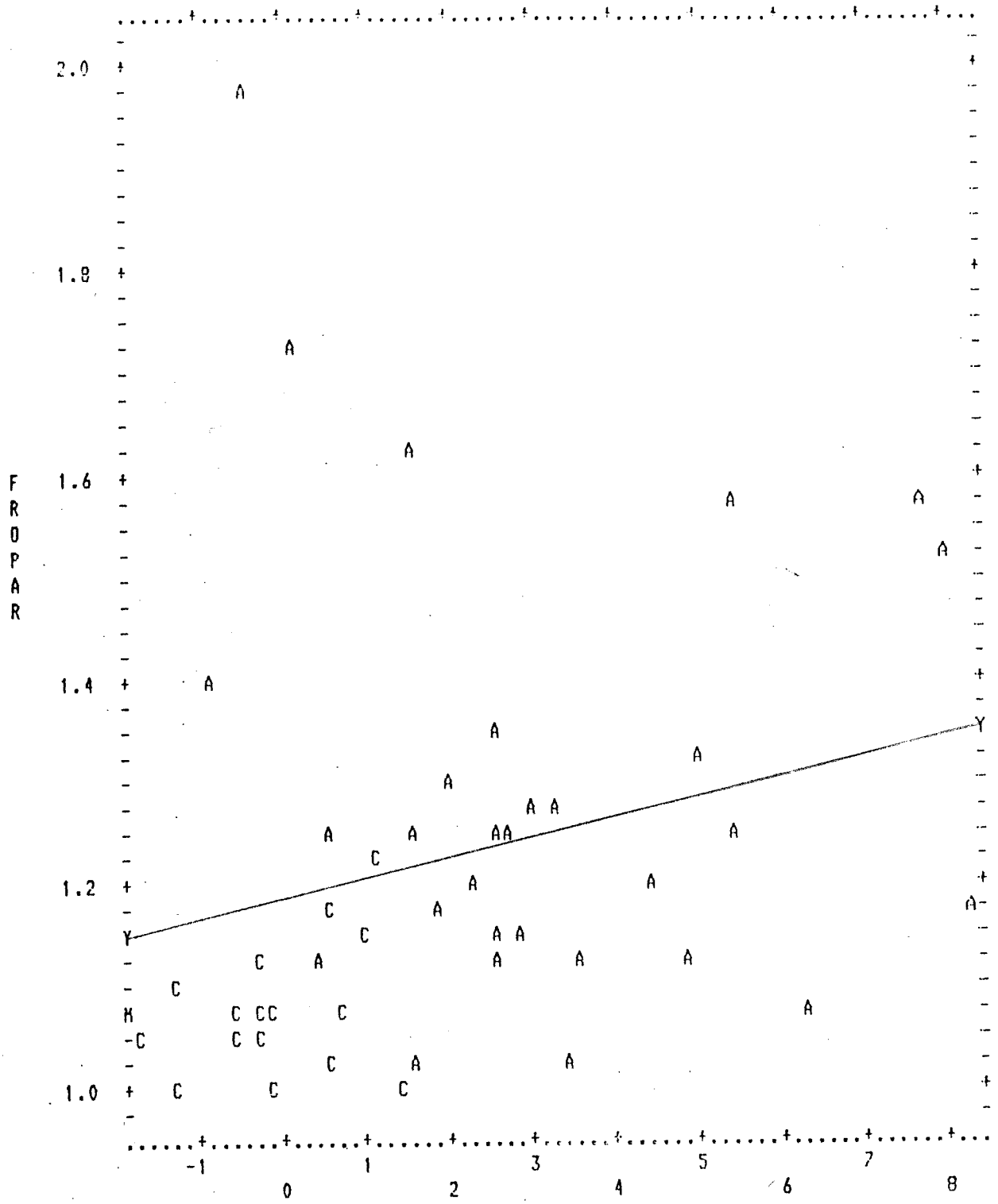
P = .1459



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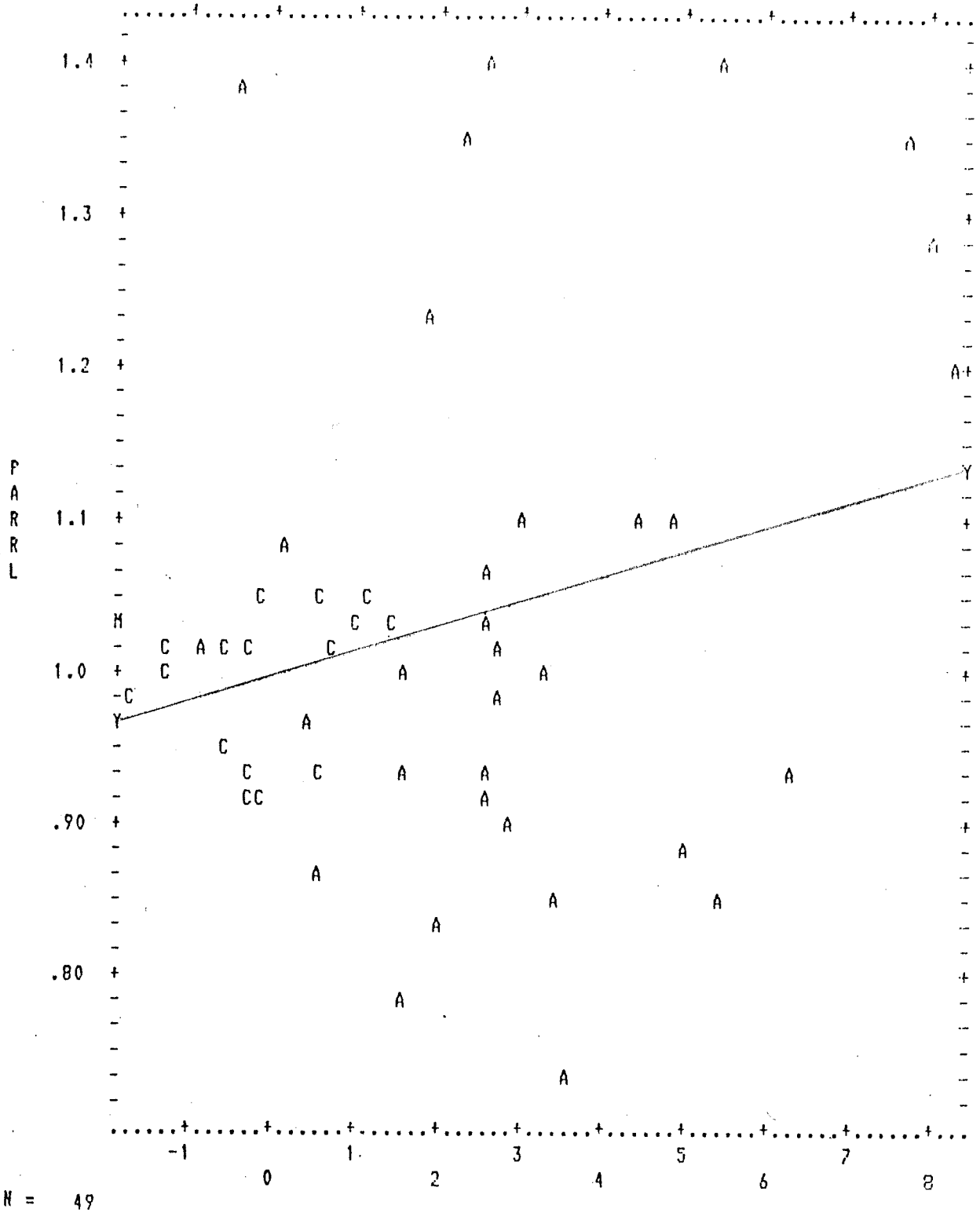
P = .0833



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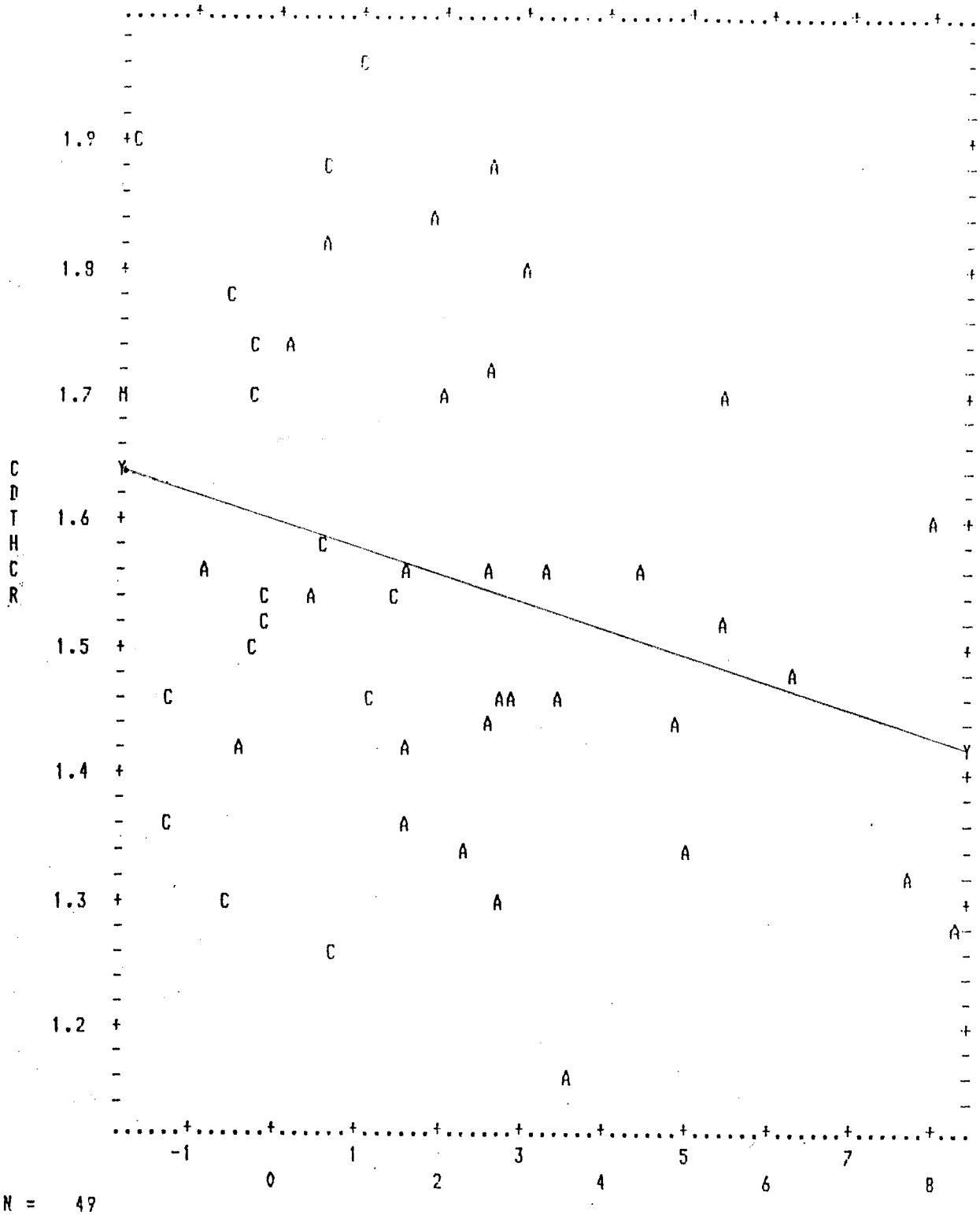
R = .2609
P = .0701



N = 49
R =-.2687
P = .0617

Descriptive Statistics

VARIABLE	CODE OR OBS. RANGE	N (%) OR MEAN	STAND. DEVIATION SAMPLE/POP. EST.	
GROUP		49 (100%)		
DEMENT	1	32 (65.3)		
NORMAL	2	17 (34.7)		
AGE	51- 76	65.939	6.457	6.524
P300LAT	290- 575	395.918	67.949	68.653
P3SD	-1.66- 8.22	2.139	2.335	2.359
SEVERITY		49 (100%)		
CDR0	0	17 (34.7)		
CDR5	5	18 (36.7)		
CDR1	1	14 (28.6)		
MMS	20- 30	25.939	3.067	3.098

Total N = 49

Correlation Coefficients

Variables	2.	3.	4.	6.
2. AGE	1.00			
3. P300LAT	.21	1.00		
4. P3SD	-.03	.95	1.00	
6. MMS	-.31	-.65	-.59	1.00

N = 49

All Subjects by Diagnosis

ANALYSIS OF VARIANCE
SUMMARY TABLE FOR AGE

VARIABLE	EFFECT SIZE	PALLAI-BARTLETT V	DF1	CHI SQ. OR F RATIO	p
GROUP	R = .23	.05	1	2.52	.1

df2 = 47

Notes: N = 49

AGE MEANS

GROUP	MEAN	N
DEMENT	67.0000	32
NORMAL	63.9412	17

AGE Mean = 65.9 Standard deviation = 6.5

All Subjects by CDR

ANALYSIS OF VARIANCE
SUMMARY TABLE FOR AGE

VARIABLE	EFFECT SIZE	PALLAI-BARTLETT V	DF1	CHI SQ. OR F RATIO	p
SEVERITY	R = .28	.08	2	1.88	.2

df2 = 46

Notes: N = 49
Effect size is multiple correlation/eta (R).

AGE MEANS

SEVERITY	MEAN	N
CDR0	63.9412	17
CDR5	65.8889	18
CDR1	68.4286	14

AGE Mean = 65.9 Standard deviation = 6.5

All Subjects

F TEST OF CORRELATION
SUMMARY TABLE FOR AGE

VARIABLE	EFFECT SIZE	PALLAI-BARTLETT V	DF1	CHI SQ. OR F RATIO	p
MMS	r = -.31	.10	1	5.01	.03

df2 = 47

Notes: N = 49
Effect size is product-moment correlation (r).

Tests are two-tailed. For a one-tailed test, divide the p of any variable with df = 1 by two IF the results are in the predicted direction.

ESTIMATING SCORES FOR AGE FROM MMS

Samples of MMS	Estimated AGE
20.0	69.820
23.0	67.860
25.0	66.552
28.0	64.592
30.0	63.284

SE of estimate = 6.1378

Linear equation = 82.89203 + (-.65359) * MMS

AGE Mean = 65.9 Standard deviation = 6.5

All Subjects by CDR

ANALYSIS OF VARIANCE
SUMMARY TABLE FOR P3SD

VARIABLE	EFFECT SIZE	PALLAI-BARTLETT V	CHI SQ. OR DF1	F RATIO	p
SEVERITY	R = .64	.41	2	15.98	<.0005

df2 = 46

Notes: N = 49
Effect size is multiple correlation/eta (R).

P3SD MEANS

SEVERITY	MEAN	N
CDR0	.0929	17
CDR5	3.1056	18
CDR1	3.3800	14

P3SD Mean = 2.1 Standard deviation = 2.3

All Subjects by CDR

ANALYSIS OF VARIANCE
SUMMARY TABLE FOR P300LAT

VARIABLE	EFFECT SIZE	PALLAI-BARTLETT V	DF1	CHI SQ. OR F RATIO	p
SEVERITY	R = .66	.44	2	17.98	<.0005

df2 = 46

Notes: N = 49
Effect size is multiple correlation/eta (R).

P300LAT MEANS

SEVERITY	MEAN	N
CDR0	334.7059	17
CDR5	421.9445	18
CDR1	436.7857	14

P300LAT Mean = 395.9 Standard deviation = 67.9

All Subjects by CDR

ANALYSIS OF VARIANCE
SUMMARY TABLE FOR MMS

VARIABLE	EFFECT SIZE	PALLAI-BARTLETT V	DF1	CHI SQ. OR F RATIO	p
SEVERITY	R = .92	.84	2	122.24	<.0005

df2 = 46

Notes: N = 49
Effect size is multiple correlation/eta (R).

MMS MEANS

SEVERITY	MEAN	N
CDR0	29.5882	17
CDR5	25.0000	18
CDR1	22.7143	14

MMS Mean = 25.9 Standard deviation = 3.1

All Subjects by P300 Z-Score

F TEST OF CORRELATION
SUMMARY TABLE FOR MMS

VARIABLE	EFFECT SIZE	PALLAI-BARTLETT V	DF1	F RATIO	CHI SQ. OR p
P3SD	r = -.59	.35	1	25.25	<.0005

df2 = 47

Notes: N = 49
Effect size is product-moment correlation (r).
Tests are two-tailed. For a one-tailed test, divide the p of any variable with df = 1 by two IF the results are in the predicted direction.

ESTIMATING SCORES FOR MMS FROM P3SD

Samples of P3SD	Estimated MMS
-2.0	29.152
.0	27.599
2.0	26.047
5.0	23.718
7.0	22.165

SE of estimate = 2.4734

Linear equation = 27.59919 + (-.77634) * P3SD

MMS Mean = 25.9 Standard deviation = 3.1

All Subjects by P300 Raw Latency Score

F TEST OF CORRELATION
SUMMARY TABLE FOR MMS

VARIABLE	EFFECT SIZE	PALLAI-BARTLETT V	DF1	CHI SQ. OR F RATIO	p
P300LAT	r = -.65	.42	1	33.77	<.0005

df2 = 47

Notes: N = 49
Effect size is product-moment correlation (r).
Tests are two-tailed. For a one-tailed test, divide the p of any variable with df = 1 by two IF the results are in the predicted direction.

ESTIMATING SCORES FOR MMS FROM P300LAT

Samples of P300LAT	Estimated MMS
290.0	29.030
351.0	27.250
411.0	25.499
472.0	23.718
532.0	21.967

SE of estimate = 2.3393

Linear equation = 37.49298 + (-2.9180000E-02) * P300LAT

MMS Mean = 25.9 Standard deviation = 3.1

CDR 0.0 versus CDR 0.5

ANALYSIS OF VARIANCE
SUMMARY TABLE FOR P3SD

VARIABLE	EFFECT SIZE	PALLAI-BARTLETT V	DF1	CHI SQ. OR F RATIO	p
SEVERITY	R = .70	.48	1	30.90	<.0005

df2 = 33

Notes: N = 35
Effect size is multiple correlation/eta (R).
Tests are two-tailed. For a one-tailed test, divide the p of any variable with df = 1 by two IF the results are in the predicted direction.

P3SD MEANS

SEVERITY	MEAN	N
CDR0	.0929	17
CDR5	3.1056	18

P3SD Mean = 1.6 Standard deviation = 2.2

CDR 0.0 versus CDR 0.5

ANALYSIS OF VARIANCE
SUMMARY TABLE FOR P300LAT

VARIABLE	EFFECT SIZE	PALLAI-BARTLETT V	DF1	CHI SQ. OR F RATIO	p
SEVERITY	R = .71	.50	1	33.66	<.0005

df2 = 33

Notes: N = 35
Effect size is multiple correlation/eta (R).
Tests are two-tailed. For a one-tailed test, divide the p of any variable with df = 1 by two IF the results are in the predicted direction.

P300LAT MEANS

SEVERITY	MEAN	N
CDR0	334.7059	17
CDR5	421.9445	18

P300LAT Mean = 379.6 Standard deviation = 61.4

CDR 0.0 versus CDR 0.5

ANALYSIS OF VARIANCE
SUMMARY TABLE FOR MMS

VARIABLE	EFFECT SIZE	PALLAI-BARTLETT V	DF1	CHI SQ. OR F RATIO	p
SEVERITY	R = .89	.80	1	131.70	<.0005

df2 = 33

Notes: N = 35
Effect size is multiple correlation/eta (R).
Tests are two-tailed. For a one-tailed test, divide the p of any variable with df = 1 by two IF the results are in the predicted direction.

MMS MEANS

SEVERITY	MEAN	N
CDR0	29.5882	17
CDR5	25.0000	18

MMS Mean = 27.2 Standard deviation = 2.6

PAD Subjects by CDR

ANALYSIS OF VARIANCE
SUMMARY TABLE FOR P3SD

VARIABLE	EFFECT SIZE	PALLAI-BARTLETT V	DF1	CHI SQ. OR F RATIO	p
SEVERITY	R = .06	.00	1	.12	n.s.
			df2 = 30		

Notes: N = 32
Effect size is multiple correlation/eta (R).
Tests are two-tailed. For a one-tailed test, divide the p of any variable with df = 1 by two IF the results are in the predicted direction.

P3SD MEANS

SEVERITY	MEAN	N
CDR5	3.1056	18
CDR1	3.3800	14

P3SD Mean = 3.2 Standard deviation = 2.1

PAD Subjects by CDR

ANALYSIS OF VARIANCE
SUMMARY TABLE FOR P300LAT

VARIABLE	EFFECT SIZE	PALLAI-BARTLETT V	DF1	CHI SQ. OR F RATIO	p
SEVERITY	R = .12	.01	1	.44	n.s.

df2 = 30

Notes: N = 32
Effect size is multiple correlation/eta (R).
Tests are two-tailed. For a one-tailed test, divide the p of any variable with df = 1 by two IF the results are in the predicted direction.

P300LAT MEANS

SEVERITY	MEAN	N
CDR5	421.9444	18
CDR1	436.7857	14

P300LAT Mean = 428.4 Standard deviation = 61.3

PAD Subjects By MMS

F TEST OF CORRELATION
SUMMARY TABLE FOR AGE

VARIABLE	EFFECT SIZE	PALLAI-BARTLETT V	DF1	CHI SQ. OR F RATIO	p
MMS	r = -.31	.10	1	3.25	.08

df2 = 30

Notes: N = 32
Effect size is product-moment correlation (r).
Tests are two-tailed. For a one-tailed test, divide the p of any variable with df = 1 by two IF the results are in the predicted direction.

ESTIMATING SCORES FOR AGE FROM MMS

Samples of MMS	Estimated AGE
20.0	70.889
22.0	68.944
24.0	67.000
26.0	65.056
28.0	63.111

SE of estimate = 5.4254

Linear equation = 90.33333 + (-.97222) * MMS

AGE Mean = 67 Standard deviation = 5.7

PAD Subjects by CDR

ANALYSIS OF VARIANCE
SUMMARY TABLE FOR MMS

VARIABLE	EFFECT SIZE	PALLAI-BARTLETT V	DF1	CHI SQ. OR F RATIO	p
SEVERITY	R = .62	.38	1	18.46	<.0005

df2 = 30

Notes: N = 32
Effect size is multiple correlation/eta (R).
Tests are two-tailed. For a one-tailed test, divide the p of any variable with df = 1 by two IF the results are in the predicted direction.

MMS MEANS

SEVERITY	MEAN	N
CDR5	25.0000	18
CDR1	22.7143	14

MMS Mean = 24 Standard deviation = 1.8

PAD Subjects by P300 Z-Score

F TEST OF CORRELATION
SUMMARY TABLE FOR MMS

VARIABLE	EFFECT SIZE	PALLAI-BARTLETT V	DF1	F RATIO	p
P3SD	r = -.11	.01	1	.37	n.s.

df2 = 30

Notes: N = 32
Effect size is product-moment correlation (r). Tests are two-tailed. For a one-tailed test, divide the p of any variable with df = 1 by two IF the results are in the predicted direction.

ESTIMATING SCORES FOR MMS FROM P3SD

Samples of P3SD	Estimated MMS
.0	24.308
2.0	24.117
4.0	23.926
5.0	23.831
7.0	23.640

SE of estimate = 1.8258

Linear equation = 24.30806 + (-9.5500000E-02) * P3SD

MMS Mean = 24 Standard deviation = 1.8

Appendix C

Flow Chart of Evaluation Process*

Stage 0: Recruitment

Stage 1: Initial Assessment

(Completed by the Public Health Nurse or Clinic Therapist)

Stage II: Primary Dementia Evaluation

- Social work evaluation
- Psychiatric Interview
  - mini-mental state exam
  - portion of Hachinski
  - Hamilton Depression Scale
- Clinical Neuropsychological Evaluation
- Neurolinguistic Evaluation
- Blood, Urine, Lab tests
- CT Scan
- EEG

Stage III: Referral to Project

- Neurological Evaluation
  - complete Hachinski
- Review of data
- Decision to include in study

Stage IV: Study Group

PET FDG Scan

Multivariate Memory Test

P300 Latency Recordings

*

Kuhl, D.E. (1983), Emission computed tomography of local cerebral functions, Unpublished grant proposal, University of California, Los Angeles.

Appendix D

Neuropsychological Battery

General Intelligence

Wechsler Adult Intelligence Scale

Memory

Benton Visual Retention Test (Benton, 1974)

Rey Auditory Verbal Learning Test (Rey, 1964)

Attention and Concentration

Number Cancellation Protocol (Lezak, 1983)

Smith Symbol-Digit Modalities Test (Smith, 1973)

Trail Making Test A and B

Test of Abstract Reasoning

Raven's colored Progressive Matrices

Test of Visuoconceptual Abilities

Hooper Visual Organization Test (Hooper, 1958)

Appendix E

Clinical Dementia Rating Scale

The Clinical Dementia Rating (CDR) scale utilized information gathered through interviews to determine what stage of dementia the patient has reached. The stages include: questionable; moderate or severe. There are six categories of functioning that are assessed which include: memory, orientation, judgment/problem solving, community affairs, home/hobbies and personal care (see chart). The numerical ratings are as follows: A score of 0 = healthy functioning, no difficulties in any category; 0.5 = mild impairment; 1.0 = moderate memory loss, mild dementia; 2.0 = moderate dementia, severe memory loss and disorientation to time or 3.0 = severe dementia, severe memory loss, disorientation to person, and personal care minimal or non-existent.

A New Clinical Scale for the Staging of Dementia

Clinical dementia rating (CDR)

	Healthy	Questionable dementia	Mild dementia
	CDR 0	CDR 0.5	CDR 1.0
Memory	No memory loss or slight inconstant forgetful-ness	Mild consistent forgetfulness; partial recollection of events; 'benign' forgetfulness	Moderate memory loss more marked for recent events; defect interferes with every-day activities
Orientation	Fully oriented	Fully oriented	Some difficulty with time relationships oriented for place and person at exam but may have geo-graphic disorienta-
Judgment/Problem Solving	Solves everyday problems well; judgment good in relation to past performance	Only doubtful impairment in solving problems, similarities, differences	Moderate difficulty in handling complex problems; social judgment usually maintained

	CDR 0	CDR 0.5	CDR 1.0
Community affairs	Independent function at usual level in job, shopping, business, and financial affairs, volunteer and social groups	Only doubtful or mild impairment, if any in these activities	Unable to function independently at these activities though may still be engaged in some; may still appear normal to casual inspection
Home and Hobbies	Life at home, intellectual interests well maintained	Life at home, hobbies intellectual interests well maintained or only slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned
Personal care	Fully capable of self care	Fully capable of self care	Needs occasional prompting

	Moderate dementia CDR 2.0	Severe dementia CDR 3.0
Memory	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Usually disoriented in time, often to place	Orientation to person only
Judgment/problem solving	Severely impaired in handling problems, similarities, differences; social judgment usually impaired	Unable to make judgments or solve problems
Community affairs	No pretense of independent function outside home	No pretense of independent function outside home
Home and hobbies	Only simple chores preserved; very restricted interests, poorly sustained	No significant function in home outside of own room
Personal care	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; often incontinent

CDR Score_____

Instructions for CDR

Use all information and make the best judgment. Score each category as independently as possible. Mark in only one box, rating each according to subject's cognitive function. For determining the CDR, memory is considered the primary category; all others are secondary. If at least three secondary categories are given the same numerical score as memory, the CDR = memory. If three or more secondary categories are given a score greater or less than the memory score, CDR = score of majority of secondary categories, unless three secondary categories are scored on one side of memory and two secondary categories are scored on the other side of memory. In this last circumstance, CDR = memory.

When memory = 0.5, CDR = 1 if at least three of certain others (Orientation, Judgment, Community Affairs, Home and Hobbies) are scored 1.0 or greater (Personal care is not influential here). If Memory = 0.5, CDR cannot be 0, CDR can only be 0.5 or 1.0. If memory = 1, CDR = 1 unless there is slight impairment in two or more secondary categories, in which case CDR = 0.5.

Hughes, C.P., Berg, L., Danziger, W.L., Coben, L.A., & Martin, R.L., (1982). A new clinical scale for the staging of dementia. British Journal of Psychiatry, 140, 566-572.

Appendix F

Mini-Mental State

The Mini-Mental State Exam (MMS) was developed by Folstein, Folstein and McHugh (1975) as a formalized, normed mental status exam consisting of 30 questions. The subsections of the MMS include: orientation, memory, attention, expressive/receptive abilities and visuographic tasks (see protocol). The MMS is sensitive to changes in cognitive impairment. High scores (28-30) are indications of little or no impairment. Lower scores suggest moderate to severe impairment. An increase in the MMS score across time occurs in reversible dementia.

Patient's Name_____

Mini-Mental State

Test Date_____

by M.F. Folstein,

Testor Name_____

S,E. Folstein, and

P.R. McHugh

Score 1 = correct

2 = incorrect

I. Orientation

Ask, "What is today's date?"	Date (e.g. Jan. 21)	1____
Then ask specifically for	Year	2____
parts omitted; e.g., "Can	Month	3____
you also tell me what season	Day (e.g. Monday)	4____
it is?"	Season	5____
Ask, "Can you tell me the	Hospital	6____
name of this hospital?"	Floor	7____
"What floor are we on?"		
"What town (or city) are we	Town	8____
in?"		
"What county are we in?"	County	9____
"What state are we in?"	State	10____

II. Registration

Ask the subject if you may test his/her memory. Then say "ball," "flag," "tree" clearly and slowly, about one second for each. After you have said all 3, ask him/her to repeat them. This first repetition determines his/her score (0-3) but keep saying them until s/he can repeat all 3, up to 6 trials. If s/he does not eventually learn all 3, recall cannot be meaningfully tested.

"Ball".....11____

"Flag".....12____

"Tree".....13____

Number of trials....14____

(number 14 not included in in score)

III. Attention and Calculation

Ask the subject to begin with 100 and count backwards by 7. Stop after 5 subtractions (93, 86, 79, 72, 65). Score the total number of correct answers. If the subject cannot or will not perform this task, ask him/her to spell the word "world" backwards. The score is the number of letters in correct order.

"93".....15____

"86".....16____

"79".....17____

"72".....18____

"65".....19____

For example, dlrow = 5, dlorw = 3,

Records how the subject spelled

"world" backwards _____ Number of letters in
d l o r w

correct order.....20____

(include either number 19

or 20 in score)

IV. Recall

Ask the subject to recall "Ball".....21____

the 3 words you previously "Flag".....22____

asked him/her to remember. "Tree".....23____

Score 0-3.

V. Language

naming: Show the subject Watch.....24____

a wrist watch and ask him/her Pencil.....25____

what it is. Repeat for

pencil.

repetition: Ask the Repetition.....26____

subject to repeat, "No ifs,

and, or buts."

3-stage command: Give Takes paper in

the subject a piece of in right hand.....27____

plain blank paper and say, Folds paper in

"Take the paper in your right half.....28____

hand, fold it in half and put it on the floor." Puts paper on floor.....29____

---

reading: On a blank piece of paper print the sentence, "Close your eyes," in letters large enough for the subject to see clearly. Ask him/her to read it and do what it says. Score correct only if s/he actually closes his/her eyes. Closes eyes.....30____

writing: Give the subject a blank piece of paper and ask him/her to write a sentence. It is to be written spontaneously. It must contain a subject and verb and be sensible. Correct grammar and punctuation are not necessary. Writes sentence....31____

copying: On a clean piece of paper, draw intersecting pentagons, each side about 1 inch, and ask subject to copy it exactly as it is. All 10 angles must be present and two must intersect to

score 1 point. Tremor and rotation are ignored.

e.g.

Draws pentagons....32____

Rate subject's level of consciousness

(a) coma

(b) stupor

(c) drowsy

(d) alert 33____

(number 33 not included in score)

TOTAL CORRECT _____

Appendix G

Hachinski Ischemic Score

Hachinski et al. (1975) studied cerebral blood flow of 24 patients in an attempt to differentiate demented patients from non-demented patients. The variables measured included blood flow through fast-clearing tissue mainly gray matter (Ff); Blood flow through slow-clearing tissue, white matter (Fs); the portion of tissue clearing at the fast rate (Wf); flow measured from the slope of the first two minutes of the logarithmically displayed isotope clearance curve (F initial); and weighted mean flow (F). Their results indicated that patients fell into two groups with 10 patients scoring 7 and above on the Ischemic Scale and 14 patients scoring 4 and below. Patients with a score of 7 and above were classified as having multi-infarct dementia. Those with a score of 4 and below were classified as having primary degenerative dementia.

Clinical Features of Ischemic Scale

Feature	Score
Sudden onset	2
Stepwise deterioration	1
Fluctuating course	2
Nocturnal confusion	1
Relative preservation of personality	1
Depression	1
Somatic complaints	1
Emotional incontinence	1
History of hypertension	1
History of strokes	2
Evidence of associated atherosclerosis	1
Focal neurological symptoms	2
Focal neurological signs	2

Hachinski, V.C., Iluff, L D., Phil M., Zilhka, E., Du Boulay, G. H., McAllister, V.L., Marshall, J., Russell, R.W.R., & Lymon, L (1975) Cerebral blood flow in dementia, Archives of Neurology, 32, 632-637

Appendix H

Epilogue

Following completion of this study, it became evident that multiple runs are very important to ensure obtaining the most clear P300 latency record possible. Making sure that at least two complete runs were obtained from each patient and control would be one improvement that could be made from the onset of the study.

For future studies it would be interesting to study the P300 latency measures for each subsequent year in order to discover if there are any patterns that might be particular to Alzheimer's patients. It may also be informative to correlate these follow-up P300 latencies with corresponding PET scans. With this particular group of subjects, analyses of memory, neuropsychological and/or psycholinguistic data could also be completed and compared with the initial P300 latency measures.

Furthermore, it would be advantageous to obtain PET scans and P300 latency measurements on patients with dementia secondary to Huntington's Disease, and compare the findings with the Alzheimer's patients in order to note similarities and differences between the two groups. It is known that both groups have prolonged P300 latencies, but different patterns of cerebral degeneration.

Curriculum Vita

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I. EDUCATION

Past:

Charles Francis Adams High School, Clarkston, WA. August 1972 - June 1976

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1984-1986 Lab Tech II, University of California Los Angeles, Brain Research Institute, Neuropsychiatric Institute, UCLA Medical Center

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O'Malley, Michael & Schubarth, Glena, (Dec, 1984), Fairness and appeasement: achievement and affiliation motives in interpersonal relations, Social Psychology Quarterly, 47(4), 364-371.

V. PRESENTATIONS

Schubarth, Glena L.N., Marsh, James, T., Brown, Warren, S., & Kuhl, David E., (October, 1987) "Alzheimer's Dementia: The Relationship Between P300 Latency and PET Scan Ratios". Presented at the Society for Psychophysiological Research International Convention, Amsterdam, Holland.

Schubarth, Glena & O'Malley, Michael, (April, 1984) The Effects of Interpersonal Orientation, Type of Partner and Performance on Distributive Justice. Presented at the Western Psychological Association convention, Los Angeles, CA.

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