To the Graduate Council:

I am submitting herewith a dissertation written by Gary Scott Holder entitled "A Quantitative and Correlative Study of the Dominant Occipital Rhythm in Senile Dementia of the Alzheimer's Type." I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Psychology.

Joel F. Lubar, Major Professor

We have read this dissertation
and recommend its acceptance:

Accepted for the Council:

Vice Provost
and Dean of The Graduate School

A QUANTITATIVE AND CORRELATIVE STUDY OF THE DOMINANT OCCIPITAL RHYTHM IN SENILE DEMENTIA OF THE ALZHEIMER'S TYPE

A Dissertation

Presented for the

Doctor of Philosophy

Degree

The University of Tennessee, Knoxville

Gary Scott Holder

May 1990

DEDICATION

This dissertation is dedicated to my wife, Bonita. She has been with me the whole of this long journey, enduring more than anyone ought to.

Also to two sojourners we picked up along the way, Scott and Tiffany, our son and daughter.

They are all wonderful people, and I look forward to getting to know them again as a new journey begins.

ACKNOWLEDGEMENTS

The help and advice of several people and institutions made this project possible. My mentor, Joel F. Lubar, Ph.D., of the University of Tennessee at Knoxville Psychology Department, supervised my training in performing the type of EEG analysis embodied in this research, and the basic technology used was nurtured in his laboratory.

John M. Dougherty, M.D., and Michael L. Eisenstadt, M.D., Ph.D., of the Knoxville Neurology Clinic were instrumental in the establishment of the neurodiagnostics research facility at the University of Tennessee Medical Center at Knoxville, the location of this study. It was Dr. Eisenstadt's clinical observations of the EEG in Alzheimer's Disease patients, and his challenge to me to quantify the effects on the alpha rhythm he saw which lead to this project.

The core components of the PDP-11/73 FFT software, transferred from Dr. Lubar's facility, were written by George Halsey, Ph.D.

For the selection of psychometric and neuropsychologic test instruments, I leaned heavily upon the advice of Odacir H. Oliveira, Ph.D., a psychologist with special expertise in the evaluation of Alzheimer's Disease. Paul Wright, of the University of Tennessee at Knoxville Statistics Department, was invaluable in the final stages of the project, as he guided me through the thicket of the SAS Statistical Analysis software package.

This project was funded by the Cole Neurosciences Foundation, of Knoxville, Tennessee.

ABSTRACT

Parameters derived from power spectral analysis of the electroencephalogram (EEG) were examined in normal aging and Senile Dementia of the Alzheimer's Type (SDAT) and correlated with neuropsychologic measures of cognitive function. The parameters chosen for study focussed on quantifying aspects of the Dominant Occipital Rhythm (DOR) as it changed across time and across several stimulus conditions (eyes closed, eyes open, and listening to speech). In contrast with most prior spectral analysis studies which used fixed frequency bands, in this study algorithms to locate and measure DOR frequency, amplitude, bandwidth, and sharpness characteristics were applied to individual data epochs. Total 0.25-32.00 Hz spectrum power, weighted mean frequency, and power in the frequency bands adjacent to DOR were also measured. Data was collected from a group of 11 normally aged subjects (5 males, 6 females, mean age 64.7 years) and a group of 11 SDAT patients (2 males and 9 females, mean age 72.7

years). The SDAT patients demonstrated lower DOR frequency and weighted mean frequency than normals in each stimulus condition. On amplitude variance measures, the DOR of SDATs was seen to be less reactive to condition change and less modulated within conditions than that of normals. A number of EEG measures, including some of the variance measures, correlated with psychologic measures by rank. Thus, spectral parameter variance measures, particularly those related to DOR amplitude, are sensitive to moderate SDAT and are worthy of further investigation.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

FIGURE PAGE

LIST OF FIGURES (Continued)

FIGURE PAGE

I. INTRODUCTION

Alzheimer's Disease (AD) is a progressively dementing illness of unknown etiology for which no effective treatment has yet been devised. In life, the diagnosis of AD as the cause of dementia in an individual is difficult, time consuming, and ultimately uncertain. A diagnosis of AD is not considered proven without postmortem histologic confirmation of the presence of characteristic microscopic abnormalities in brain tissues. (Khachaturian, 1985; McKhann, Folstein, Katzman, Price, Stadlan, 1984). While antemortem diagnostic accuracy has improved from as low as 70 percent before 1975 (Ron, Tooney, Garralda, & Lishman, 1979) to rates approaching 90 percent more recently (Katzman, 1986; Wade, Mirsen, Hachinski, Fisman, Lau, & Merskey, 1987), the development of techniques to further improve diagnostic speed and accuracy, particularly in the early stages of AD, would be of great help in the management of AD patients and in AD research.

The electroencephalogram (EEG) has long been known to be abnormal by the late stages of AD. Indeed, as Fenton (1986) notes, the first report of EEG abnormalities in AD was made by Hans Berger in 1932, only three years after Berger announced his discovery of the human EEG itself. Numerous studies, to be detailed below, have confirmed Berger's findings and extended them to show at least group differences between the EEG characteristics of healthy individuals and those of middle-stage AD patients. A few recent studies have reported success in distinguishing early-stage AD patients from normals with EEG techniques. However, in current practice, EEG-based techniques play a relatively minor and supportive role in AD diagnosis. A report of a consensus conference convened by the National Institute on Aging, the National Institute of Neurological and Communicative Disorders and Stroke, the National Institute of Mental Health, and the National Institutes of Health's Office of Medical Applications of Research (1987) recommended against the routine use of EEG or other electrophysiological techniques in the diagnosis of AD. The exception would be if the suspected AD patient

displayed altered consciousness or possible epileptic seizures, which would be indications for clinical EEG testing in any patient. Thus, despite the large and rapidly increasing number of studies in this field, the medical establishment has not been convinced that any EEG-based technique is powerful enough to produce clinically relevant information in the differential diagnosis of AD in individual patients.

While many medical practitioners and EEG researchers would probably disagree with this gloomy assessment regarding the use of EEG techniques for the evaluation of AD (McIntyre, 1985), the mass of significant, if insufficiently specific, findings continues to stimulate many attempts to demonstrate clinically useful EEG patterns in AD. As compared with other diagnostic modalities available, EEG testing is noninvasive, relatively easy to perform, and typically less expensive. Even though Fenton (1986) and others consider it unlikely that AD could ever be diagnosed solely on the basis of EEG, EEG-based techniques could become more acceptable as part of the routine AD diagnostic workup, if they could demonstrate diagnostic power at a level similar to other modalities. My study

represents an initial investigation of EEG parameters beyond those usually studied in AD, in an attempt to assess the potential value of these parameters in increasing the sensitivity of EEG-based testing in AD.

Measures of the alpha rhythm component of the EEG derived from computer-analyzed power spectral data were applied to a population of moderately demented AD patients whose disease onset occurred later in life and to a population of similarly aged healthy individuals. Slowing and loss of the alpha rhythm are the strongest and longest documented effects of AD on the EEG. However, the slowing of alpha has not typically been found to distinguish reliably between late-onset AD patients and normals until the moderate stage of dementia. Measures of alpha activity beyond its characteristic frequency were used in this study, in the belief that in parameters such as alpha bandwidth, frequency and amplitude variance, and power spectral distribution will be found more subtle but more distinctive AD-produced changes than gross slowing. Several of these subtle effects proved to be present in the current study of the moderately demented, and are likely candidates for further study in a mildly

demented, early stage AD population or in comparative studies of other dementing conditions. The task of this initial study was to demonstrate whether differences exist between a normal group and a clearly demented group on these measures. The EEG measures which did show normal vs. AD differences were then checked for the degree to which they correlated with psychologically-based measures of cognitive decline.

In order to set the stage for the current study, a number of topics need to be reviewed. First, dementia and AD will be described. Then an orientation to the EEG, its alpha rhythm, and its measurement with computer-based spectral analysis techniques will be presented. The known EEG findings in normal aging and AD will be summarized. Finally, a description of the specific measures developed and applied in this study will be given, concluding with the hypotheses formulated concerning those measures.

Alzheimer's Disease

Dementia

As mentioned above, AD is a dementing illness. Mahendra (1984, pp. 1-18) relates the history of the term dementia and its clinical use through the 20 centuries since its first appearance. Within this century, its meaning and usage has evolved from a catchall psychiatric diagnosis encompassing several psychotic conditions to a relatively precise descriptive term for a clinically recognizable set of symptoms involving a certain type of decline in cognitive abilities (Mahendra, 1984; Wang, H.S., 1977; Consensus Conference, 1987). That is, dementia is now used to describe a syndrome characterized by deficits of memory and cognition. Though the demented state is presumed to be caused by any of a number of underlying physiologic pathologies, its diagnosis is based solely on an observed set of behaviors (American Psychiatric Association, 1980; McKhann, Folstein, Katzman, Price, Stadlan, 1984).

The meaning of dementia, particularly as it relates to AD, was standardized in 1984 with the publication of the report of the National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association Work Group on the Diagnosis of Alzheimer's Disease. This report codified a definition of dementia, within the framework of the existing APA DSM III definition, and set provisional standards for diagnosing and classifying AD. Its diagnostic criteria for dementia in general include a basic definition of dementia, along with a description of the overall clinical factors necessary for an accurate diagnosis of dementia, and adds a final emphasis that dementia is a recognizable clinical state without reference to an underlying pathology. In the verbatim language of the NINCDS-ADRDA Work Group report:

> Dementia is the decline of memory and other cognitive functions in comparison with the patient's previous level of function as determined by a history of decline in performance and by abnormalities noted from clinical examination and neuropsychological test. A diagnosis of dementia cannot be made when consciousness is impaired by delirium, drowsiness, stupor, or coma or when other

> clinical abnormalities prevent adequate evaluation of mental status. Dementia is a diagnosis based on behavior and cannot be determined by computerized tomography, electroencephalography, or other laboratory instruments, although specific causes of dementia may be identified by these means. (p. 940)

Alzheimer's Disease, then, is one of a number of "specific causes" of dementia, though, as stated earlier, the etiology of AD is itself currently unknown. The Work Group notes that there are a number of other causes of dementia which must be excluded before AD is considered as a possible cause. As a non-exhaustive list, they mention "manic-depressive disorder, Parkinson's disease, multi-infarct dementia, and drug intoxication" (pp. 940-941) as more common sources of diagostic error. Many other authors, including those of the 1987 Consensus Conference, have noted the importance of correctly identifying other possible causes, as effective treatments are available for several of them. One additional condition not specifically mentioned by the Work Group, but often noted by others, including Lazarus, Newton, Cohler, Lesser, and Schweon (1987), Reifler (1988), and Terry and Katzman (1983), is a depressive functional disorder

often occurring in the aged and severe enough to produce an apparently demented state. This condition is often called psuedodementia and is usually responsive to antidepressant medications.

History of Alzheimer's Disease

Alzheimer's Disease was first definitively described in 1907 by Alois Alzheimer. His archetypical case involved a relatively young patient, who died at age 55 after a five-year course of progressive memory loss and associated symptoms which seemed to simulate senile dementia (Katzman, 1986). That is, though relatively young, her symptoms were similar to those seen in what was commonly called "senility" in older people, long thought to be an unavoidable consequence of aging in many people. Through postmortem histological examination of this patient's brain, Alzheimer discovered and described the distinctive abnormal microscopic structures known as neurofibrillary tangles and neuritic plaques. The presence of an excess of these structures became and has remained the final conclusive evidence necessary for a diagnosis of AD.

While the similarities between the presenile dementia caused by AD and at least certain types of senile dementia were long known, it was not until a series of clinical and histologic studies were performed in the nineteen-sixties (Blessed, Tomlinson, & Roth, 1968; Kidd, 1963; Terry, Gonatas, & Weiss, 1964) that it was accepted that senile dementia accompanied by the traditional histologic and clinical signs of AD was indeed AD. Thus it was realized that rather than a rare presenile condition, AD is a common condition associated with aging.

It took several more years for the implications of this readjustment in the definition of the AD population to be fully absorbed. As summarized by Katzman (1986) with additional previously unpublished data, the current and likely future impact of AD on the health care system and society in general is huge. Aging is clearly the most important risk factor for AD, and the size of the aged population is expected to grow markedly in the next several decades. Katzman estimates the 1986 AD population at two million, with the incidence of new AD cases in the 75-85 year old group higher than that of strokes (2.4 cases per 100 persons

a year for AD). Katzman also reported a study of patients in a large nursing home, in which 65 percent of the patients were found to be demented and 55 of 100 demented patients autopsied were found to have AD. The cost of institutional care for all AD patients was estimated at 25 billion dollars a year.

The full realization of the importance of AD has caused a vast increase in research interest, represented by an ever-increasing number of articles on the clinical, demographic, neuropathologic, neuropsychologic, and many other aspects of AD. Other than the findings relating to EEG research, space here allows for only the briefest mention of the status of knowledge in these related areas.

The Clinical Course of AD

With the recognition that AD is much more prevalent than once thought, and that a wide range of medical practitioners needed to be better able to recognize its symptoms, many summary and overview articles aimed at describing the basic features of AD have been published in the 1980s. A particularly

succinct one by Kvale (1986) is the basis for the following summary, with additional information from Powers and Dougherty (1985) as well as the previously mentioned sources also used.

The course of AD can be divided into three stages: early, middle, and late, corresponding to three stages of dementia: mild, moderate, and severe. The onset of the disease is insidious, extending over a number of months to several years. During this time the patient may continue normal living and work patterns, but with increasing difficulty as short-term memory and organizational problems worsen. There is considerable variation from individual to individual in the pattern of specific cognitive deficits shown and in their rate of progression.

The moderate stage is entered when it becomes evident that the patient can no longer safely live independently and needs round-the-clock supervision. The patient is likely to wander and get lost, forget tasks in the middle of them, and may approach the near-complete loss of recent memory formation. Affect becomes blunted and speech is markedly affected. Frank neurological signs may appear as well, such as gait and coordination disturbances and incontinence.

The severe stage is marked by the almost complete loss of memory and sensible speech. Nursing home care is usually indicated by this stage. Given long enough survival, a vegetative, bedridden state is reached in which all cognitive abilities are lost and complete nursing support is needed to maintain life. Patients can survive in this state for periods ranging up to years. Alzheimer's Disease is rarely considered the direct cause of death, but most often is a contributing factor in death due to other causes associated with the individual's increasing inability for self care or with other age-related conditions.

Diagnostic Categories

The NINCDS-ADRDA Work Group set forth three categories of AD diagnosis: Possible AD, Probable AD, and Definite AD. The finding at autopsy, or in rare cases by brain biopsy in life, of an excess of plaques and tangles remains the criterion for a diagnosis of Definite AD. The two additional types of AD diagnosis are for use prior to the patient's death and autopsy. Most relevant to this study is "Probable AD", which is

the diagnosis given to patients who present with the typical AD dementia pattern, uncomplicated by other conditions. "Possible AD" is the appropriate diagnosis when the clinical picture is atypical, but mainly AD-like, or when AD symptoms are present in conjunction with other conditions (such as Parkinson's Disease).

One term predating the Work Group report (Tomlinson, 1977, p. 26) and equivalent to "Probable AD" in older patients is still current in much research literature. This is "Senile Dementia of the Alzheimer's Type" (SDAT), which will be the term used for the experimental group in my study.

It has long been suspected, and there has been increasing evidence, that AD may not be a single disorder, but a collection of pathologies that produce similar effects (Chui, Teng, Henderson, & Moy, 1985; Huff, Growdon, Corkin, & Rosen, 1987; Consensus Conference, 1987; Mayeux, Stern, & Spanton, 1985). These individual findings provide varying levels of support for the existence of AD subgroups based on age at onset, patterns of cognitive deficit, and patterns of specific pathologic neurological signs. It has long been accepted that a rare form of AD exists which is

clearly familially-linked. Genetic predisposition may also play a role in the majority of AD cases (Mahendras, pp 40-41).

The Issue of AD as Accelerated Aging

The question of whether or not AD represents an accelerated form of normal aging impacts all areas of interest in AD, from clinical diagnosis by the medical practitioner to the most advanced studies of the brain chemistry in AD. Virtually every deficit or change produced by AD, as measured by virtually all diagnostic techniques, can also be seen to a lesser extent in many apparently normal elderly people. This would include a degree of memory loss and the presence of plaques and tangles in brain tissues, as well as many others. As will be detailed later, many of the known EEG effects of AD are also echoed in normal aging. A philosophical and balanced presentation of this issue is presented by Gubrium in the book Oldtimers and Alzheimer's: The Descriptive Organization of Senility (1986, pp. 50-61) and more briefly in an article by Berg (1985). Gubrium presents evidence and forcefully points out

that in an absolute sense the definition of AD as a disease process separate from the aging process is circular--that, as there are cases of AD-like histologic changes in the brains of undemented elderly people and cases of elderly people that had AD-like dementia which lacked such changes, even the "gold standard" of AD diagnosis, the histologic examination of the brain at autopsy for plaques and tangles, must be done with reference to the antemortem cognitive status of the patient. Current knowledge cannot explain the cases of contrary autopsy results, so it remains possible that AD represents an accumulation of normal aging changes which trigger dementia in some individuals when some individually determined threshold is reached. Berg details a number of aging/AD similarities and delineates the handful of possible differences shown in brain chemistry studies, while also admitting a definitive conclusion is not yet possible. Both conclude that the assumption that AD is a distinct disease is at least useful, with Berg going so far as to say he believes this can eventually be proven.

In more practical terms, and relevant to the current study, this situation means that every study of AD should seek to compare any demonstrated AD changes to potential similar changes in normal aging.

Neurophysiological and Neurochemical Effects of AD

While the cause or causes of AD are not yet known, much has been learned about the details of the damage AD causes to the central nervous system. Long known are the gross effects of AD on neural tissues and structures. These are neuronal loss, ventricular enlargement, and the development of senile neuritic plaques and neurofibrillary tangles. An abundance of plaques and tangles seem to mark the brain regions most affected by AD, as indicated by neuronal loss and correlation between clinical patterns of cognitive deficits and the probable function of affected brain regions. It is not known if these structures represent the debris of degenerated neurons, or develop independently as part of the AD disease process. The distribution, particularly of tangles and neuronal loss, is concentrated in association cortex,

hippocampus, amygdala, entorhinal cortex, and in several nuclei from which different neurotransmitter projection systems arise (Davison, 1987; Henderson & Finch, 1989; Katzman, 1986; Pepeu, 1988).

The findings of focussed effects of neurotransmitter systems, particularly that of the acetylcholine system and the nucleus basalis of Meynart (Davies & Maloney, 1976; Whitehouse, Price, Clark, Coyle and DeLong, 1981) have driven much research since (Pomara & Stanley, 1986). Strong support for the concept that the majority of AD effects are caused by marked defects in the acetylcholine system has been found, though increasing importance is placed on damage to the serotoninergic systems and noradrenergic systems as well (Henderson & Finch, 1989). However, attempts to treat AD with neurotransmitter-replacement therapies much like the application of dopamine to Parkinson's Disease have not been markedly successful, though one relevant study showed memory improvement and some EEG normalization upon application of cholinergic drugs (Agnoli, Martucci, Manna, Conti, & Fioravanti, 1983).

Origins, Characteristics, and Components of the EEG

Neurophysiologic Source of the EEG Signal

Despite the now 60-years-long interval between the announcement of the existence of the human EEG by Hans Berger in 1929 and the present, it remains valid to state as did Empson in 1986 that "neurophysiologists simply do not know for certain how the human EEG is generated" (p. 16). This is meant primarily in the absolute sense that the probably definitive animal studies which used depth electrodes have not been, nor can they ethically be, confirmed in humans. He goes on to state, "there is, however, absolutely no doubt that electrical activity originating in the human cortex can be measured from the scalp" (p. 16). Moreover, while theorists with opposing points of view can still be found, it is generally accepted that the varying electrical potentials found on the scalp which constitute the electroencephalogram, are produced almost exclusively by the electrical activity of certain neurons in the surface layers of the cortex (Ebersole, 1987; Gabor, 1978).

As particularly well summarized by Ebersole (1987), the surface of the cortex is organized into six neuronal layers, with each layer differing by neuron type and neuron input (dendritic) and output (axonal) connections. There are two general neuron types in these layers: stellate and pyramidal. It is neurons of the elongated pyramidal type which seem to have the proper characteristics and orientation for the production of potentials on the scalp. These pyramidal neurons tend to be oriented perpendicularly to the surface of the cortex, their dendrites branching towards the surface and their axons projecting towards deeper and collateral levels. Particularly important are the giant pyramidal cells of layer 5 (the layer defined by the location of the cell body), whose projections can extend through all the other layers.

The EEG is thought to arise from the summation and transmission into the extracellular space of the graded excitatory post-synaptic potentials and inhibitory post-synaptic potentials (EPSPs and IPSPs) spreading along the cell membrane from the synapse sites in the dendritic tree and cell body of these pyramidal neurons. Since the dendrites run in one direction, and

are on average a significant distance from the cell body (giant pyramidal cells can be over 1 mm in length), current flow produced by the synapses creates a miniature dipole between the dendrites and cell body. Though the convolutions of the cortex complicate the picture considerably, the pyramidal layers thus constitute a sheet of dipoles oriented toward the cortical surface, which in turn is most often oriented parallel to the surface of the scalp. For a measurable potential to be produced on the scalp, a rather large area of this dipole sheet (on the order of 6 square centimeters) must build up a potential through synchronous action. This potential is transmitted with degraded voltage through the intervening tissue and bone to the scalp and spreads, creating a field of potential differences between scalp locations. Properly placed pairs of scalp electrodes can then be used to detect potential differences between different parts of the potential field.

Gross Characteristics of EEG Tracings

The EEG signal thus recorded consists primarily of a mixture of a nearly random background waveform, a number of possible sporadic waveform types, and several types of rhythmic activities which wax and wane in amplitude and have characteristic frequencies, wave shapes, and scalp distributions. While the actual mixture of components exhibited varies markedly across individuals and across time within individuals, there are a relatively limited number of such patterns. The patterns can be indicative of such things as level of arousal, depth of sleep, and many disease conditions. The EEG signal typically ranges from zero to about 100.0 microvolts in amplitude and from zero to about 30.0 Hertz (Hz) in frequency, though some difficult to record but genuine potentials extending well beyond 30.0 Hz have been detected and studied. See Figure 1 for an example of a typical run of multichannel EEG tracings from a normal individual.

As demonstrated in Figure 1, the most prominent features of the EEG are the trains of rhythmic activity. Particularly impressive is that activity

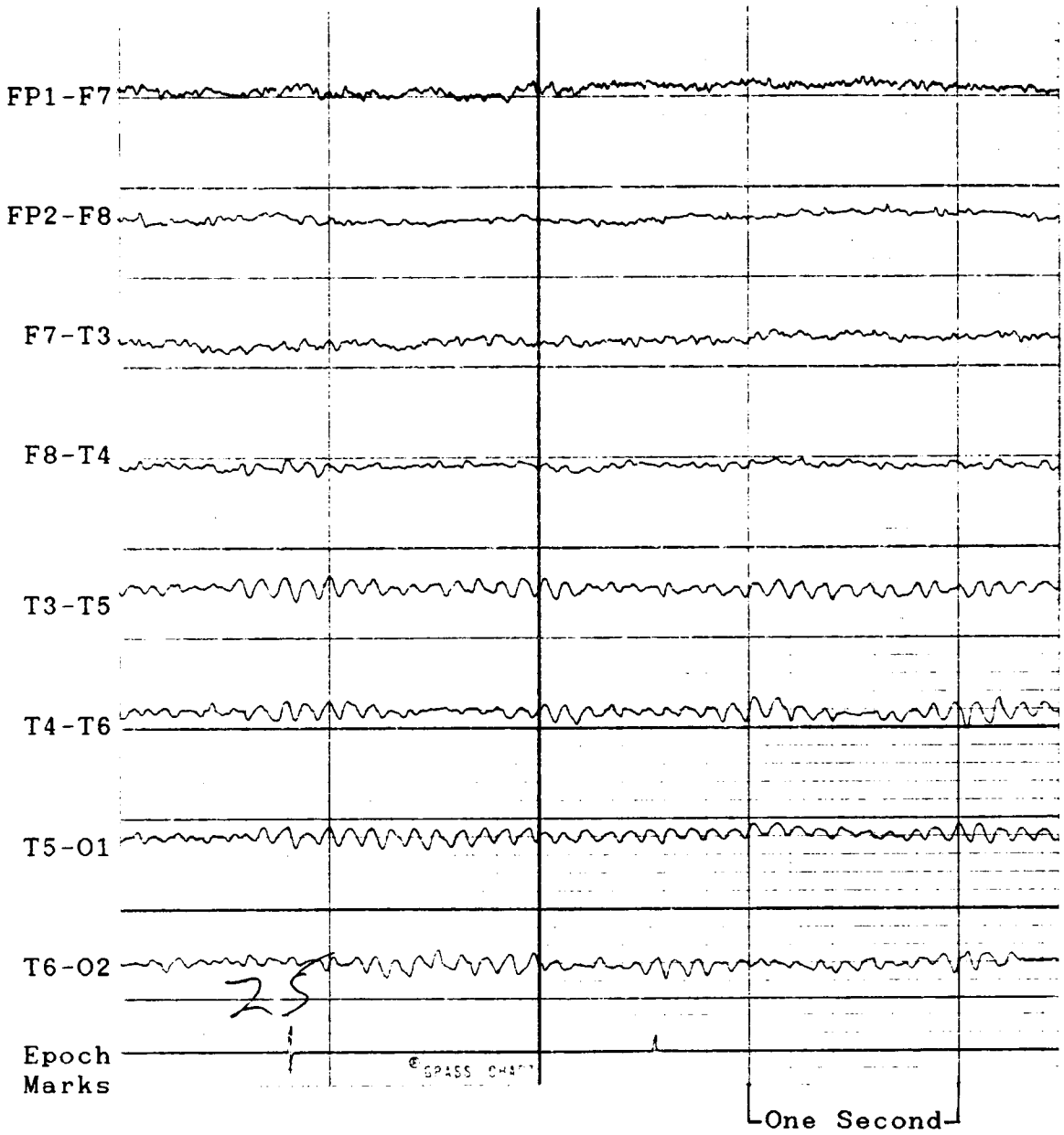


Figure 1. Example of EEG from normal subject.
Note: 30.0 mm/sec paper speed, 10uV/mm vertical scale.

known as the alpha rhythm. The alpha rhythm is traditionally defined as the waxing and waning 8.0 to 12.0 Hz sinusoidal rhythmic activity recorded maximally over the occipital cortex. A vast majority of people exhibit this rhythm, and in most people its most frequent and largest amplitude runs occur in a state of relaxed wakefulness with the eyes closed (Empson, p. 17). Visual processing (either real, as with eyes opened, or imagined), mental effort, drowsiness, and sleep tend to abolish, that is "desynchronize" or "block" the alpha rhythm. The frequency of the alpha rhythm tends to be characteristic of an individual, with relatively little wandering of its center frequency across time. Thus, the alpha rhythm can be viewed as encoding a large amount of information about an individual and that individual's current behavioral and cognitive state.

Much less prominent in the normal, waking EEG are several other rhythmic activities. The most important of these are, along with their typical frequency ranges: delta (0.5-3.5 Hz), theta (4-7 Hz), and beta (> 13 Hz) (Empson, p. 10). Particularly relevant to this study are delta and theta-range waves, which normally

occur in deep sleep, and light sleep or drowsiness respectively. Excessive or localized appearance of delta or theta activity is a pathologic sign for a number of brain-affecting disorders (Katz & Harner, 1987, p.119-122). As will be detailed later, the characteristic frequency of the alpha rhythm in AD slows as the disease progresses into what would normally be considered the theta or delta frequency bands. It is nonetheless assumed in this study, with support in the literature (Katz & Harner, p. 120-121, for example), that this slowed alpha activity remains essentially alpha-like in character and generation, and that this frequency change does not represent a transformation of alpha into theta or delta. Thus, as a background presentation leading to a discussion of the aspects of the EEG affected by AD, it is valid to remain focused on issues surrounding the alpha rhythm.

Generation of the Alpha Rhythm

Though it was the alpha rhythm itself which Berger first detected with his primitive string galvanometer, and the alpha rhythm has been the subject of intense

study since, the understanding of its generation by the brain is still incomplete. As mentioned above, rather large areas of the cortical dipole layers must act in synchrony to produce EEG potentials on the scalp. The existence of alpha and other rhythmic activities implies that whatever mechanism produces this regional cortical synchrony is either inherently rhythmic at alpha frequencies or is driven at alpha frequencies by an external source. Both sorts of mechanisms as well as combinations of the two have theoretical adherents. The most accepted idea is that driving pulses originate in the subcortical structures of the thalamus (Andersen & Andersen, 1963). By this concept, these ascending pulses initiate synchronous action within the heavily cross-connected cortex, which in turn sends inhibitory feedback pulses to the thalamus. While many consider Andersen and Andersen's concepts to be basically correct, numerous more recent studies, summarized by Osorio (1987), imply that many more subcortical nuclei may be involved as well. Of these, several may be relevant to the AD effects on EEG and alpha, in particular the nucleus basalis of Meynart, amygdala, and locus coeruleus.

An alternative view is strongly argued by Nunez (1981), who emphasizes the strong predominance of cortical-to-cortical projections over cortical-to-subcortical ones. In his view the EEG and its rhythms represent a summated standing wave from all the cortex as electrically influenced by its shape and surrounding tissues. Nunez argues, as does Basar (1980) that the rhythmic aspects of the EEG represent natural vibratory modes of the entire system, which wax and wane as underlying inputs from cortical and subcortical structures excite different harmonic resonances. Presumably, from this point of view AD effects on the EEG might as likely arise from the overall cortical degeneration in AD thus altering the resonance frequencies, as from the marked degeneration of a number of particular subcortical driving nuclei.

Spectral Analysis of EEG Signals

Background

The EEG signal can, like any time-varying waveform, be processed by various techniques to reveal

its spectral content. That is, a waveform representing a quantity changing in the time domain can be transformed into a frequency-domain representation, usually displayed as a spectrum, a plot of some measure of amplitude across a range of frequencies. An equivalent way of describing this is to say that the waveform has been decomposed into component frequencies. Techniques based on the classic Fourier series usually present this as decomposition into a series of fixed amplitude and frequency sine wave components, which if added together would reproduce the original input waveform. This is completely analogous to the splitting of white light into a rainbow spectrum of its component colors (frequencies) by a prism. The application of such techniques, especially in the field of EEG, does not mean to imply the reality of multiple sine wave generators in the brain (Gevins, 1987, pp. 43-45).

Methods for quantifying the spectral content of EEG signals were developed early on in the study of EEG. In the 1930s and 1940s, an opto-mechanical method of Fourier analysis was used in an extensive series of patients by Gibbs and his colleagues (Gibbs, Lennox, &

Gibbs, 1941; Grass & Gibbs, 1938; Knott, Gibbs, & Henry, 1942). Though the techniques were laborious, and little understood by other workers at the time, the applications and results foreshadowed much of what is done with relative ease through computer-produced spectral analysis today (Grass, 1984, p. 28).

Computer-based methods of EEG spectral analysis were developed in the 1960s, refined and adapted to affordable small computers in the 1970s (Bickford, Fleming, & Billinger, 1971), and have seen explosive growth in use and usefulness in the 1980s (Gevins, pp. 1-4). By far the most common method of EEG spectral analysis is that of power spectral analysis by the Fast Fourier Transform (FFT) technique, a computationally efficient method developed by Cooley and Tukey (1965). This was the technique applied in the current study.

A full presentation of the FFT algorithm, its method of computation, and full details of its application to EEG analysis are not needed here. However, a short orientation is called for to ensure the reader has a general understanding of the method and terminology used in this study. A more complete presentation is available in the chapters by Gevins

(pp. 1-83) and by Dummermuth and Molinari (pp. 85-130) of the Handbook of Electroencephalography and Clinical Neurophysiology, Revised Series, Volume 1 (1987). The following summary is derived from that material.

Application of the FFT to the EEG

An individual FFT computation, which produces a single output spectrum, operates on a finite-length portion of a running waveform, in this case, an EEG signal. This finite-length period is called an epoch. Within an epoch, the voltage values of individual points of the EEG waveform under analysis are collected at regular intervals, that is, the waveform is digitized at a particular sampling rate. This collection of digitized values is the raw data needed by the FFT algorithm to compute a spectral representation of the EEG epoch. In its basic form, as used in this study, the output spectrum is a power spectral density (PSD) spectrum in which the resulting amplitude measure for each frequency point on the spectrum is a power value. Thus, the FFT power spectrum

is a decomposition of the EEG waveform into component frequencies as measured by the power present at those frequencies.

Just as the FFT does not collect an infinite number of sample points in an attempt to continuously follow the input waveform, the FFT does not produce a spectrum of power values over a continuous spectrum of frequencies. Rather, it computes a set of spectral coefficients at fixed number of frequency values over a limited frequency range. The sample rate, and thus the number of points provided to the FFT algorithm, determines the frequency resolution of the resulting spectrum. The sample rate and total number of data points needed to adequately represent an input waveform is determined by the frequency band of interest contained in that waveform. For reasons of computational efficiency, the total number of points is usually an exponential power of two. The Nyquist theorem dictates that a waveform must be sampled at a rate at least twice the maximum frequency of interest in order for a digitized waveform to accurately describe that highest frequency of interest. The number of points provided to the FFT algorithm is inversely

proportional to the number of spectral coefficients it will produce. That is, the higher the frequency resolution desired for the output spectrum, the more data points the FFT algorithm needs, and for a fixed sample rate (determined by the Nyquist Theorem), the longer an epoch length is needed.

As applied to EEG analysis, the various parameters used in this study are typical. The frequency band of interest was zero to about 30.0 Hz, and a spectral resolution of one quarter Hertz (four spectral points plotted per division) was desired. For reasons to be discussed a bit more fully in the Method section, the FFT algorithm needs to compute its spectral coefficients over a frequency range twice the maximum frequency of interest. A usable set of parameters then works out to be 512 data points collected over a four-second epoch (a rate of 128 samples/second--twice the doubled maximum frequency of interest fixed at 32.0 Hz), enabling a FFT computation at 0.25 Hz resolution over a usable spectrum of 0.25-32.0 Hz.

Figure 2 is an example of a compressed spectral array (CSA) of repeated FFT PSD spectra from a series of input EEG epochs. The CSA technique involves the

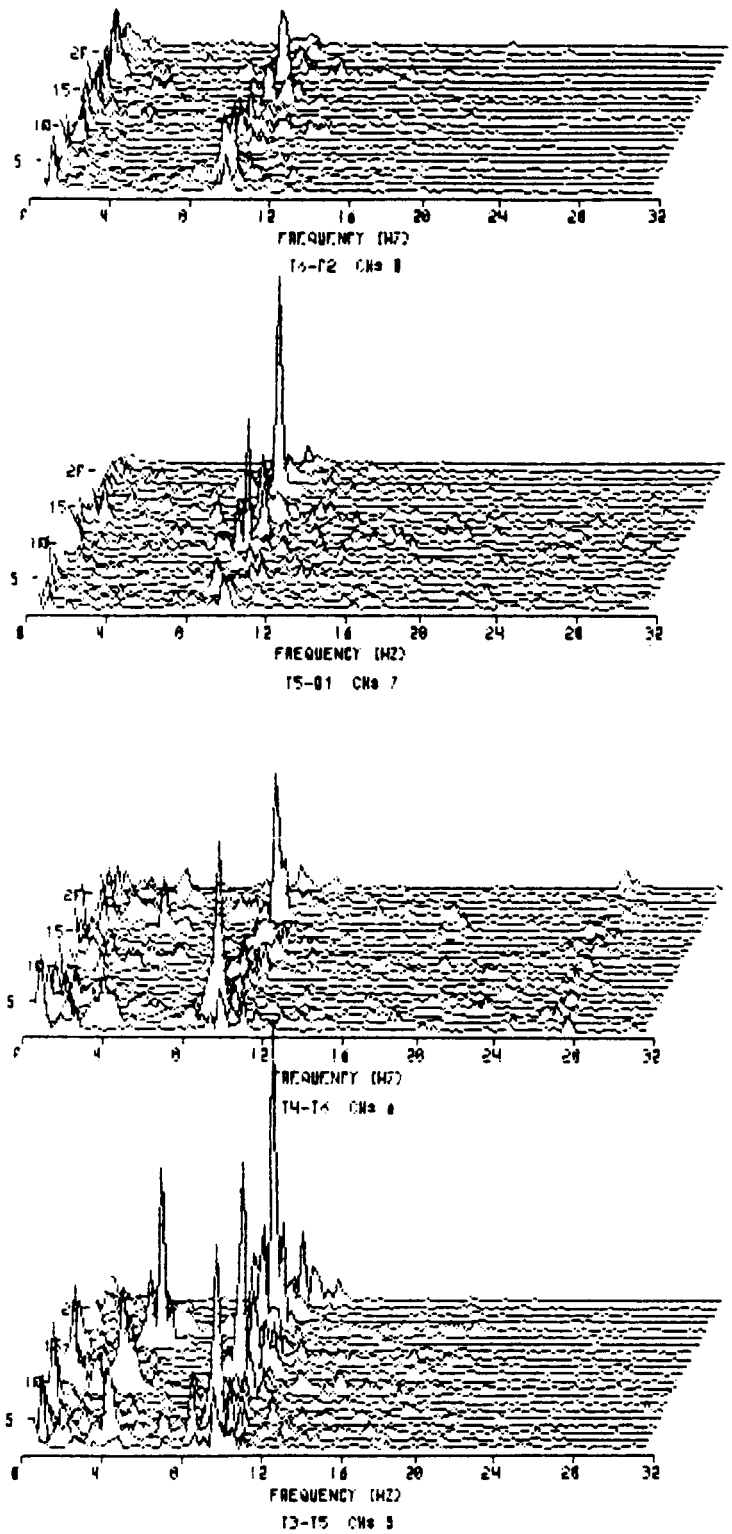


Figure 2. Compressed spectral arrays of percent power spectra.

plotting of successive FFT epoch spectra with offsets simulating a third spatial dimension for time, while making use of hidden line drawing of later spectra (Bickford, Fleming, & Billinger, 1971). This figure demonstrates the prominence of the alpha rhythm in the underlying EEG signal as the prominent "hump" in the PSD spectra at about 10.0 Hz. The waxing and waning of the alpha activity over time are reflected in the changing PSD amplitudes in succeeding FFT epochs. Changes in peak and mean alpha frequency, as well as alpha bandwidth, can also be discerned across epochs.

A grand average spectrum can be computed from a number of individual FFT epochs. A set of such average spectra from several EEG channels is shown in Figure 3, accompanied by curves representing a point-by-point plotting of the two-standard-deviation distance above the plotted PSD curve. The figure shows actual data from a normal subject in this study, as well as the actual channels and channel electrode derivations used in this study.

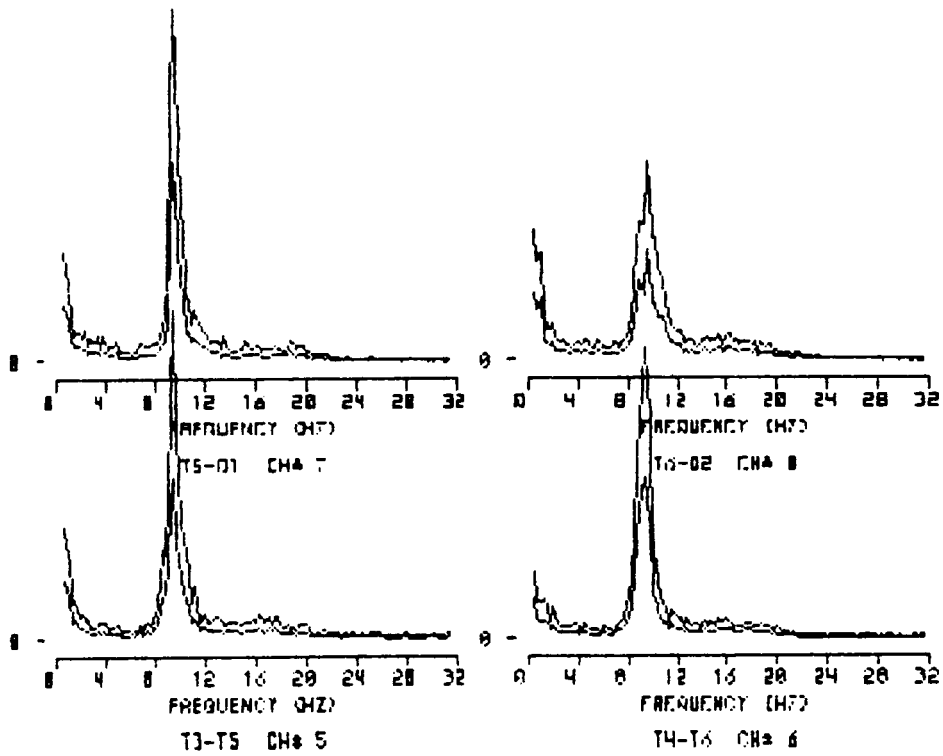


Figure 3. Example of grand average epoch percent power spectra.

Normal Aging and AD Effects on the EEG

Before describing the known effects of aging and AD on the EEG, briefly summarizing three basic background issues is in order. Over the past 40 years of EEG research into aging and AD, researchers have changed and refined their positions on these issues. As a result, an often confusing set of older findings is being clarified and sometimes overturned by more recent work. These issues are embodied in the questions: what is a normally aged subject, what is AD, and what method of EEG analysis is most sensitive to AD?

It has often been stated that the effects of AD on the EEG are mainly an exaggeration of the effects of normal aging on the EEG (Soininen, Partanen, Helkala, & Riekkinen, 1982; Fenton, 1986). The degree of perceived overlap between aging effects and AD effects, particularly early in the disease, has been the primary factor limiting the usefulness of EEG methods in AD diagnosis and evaluation (Harner, 1975). Ironically, in recent years several studies have cast considerable

doubt on the reality of the previously accepted normal aging effects (Duffy, Albert, McAnulty, & Garvey, 1983; Giaquinto, & Nolfe, 1986; Katz & Horowitz, 1982). The authors of these later studies claim that earlier researchers had not selected truly healthy older subjects for their normal control groups, thus contaminating their "normal" findings with those actually caused by disease conditions common in aging. The open question is how clinically useful a technique can be if it can only distinguish between exceptionally healthy older people and AD patients. It is much more likely in practice that a suspected AD case would need to be distinguished from similarly aged people of average health (Katz & Horowitz; Pedley & Miller, 1983, p. 34).

Likewise, there has been considerable doubt about how well EEG methods can distinguish between AD and other dementing conditions in the aged (Khachaturian, 1985). Such distinctions were not even attempted by many early researchers, who often classified all senile dements into one experimental group, or even lumped them with a general group of psychiatric patients (McAdam, & Robinson, 1956, Mundy-Castle, Hurst,

Beerstecher, & Prinsloo, 1954; Weiner & Schuster, 1956). Of course, these studies predated the clarification of AD as identical to its presenile form and distinct from other senile dementias, and thus earlier studies of AD were limited to the presenile form. As it is now realized that by far the largest AD population is the aged group, almost all current studies concern the senile form (SDAT). A number of more recent studies, including those of Brenner, Ulrich, Spiker, Sclabassi, Reynold, Marin, and Boller (1986); O'Connor, Shaw, and Ongley (1979); and Verma, Greiffenstein, Verma, King, and Caldwell (1987) have shown that SDAT groups can be differentiated from other demented and depressed groups with EEG techniques.

There has been an increasing trend towards studying AD and aging effects with spectral analysis and other computer analysis techniques, allowing for better quantification of EEG parameters. Indeed, virtually all studies done since 1980 use such techniques, while nearly all studies before 1970 quantified aspects of the EEG through various types of visual inspection and scoring of the EEG tracings (Ottomo, 1966; Busse & Obrist 1965). The number and

types of EEG abnormalities that can be accurately quantified by visual inspection are limited. However, such analysis does have an advantage in that it ties observed differences to clearly distinguishable characteristics of the EEG waveform. Spectral analysis is often applied with little reference to the character of the underlying waveform, making the relevance of observed differences sometimes obscure. Moreover, as Gevins (1987, p. 44) points out, such blind application of spectral techniques may throw away information which could have been detected had the spectral techniques been adjusted for characteristics of the waveform. The measures applied in this study are an example of such adjustment.

It should be noted that the issue of whether or not spectral analysis offers a significant increase in diagnostic power is still debated. A recent study by Brenner, Reynolds, and Ulrich (1988) found that moderately demented AD patients could be distinguished from normals by standard visual inspection EEG interpretation nearly as well as could be done with a spectral analysis technique. Mildly demented patients were detected in a majority of cases by either

technique, though with a high rate of false positive and false negative classifications.

Normal Aging Effects On the EEG

In their standard reference work on the characteristics of EEG, The Atlas of Electroencephalography, first published in 1951 and revised in 1958, Gibbs and Gibbs were already able to accurately describe several of the EEG changes associated with aging. They noted that the features of the adult EEG are not fully present in the majority of individuals until around the age of 20. Between the ages of 20 and 60, EEG changes are gradual, with a tendency toward flatter records, less alpha, and increased beta activity. After the age of 60, these trends accelerate, while periodic slow waves, especially anteriorly, may also appear. Gibbs and Gibbs do note, however, that completely normal adult pattern EEGs are not uncommon in the elderly, and that some of the changes they describe may well be due to other factors common to aging such as cardiovascular and metabolic problems.

With respect to the slow (delta and theta) activity, more modern studies support this latter conclusion. Reports by Harner (1975, pp. 65-69) and Katz and Horowitz (1982), among others, show that intermittent delta or periodic theta activity is strongly associated with transient ischemic attack and is extremely rare in subjects for which such cardiovascular problems have been rigorously excluded. Such slowing is nonetheless rather common in older people in apparent good health, and many studies note its presence in the temporal region of their normal groups (Busse & Obrist, 1965; Kooi, Guvener, Tupper, & Bagchi, 1964; Ottomo, & Tsubaki, 1966; Silverman, Busse, & Barnes, 1955). There is a strong tendency for these slow activities to appear on the left side of the head, a finding which has never been adequately explained (Pedley & Miller, 1983).

Support for the claim of Gibbs and Gibbs that beta activity increases throughout adulthood has been limited. Busse and Obrist (1965) find that this is true only for females, while Fenton (1986) notes that beta activity declines after age 80. Roubicek (1977) examined higher beta frequencies through spectral

analysis, and noted an increase in diffuse, low amplitude, very fast beta (30-40 Hz) with age. The plotted data Roubicek presents in support of this finding show a great deal of dispersion, however, and the linear regression shown must be considered a statistically significant finding only.

Of primary relevance to this study is the frequently reported finding of alpha slowing in normal aging. This seems to be the finding most affected by the issue of the proper definition of the aged normal subject. Earlier studies often found a rather pronounced slowing effect, though even these rarely noted a shift to less than 8.0 Hz (Obrist, 1953). These early researchers were quite aware of the potential problems of poor selection for their normal groups (Obrist, 1953; Mundy-Castle, et. al., 1954). The more recent studies with extraordinarily healthy normals have generally found a slowing effect, but to a much lesser degree. It is now a generally accepted clinical criterion that an alpha frequency of less than 8.00 Hz is abnormal at any age (Katz & Harner, 1987, pp. 116-117; Pedley & Miller, 1983). Katz and Harner and others note that such slowing can be produced by a

number of conditions, including cardiovascular disease, metabolic abnormalities, and vitamin B12 deficiency (p.126). Given these limitations, some studies that verified the finding of alpha slowing in aging include: Hughes & Cayaffa, 1977; Mundy-Castle, Hurst, Beersteicher, & Prinsloo, 1954; Obrist, 1953; Ottomo, 1966; Roubicek, 1977; & Soininen, Partanen, Helkala, & Riekkinen, 1982.

In recent years one center has used an advanced computer analysis technique for a study of very well documented healthy normal volunteers (Duffy, Albert, McAnulty, & Garvey, 1984). The technique used was that of topographic mapping, which involves taking FFT spectral analysis parameters from multiple EEG channels spread over the scalp, computing interpolated values for the parameters for all scalp positions between actual electrode sites, and plotting the resulting whole-scalp set of values with color coding onto a representation of the top of the head. The result is a "topographic map" of the distribution of parameter values, which can then be statistically compared to an average map derived from an appropriate normal group. Duffy and his colleagues found much less of the

supposed age-related changes than most earlier investigators had. Some of the EEG trends he did find ran counter to those of earlier studies. Specifically, Duffy's group found only a slight and non-significant decrease in alpha frequency with age. They did note a significant decrease in alpha blocking reactivity, when comparing eyes closed (alpha maximized) and eyes open (alpha blocked) conditions. The topographical analysis revealed a decrease with age for delta and theta activity and an increase with age for beta. These results are interpreted as indicative of EEG desychronization, that is, the disruption of the rhythmic delta and theta activity by beta.

Two similarly well-controlled studies using more standard spectral analysis methods found alpha slowing effects so small that significant differences could not be demonstrated. As part of a longitudinal study of SDAT, Coben, Danziger and Storandt (1985) followed a normal aged group for two and a half years. Their measure of overall average spectrum frequency, weighted mean frequency, which is most strongly influenced by alpha frequency, fell from 9.3 Hz at entry to 8.8 Hz at the end of the study. Giaquinto and Nolfe (1985)

compared a middle-aged normal group (40-60 years old) to an elderly group (60-80 years old), and found that "alpha rhythm undergoes a deceleration of about 0.5 Hz in the lifespan" (p. 544).

Hughes and Cayaffa (1977) reported decreased reactivity to standard clinical EEG activation procedures (hyperventilation and photic flash stimulation) in a significant minority of cases. Ottomo and Tsubaki (1965) also noted a significant decrease in alpha blocking due to opening the eyes in an elderly group.

The Effects of AD on the EEG

As mentioned earlier, Fenton (1986) notes that Hans Berger was the first to report EEG abnormalities in AD, doing so in 1932. Berger's patient had been confirmed histologically at autopsy. The histological confirmation is especially notable in light of the fact that most researchers since then have had to rely on unconfirmed patient populations. This and several other factors complicate the evaluation of the EEG literature

in AD. First, as mentioned, the most reliable method of confirming a case of AD is by postmortem microscopic studies of brain tissue. Few EEG studies, with certain exceptions (Gordon & Sim, 1967; Letemendia & Pampiglione, 1958) have been of long enough duration or in the proper setting for the postmortem studies to be done on a significant number of their subjects. Thus, there is some doubt about how many of the supposed AD or SDAT subjects in given studies actually suffered from AD. Furthermore, all the methodological problems mentioned in the EEG aging studies also apply to SDAT studies, that is, late-onset AD patients may very well have other medical problems related to aging in addition to AD.

The changing concept of what constitutes AD over the years means that the earlier studies of AD, and especially the few early studies which did include postmortem histological confirmation, were almost exclusively concerned with early, presenile onset dementia (PDAT). Also, early studies of "primary senile dementia", or "simple senile dementia" tended to have poor preselection for what is now called SDAT. Their experimental groups often included patients with

dementia or pseudo-dementia caused by such conditions as Pick's Disease, multi-infarct dementia (MID), depression, and Creutzfeldt-Jakob disease. The inclusion of MID patients is probably most important, as the multiple small strokes which cause it are known to affect the EEG (Katz & Harner, 1987), it is the second most common dementing illness of old age, and it often occurs in combination with AD (Katzman, 1986). As was the case for studies of normal aging effects on the EEG, more recent studies with better selection of subjects have results somewhat at odds with the earlier ones.

The early studies tended to support the argument that AD-related EEG changes that were like those then expected in normal aging, only greater in magnitude. That is, they showed marked slowing of the alpha rhythm, often into the theta range of frequency, a decrease in beta activity, and the appearance of markedly abnormal amounts of delta and theta (Gordon, 1968; Gordon & Sim, 1967; and Letemendia & Pampiglione, 1958). These studies also noted the disorganization of the alpha rhythm in late AD, usually leading to its absence entirely in late AD cases. Letemendia and

Pampiglione (1958) also reported the appearance of general EEG abnormalities of the type associated with epilepsy (such as spikes), and indeed reported a significant minority of patients had seizures.

By the early 1980s there was general agreement that by the moderate stage of AD it was rare to see a completely normal EEG, with marked slowing and reduction of alpha being the most consistent sign (Gordon, 1968; Gordon & Sim, 1967; Johannesson, Brun, & Ingvar, 1977; Prinz, Peskind, Vitaliano, Raskind, Eisdorfer, Zemcuznikov, & Gerber, 1982; & Soininen, et. al., 1982). Several studies confirmed that the alpha changes were relatively specific to AD, tending to distinguish it from other possible dementias, including multi-infarct, Pick's, and Creutzfeldt-Jakob (Letemendia & Pampiglione, 1958; Gordon & Sim, 1967; and Swain, 1959). The studies which also addressed the question of whether increased levels of dementia were also accompanied by increased amounts of EEG abnormalities, especially more severe alpha disruption, almost universally found this to be the case (Gordon & Sim, 1967; Johannesson, Hagberg, Gustafson, & Ingvar, 1979; McAdam & Robinson, 1956; Roberts, McGeorge, &

Caird, 1978; Soininen, et. al.; and Weiner & Schuster, 1956), though it should be noted that Weiner and Schuster saw no differences between the different dementias. Only Letemendia and Pampiglione (1958) did not find an increase in EEG abnormalities across time, a result which is probably due to their use of patients near death only. Given these findings, it is rather remarkable that EEG testing never gained wide acceptance as a discriminator of AD. This is probably due to the mixed nature of the specific findings of each researcher, though they almost uniformly had positive results, and the fact that the changes noted were not distinctively different from the then accepted normal aging signs until the disease was well advanced.

Results of Computer-Analyzed EEG Studies

Two studies by Coben and his colleagues relate very closely to my project (Coben, Danziger, & Berg, 1983; Coben, Danziger, & Storandt, 1985). These studies are the first and second reports of an ongoing

longitudinal study of the EEG and evoked response characteristics of a group of mild SDAT patients and their matched controls. As measured by group statistics, this center was able to distinguish between the mild SDAT subjects and normals using FFT measures applied at intake to the program and at followups at 1 and 2.5 years following intake. By the time of the followups, a number of the SDAT patients had progressed to moderate and severe dementia, and FFT measures distinguishing between these subgroups were also successful. The one measure successful in all cases was a normalized measure of theta power divided by the overall power, which showed higher levels of theta power in SDAT patients and trended upward with dementia severity. A measured decrease in normalized alpha power could distinguish milds from moderates and moderates from severes, but could not distinguish milds from normals. In the first study it was also reported that beta power in SDAT patients was significantly lower than that of normals. The combined theta and beta differences produced a significant difference in the measured average frequency between the groups.

Duffy's group has also applied his topographic techniques to AD-related EEG changes in mild to moderately demented subjects (Duffy, Albert, & McAnulty, 1984). Duffy's study included PDAT and SDAT groups. His group was able to find topographic differences between the groups and between each group and matched normals. Surprisingly, they found that alpha and the occipital region was of little usefulness in making the distinction. For the PDAT group, temporal lobe activity was most different from normals, while frontal regions were most distinctive for the SDAT group. They did confirm that an increase in slow activity and a decrease in fast activity is associated with poorer performance on neuropsychologic cognitive measures.

A further series of less comprehensive spectral analysis studies has tended to confirm the findings of Coben's and Duffy's groups (Brenner, Reynolds, & Ulrich, 1988; Brenner, Ulrich, Spiker, Sclabassi, Reynolds, Marin, & Boller, 1986; Breslau, Starr, Sicotte, Higa, & Buchsbaum, 1989; Giaquinto & Nolfe, 1986; Leuchter, Spar, Walter, & Weiner, 1987; Penttila, Partanen, Soininen, & Riekkinen, 1984; Soininen,

Partanen, Laulumaa, Helkala, Laakso, & Riekkinen, 1989). All of these studies made use of broad-banded FFT spectral parameters to measure amounts of EEG activity across the spectrum. That is, the spectrum was split into fixed segments according to the standard cutoff frequencies for the different EEG rhythms, and the average amount of activity found in each of these frequency bins was analyzed. The studies varied as to the number of channels, the actual bin cutoff points and number of bins, and in the details of data manipulation. However, it was a general finding that SDAT groups displayed an increase in very slow activity (delta) over normals, often in the left temporal region. The similarity of this pattern to that found by older studies of cardiovascular effects on the EEG was especially noted by Breslau, et. al. and Leuchter, et. al. The slowing of overall mean or mean alpha frequency was universally noted (except in the case of Breslau, et. al., in which such measurements were not done), though not with great sensitivity in mild SDAT (Brenner, Reynolds, & Ulrich, 1988; Pentitila, et. al.). Several enhancements of raw delta power or abundance measures were used and found to be more

sensitive than the raw measures alone. These included measures of beta divided by theta (Leuchter, et. al.), alpha divided by theta (Pentitla, Partanen, Soinen, & Riekkenen, 1985), and the beta minus theta difference (Brenner, et. al., 1986). This latter study also reported an increase in theta and alpha bandwidths, and a decrease in beta amplitude in SDAT.

Synthesis of EEG Findings in AD

The findings of previous work on the EEG in aging and AD definitely show that AD has an effect on the EEG which is evident to visual EEG analysis methods at least by the late moderate stage of AD dementia, and probably causes even mild AD dements, as a group, to differ from normals on FFT measures. As a number of the researchers note, the AD changes almost certainly start to appear early in the disorder, but are difficult to separate from the normal EEG pattern. Duffy, Coben, Khachaturian, and many others make the point that finding a distinctive pattern for early AD would be an important contribution to AD research and the

management of AD cases. The almost universal finding of an effect on the alpha band lends credence to the idea that measures of that activity are especially sensitive to AD.

Correlation of EEG With Other Diagnostic Modalities

There is an extensive independent literature concerning aging and AD effects in each of several fields not yet mentioned. These include psychometric and neuropsychologic evaluation, neuroimaging and direct measures of cerebral function, and evoked response studies. It is common for studies to use one or more of these other diagnostic modalities in combination with EEG techniques. This is particularly true for psychologic methods, as almost every study from every orientation includes some such measure, if only to document cognitive impairment in their experimental groups. These findings are relevant here only in that they demonstrate that aging and AD produced changes in the EEG which are known to correlate with aging and AD changes measured by other

means. As such, a complete presentation of these findings will not be attempted here. Very good reviews of these three areas, as well as most other aspects of AD are contained in an issue of The British Medical Bulletin (1986, Volume 42, Number 1) entirely devoted to AD.

The review of all electrophysiologic techniques in AD research by Fenton (1986), already mentioned for its conclusions on the EEG, includes analyses of the findings from several types of evoked response studies. Evoked response techniques involve the averaging of scans of the EEG signal following repeated stimuli. The resulting average waveform consists of a series of peaks and troughs characteristic of the type of stimulus applied and the recording electrode location. Fenton concludes that few convincing AD effects have been shown for short-latency evoked responses, i.e., those that occur in the first few milliseconds after a stimulus and represent basic reception and routing of stimuli through the central nervous system. Strong, but nonspecific effects of aging, dementia, and psychiatric disorders have been shown for longer-latency responses, which reflect higher-level stimulus processing. These

responses, usually investigated through the P300-wave paradigm first used in dementia by Goodin, Squires, and Starr (1978), are slowed by normal aging and are further slowed by many conditions producing cognitive impairment.

Neuroimaging techniques can detect the cerebral atrophy, degeneration, and altered brain metabolism caused by AD, though patterns caused by AD are difficult to distinguish from those seen in some normal individuals and in other pathologic conditions (McGeer, 1986). EEG changes typically correlate poorly with such measures from computed tomography, magnetic resonance imaging, positron emmision tomography, and cerebral blood flow testing until AD is rather well advanced (Kaszniak, Garron, Fox, Bergen, & Huckman, 1979; Johannesson, Brun, Gustafson, & Ingvar, 1977; Merskey, Ball, Blume, Fox, Fox, Kral, & Palmer, 1980; Stigsby, Johannesson, & Ingvar, 1981; Soininen, Partanen, Puranen, & Riekkinen, 1982; Stefoski, Bergen, Fox, Morrell, Huckman, & Ramsey, 1976).

The development and use of psychometric and neuropsychologic methods for the grading of dementia and the assessment of AD represent a vast field of

work. I will focus on a few findings especially relevant to the current study. Huppert and Tym (1986) offer a brief critical review of the status of the field and its goals. There are indications that such psychologic techniques have become quite sensitive and accurate in classifying AD and distinguishing it from other dementing conditions (Burke, Miller, Rubin, Morris, Coben, Duchek, Wittels, & Berg, 1988; Huff, Becher, Belle, Nebes, Holand, & Boller, 1987; Hughes, Berg, Danziger, Coben, & Martin, 1982). The Burke, et. al. (1988) and Hughes, et. al. (1982) studies report on the Clinical Dementia Rating (CDR) instrument developed and used successfully to grade mild SDAT in a comprehensive study on aging and dementia for which the EEG findings have already been discussed (Coben, et. al., 1985). A further report by Berg (1985) compared the effectiveness of their neuropsychologic battery, including the CDR, and the EEG measures derived from the same SDAT population as predictors of the course of SDAT. Berg concluded that several of the psychologic measures were most effective at predicting the rapidity of the future course of dementia, while none of the EEG measures did so. It was true, however, that EEG

measures could separate the demented from the nondemented and the various levels of dementia.

Most of the psychologic measures applied in this study have been shown to be affected by AD previously. The Mini-Mental Status examination of Folstein, Folstein and McHugh (1975) is a very often used method of grading dementia. Though criticized as imprecise (Strub, 1985, p.159), it is very easy to administer and score, and has been used to separate levels of dementia in numerous studies which found significant differences on their other measures. Hupert and Tym (1986) note a high false-positive rate, however. The Cognitive Behavior Rating Scale (CBRS) of Williams, Klein, Little, and Haban, (1986) is a new instrument which provides a profile of different problem behaviors in dementia. The Trailmaking A test from the Halstead-Reitan Neuropsychological Battery has been used recently as part of a battery which successfully distinguished SDAT patients from normals, but not SDAT from other dementias (Tierney, Snow, Reid, Zorzitto, & Fisher, 1987). All or parts of the Wechsler Adult Intelligence Scale (WAIS) have been used in AD evaluation by many workers. WAIS scores are clearly

below normal by the moderate stage of dementia (Coolidge, Peters, Brown, & Harsh, 1985; Hart, Kwentus, Wade, & Hamer, 1987; Gandolfo, Veccia, Moretti, Brusa, & Scotto, 1986; Larrabee, Largen, & Leven, 1985). WAIS measures did not distinguish between dementia types very well. The WAIS subtests of Vocabulary, Comprehension, Similarities, and Block Design were shown to be more affected than other subtests.

EEG spectral measures of 13.0-15.0 Hz activity have been shown to be positively correlated with intelligence in the normal aged (Patterson, Gluck & Mack, 1983). Many attempts to consistently demonstrate EEG differences, particularly lateralized differences, induced by the performance of tasks meant to activate the left or right hemisphere individually have not met with much success (Gevins, Zietlin, Doyle, Schaffer, & Callaway, 1979; Grabow, Aronson, Greene, & Offord, 1979; Ramsey, Coppola, Denckla, Hamburger, & Kruesi, 1989; Rugg & Dickens, 1982). Tasks without a motor component, that is "pure" cognitive tasks such as listening to speech have shown especially weak effects.

Rationale for the Current Study

As noted above a number of studies have described a slowing of the alpha rhythm and/or an increase in theta rhythm (4Hz-8Hz activity) as aspects of aging or dementia, while some recent studies emphasize delta effects. This was particularly true of studies which used the FFT technique to derive their measures of alpha, theta, and delta activity by making use of rigid wide-band frequency bins. That is, a common FFT analysis strategy is to divide the spectrum into 4.0 Hz-wide frequency bins, which conveniently produces frequency boundaries matching the definitions of three of the main EEG rhythms: delta (0.0-4.0 Hz), theta (4.0-8.0 Hz), and alpha (8.0-12.0 Hz). I contend that this sort of analysis, though it has been able to detect AD/normal group differences, misses a good deal of information about what is happening with the underlying rhythmic activity, and can actually produce a distorted view of that activity. This may be the reason that a number of recent studies found measures of theta or theta activity more sensitive to SDAT than alpha-based measures.

As seen in Figure 2, p.33, rhythmic alpha activity is represented in the FFT power spectrum as a hump several hertz wide. This is in part due to limitations in the FFT's frequency resolution and partly due to the fact that the alpha waveform is not a true sine wave and genuinely contains a narrow band of frequency components. The boundaries of this true alpha hump respect no one's artificially defined bin edges, almost certainly straddling such edges to some degree. This is critical in studies of aging and dementia, in which alpha slows to or beyond the 8.0 Hz traditional boundary. When viewing FFT data binned as described above, this would almost certainly be seen and described as an increase in theta activity and a decrease in alpha activity, when in reality nothing has happened to the underlying rhythmic activity other than slowing of its center frequency. Thus, a strong alpha effect is split into two weaker effects which are misleadingly labeled. The study of Giaquinto and Nolfe (1985) happens to provide delta/theta/alpha/beta activity histograms by group which clearly show such an effect.

As Katz & Harner (1987, pp. 119-120) note, the idea of "slow alpha" at a frequency considered characteristic for theta is somewhat controversial. It is certainly a source of confusion when reviewing the literature, as one is never quite sure if the often-repeated claim that theta increases in AD is actually referring to slow alpha. The study by Letemendia and Pampiglione (1958) was unusual in that it offered a careful description of the EEG patterns displayed in their AD group. They saw brief occurrences of normal theta and alpha while the slow alpha pattern predominated. Katz & Harner conclude that the slow alpha concept has "pragmatic value" (p. 120) in that, despite its frequency, it maintains an alpha-like shape (spindle), scalp distribution (posterior), and reactivity (blocks on eye opening). Visual inspection of the EEG tracings of the majority of SDAT subjects in this study support those conclusions. See Figure 4 for a page of EEG tracings from an SDAT subject displaying "slow alpha" activity. This can be compared with the normal alpha seen in Figure 1, p. 23.

In order to avoid confusion with the traditional theta/alpha terminology and definitions, I turned to

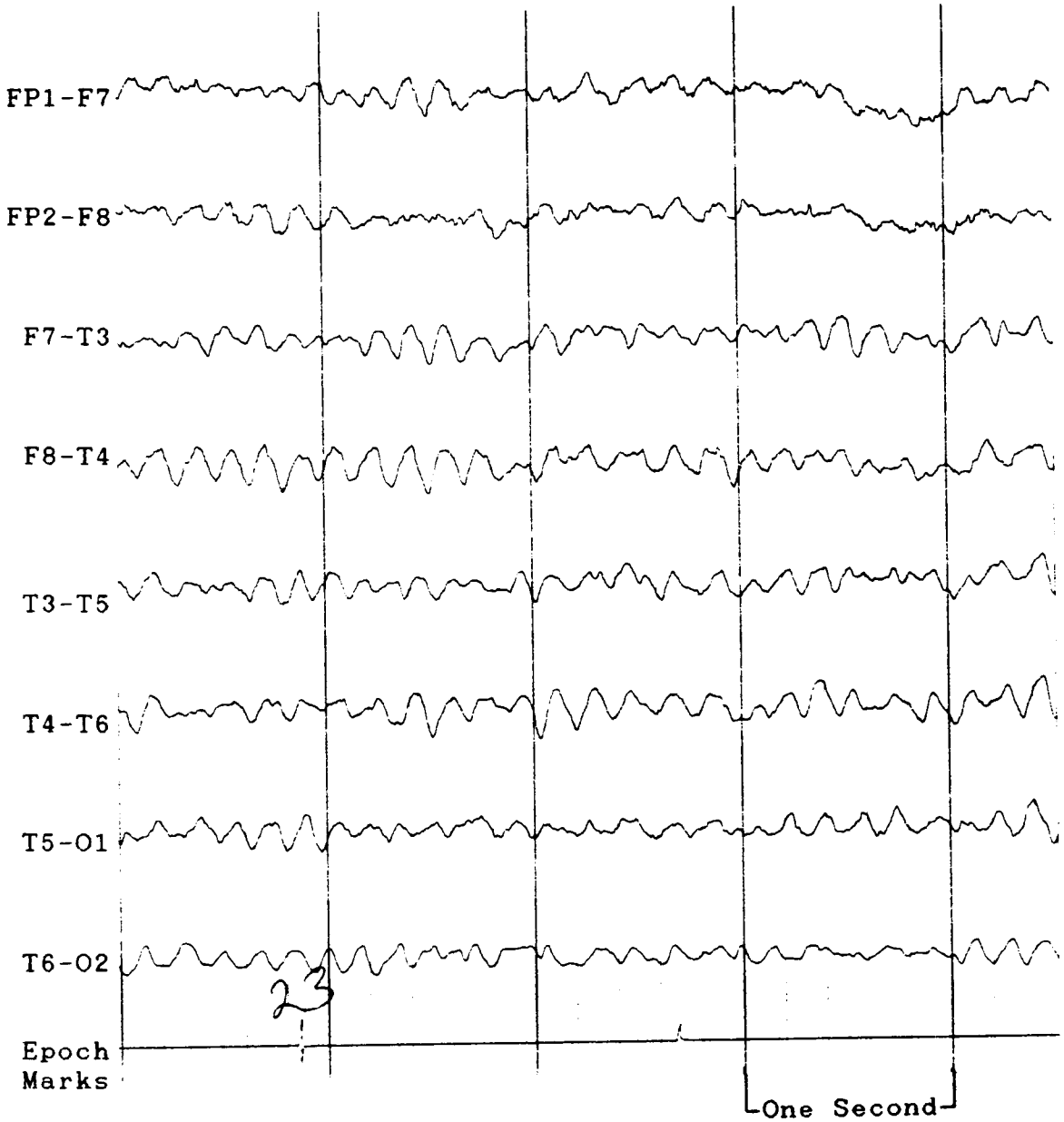


Figure 4. Example of EEG from SDAT subject.
Note: 30.0 mm/sec paper speed, 10uV/mm vertical scale.

an alternate designation sometimes used in the literature when referring to rhythmic activity occurring maximally in the occipital region, whatever its frequency. This more general designation for such activity is the Dominant Occipital Rhythm, or DOR. For the purposes of this study, the DOR will be defined as the EEG activity present in the 4.0-16.0 Hz frequency band (6.0 Hz above and below the 10.0 Hz standard for alpha), as detected by the FFT algorithm.

Thus, a main impetus for this study was the desire to test the sensitivity of DOR-oriented measures in SDAT. That is, in SDAT, the EEG component, here called DOR, slows from what has been called the alpha range down into what has been called the theta range. Descriptions and measures applied to these two ranges separately may not adequately describe the behavior of DOR. Moreover, it was hypothesized that the normal aged population might differ from the aged AD demented population not only in the degree of slowing of the DOR, but also in aspects of its frequency and amplitude variability over time. Therefore, measures applied to average values over an entire set of sampled epochs might also be missing important information present in

the EEG signal, while measures which can locate and describe the characteristics of the DOR epoch-by-epoch would be able to reflect more accurately the underlying activity and its changes over time. As a consequence of this possibility, a major task was the design of FFT-based measurements of EEG rhythmic activity which were relatively free of assumptions about frequency boundaries. The goal was to produce measures capable of locating, describing, and following the occipital spectral "hump", epoch-to-epoch, wherever it might be and however wide or narrow it was.

Preliminary Statement of Hypotheses

Stated most generally, the hypotheses about the DOR in AD are, that the known progressive slowing and eventual loss of the DOR during the course of AD is accompanied and perhaps preceded by one or both of the following:

1. The DOR becoming more stable in amplitude.

2. The DOR becoming less stable in frequency.

More specifically relevant to the current study, these proposed effects should hypothetically produce the following situation:

1. The DOR amplitude of moderately demented AD patients should vary less, from moment to moment and across changes of stimulus conditions, than the DOR of normals.

2. The DOR frequency of moderately demented AD patients should vary more from moment to moment than the DOR of normals.

If the DOR activity of AD patients does indeed differ from normal in either of those two ways, there should be measurable consequences found in the FFT spectra of such patients. Within-epoch and across-epoch effects are possible. There would be little within-epoch effect due to Hypothesis 1, but DOR amplitude across-epochs ought to display less variance in ADs than in normals. It ought also to be less reactive to the desynchronizing effects of visual and mental processing. If the frequency instability defined in Hypothesis 2 produces frequency fluctuations over periods shorter than the epoch period, it would result

in a broadening of the DOR hump. If the frequency instability is more like a frequency shift occurring a number of seconds apart, then an across-epoch effect of increased variability in the measures of DOR epoch frequency would result.

Development of FFT Measures to Test Hypotheses

A necessary preliminary step for this study was the development of FFT-based measures sensitive to the DOR characteristics to be examined, DOR variability in amplitude and frequency. Analysis of the FFT data from a number of pilot AD patients had already demonstrated the suspected weaknesses of the broad-bin and whole-run averaging techniques. At the time of data collection for this study, software development, aimed at producing measures capable of locating the DOR hump within an epoch and tracking it across epochs at the maximum frequency resolution of 0.25 Hz, was far along. Refinements continued well into the post-collection, analysis phase of the study. As mentioned above, the hypothesized DOR instabilities would have secondary

effects on the FFT spectra beyond simple DOR peak amplitude and center frequency variations. Bandwidth and peak sharpness differences and variations were also expected.

The result of an extensive development phase was a set of thirteen variables which measured characteristics of the DOR and surrounding portions of the FFT power spectrum for each epoch of FFT data. Across-epoch statistics were maintained for each variable in order to quantify the expected mean and variance effects of AD on the EEG. The statistics types used were mean, standard deviation, and coefficient of variation.

Coefficients of variation (CVs), which are SD standardized by the mean (SD divided by mean times 100, or SD as a percentage of the mean), were used as well as the more common SDs, as the variance of FFT power spectral data points was found to be highly, and nearly linearly, positively correlated with mean amplitude. That is, the higher the mean power amplitude at a given point on the FFT spectrum, the higher the underlying variance is at that point across individual epochs. Using CVs puts amplitude-based measures of variance on

an equal footing, whatever the underlying mean amplitude may be. The CV may also be used as an indicator of the stability of a variable. That is, the higher the CV, the more nearly the SD of the variable approaches (or even exceeds) the mean in amplitude. A high-CV variable would be expected to be extremely volatile across measurements, and for a small number of measurements could lead to high across-subjects variance. This situation would make it more difficult to prove genuine group differences. If it is found, as was often the case in the variable-development phase, that a proposed variable has a high CV within a subject run, it indicates the variable is probably not measuring some inherently stable aspect of the EEG. SD and CV quantities have an equal footing with the mean value of a variable in the full description of that variable's behavior within an individual subject. Likewise, for characterizing a group, the mean of group SD and the mean of group CV will be the descriptors of group variance for a variable, potentially of equal importance to the group mean.

The actual thirteen variables developed fell into five categories: measures of whole-spectrum power

amplitude and mean frequency, measures of DOR amplitude and frequency, measures of DOR bandwidth, measures of DOR shape (in particular, the "sharpness" of the DOR hump), and measures of the activity immediately adjacent to the DOR in frequency. Two similar measures were used in several of the categories, one designed as a stable measure across epochs, and one designed as a volatile measure very sensitive to individual epoch characteristics. It could not be determined a priori which type might be more successful in detecting group differences, as the stable measures would less accurately reflect the interepoch variances under investigation but would be likely to have lower variance values, making significant differences on variance values easier to demonstrate statistically. Conversely, the volatile measures would be more sensitive but more variable, possibly obscuring significant differences. Thus, the thirteen variables and their three statistics types are certainly not completely independent; indeed, a number of them are certainly measuring very similar aspects of the FFT data. However, all produce different values and exhibit different amounts of stability within a subject run.

As the literature indicates that mathematical transformation of the FFT raw power spectrum can be of value in stabilizing measures of it by reducing its non-Gaussian distribution in amplitude values, several such transforms of the underlying spectrum and the derived variables were tested as well. The transforms tried were: percent power (each point divided by the total of 2.00-32.00 Hz power in an epoch), square root of power, and natural logarithm of power. Measures derived from spectra after application of square root and logarithm transformations were extensively explored, but did not seem significantly better in sensitivity or stability than measures derived after application of the simple percent power transformation, which has the main effect of controlling for epoch-to-epoch variation in the overall EEG power. This transformation did indeed reduce the extremely high variance values obtained for the amplitude-oriented measures, while it had no effect on the purely frequency-oriented measures. Therefore, in the final form, the variables were derived from percent power spectra, that is, from raw power spectra standardized by the total power (the sum of all power amplitude

data points). Spectral information below 2.00 Hz was discarded from the total epoch power computation as that band of the spectrum is extremely sensitive to contamination by artifacts due to eye movement, eye blinks, gross head movement, and electrode-induced voltage baseline sway. The thirteenth of the measures, total 2.00-32.00 Hz power was actually added at this final step, in order to maintain some measure sensitive to overall raw power differences after all the other measures were converted to percent-power derivations.

See Table 1 for a summary of the thirteen measures and the computational method for deriving each of them from the percent power FFT spectra. Table 2 summarizes the intended purpose for each measure.

Investigating the EEG in AD

The main task of this study then was to apply these measures to a moderately demented, late onset AD patient group and a similarly aged normal control population. That the SDAT group was indeed cognitively impaired (and the control group was not) was

Table 1

Measures Applied to FFT Percent Power Spectra

Measure (Abbreviation)	Computation Method (Units)
1. Weighted Mean Frequency (WMF)	Sum of each data point times its % power value divided by the sum of 2.00-32.00 Hz % power (Hz)
2. Total Power (TP)	Sum of raw power amplitudes all data points 2.00-32.00 Hz (arbitrary power units)
3. % of Total Power in DOR window (%TP)	Sum of raw power 4.00-16.00 Hz divided by TP (percentage)
4. Maximum DOR amplitude (MAX AMP)	Value of largest % power data point 4.00-16.00 Hz (% power)
5. Frequency of maximum DOR amplitude (MAX FRQ)	Frequency of MAX AMP data point (Hz)
6. Frequency of % power median (MDN)	Frequency of data point which has half of 4.00-16.00 Hz % PWR below it and half above it (Hz)
7. Median-based DOR bandwidth (MDN WID)	Frequency band surrounding MDN which contains 80% of 4.00-16.00 Hz % power, difference between high and low frequency endpoints, computed separately MDN amplitude inclusive, 40% to left, 40% to right of MDN (Hz)
8. Drop-from-peak DOR bandwidth (DROP WID)	Difference of frequency points left and right of MAX FRQ at which rolling 3-point averages of % power amplitudes falls to 10% of MAX AMP (Hz)
9. Median-based peak/width ratio (MDN PK/WID)	MAX AMP divided by MDN WID

Table 1

(Continued)

Measure (Abbreviation)	Computation Method (Units)
10. Drop-from-peak-based peak/width ratio (DROP PK/WID)	MAX AMP divided by DROP WID
11. Average % power per point, pre-DOR (PRE PWR/PT)	Sum of % powers of points 4.00 Hz to left DROP WID endpoint divided by the number of such points (% power)
12. Average % power per point, DOR (DOR PWR/PT)	Sum of % powers of points within DROP WID divided by number of DROP WID points (% power)
13. Average % power per point, post-DOR (POST PWR/PT)	Sum of % powers of points from right DROP WID endpoint to 16.00 Hz divided by the number of such points (% power)

Notes:

1. Raw FFT power spectrum consists of 127 arbitrary power unit data points (0.25-32.00 Hz, four points per Hz). Arbitrary power units are on order of picowatts, calibrated as 1500 units total power for a spectrum output when a 1.0 V peak-to-peak, 10.0 Hz sinewave is input to the FFT.
2. % Power spectrum consists of 120 % power data points (each) raw power data point 2.00-32.00 Hz divided by TP times 100).
3. DOR frequency window is 4.00-16.00 Hz portion of spectrum (6.00 Hz below and 6.00 Hz above nominal 10.00 Hz alpha center frequency).
4. If DROP WID computation hits 4.00 Hz going left or 16.00 Hz going right, it is taken as failure of algorithm to find DOR peak, and DROP WID-based measures are not taken for epoch (DROP WID, DROP PK/WID, PRE PWR/PT, DOR PWR/PT, POST PWR/PT).

Table 2

Rationales for Measures Applied to FFT Percent Power Spectra

Abbreviation		Rationale
1.	WMF	Describes overall average frequency of epoch, weighted by each point power.
2.	TP	Measures total power of epoch, able to track total power differences despite use of % power elsewhere.
3.	%TP	Measures how much of TP is contained in DOR window. Gross measure of concentration of power in DOR.
4.	MAX AMP	Tracks mean and variation of maximum amplitude point. For describing DOR amplitude characteristics.
5.	MAX FRQ	Tracks mean and variation of frequency of MAX AMP. For describing DOR frequency changes.
6.	MDN	Similar in purpose to MAX FRQ, but less volatile.
7.	MDN WID	Width is affected by DOR frequency variation within an epoch or by number of frequency components producing DOR--a measure of "sharpness" of the DOR FFT peak.
8.	DROP WID	Similar to MDN WID, but more volatile, as it is based on morphology of peak and is more accurate at finding frequency endpoints of DOR--a "sharpness" DOR measure.

Table 2

(Continued)

Abbreviation	Rationale
9. MDN PK/WID	A sharpness or "peakiness" measure which interrelates MAX AMP with the width of the surrounding DOR.
10. DROP PK/WID	Same as 9, but using the DROP WID, so is peak morphology-based, and more volatile.
11. PRE PWR/PT	Tracks average amplitude of DOR window points lower than found DOR in frequency. Would detect power produced by a separate theta rhythm in this range.
12. DOR PWR/PT	Tracks average amplitude of points within DROP WID, that is, average amplitude of points found in DOR peak.
13. POST PWR/PT	Tracks average amplitude of DOR window points higher than found DOR in frequency. Would detect low-frequency beta activity in this range.

documented and measured with neuropsychologic and psychometric testing. EEG spectral data were gathered in a baseline condition meant to maximize DOR activity and in two stimulus/behavioral activation conditions which would be expected to produce DOR blocking or desynchronization, that is, reductions in amount of DOR with an increase in its amount of fluctuation. A baseline comparison of normal and SDAT DOR patterns was done to validate the concept of SDAT DOR as slowed alpha. The major hypotheses were addressed through within-groups comparisons of the EEG measures across stimulus conditions and between-groups comparisons within stimulus condition type. Finally, those EEG variables that successfully discriminated between the SDAT and normal group were tested for their ability to rank the SDAT subjects in a way similar to that of the psychologic testing-based measures through rank correlations.

Specific Hypotheses

A final restatement of the hypotheses of the study, in terms of the actual type of measurements applied are as follows:

I. Validation of AD group as genuine probable AD with senile onset.

A. That moderately demented SDAT subjects will demonstrate clear cognitive deficits as measured by psychometric and neuropsychologic testing instruments.

B. That as compared to the normal controls, the SDAT group will exhibit the known main differences in basic EEG parameters, i.e., slower mean frequency and DOR frequency, increased theta activity, and decreased beta activity.

II. Validation of the concept that, as seen by FFT measures, the DOR of SDAT subjects differ from that of normals only in frequency.

That the two groups will not differ significantly in the baseline condition on mean DOR measures of amplitude. Additional confirmation may be possible if the bandwidth and amplitude relative to bandwidth ("sharpness") are not significantly different. This latter would indicate that any DOR frequency instabilities present as postulated in the SDAT group do not significantly affect the DOR within epochs, at least in the baseline condition.

III. Demonstration of group differences on EEG measures.

A. That activation effects as compared to the baseline condition will be more prominent in the normal control group.

B. That the DOR measures applied to the AD group will demonstrate differences from those derived from the normal group in the following ways, by measurement type:

1. Coefficient of variation (CV) measures of DOR amplitude variance will be less in the SDAT group.

2. Standard deviation (SD) measures of DOR frequency variance will be higher in the SDAT group.

3. That the DOR bandwidth of SDAT subjects will be larger, due to increased frequency variance.

4. That "sharpness" measures of DOR amplitude divided by bandwidth will show lower mean and variance values in the SDAT group.

All four of these effects should be more strongly seen in the activation conditions which maximize DOR variability.

IV. Correlation of EEG and psychologic measures.

That it will be possible to demonstrate correlations between EEG measures which demonstrate group differences and psychometric or neuropsychologic measures which demonstrate cognitive decline in the AD group.

II. METHOD

Subjects

Eleven subjects were selected for each of the two experimental groups, the normal control group and the Senile Dementia of the Alzheimer's Type (SDAT) group. Subjects for the normal control group were solicited from members of the Knoxville, Tennessee, chapter of the Alzheimer's Disease and Related Disorders Association (ADRDA). Subjects for the SDAT group were obtained through solicitations distributed to the spouses, guardians, or other appropriate family members acting as caregivers for SDAT patients associated with the ADRDA chapter or with the St. Mary's Medical Center Alzheimer's Disease Day Treatment Center in Knoxville, Tennessee.

All prospective subjects were prescreened for age (55-70 years) and general good health for age. Membership in the SDAT group was also limited to moderately demented persons with clear diagnoses of SDAT, as determined by a neurologist's opinion supported by appropriate testing and course of disease,

with requirements of a minimum of six months since diagnosis and one year since noticeable symptom onset. These factors were determined before admission to the study by telephone interviews with the normal control volunteers or appropriate SDAT caregivers, reference to medical records, and questioning of the associated neurologist. For purposes of prescreening, moderate dementia was defined as cognitive or memory impairment sufficient to have caused a significant change in the lifestyle of the patient (e.g., retirement from employment or cessation of homemaking) while not severe enough to require permanent institutionalization. There were 5 males and 6 females in the normal control group, with an age range of 58 to 74 years (mean 64.7 years). The SDAT group contained 2 males and 9 females, with an age range of 62 to 83 years (mean 72.7 years). The protocol was not completed by one very drowsy male normal control subject and one severely demented female SDAT subject. As detailed in the Results section, the data from several other subjects were found to be unusable in all or parts of the analysis due to EEG artifacts.

Followup information was sought about the remaining ten SDAT subjects two years and ten months

after the last SDAT subject run. Two subjects were lost to followup. There is postmortem histologic confirmation of AD for the one female subject who has expired. The seven other subjects all continue treatment under a diagnosis of AD. Three female subjects remain in the moderately-demented stage of the disease, while four subjects (two male, two female) have progressed to the severely-demented stage.

Six of the eight normal control subjects whose data were used in the final analyses were also contacted for followup information. Five of these subjects remained in good health. One subject suffered a mild stroke approximately ten months after testing, with near-complete recovery by the time of the followup.

Guidelines for the ethical treatment of human subjects in medical and psychological research were followed. Particular care was taken to obtain informed consent from the subject, and in the case of SDAT subjects, from the person acting as the patient's guardian as well. Confidentiality of subject data was maintained. Approval for these and other factors insuring subject rights and welfare were obtained from the Institutional Review Board of the University of Tennessee Health Science Center, Memphis, project number IRB 2380.

Apparatus

A Digital Equipment Corporation PDP-11/73 computer system performed Fast Fourier Transform (FFT)-based power spectral analysis of the EEG signals provided by a Nihon Kohden Corporation model EEG-7209 eight-channel EEG machine. EEG signals were sampled and digitized through a 16-channel, 12-bit resolution analog-to-digital conversion board within the PDP-11/73. See Appendix A for a detailed list of the hardware used in this study.

The FFT power spectral analysis software produced and stored to disk a 0.25-32.00 Hz power spectrum for each of the eight EEG channels every four seconds. The channels were sampled and digitized at a rate of 128 Hz, providing the FFT algorithm 512 points to analyze per channel for each four-second epoch. Hann cosine-tapered windowing was applied within the FFT algorithm. The program was able to maintain continuous data collection at 128 samples per second while also computing the PSD coefficients in real time by supporting two epoch data buffers in memory and filling them alternatively. The PSD computation and storage for

an epoch occurred while the alternate buffer was being filled.

In terms of the International 10-20 System of electrode placement, the electrode locations and channel derivations for the eight channel FFT procedures were as follows:

Channel	Derivation	Channel	Derivation
1	FP1-F7	2	FP2-F8
3	F7-T3	4	F8-T4
5	T3-T5	6	T4-T6
7	T5-O1	8	T6-O2

Thus, the channels record the EEG in four left/right pairs (odd/even channel numbers), stepping by pairs from the front of the head to the back. The channels on each side form a chain following a path around the side of the head. As will be explained below, data from the front four channels contained an unacceptable level of artifact and usable data could only be obtained from the rear four channels (numbered 5 through 8).

Psychometric and neuropsychologic testing was carried out with selected standard testing materials from the Wechsler Adult Intelligence Scale, the Halstead-Reitan Neuropsychological Battery, the Mini Mental Status Examination, and the Cognitive Behavior Rating Scale.

Procedure

A number of the measures derived from the data collected in this study required extensive analysis, the creation of new scoring techniques, or the use of custom-designed software algorithms. As this warrants detailed explanation of each measure and the procedure for obtaining it from the data, the Procedure section will be broken into two parts: Data Collection and Analysis. The Data Collection section will describe the order of events as data were collected from each subject with details as to how the apparatus was used. The Analysis section will describe how the various pieces of raw data were scrutinized and manipulated in order to produce comparable and analyzable measures.

Data Collection

Demographic/medical history data collection.

Subjects and caregivers were first interviewed to collect demographic and medical history data. The demographic data collected included age, sex, level of education, and occupation (or former occupation in the case of retirees). All subjects were right-handed. The medical history queries focussed on discovering any prior or existing medical conditions or medications being taken which would be likely to affect the EEG or evoked response. In the case of SDAT subjects, additional information on the length of time since official SDAT diagnosis and since first signs of AD onset was also collected. All subjects were asked if they had positive medical histories in the categories of general neurologic disorders (other than AD), cardiovascular disorders, metabolic disorders, and trauma. When a positive history in any category was indicated, further questions ascertained the level of involvement and any medications being taken for the conditions. Subjects were then asked to list all medications being taken and whether or not alcohol or

other psychoactive drugs had been taken within the last 48 hours. None had done so.

Finally, subjects were asked to estimate if their amount and quality of sleep over the past 24 hours had been above, at, or below their usual levels. They were also asked to estimate whether their current general feeling of physical and mental well-being was above, at, or below what they customarily experienced. All subjects reported feeling well-rested and at typical physical and mental levels.

Neuropsychologic and psychometric data collection. Subjects were then given a 1 1/2 to 2 1/2 hour battery of neuropsychological tests. The neuropsychological battery included the Trailmaking A, Trailmaking B, and Aphasia Screening Test subtests of the Halstead-Reitan Neuropsychological Battery; the Information, Digit Span, Similarities, Block Design, Object Assembly, and Digit Symbol portions of the Wechsler Adult Intelligence Scale-Revised (WAIS-R); and the Mini Mental Status Examination (MMS). The first ten questions of the MMS constitute the Mental Status

Questionnaire (MSQ), which was scored and analyzed separately. The Cognitive Behavior Rating Scale (CBRS) is an instrument intended to evaluate the cognitive and behavioral effects of dementing conditions as perceived by persons closely associated with the demented patient. While the experimenter administered the neuropsychologic battery, the caregivers accompanying the SDAT patients were asked to complete the CBRS. The normal control group subjects were asked to complete the CBRS for themselves, by comparing themselves to what they perceived as average for their age.

Electrophysiologic data collection.

Approximately 2 hours of electrophysiologic procedures followed, comprised of FFT analyses of the EEG under several behavioral and stimulus conditions and P300 evoked response studies to two different types of stimuli. The P300 stimulus types were visual (circle, square, and triangle shapes flashed on a video monitor) and auditory (low, medium, and high pitched beeps presented through headphones). The FFT EEG data were obtained during five behavioral/stimulus conditions:

resting with eyes open, resting with eyes closed, listening to speech, doing mental arithmetic, and photic flash stimulation. The order of presentation of the seven electrophysiologic procedures was randomized across subjects by reference to a table of random numbers.

This study will report and analyze the results from the baseline resting with eyes closed condition and two of the activation from baseline conditions, resting with eyes open and listening to speech. These conditions will be designated CLOSED, OPEN, and LISTEN. Too much data were lost due to subject-induced artifacts for successful analysis of the mental arithmetic and photic flash stimulation conditions, particularly in the SDAT group. The P300 data were also unusable due to artifact.

FFT of EEG data collection. For all neurophysiologic studies the subjects were seated comfortably in a reclining chair. The experimenter instructed each subject in the relaxation of face, jaw, and scalp muscles in order to minimize electromyogram

(EMG) contamination of the neurophysiologic signals. Subjects were also asked to minimize eye movements and eye blinks as much as comfort allowed in order to reduce signal artifacts due to these behaviors. This instruction continued throughout the recordings as the need arose. The latter was indicated by the visually-assessed quality of the ongoing EEG tracings. The comfort level and alertness level of the subject was continually monitored and assessed by the experimenter, and maximized as much as possible by talking with the subject or allowing breaks in the procedure as needed. Special care was taken in the case of SDAT subjects to maintain their vigilance to the tasks, minimize any frustration, and ensure continued cooperation.

A minimum of 30 four-second-long epochs of eight-channel EEG data were collected using the FFT software in each of following three experimental conditions relevant to this study:

> Resting, eyes closed. Subjects were asked to relax with eyes closed, minimizing eye movements.

Resting, eyes open. Subjects were asked to relax and minimize eyeblinks while fixing their gaze on a picture presented on a video graphics display.

Listening to speech, eyes closed. Subjects were asked to follow the eyes closed instructions while listening to an audio tape of the experimenter reading an editorial from the USA Today newspaper, as presented through headphones. The tape was briefly previewed for each subject prior to running this condition in order to adjust the volume to an audible and comfortable level.

Analysis

The medical history data and several of the neuropsychologic tests used do not have existing or inherent numeric scores. While the number of subjects in this study are certainly far too few to allow for creation and standardization of a new testing battery, some method for comparing the results derived from these data across subjects and groups was needed. As the CBRS form (described below) already made use of a five-point scale, it was used as a guide in the creation of criteria for five-point scales for those subtests which lacked standard scores.

Scoring of medical history and prescribed drug information. See Tables 3 and 4 for summaries of the scales used to score the medical history and the prescribed medication history data, respectively. As can be seen, the scores were based on the severity of potential effects on the neurophysiologic measures.

Scoring of psychometric and neuropsychologic tests. The WAIS-R subtest scores were converted to age-corrected Scaled Score Equivalents of raw scores. For subjects older than the maximum WAIS-R standardized age group, the oldest group was used.

The MMS and its subtest, the MSQ, are simple counts of correct answers out of 30 and 10 respectively.

Save for a few demographically-oriented questions, each item of the CBRS consists of a description of a potential problem behavior that might be exhibited by the patient. The caregiver completing the form must check off the most relevant column of the provided five-point scale.

Table 3

Scoring of Medical Conditions

Numeric Score	Probable Effect on EEG or Evoked Response	Scoring Criteria
1	No effect.	Negative history
2	No effect likely.	Minor positive history (condition which almost certainly has no effects, is untreated, or far in past)
3	Possible effect.	Moderate positive history (potentially serious condition or one known to affect, at a moderate or controlled level in this subject)
4	Definite effect.	Positive history (current conditon with known minor or uncertain effects)
5	Severe effect.	Positive history (current condition with known severe effects)

Table 4

Scoring of Currently Prescribed Medications

Numeric Score	Probable Effect on EEG or Evoked Response	Scoring Criteria
1	No effect.	No medications.
2	No effect likely.	Medication with no known effects.
3	Possible effect.	Medication with uncertain effects or known only at higher levels.
4	Definite effect.	Medication with known but minor to moderate effects.
5	Severe effect.	Medication with known severe effects.

The criteria for the five-point scale are summarized in Table 5. Thus, for each problem behavior described, the higher the score, the more nearly that behavior describes a characteristic of the patient under study. The CBRS has been standardized into several subscales and a dementia profile created. The form used in this study was an intermediate form no longer available, then called the Memphis Dementia Rating Scale. See Appendix B for a copy of this instrument and a summary of its standards.

The subscales are: Memory, Language, Need for Routine, Orientation, Denial, Suspiciousness, Apraxia, Agitation, Dementia, Neurological, Depression, Higher Cognitive, and Ischemia.

As used in the Halstead-Reitan Battery, the Trailmaking A, Trailmaking B, and the Aphasia Test are not scored numerically. For purposes of this study, a five-point scale was created in terms of how difficult the test was for the subject. Criteria for this scale are shown in Table 6.

Table 5

Scoring Criteria for Cognitive Behavior Rating Scale (CBRS)

Numeric Score	Criteria
1	Not at all like the person
2	A little bit like the person
3	Moderately like the person
4	A lot like the person
5	Extremely like the person

Table 6

Scoring Criteria for Halstead-Reitan Neuropsychological Battery

Numeric Score	Difficulty level of task	Scoring Criteria
1	No difficulty	Performed within time norms without errors.
2	Minor difficulty	One error or minor time overrun.
3	Moderate difficulty	2 or 3 errors, minor time overrun (but could do).
4	Severe difficuly	More than 3 errors, major time overrun, some idea how to do.
5	Failure	Could not do task, or did not attempt due to severity of dementia.

Processing of FFT power spectral analysis.

The process of analyzing the stored FFT PSD data from subject runs proceeded in three steps, corresponding to the functions of the three processing programs of the system. These were a program to encode artifactual epoch information from the visual inspection procedure into database files, a program to display the PSD data, and a program to read the PSD data files and compute the measures to be used in testing the hypotheses of this study.

Removal of artifactual epochs from analysis. All EEG recordings are contaminated by sporadic artifacts to a greater or lesser degree. With proper recording techniques, few artifacts are induced by the equipment itself; most artifacts are subject-induced. The most common subject-induced artifacts are due to EMG activity from the muscles of the scalp, jaw, and forehead (the frontalis, temporal, and masseter muscles). Electro-oculogram (EOG) signals from eye movements, spike potentials from eye blinks, and large potentials from gross head movements can also be

common, particularly in subject groups unable to comply well with instructions for minimizing such effects, as in the demented group under study here. Equipment artifacts can be due to excessive environmental electronic noise and signal pops and baseline sways, both due to problems at the electrode-to-skin interface.

It was found that both the normal subject population and the SDAT population were prone to producing signal artifacts. The OPEN condition was particularly troublesome, as it made eyeblink artifacts inevitable. If the group of normal controls used in this study is typical, it would seem likely that a general feature of the older population may be chronic jaw and forehead muscle tension. It was often difficult to guide subjects into a sufficiently relaxed condition for the collection of EMG-free samples. As mentioned above, the SDAT population was particularly prone to artifacts due to gross head movement, eye movement, and eyeblinks.

If reliable information is to be obtained from the application of the FFT technique to EEG data, very stringent artifact rejection criteria must be used in

order to prevent FFT analysis of artifactual data. All of the possible artifact types contain a significant amount of power in the 0.25-32.00 Hz spectrum of interest, often much more power than that of any genuine EEG component. Moreover, application of the FFT algorithm can produce types of artifact inherent in this technique. Chief among these is one which is due to the fact that the algorithm actually computes its spectrum over the range of 0.25 to 64.00 Hz, with the 32.25-64.00 Hz half being "folded back" in mirror image over the 0.25 to 32.00 Hz spectrum. Any incoming data producing genuine frequency information in the upper half of the spectrum is computationally and artifactually transformed to appear in the lower half of the spectrum. Ideally, this effect would be minimized with preprocessing low-pass filters set at 32.00 Hz (or some lower value, determined by the real spectrum of interest). Such filters were not available for this study. The extremely low (0.25-2.00 Hz) and high (>20.00 Hz) frequency portions of the spectrum are of particular concern, due to their sensitivity to eye movement and EMG artifacts respectively. The software available to this project was not able to detect and

reject artifactual epochs satisfactorily. It was necessary to apply visual inspection of each individual epoch in order to do so. This was made possible by the use of a marker channel on the EEG polygraph, which was driven by the data collection and FFT production software, to mark the start and end of each epoch.

The EEG tracings were visually inspected epoch-by-epoch for artifacts by the experimenter in a blind fashion. The group and subject number identifications were covered on all of the EEG records, the records scrambled, and a new subject scoring identification number was written on the cover sheet. The records were then inspected by channel and epoch for artifacts, with the results marked on score sheets by scoring ID number. Once the entire set of records was scored, the scoring ID numbers were decoded into true subject ID numbers by uncovering the original top sheet. The information from the decoded score sheets was then entered into a rejected-epochs disk file for each subject. All subsequent analysis of the raw FFT data files referred to the rejected-epochs files to determine the good epochs for that subject.

As a result of this procedure it was found that the number of remaining good epochs at an individual

channel level was highly variable, with numerous subjects having very few remaining good epochs in the frontal four channels most subject to EMG and eyeblink artifacts. As it would be highly desirable for the subsequent analyses to be based on epochs of data derived from multiple channels concurrently, and such a requirement placed on all eight channels would eliminate a large number of the subjects, it was decided that channels one through four should be dropped from further consideration. While unfortunate, it was felt that this would have a minor impact on questions relating to the main hypotheses, as the activity of interest, the DOR, is by far most detected in the posterior four channels.

Therefore, for purposes of this study, concurrent good epochs of data on all four posterior channels were required for an epoch to be considered good overall. Even at this level, several subjects had very few good epochs left. As computations of variance were necessary for hypothesis testing, some minimum number of good epochs per condition would be needed for such computations to have any validity. Practical considerations of how many subjects would be lost to analysis at different good-numbers-of-epochs criteria

were balanced against estimations of absolute minimum number needed. A criterion of five good epochs was settled on, with the actual minimum in one case being six good epochs.

Display of FFT power spectra. The display program could produce output on a color video graphics monitor or on a X-Y pen plotter. Compressed spectral array plots of all good epochs, grand average epoch curves and point-by-point amplitude standard deviation curves for each channel could be displayed, as seen in Figures 2 and 3 (p. 33 and p.35, respectively). Visual inspection of these displays was used to ensure further that all artifactual data had been eliminated from the analysis.

Computation of FFT-derived measures of DOR activity. The set of measures derived from the FFT power spectra, described above, were computed for each good epoch and stored to disk by running a final program which read the PSD data files with reference to the artifactual epochs database files.

III. RESULTS

Considerations

The choice of subjects and conditions actually used in each of the succeeding data analysis steps was influenced by the criterion for a minimum of five artifact-free epochs of EEG data per activity condition (CLOSED, OPEN, LISTEN). The normal control group lost two subjects and the AD group lost one subject at this stage, because they had good data in fewer than two of the activity conditions. Several subjects with good CLOSED data had insufficient data in either one of the OPEN or LISTEN conditions. Parallel analyses were done with slightly different sets of subjects when comparing the CLOSED condition pairwise with the OPEN or LISTEN condition, so that identical sets of subjects were compared across condition pairs. As a result, the group data for the CLOSED condition will hereafter be referred to as two separate subconditions, CLOSED/O for the set of CLOSED condition data from subjects with good OPEN data, and CLOSED/L for the set of CLOSED condition data from subjects with good LISTEN data. The resulting ns for each analysis are summarized below:

Condition	SDAT	Normal
CLOSED	9	8
OPEN, CLOSED/O	8	7
LISTEN, CLOSED/L	8	8

Equal ns do not necessarily imply identical members across groups/conditions.

The three subjects lost due to EEG artifact were also removed from the groups used for analysis of the subject background, neuropsychologic, and psychometric data. The Wilcoxon rank sums test was the source for all significance values quoted for the non-EEG measures.

Subject Background Data

Demographic Data

The two groups did not significantly differ in their numbers of males and females or in the mean number of years of education. The SDAT group mean was older on average than the normal control group (72.56 years vs. 63.75 years, $p = .018$).

Medical History Data

The medical history data is summarized in Table 7. The only category in which either group averaged over 2 on the five point scale was in the Medication category for the SDAT subjects. The group difference in that category was the only significant difference (2.778 vs. 1.375, p = .011).

Neuropsychologic and Psychometric Tests

Mental Status Questionnaire and Mini Mental Status

The mean MMS and MSQ scores for the SDAT group were 12.67 and 4.11, respectively. The corresponding scores for the normal group were 26.25 and 9.88. The difference in scores between groups was significant, $p < .01$ for both tests. Interestingly, the rank correlations for these two tests did not reach significance in either group (r = .1067 for SDATs, r = .1653 for normals),

Table 7

Medical History Data

	GROUP			
	AD		NC	
	MEAN	SD	MEAN	SD
NEUROLOGICAL	1.667	0.866	1.250	0.707
CARDIOVASCULAR	2.000	1.000	1.375	0.518
METABOLIC	1.444	0.726	1.125	0.354
TRAUMA	1.000	0.000	1.250	0.463
MEDICATIONS	2.778	0.833	1.375	0.518 *

* $p < .05$
AD = Alzheimer's Disease subjects
NC = Normal Control subjects
SD = Standard Deviation

despite the fact that the MSQ is a subtest of the MMS.

Halstead-Reitan Subtests

The results from the three subtests of the Halstead-Reitan Neuropsychological Battery, for which a five point scale was created, are shown in Table 8. The normal control group had virtually no problem with any of these tests, as shown by group means less than 2.0. The SDAT means were all above the 3.0, moderate problem with task level, with the Trails B score approaching 5.0, severe problem with task (actual mean of 4.778). The group differences were all significant at the $p < .01$ level.

Wechsler Adult Intelligence Scale-Revised

See Table 9 for the WAIS-R results. The average Scaled Score Equivalent value expected from the norms for the WAIS-R is 7.0. As can be seen, the normal group averaged above that number

Table 8

Halstead-Reitan Neuropsychological Battery Subtests Data

	GROUP				
	AD		NC		
	MEAN	SD	MEAN	SD	
TRAILS A	4.111	1.269	1.000	0.000	**
TRAILS B	4.778	0.441	1.500	1.069	**
APHASIA	3.556	0.726	1.625	0.518	**

** $p < .01$
AD = Alzheimer's Disease subjects
NC = Normal Control subjects
SD = Standard Deviation

Table 9

Wechsler Adult Intelligence Scale-Revised (WAIS-R) Data

	GROUP				
	AD		NC		
	MEAN	SD	MEAN	SD	
INFORMATION	3.778	2.728	10.500	3.703	**
DIGIT SPAN	6.444	2.555	10.625	2.973	*
SIMILARITIES	5.667	2.784	12.000	2.619	**
BLOCK DESIGN	4.333	2.784	11.125	2.532	**
OBJECT ASSEMBLY	3.444	3.395	8.500	3.854	*
DIGIT SYMBOL	2.444	2.963	11.875	2.748	**
MEAN WAIS SCORE	4.538	2.198	10.771	1.539	**

NOTE: Scores given are scaled score equivalents of raw scores.

* $p<.05$ ** $p<.01$
AD = Alzheimer's Disease subjects
NC = Normal Control subjects
SD = Standard Deviation

for every subtest and the SDAT group averaged below 7.0 on every subtest. The group differences were all significant at either the $p < .05$ or $p < .01$ levels.

Cognitive Behavior Rating Scale

Table 10 shows the scores for the various CBRS subscales. All group differences were significant ($p < .01$ or better), except for the Neurological and Ischemia subscales. The Ischemia difference was not significant, while the Neurological difference was significant at the $p < .05$ level. It should be noted that the Ischemia subscale in this intermediate form of the CBRS was based on two questions concerning a positive medical history for heart disease or high blood pressure. It was dropped as a separate subscale in later versions of the CBRS. Compare group scores with those of the initial standardization group in Appendix B.

Table 10

Cognitive Behavior Rating Scale (CBRS) Subscale Data

	GROUP				
	AD		NC		
	MEAN	SD	MEAN	SD	
MEMORY	3.326	0.641	1.215	0.112	**
LANGUAGE	2.953	0.580	1.068	0.158	**
ROUTINE	3.296	1.013	1.125	0.291	**
SUSPICION	2.370	1.241	1.041	0.117	**
DENIAL	2.999	1.491	1.041	0.117	**
ORIENTATION	3.409	0.762	1.016	0.046	**
APRAXIA	2.258	0.741	1.000	0.000	**
AGITATION	2.327	0.594	1.101	0.120	**
NEUROLOGICAL	1.417	0.385	1.088	0.072	*
DEMENTIA	2.599	0.466	1.011	0.016	**
HIGHER COGNITIVE	3.667	0.995	1.050	0.093	**
DEPRESSION	2.259	0.658	1.233	0.388	*
ISCHEMIA	1.833	0.935	1.313	0.704	

* $p<.05$ ** $p<.01$
AD = Alzheimer's Disease subjects
NC = Normal Control subjects
SD = Standard Deviation

Correlations Between Non-EEG Measures

Spearman rank correlations between all pairs of non-EEG measures (background data as well as psychologic testing scores) was done both to check for any strong effects of the subject background characteristics on psychologic measures and to roughly assess the independence vs. relatedness among the psychologic measures. The information revealed by this analysis does not directly bear on the main questions under study here, but will be useful in understanding some of the results of the final section on correlations between EEG measures and non-EEG measures. As such, a complete description of the 37 variable by 37 variable correlation table for each group will not be attempted, but rather, a brief summary of the patterns of $p < .01$ correlations will be given. Unless otherwise stated, all correlations mentioned will be positive correlations.

The normal group showed fewer correlations at this level of significance than the SDAT group,

as well as a somewhat different pattern of correlations. Neither group displayed strong patterns of correlation between psychologic measures and background measures. There were no such correlations in the SDAT group. In the normal group, a positive correlation was found between sex and the WAIS Information subscale score. There were a number of normal group significant or near significant positive correlations between two of the medical history measures, those for history of neurological problems and cardiovascular problems, with a number of the CBRS subscales. Since the normal group data for both of these types of measures remains very near the 1.00 floor on these measures, meaning "no problem" with the associated measure, these relationships are probably not clinically meaningful. Beyond this, the normal data show a few scattered correlations between subscales of given test types (Halstead-Reitan, WAIS, CBRS), but none across test types. Ranking by mean WAIS score correlates with the ranking by the WAIS subscales of Block Design and Object Assembly.

The SDAT data contain several interesting clusters of correlations, including subscales within test types as well as a few across test types. As in the normal group CBRS scores rank relatively independently from the other scores, with only the CBRS Suspiciousness subscale correlating with mean WAIS score and WAIS Digit Symbol, and the CBRS Ischemia subscale correlating with the cardiovascular medical history score. MSQ correlates with WAIS Digit Span, while MMS correlates with WAIS Information. The Trails A, Trails B, and Aphasia scores all correlated significantly or near significantly, and negatively with mean WAIS and WAIS Block Design, Object Assembly, and Digit Symbol. Recall that a negative correlation in this case means a poorer performance on the Trails and Aphasia tests (high score) correlating with poorer WAIS scores (low scores). Trails B correlated negatively with the metabolic disorders history measure. Within the WAIS data, mean WAIS score correlated with Digit Span and Digit Symbol, and nearly significantly with Block design. Block Design, Object Assembly,

and Digit Symbol all correlated pairwise with each other.

FFT of EEG Data

Percent Power Grand Average Epoch Spectra

Figures 5 through 21 are plots of the grand average epoch spectra for each subject used in the following analyses. There are three parts to each figure, showing the four-channel spectra from each of the three stimulus conditions. Each figure is ordered such that the subject's baseline CLOSED condition spectra are in the middle of the page, for ease of comparison with the OPEN condition plotted at the top and the LISTEN condition plotted at the bottom.

Each figure shows the 0.25-32.00 Hz grand average epoch spectrum (the point-by-point mean percent power of all good epochs) for each of the four channels, arranged with the posterior left/right channel pair over the anterior left/right channel pair. Each channel plot

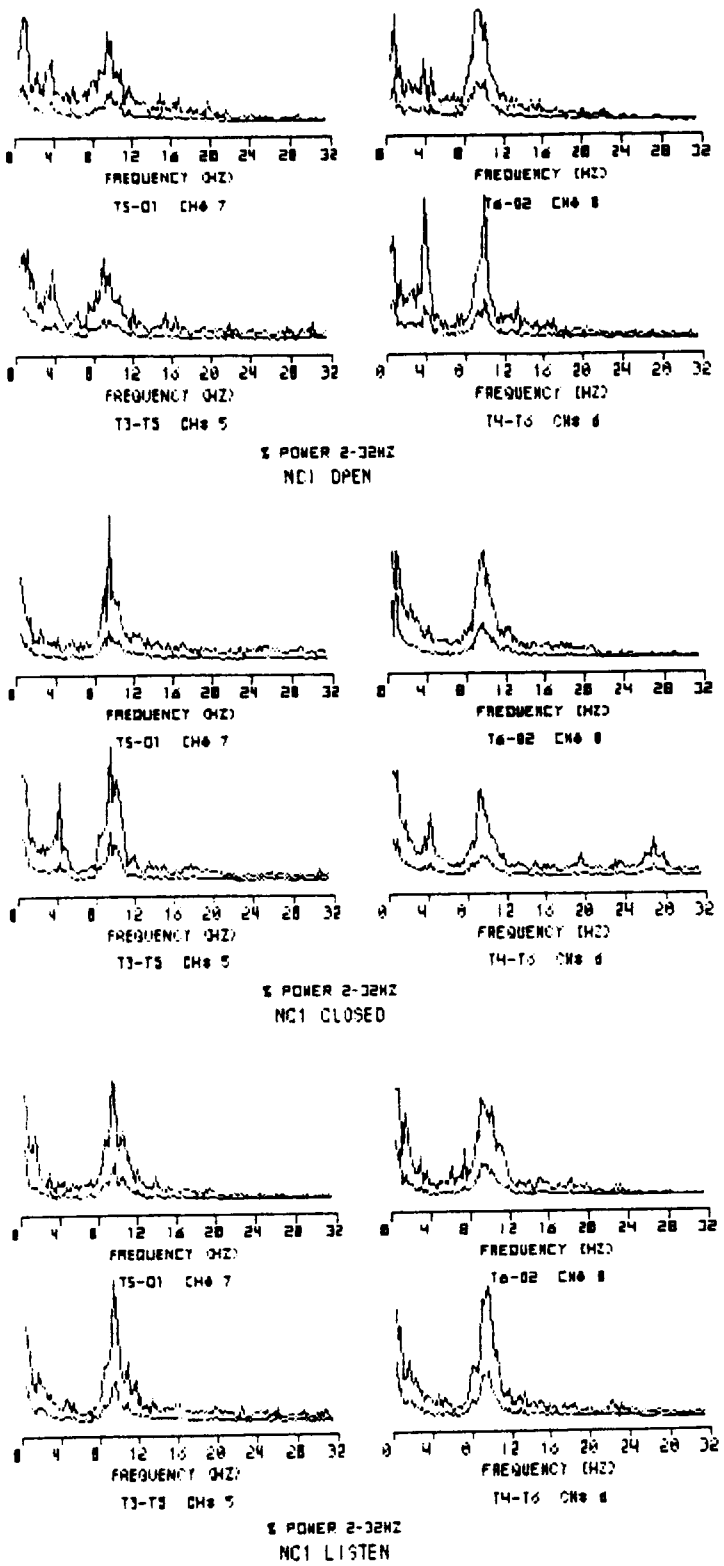


Figure 5. Normal control #1 average percent power spectra.

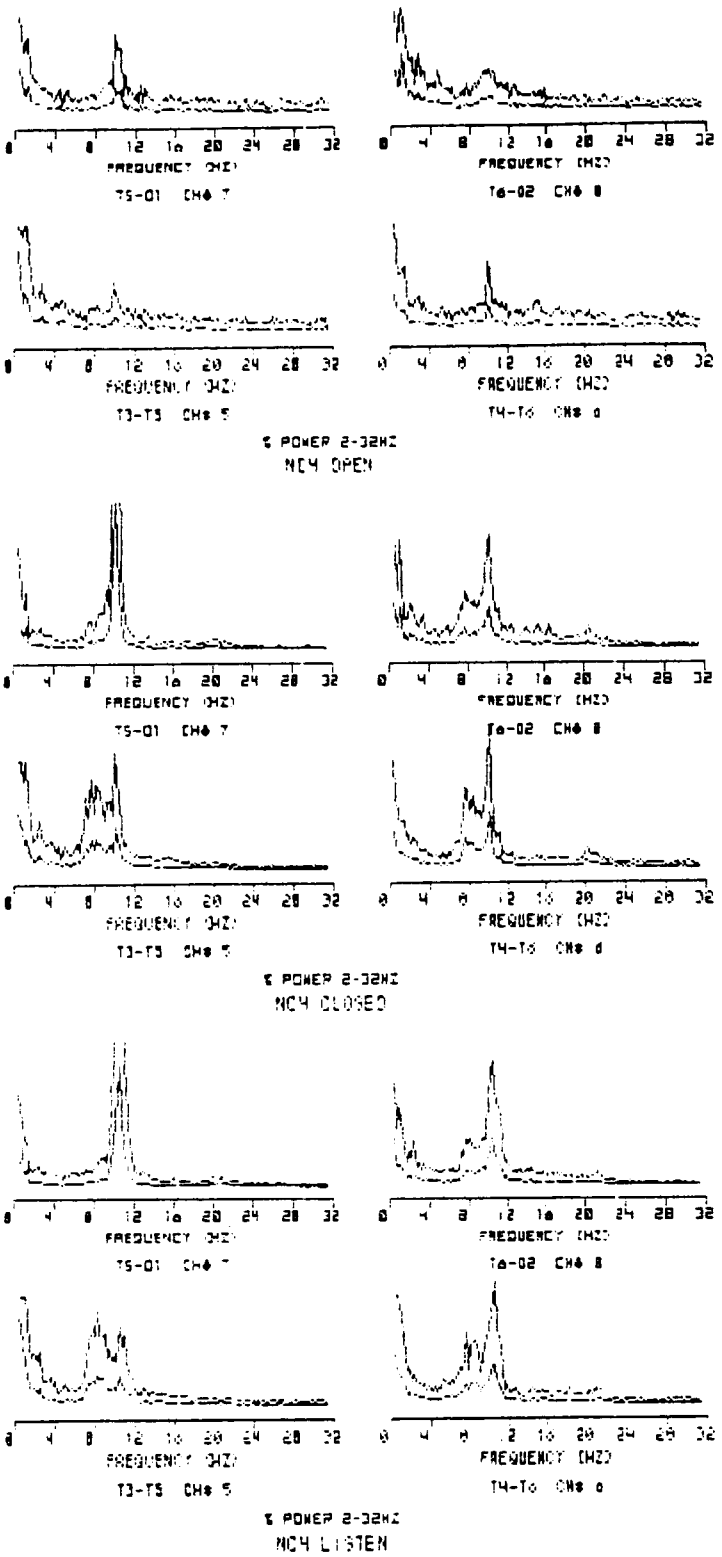


Figure 6. Normal control #4 average percent power spectra.

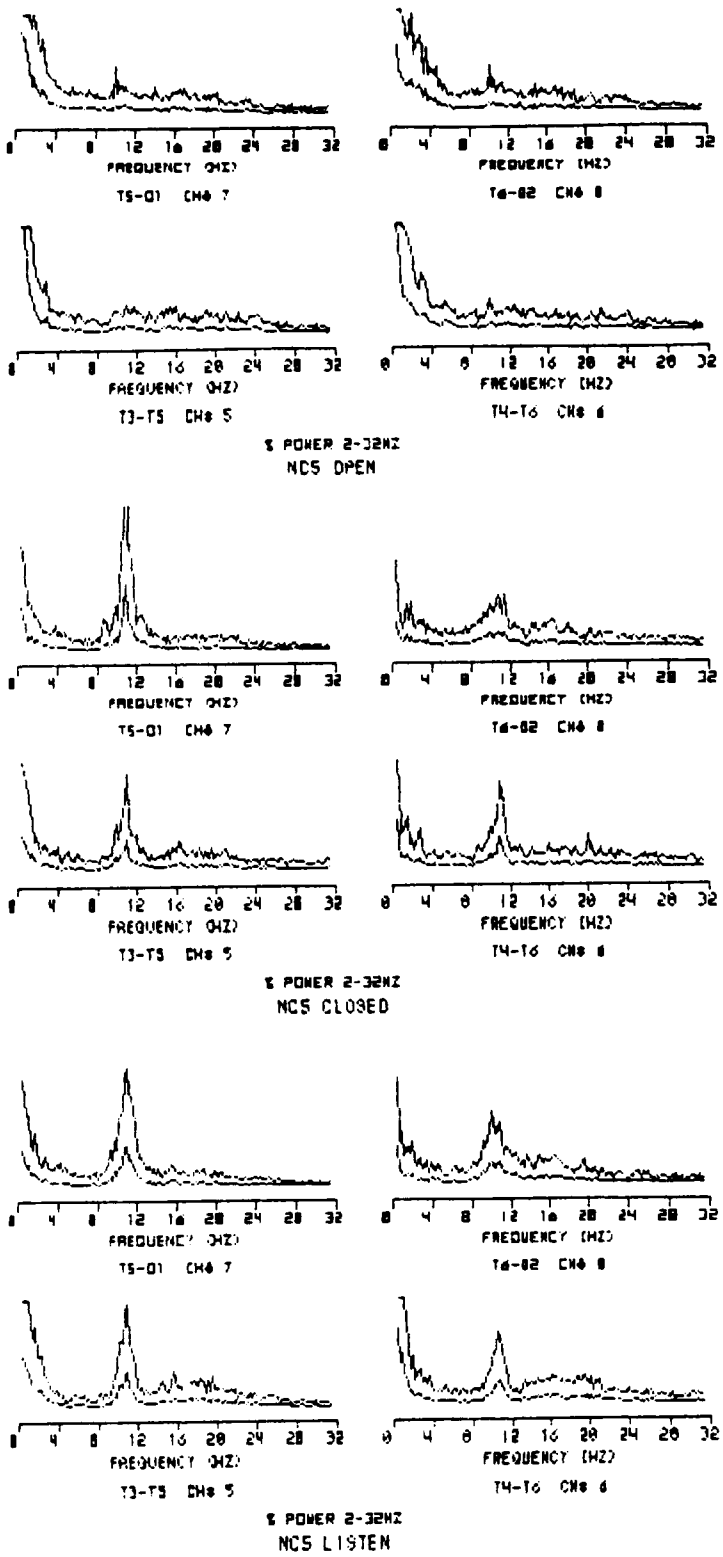


Figure 7. Normal control #5 average percent power spectra.

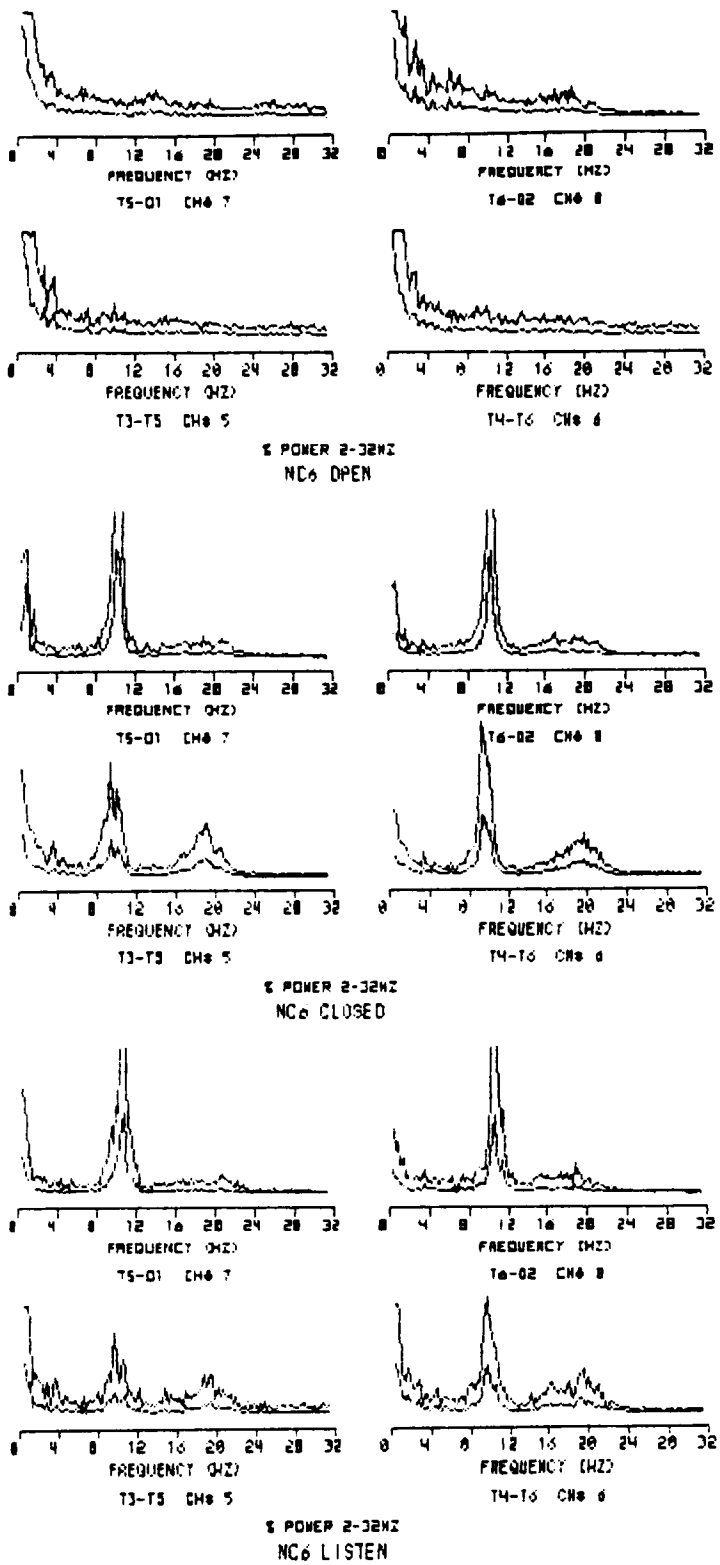


Figure 8. Normal control #6 average percent power spectra.

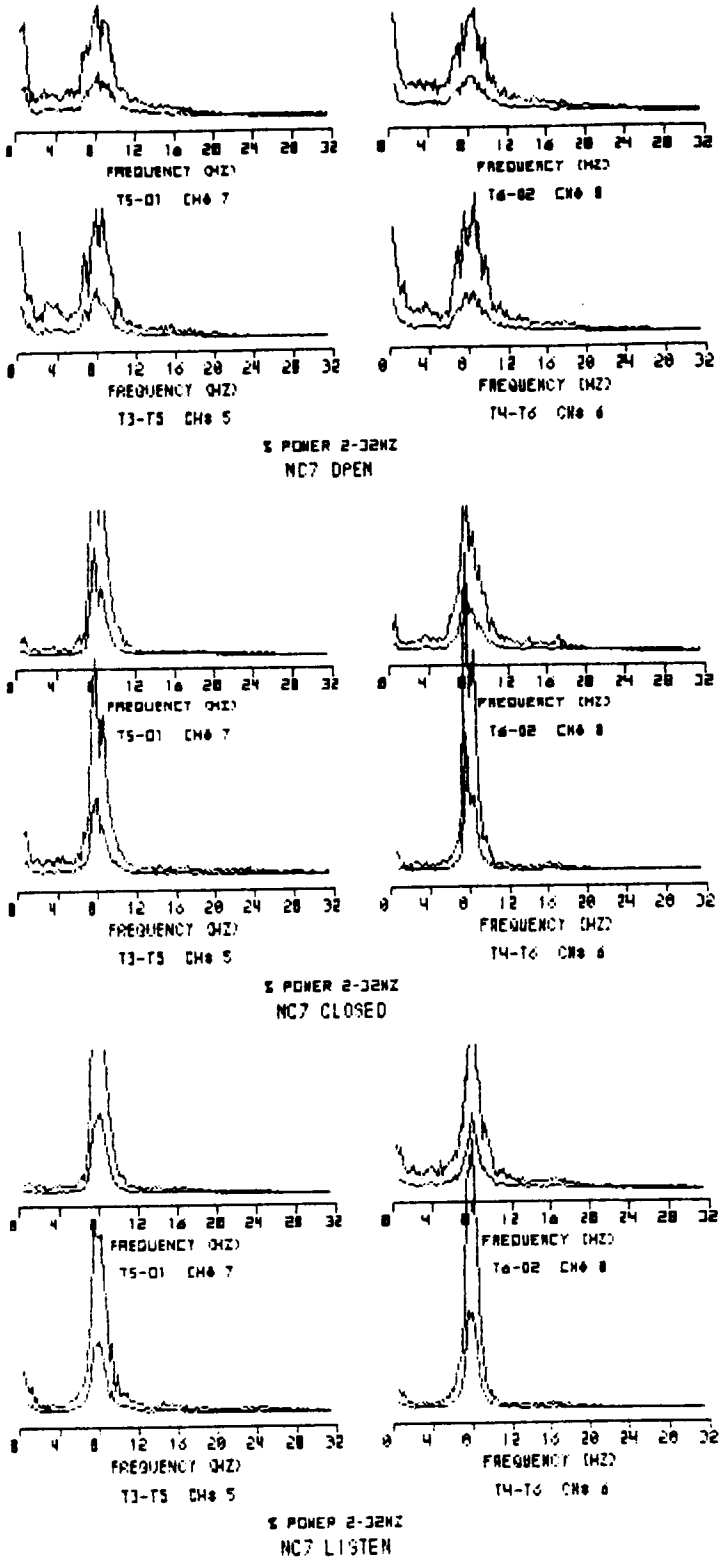


Figure 9. Normal control #7 average percent power spectra.

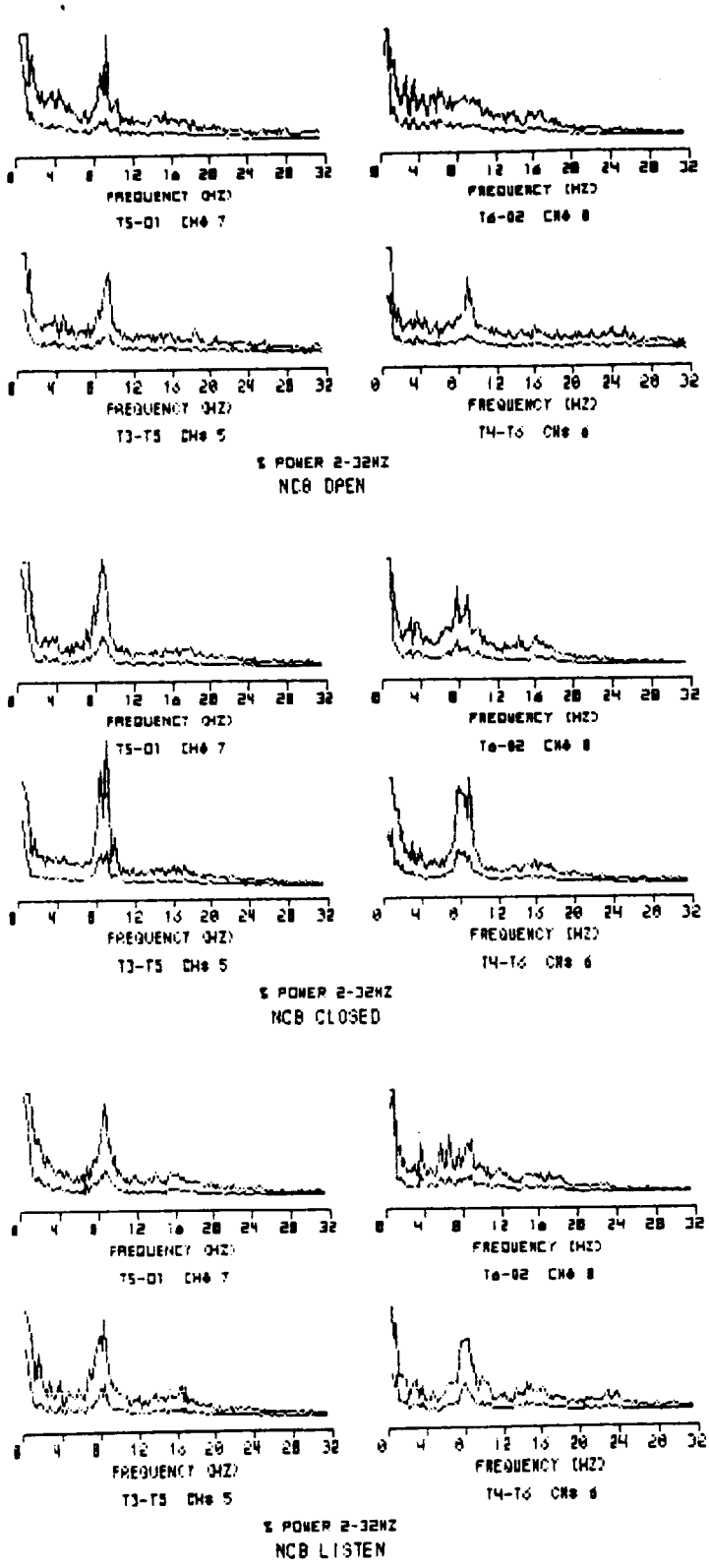


Figure 10. Normal control #8 average percent power spectra.

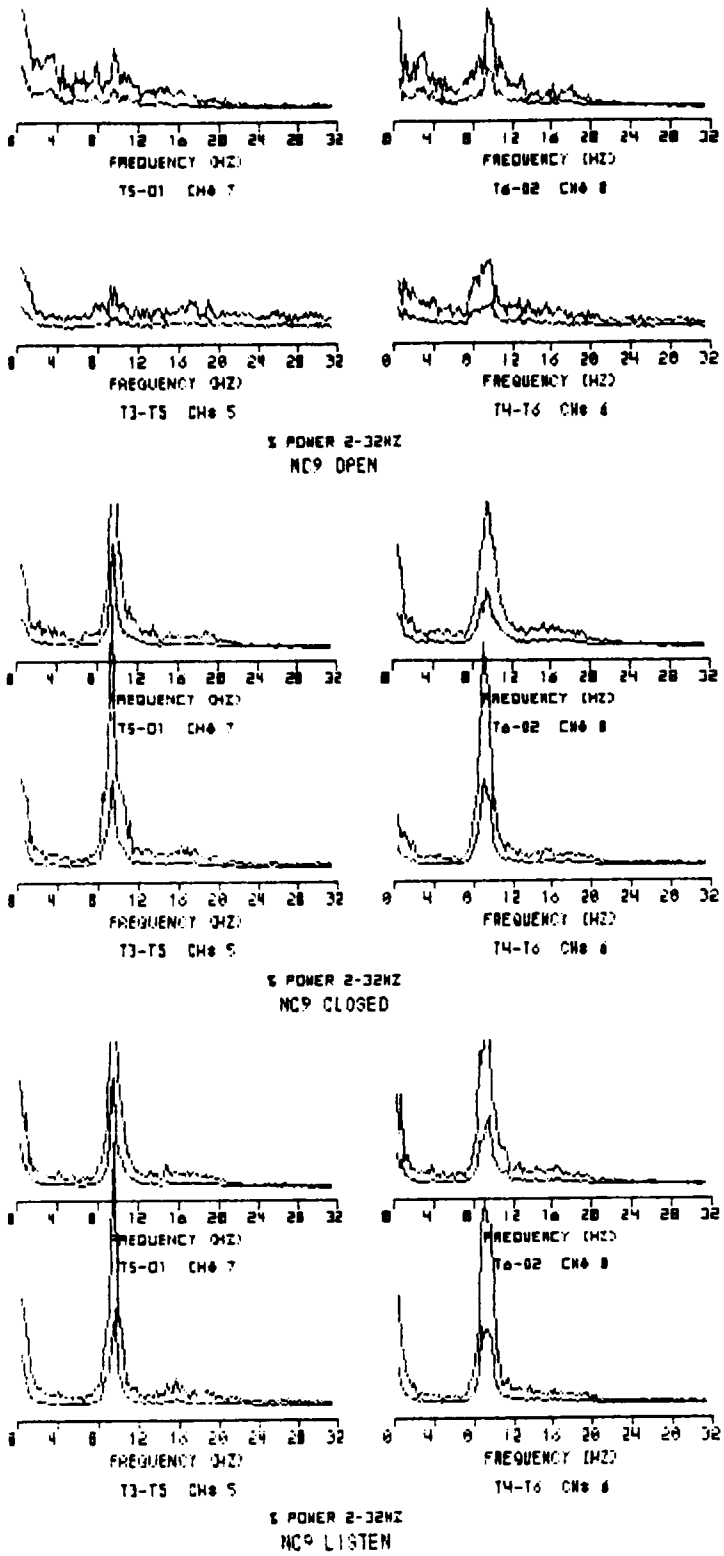


Figure 11. Normal control #9 average percent power spectra.

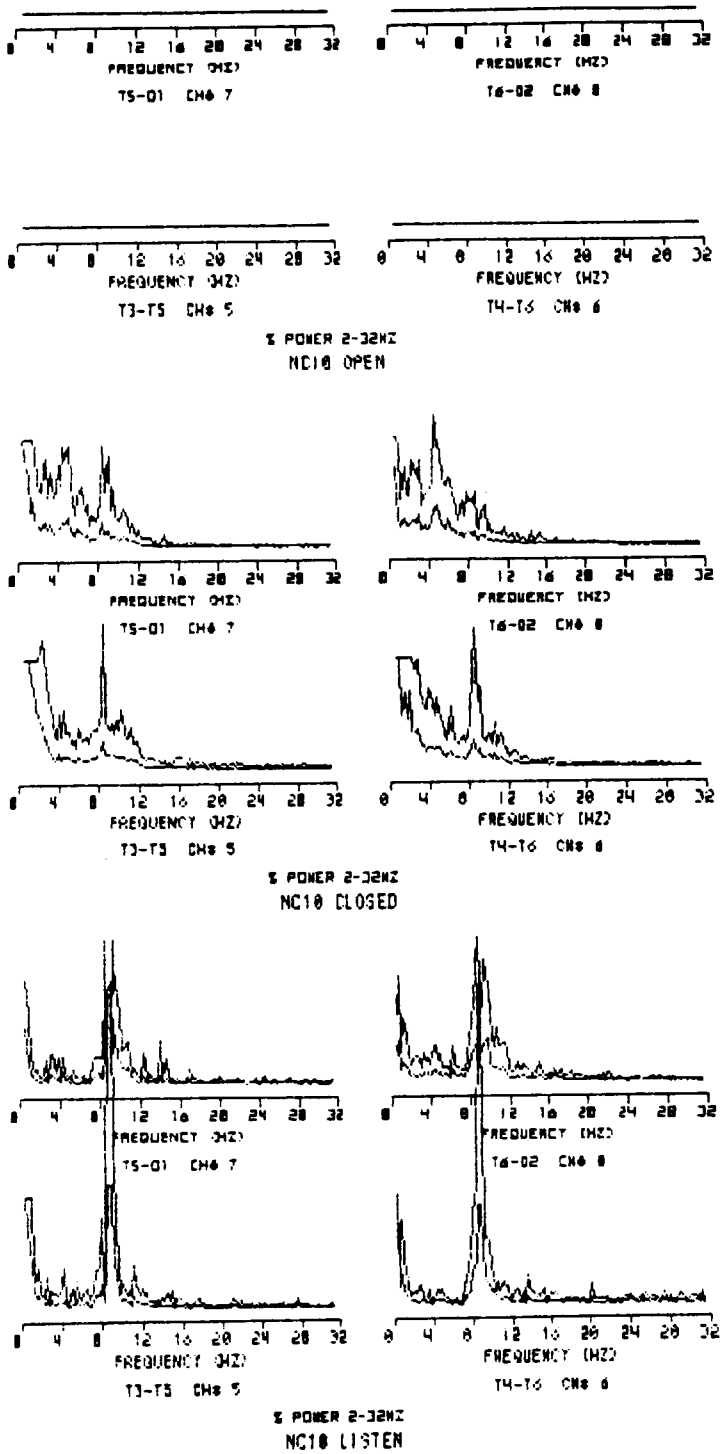


Figure 12. Normal control #10 average percent power spectra.

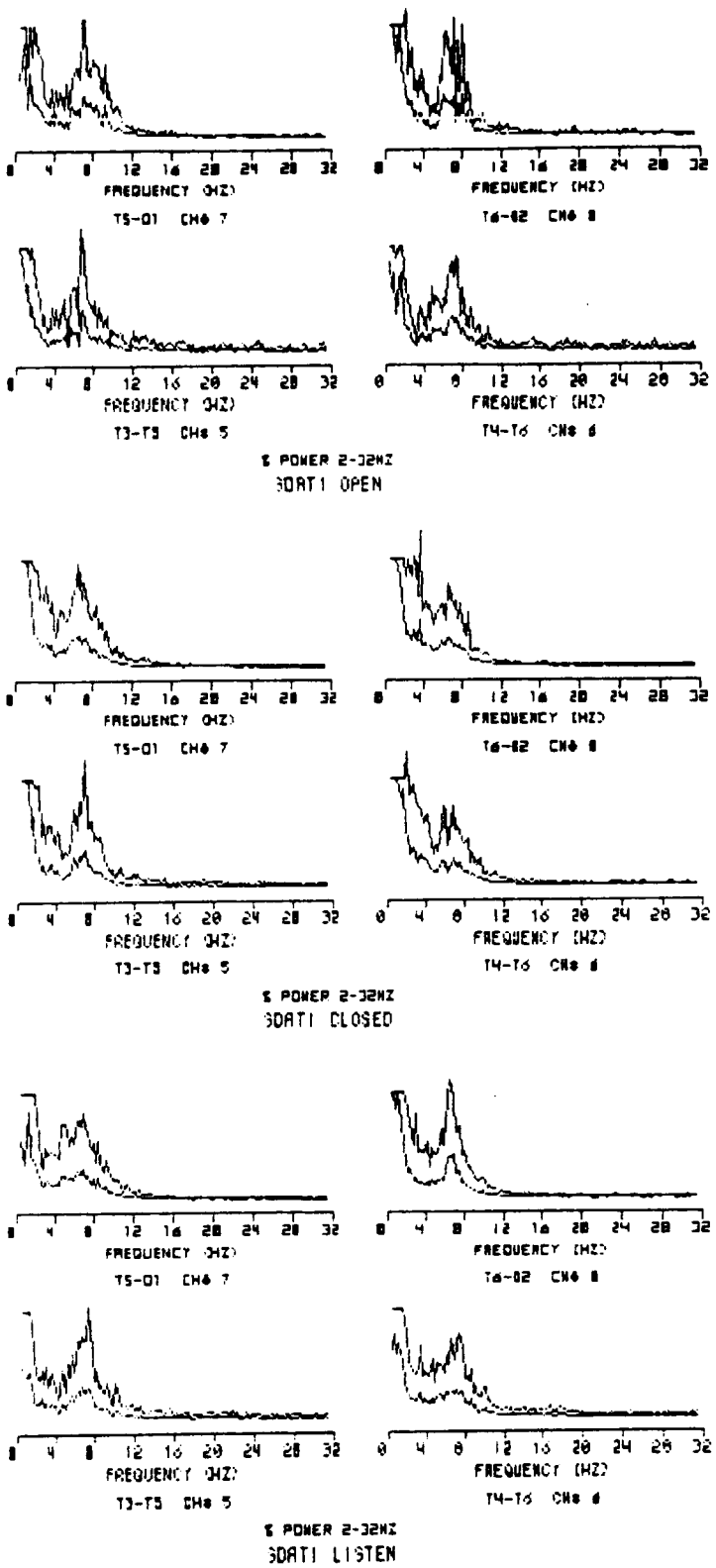


Figure 13. SDAT #1 average percent power spectra.

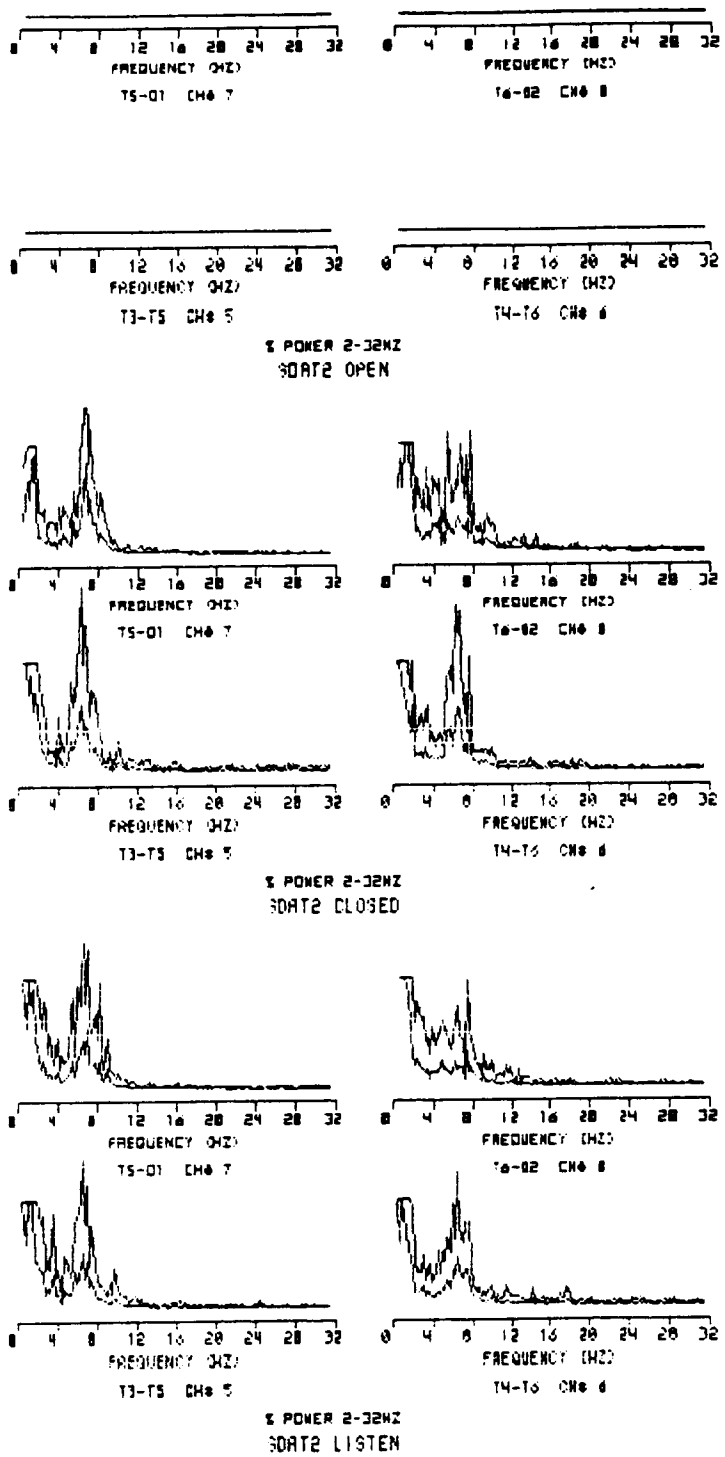


Figure 14. SDAT #2 average percent power spectra.

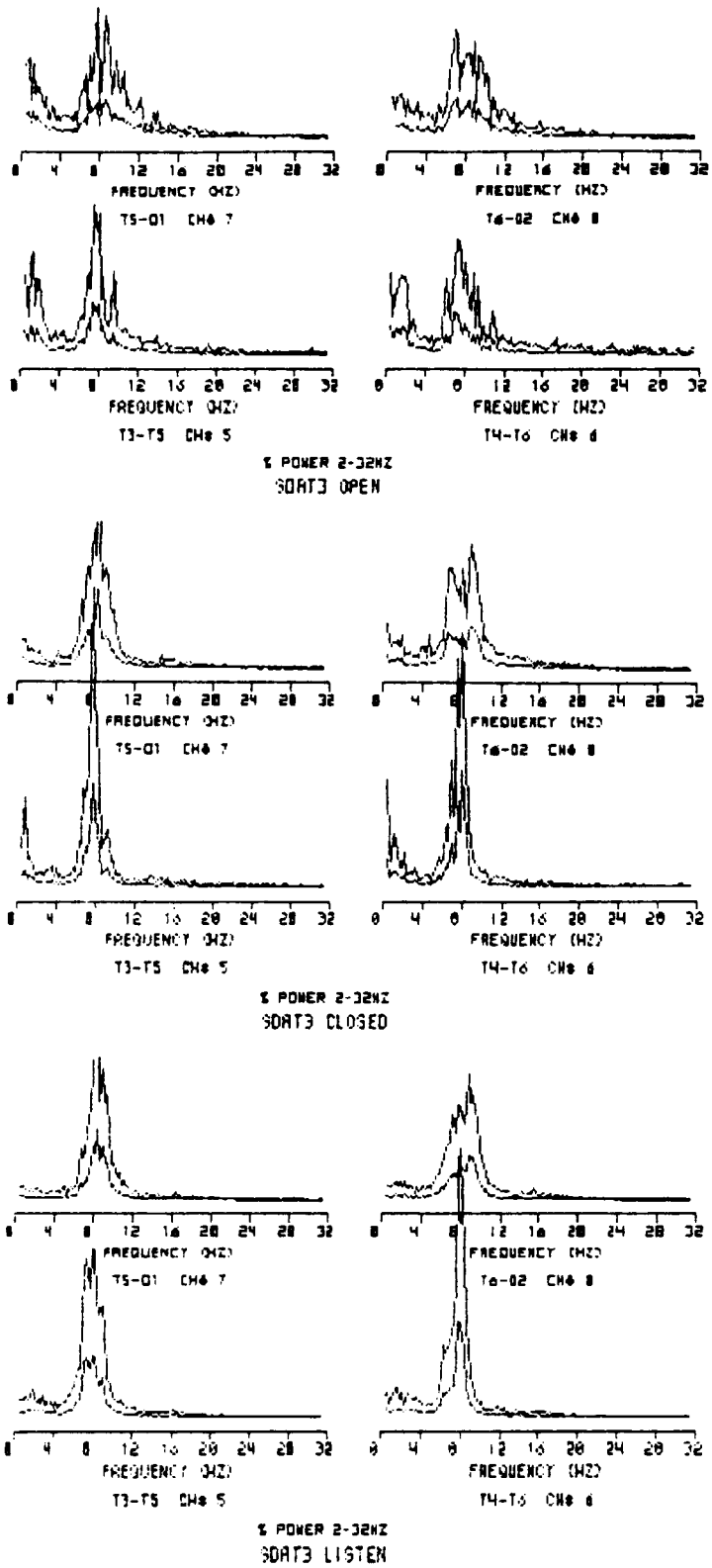


Figure 15. SDAT #3 average percent power spectra.

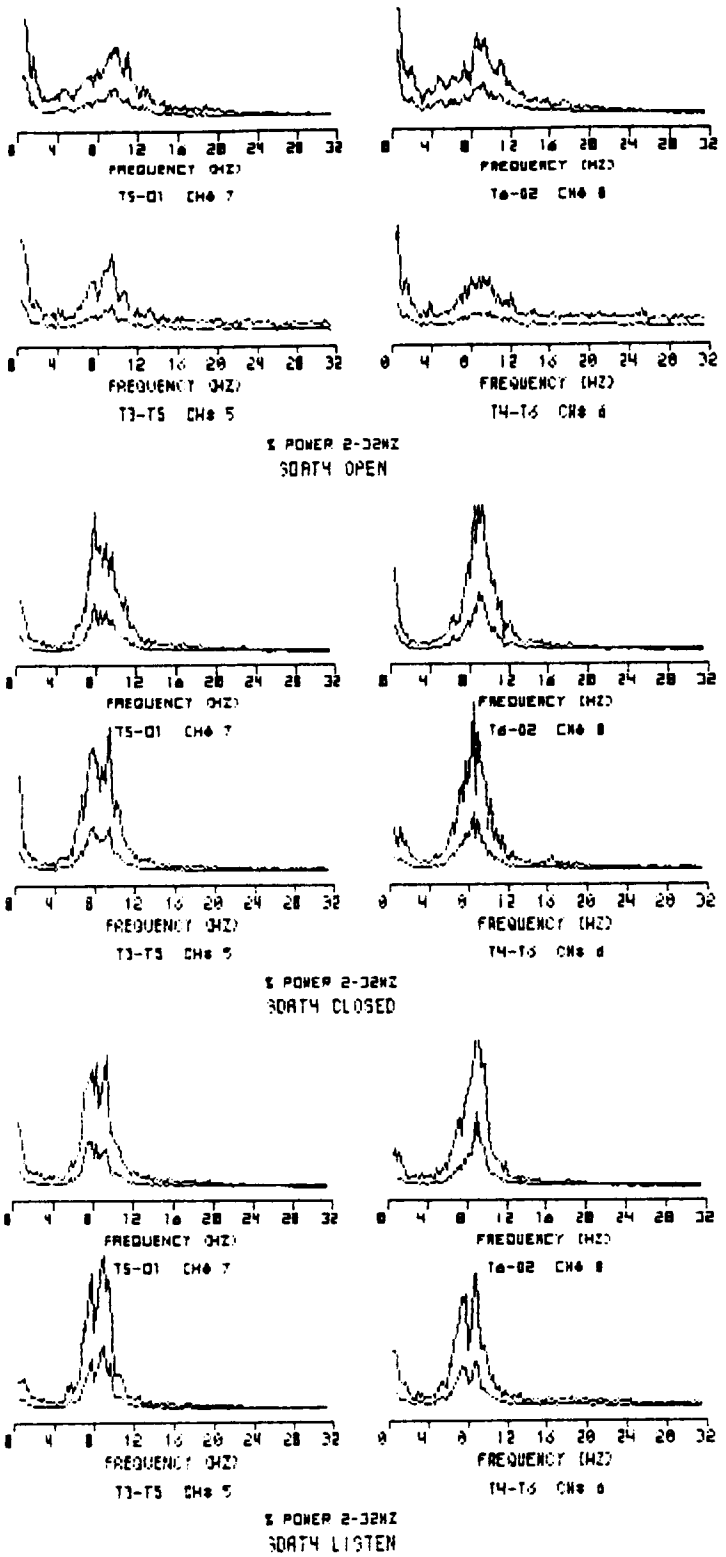


Figure 16. SDAT #4 average percent power spectra.

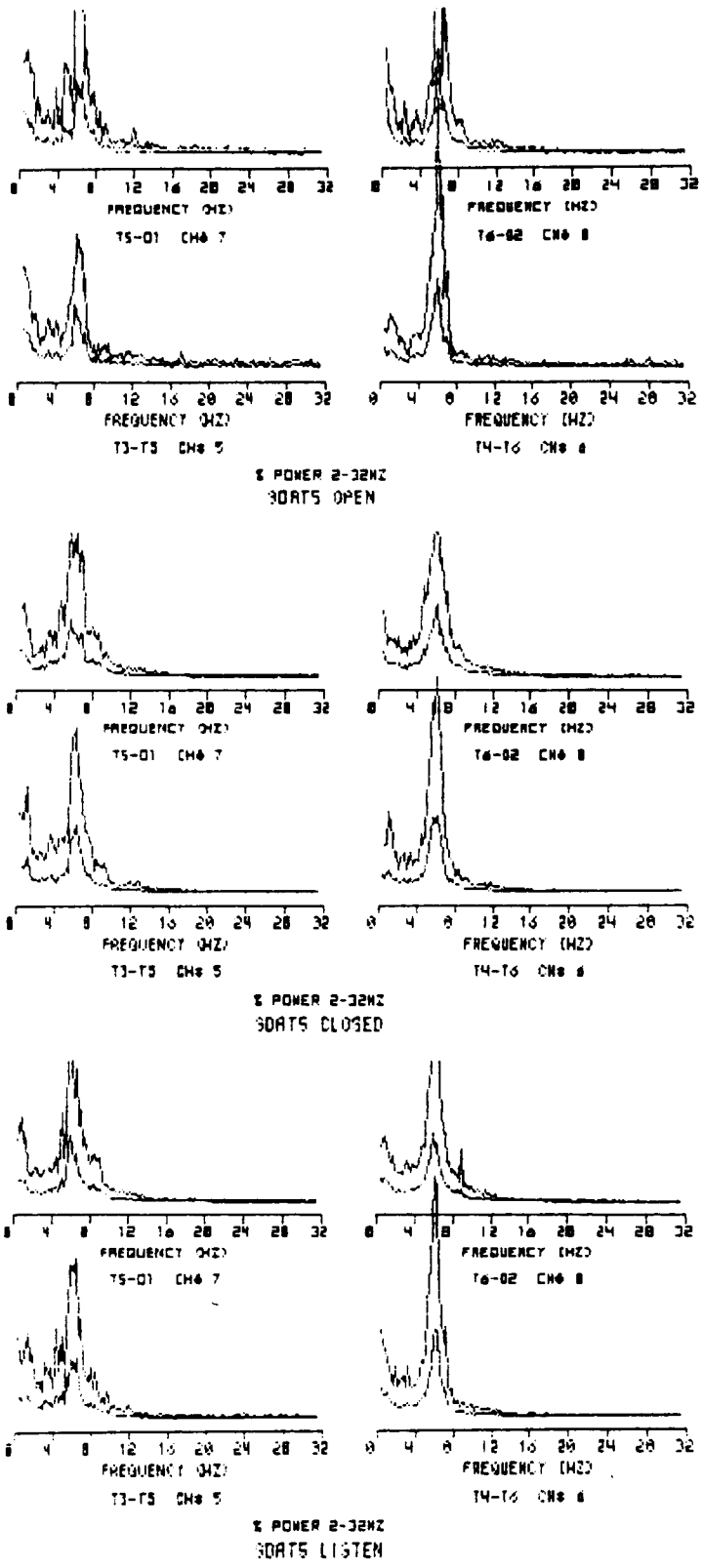


Figure 17. SDAT #5 average percent power spectra.

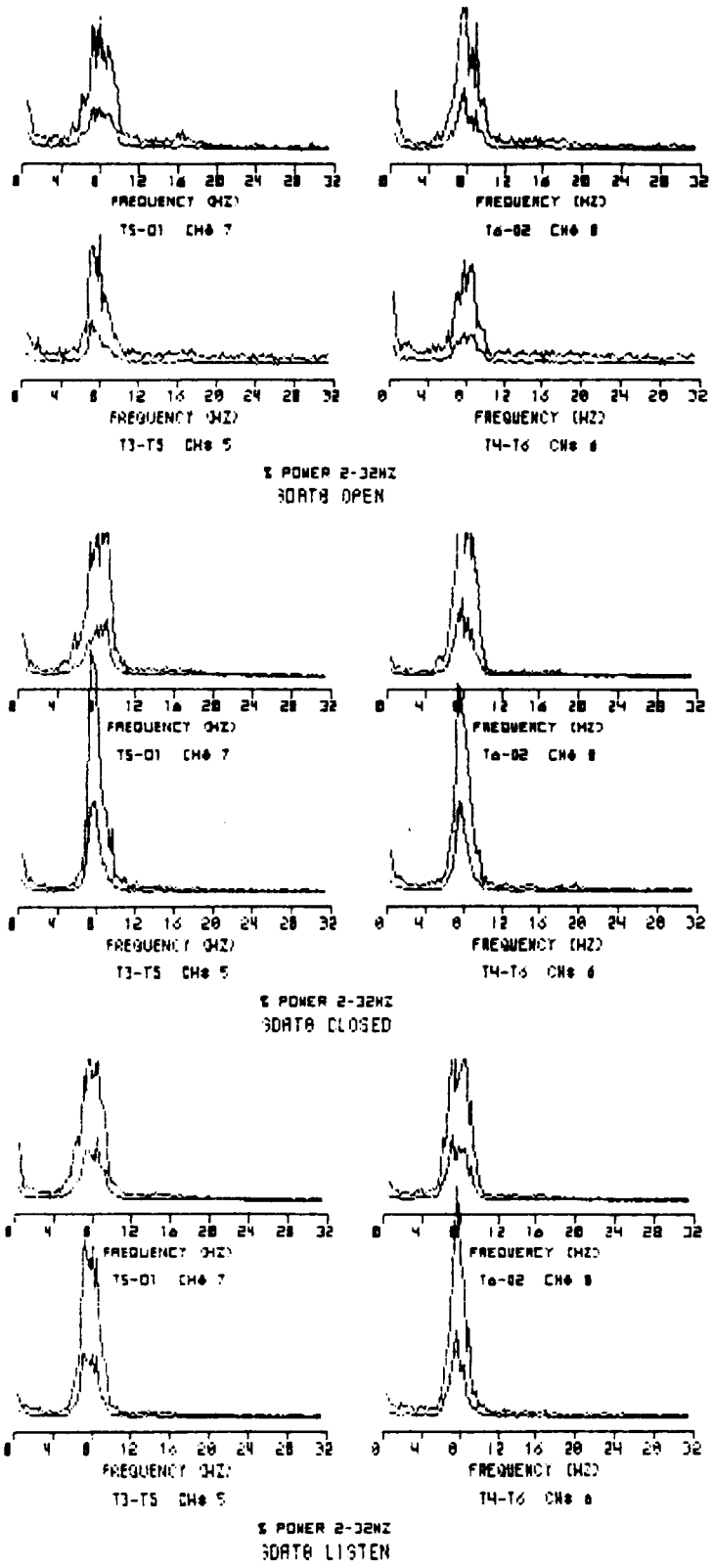


Figure 18. SDAT #8 average percent power spectra.

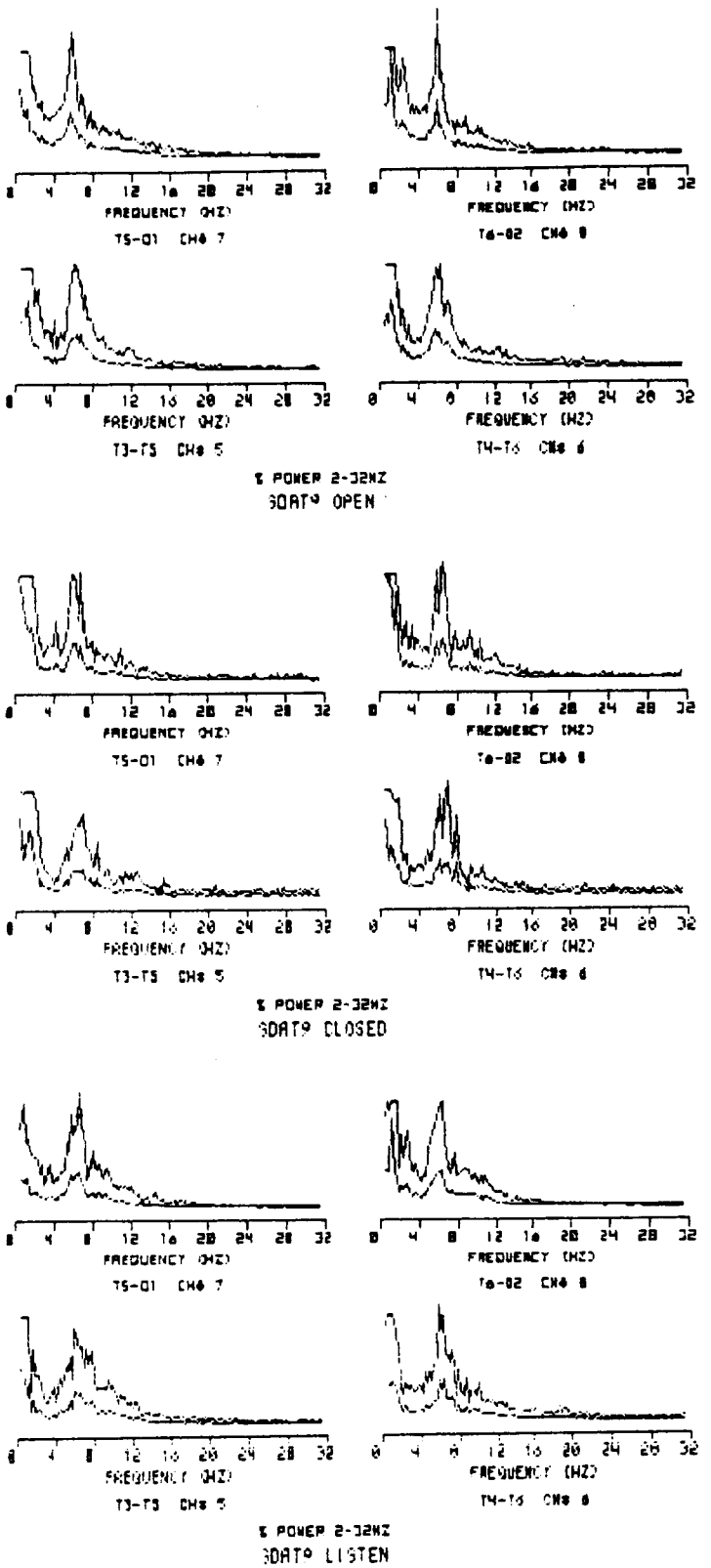


Figure 19. SDAT #9 average percent power spectra.

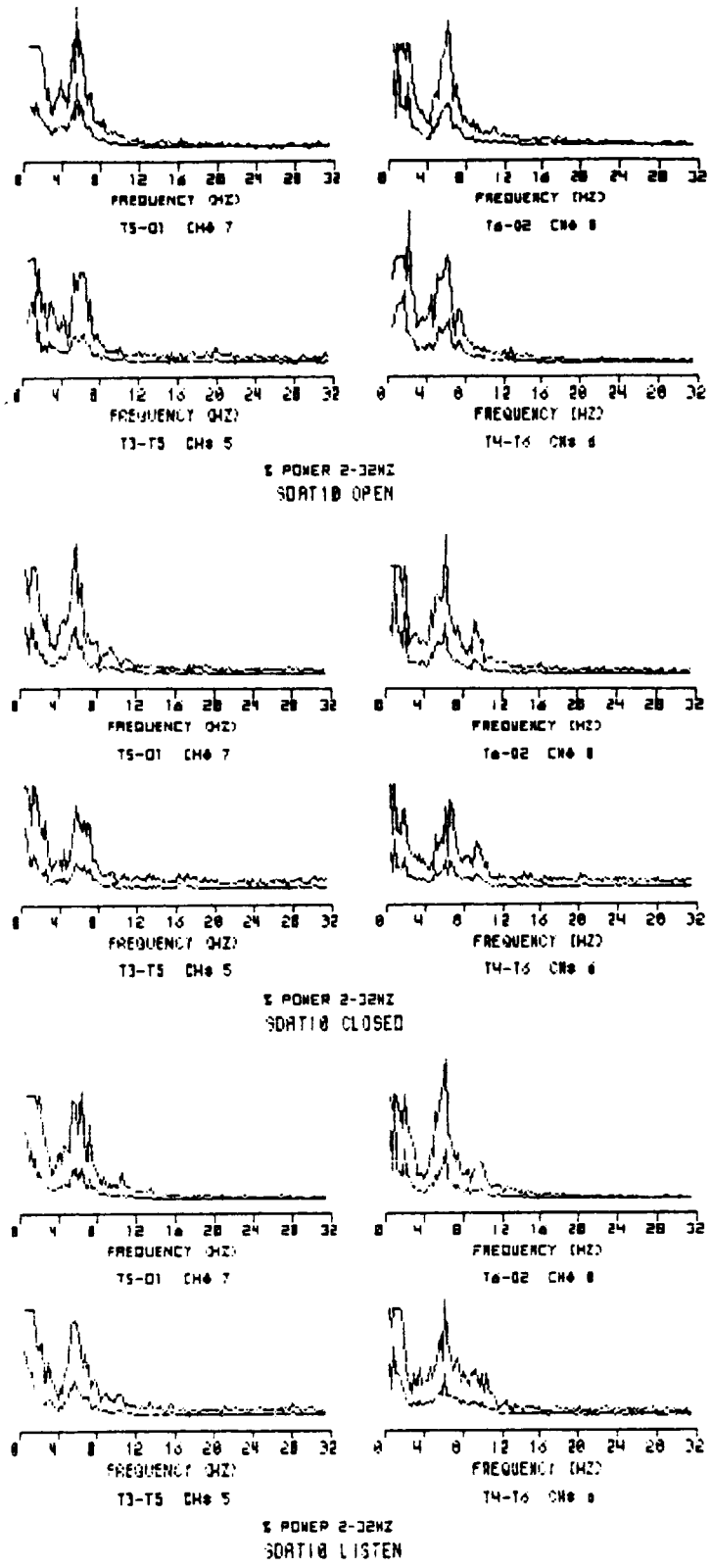


Figure 20. SDAT #10 average percent power spectra.

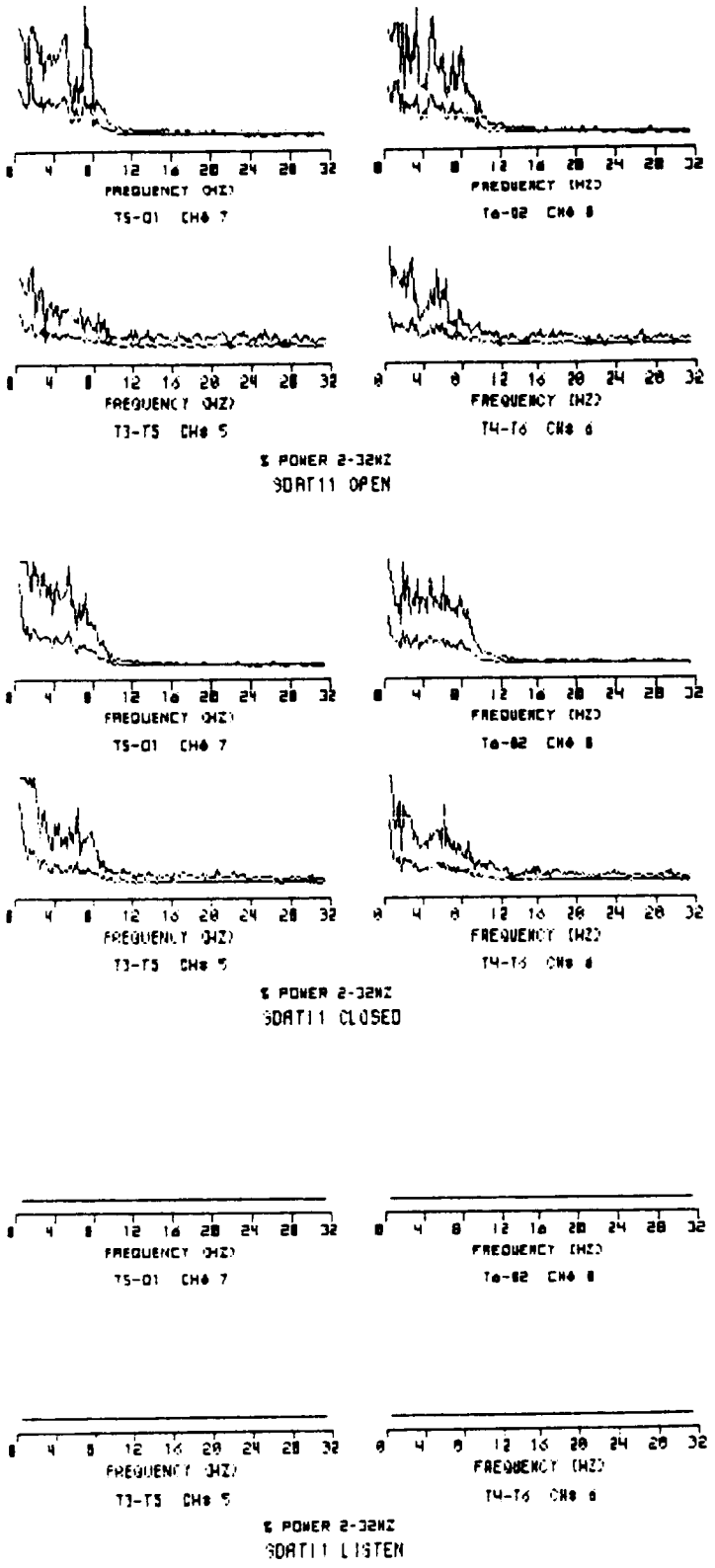


Figure 21. SDAT #11 average percent power spectra.

consists of two curves. The lower curve is the actual grand average epoch spectrum. The upper curve is a representation of the point-by-point standard deviations of each point in the grand average epoch. Each standard deviation point is plotted two standard deviations above the corresponding grand average epoch point.

These figures are presented to provide a visual reference for understanding the FFT measures findings below. Remember, however, that the FFT measures were applied to each individual epoch and the grand average epoch curve may mask underlying interepoch variations. Thus, a direct application of the FFT measures to the grand average epoch would produce somewhat different values than those described below, which are the means of values derived from each epoch.

Analysis Strategy

Mean, standard deviation, and coefficient of variation. The analysis of the EEG-derived data was done by applying the repeated measures analysis of

variance procedure from the SAS System, Version 5 to data sets consisting of each subject's across epochs means, standard deviations, and coefficients of variation values for the thirteen EEG measures for each of the four channels. Prior SAS processing had produced these data sets from each subject's individual epoch data. Overall, a two-stage analysis strategy was adopted. First, tests of each group separately across condition pairs were done to enable examination of activation from baseline effects on the FFT measures. Then across-groups tests were done for each of the three conditions to demonstrate group differences within condition types.

The two types of analyses of variance done, within groups across conditions, and across groups within conditions were designed in order to be able to detect interaction effects by condition or group, as appropriate, and by scalp location. As the normal EEG is highly symmetric bilaterally, and since the DOR would be expected to be maximally seen in the posterior two channels (T5-O1 and T6-O2), additional analyses of variance were done by left/right channel pairs and anterior/posterior channel pairs. Thus, main effect

differences by individual channel location, side, and anterior/posterior pair could be found. Differential effects of group or condition manipulation allowed for the examination of interaction effects at this level.

The ultimate result is that for the main group and condition effects to be discussed below, it is generally possible to determine if a single channel or channel pair is causing the effect. As these channel-level main effects have little bearing on the questions under consideration, save in how their patterns differ between groups, these results will not be presented in detail. Their presence will be noted without associated statistics in the across-conditions, within-groups tests in order to make such group pattern comparisons possible.

The selection of an appropriate criterion for declaring analysis of variance findings statistically significant was problematic and influenced by several factors. The total number of variables studied per group was large (13 variables x 4 input channels x 3 statistic types x 3 activity conditions = 468), and the group size small (varying from seven to nine subjects per analysis). A straight application of a .05-level

criterion was would be clearly inappropriate, as a large number of chance significances would occur at that level. On the other hand, strict application of rules for adjusting p-value criteria for multiple analyses would result in an extremely stringent criterion ($p < .0001$, at least), likely to eliminate virtually all significances, particularly with such small groups.

There were both subjective and objective factors which lent support to the use of a less stringent criterion. Subjectively, a main purpose of this study was to find FFT measures which showed promise worth further investigation. As such, it seemed inappropriate to ignore consistent findings, albeit at a lower level of significance than strictly required. More objectively, there is a source of "internal calibration" of appropriate significance levels within the data set. That is, it can be argued that any of the subtle DOR effects I am searching for would not be likely to display differences at a significance level any higher than that seen for the DOR frequency differences. Assuming that I have chosen my groups properly, the DOR frequency measures should replicate

the long-known DOR slowing effects of AD. By this argument, the significance levels actually achieved in the data set on DOR frequency measures differences ought to represent both an indication of what a "true difference" is for the data set and of what the ceiling of effect magnitude is likely to be for the data set. Most of the SDAT vs. normal DOR frequency differences are significant at the $p < .01$ level.

Therefore, in consultation with a statistician, it was decided that a reasonable compromise would be to attend to all findings at the $p < .01$ level or better, while reserving more definitive statements of significance to those of $p < .001$. As an additional safeguard against overinterpretation of the results, it was also decided to use two-tailed test criteria throughout, though the hypotheses would allow for the use of one-tailed criteria in most cases.

Within-groups Comparisons of Condition Pairs

For each group, a set of repeated measures analyses of variance was done comparing the appropriate baseline CLOSED condition subgroup pairwise with each

of the activation conditions, OPEN and LISTEN. Thus, separate analyses were done for each group CLOSED/O vs. OPEN and for CLOSED/L vs. LISTEN. The analysis of variance model for these tests was Condition x Measure x Channel. Additional analyses were done with the channels paired left/right and front/back.

CLOSED/O vs. OPEN, normal subjects. Several of the measures showed significant change in the CLOSED/O vs. OPEN analysis. Table 11 summarizes the findings from the latter analysis. There was a highly significant change in the mean group coefficient of variation shown for the weighted mean frequency (WMF) measure ($p < .001$). At the $p < .01$ level several other variables differed significantly between these conditions. Maximum DOR amplitude (MAX AMP) mean and standard deviation dropped upon opening eyes, as did the mean and mean standard deviation of DOR sharpness measure DROP PK/WID. The measure of average percent power per DOR data point (DOR PWR/PT) also showed drops in group mean and group mean standard deviation values. DOR bandwidth, as defined by the median-based method

Table 11

CLOSED/O vs. OPEN Comparison, Normal Group

		Condition				
		CLOSED		OPEN		
		MEAN	SD	MEAN	SD	
WMF	Mean	11.450	1.666	11.779	1.896	
	Mean SD	0.772	0.375	1.042	0.320	
	Mean CV	6.597	2.665	8.866	2.615	**
TP	Mean	302.661	497.018	160.418	177.197	
	Mean SD	98.853	150.468	53.480	73.093	
	Mean CV	35.490	8.805	26.388	11.679	
%TP	Mean	71.539	12.229	60.079	12.439	
	Mean SD	6.891	1.996	6.807	1.397	
	Mean CV	10.261	4.141	11.767	3.145	
MAX AMP	Mean	14.777	6.707	7.374	3.062	*
	Mean SD	5.854	2.109	2.802	1.553	*
	Mean CV	41.995	10.996	36.840	11.647	
MAX FRQ	Mean	9.220	1.002	8.727	1.061	
	Mean SD	1.044	0.700	2.242	1.000	
	Mean CV	11.312	7.540	25.848	11.354	
MDN	Mean	9.414	0.830	9.360	0.627	
	Mean SD	0.488	0.241	0.817	0.286	
	Mean CV	5.196	2.522	8.702	2.925	
MDN WID	Mean	6.050	1.958	8.485	1.279	*
	Mean SD	1.477	0.389	1.007	0.322	
	Mean CV	26.681	9.875	12.668	6.197	
DROP WID	Mean	3.146	0.804	4.241	0.668	
	Mean SD	1.267	0.459	1.889	0.569	
	Mean CV	39.675	8.091	44.188	10.050	

Table 11

(Continued)

		Condition				
		CLOSED		OPEN		
		MEAN	SD	MEAN	SD	
MDN PK/WID	Mean	3.994	3.545	1.035	0.735	
	Mean SD	2.961	2.659	0.617	0.652	
	Mean CV	74.559	26.356	50.419	20.972	
DROP PK/WID	Mean	7.105	4.506	2.531	1.167	*
	Mean SD	5.184	2.673	2.151	1.294	*
	Mean CV	79.108	23.599	81.678	23.406	
PRE PWR/PT	Mean	0.728	0.196	1.045	0.203	*
	Mean SD	0.280	0.096	0.444	0.184	
	Mean CV	38.696	9.023	41.929	13.749	
DOR PWR/PT	Mean	4.279	1.906	2.132	0.926	*
	Mean SD	1.513	0.542	0.772	0.452	*
	Mean CV	37.927	11.287	35.031	12.210	
POST PWR/PT	Mean	0.639	0.146	0.752	0.109	
	Mean SD	0.237	0.074	0.293	0.110	
	Mean CV	37.323	8.064	38.499	11.121	

* $p<.01$ ** $p<.001$
SD = Standard Deviation
CV = Coefficient of Variation

(MDN WID) increased with eye opening, as did the average percent power of data points lower in frequency than the DOR (PRE PWR/PT).

Several condition by channel or channel pair interactions were seen at the $p < .01$ level. For the DOR frequency measures, MAX FRQ and MDN, there was a drop in frequency seen in the posterior channel pair upon eye opening. The other interaction in this comparison was a significant shift in the MDN WID bandwidth pattern at the individual channel level.

CLOSED/O vs. OPEN, SDAT subjects. There were no significant main effects differences shown in the SDAT group upon opening eyes. For purposes of comparison with the normal CLOSED/O vs. OPEN results, Table 12 is included here, which summarizes the corresponding analysis for the SDAT group.

There were two Condition x Channel Pair interactions seen at the $p < .01$ level. These were due to differential effects at each channel seen in DROP WID SD, and a PRE PWR/PT SD increase in the posterior channels on eye opening.

Table 12

CLOSED/O vs. OPEN Comparison, SDAT Group

		Condition			
		CLOSED		OPEN	
		MEAN	SD	MEAN	SD
WMF	Mean	8.516	1.496	9.182	1.929
	Mean SD	0.865	0.392	0.907	0.387
	Mean CV	9.992	3.641	9.815	3.439
TP	Mean	298.796	219.841	222.788	159.464
	Mean SD	96.968	86.753	65.256	60.264
	Mean CV	28.875	9.030	27.958	12.378
%TP	Mean	77.161	12.421	72.222	8.973
	Mean SD	6.255	2.486	7.847	2.361
	Mean CV	8.790	4.696	11.160	3.965
MAX AMP	Mean	14.145	4.995	12.121	3.694
	Mean SD	4.721	1.917	4.293	1.637
	Mean CV	33.487	5.716	35.011	6.320
MAX FRQ	Mean	6.788	1.087	6.748	1.246
	Mean SD	0.924	0.447	0.880	0.350
	Mean CV	14.003	6.912	12.998	4.813
MDN	Mean	7.331	0.841	7.352	1.036
	Mean SD	0.565	0.203	0.538	0.188
	Mean CV	7.778	2.821	7.277	2.396
MDN WID	Mean	5.302	1.721	6.438	1.210
	Mean SD	1.081	0.235	1.192	0.361
	Mean CV	22.115	7.255	19.574	8.554
DROP WID	Mean	3.253	0.570	3.420	0.704
	Mean SD	1.079	0.251	1.177	0.390
	Mean CV	33.184	5.425	33.862	6.516

Table 12

(Continued)

	Condition			
	CLOSED		OPEN	
	MEAN	SD	MEAN	SD
MDN PK/WID Mean	3.756	2.916	2.294	1.408
Mean SD	2.120	2.123	1.263	1.252
Mean CV	51.217	12.297	49.138	14.988
DROP PK/WID Mean	5.804	2.838	4.806	2.346
Mean SD	3.885	2.371	3.051	1.720
Mean CV	65.732	14.533	63.963	17.087
PRE PWR/PT Mean	1.389	0.730	1.582	0.765
Mean SD	0.900	0.515	0.901	0.589
Mean CV	63.554	15.458	55.246	17.196
DOR PWR/PT Mean	4.300	1.530	3.561	1.118
Mean SD	1.203	0.482	1.050	0.383
Mean CV	28.218	5.901	29.922	7.391
POST PWR/PT Mean	0.518	0.143	0.599	0.135
Mean SD	0.204	0.066	0.199	0.079
Mean CV	40.381	11.164	33.786	13.253

SD = Standard Deviation
CV = Coefficient of Variation

Channel-level effects were seen ($p < .01$) for the WMF, %TP, and MAX AMP measures. The WMF mean and WMF mean standard deviation measures were higher in the anterior channels. There was a higher mean %TP value found in the anterior channels. The MAX AMP coefficient of variation measure was lower in the posterior channels.

CLOSED/L vs. LISTEN, normal subjects. There were no significant main condition effects shown in the CLOSED/L vs. LISTEN analysis. There were some $p < .01$-level main effects by channel and channel pair which existed in both conditions. Weighted mean frequency was lower in the posterior channels, and a lower mean MDN WID and POST PWR/PT was seen for the left rear channel, T5-O1.

CLOSED/L vs. LISTEN, SDAT subjects. The SDAT subjects did not show any significant condition effects due to listening to speech. Two effects common to both conditions were seen at the channel level. There was a lower WMF and a higher percent of total

power in the 2.00-32.00 Hz band (%TP) in the posterior channels.

Between-groups Comparisons Across Conditions

For each of the three conditions, CLOSED, OPEN, and LISTEN, a set of repeated measures analyses of variance was done across the SDAT and normal groups. Thus, separate analyses were done for SDAT vs. normal CLOSED, for SDAT vs. normal OPEN, and for SDAT vs. normal LISTEN. The analysis of variance model for these tests was Group x Measure x Channel. Additional analyses were done with the channels paired left/right and front/back.

SDAT vs. normal CLOSED analysis. This analysis is summarized in Table 13. It demonstrated that the two groups do indeed differ on a number of the measures. The $p < .001$ level was seen for the WMF group mean measure, with the SDAT group showing an average weighted mean frequency of 8.42 Hz, while the normal group had a value of 10.96 Hz. The two groups did not

Table 13

Group Comparisons, CLOSED Conditions

		Group				
		SDAT		Normal		
		MEAN	SD	MEAN	SD	
WMF	Mean	8.415	1.455	10.956	2.058	**
	Mean SD	0.828	0.385	0.845	0.409	
	Mean CV	9.665	3.559	8.025	4.633	
TP	Mean	283.485	211.835	276.100	469.327	
	Mean SD	89.513	84.493	91.485	141.827	
	Mean CV	27.723	9.278	36.594	8.756	
%TP	Mean	77.108	11.790	70.944	11.567	
	Mean SD	6.306	2.457	7.574	2.718	
	Mean CV	8.802	4.546	11.307	4.958	
MAX AMP	Mean	14.175	4.717	14.281	6.424	
	Mean SD	4.712	1.823	5.886	1.987	
	Mean CV	33.332	5.594	44.071	12.877	*
MAX FRQ	Mean	6.765	1.027	8.890	1.311	*
	Mean SD	0.884	0.440	1.169	0.741	
	Mean CV	13.406	6.784	13.797	9.813	
MDN	Mean	7.262	0.818	9.163	1.067	*
	Mean SD	0.549	0.204	0.581	0.341	
	Mean CV	7.599	2.803	6.652	4.668	
MDN WID	Mean	5.306	1.652	6.143	1.847	
	Mean SD	1.072	0.245	1.506	0.380	*
	Mean CV	21.724	7.053	26.486	9.284	
DROP WID	Mean	3.219	0.549	3.205	0.835	
	Mean SD	1.080	0.257	1.297	0.497	
	Mean CV	33.583	6.107	39.810	8.770	

Table 13

(Continued)

		Group				
		SDAT		Normal		
		MEAN	SD	MEAN	SD	
MDN PK/WID	Mean	3.661	2.769	3.757	3.372	
	Mean SD	1.997	2.031	2.899	2.543	
	Mean CV	49.410	12.862	79.529	33.504	*
DROP PK/WID	Mean	5.829	2.676	6.759	4.312	
	Mean SD	3.868	2.242	5.048	2.619	
	Mean CV	65.281	13.911	82.036	32.892	*
PRE PWR/PT	Mean	1.451	0.734	0.864	0.490	
	Mean SD	0.916	0.492	0.381	0.362	*
	Mean CV	62.727	15.601	40.925	12.105	**
DOR PWR/PT	Mean	4.297	1.454	4.139	1.822	
	Mean SD	1.219	0.472	1.540	0.591	
	Mean CV	28.564	6.036	40.129	15.666	*
POST PWR/PT	Mean	0.515	0.142	0.618	0.149	
	Mean SD	0.199	0.065	0.231	0.073	
	Mean CV	39.586	10.756	37.778	8.303	

* $p < .01$ ** $p < .001$
SD = Standard Deviation
CV = Coefficient of Variation

differ significantly on group average interepoch standard deviations and coefficients of variation for the WMF measure.

The DOR frequency, as measured by both the frequency of the maximum DOR amplitude point (MAX FRQ) as well as the median DOR frequency (MDN) were higher in the normal group than in the SDAT group, 8.89 Hz vs. 6.76 Hz ($p < .01$), and 9.14 Hz vs. 7.26 Hz ($p < .01$) respectively.

The group average standard deviation variability measures differed at the .01 level on the median based bandwidth measure, with the normals having a larger DOR bandwidth. The SDAT group displayed a higher amount of variability at a similar significance level on the PRE PWR/PT average standard deviation measure.

The group average coefficient of variation category differed between groups for several measures. Normals had higher values for both the MDN PK/WID and DROP PK/WID measures of peak sharpness variation ($p < .01$), while the SDATs had a significantly higher coefficient of variation for the PRE PWR/PT measure ($p < .001$).

SDAT vs. normal OPEN analysis. Table 14 summarizes the OPEN across-groups results. No differences achieved the $p < .001$ level for this analysis, while several did so at the $p < .01$ level. Once again, the SDAT group had a slower WMF, 9.18 Hz vs. 11.78 Hz. The group means of the frequency measures of the DOR were also lower in the SDAT group (MAX FRQ and MDN), with the group means of the MAX FRQ standard deviation and coefficient of variation measures also showing significantly lower values in the SDAT group.

The DOR mean bandwidth measures were higher in the normal group as determined with both bandwidth measures, with the DROP WID standard deviation measure also higher than that of the SDAT group. The group average coefficient of variation DROP PK/WID measure of variance of DOR peak sharpness was higher in the normal group.

The group average standard deviation POST PWR/PT variation measure was higher in the normal group.

SDAT vs. normal LISTEN analysis. Despite a somewhat different set of subjects in each group than

Table 14

Group Comparisons, OPEN Conditions

		Group				
		SDAT		Normal		
		MEAN	SD	MEAN	SD	
WMF	Mean	9.182	1.929	11.779	1.896	*
	Mean SD	0.907	0.387	1.042	0.320	
	Mean CV	9.815	3.439	8.866	2.615	
TP	Mean	222.788	159.464	160.418	177.197	
	Mean SD	65.256	60.264	53.480	73.093	
	Mean CV	27.958	12.378	26.388	11.679	
%TP	Mean	72.222	8.973	60.079	12.439	
	Mean SD	7.847	2.361	6.807	1.397	
	Mean CV	11.160	3.965	11.767	3.145	
MAX AMP	Mean	12.121	3.694	7.374	3.062	
	Mean SD	4.293	1.637	2.802	1.553	
	Mean CV	35.011	6.320	36.840	11.647	
MAX FRQ	Mean	6.748	1.246	8.727	1.061	*
	Mean SD	0.880	0.350	2.242	1.000	*
	Mean CV	12.998	4.813	25.848	11.354	*
MDN	Mean	7.352	1.036	9.360	0.627	*
	Mean SD	0.538	0.188	0.817	0.286	
	Mean CV	7.277	2.396	8.702	2.925	
MDN WID	Mean	6.438	1.210	8.485	1.279	*
	Mean SD	1.192	0.361	1.007	0.322	
	Mean CV	19.574	8.554	12.668	6.197	
DROP WID	Mean	3.420	0.704	4.241	0.668	*
	Mean SD	1.177	0.390	1.889	0.569	*
	Mean CV	33.862	6.516	44.188	10.050	

Table 14

(Continued)

	Group				
	SDAT		Normal		
	MEAN	SD	MEAN	SD	
MDN PK/WID Mean	2.294	1.408	1.035	0.735	
Mean SD	1.263	1.252	0.617	0.652	
Mean CV	49.138	14.988	50.419	20.972	
DROP PK/WID Mean	4.806	2.346	2.531	1.167	
Mean SD	3.051	1.720	2.151	1.294	
Mean CV	63.963	17.087	81.678	23.406	*
PRE PWR/PT Mean	1.582	0.765	1.045	0.203	
Mean SD	0.901	0.589	0.444	0.184	
Mean CV	55.246	17.196	41.929	13.749	
DOR PWR/PT Mean	3.561	1.118	2.132	0.926	
Mean SD	1.050	0.383	0.772	0.452	
Mean CV	29.922	7.391	35.031	12.210	
POST PWR/PT Mean	0.599	0.135	0.752	0.109	
Mean SD	0.199	0.079	0.293	0.110	*
Mean CV	33.786	13.253	38.499	11.121	

* $p < .01$
SD = Standard Deviation
CV = Coefficient of Variation

those used in the CLOSED analysis, the patterns of significant findings for the CLOSED analysis and the LISTEN analysis are similar. The LISTEN results are shown in Table 15. The only differences in significance as compared to the OPEN analysis are the findings for WMF, group standard deviation and coefficient of variation (SDATs higher than normals in each case), a total power (TP) difference on group coefficient of variation (normals higher than SDATS), and a difference on mean PRE PWR/PT (SDATs higher). Several of the significant findings are at a higher level than the corresponding CLOSED findings.

The MDN PK/WID DOR SD and CV sharpness variation measures displayed a Side x Group interaction at the $p < .01$ level, due to high values in the left channel pair of the normal group. The groups also differed in their channel-level distribution of mean POST PWR/PT values, with the normal group showing highest values on the right and the SDAT group showing highest values on the left side.

Table 15

Group Comparisons, LISTEN Conditions

		Group				
		SDAT		Normal		
		MEAN	SD	MEAN	SD	
WMF	Mean	8.307	1.068	11.271	1.551	**
	Mean SD	0.626	0.265	0.818	0.352	
	Mean CV	7.534	3.022	7.180	2.891	
TP	Mean	305.420	218.386	293.942	534.534	
	Mean SD	78.235	60.938	89.728	135.742	
	Mean CV	24.618	6.193	38.355	11.449	*
%TP	Mean	80.069	8.997	73.634	11.726	
	Mean SD	5.970	2.765	7.124	2.476	
	Mean CV	7.849	4.244	10.230	4.382	
MAX AMP	Mean	14.827	4.383	14.672	6.610	
	Mean SD	4.753	1.604	5.857	2.819	
	Mean CV	32.248	5.707	40.637	8.622	
MAX FRQ	Mean	6.812	0.981	9.365	0.954	**
	Mean SD	0.776	0.275	0.974	0.739	
	Mean CV	11.702	4.725	10.364	7.900	
MDN	Mean	7.292	0.769	9.501	0.826	**
	Mean SD	0.472	0.162	0.516	0.229	
	Mean CV	6.565	2.433	5.448	2.453	
MDN WID	Mean	5.119	1.468	6.085	1.905	
	Mean SD	0.955	0.221	1.622	0.595	*
	Mean CV	19.533	4.792	29.639	15.603	
DROP WID	Mean	3.193	0.442	3.272	0.734	
	Mean SD	1.137	0.335	1.391	0.530	
	Mean CV	35.494	8.421	41.951	12.621	

Table 15

(Continued)

	Group				
	SDAT		Normal		
	MEAN	SD	MEAN	SD	
MDN PK/WID Mean	3.677	2.251	3.982	3.321	
Mean SD	1.662	1.141	2.849	2.419	
Mean CV	44.419	8.810	71.379	23.805	*
DROP PK/WID Mean	6.120	2.687	6.631	4.066	
Mean SD	4.082	2.494	4.726	2.920	
Mean CV	63.832	18.470	73.713	16.326	
PRE PWR/PT Mean	1.493	0.671	0.731	0.199	*
Mean SD	0.985	0.507	0.295	0.125	**
Mean CV	66.890	21.446	39.932	10.422	**
DOR PWR/PT Mean	4.408	1.242	4.267	1.794	
Mean SD	1.209	0.415	1.534	0.654	
Mean CV	27.663	6.446	37.220	9.524	*
POST PWR/PT Mean	0.528	0.132	0.667	0.165	
Mean SD	0.199	0.050	0.264	0.095	
Mean CV	38.686	9.864	39.679	10.579	

* $p<.01$ ** $p<.001$
SD = Standard Deviation
CV = Coefficient of Variation

Correlation of EEG and non-EEG Measures

Strategy

It was decided that some method for preselecting EEG variables to correlate with non-EEG variables must be applied, else the hundreds of channel-level measures correlated against the rather large set of non-EEG measures would produce an unwieldy and probably meaningless set of findings. So, EEG variables were selected for correlation with nonelectrophysiologic measures by choosing those variables on which the prior analysis had shown significant group or group interactions effects. In addition, all "core variables" which directly related to the hypotheses about DOR instability were included. These would be the mean, SD, and CV measures of weighted mean frequency, DOR maximum amplitude, frequency of DOR maximum amplitude, median frequency, and average DOR power per point.

By these criteria, 52 EEG measures were selected for correlations. The individual channel values for these measures were collapsed by front/back channel pairs, as few side differences had been noted in the

previous EEG analysis, while front/back differences were relatively common. Three measures did demonstrate strong left/right differences and these were also computed in left/right pairs. Thus, a total of 110 variables were created for correlation with the psychologic, demographic, and medical history data. As the groups were small, and a number of the variables were ordinal scale measures, Spearman rank correlations were done as opposed to Pearson product-moment correlations. As in the EEG analyses of variance, significance values of less than .01 were required in order for a given correlation to be attended to.

Normal Subjects

A number of the non-EEG measures were inappropriate for correlation in the normal group, as their individual values hovered near the ceiling on those measures. Indeed, the WAIS-R scores were probably the only measures displaying a good dispersion of values. For the sake of completeness, I will report demographic and medical history correlations for this group as well as the WAIS-R. In any case, the normal

group displayed few significant correlations at the $p < .01$ level for any non-EEG measure.

There were three EEG measure correlations with demographic and medical history variables. These were: sex of subject with the LISTEN MAX AMP CV, back channel pair; years of education with the LISTEN POST PWR/PT mean, right pair; and medication level with the OPEN DROP WID mean, front pair.

There was a group of $p < .01$ correlations found between EEG variables and WAIS-R variables. Overall average WAIS-R score correlated with CLOSED PRE PWR/PT CV, back pair, as did this same EEG variable with the Object Assembly subtest. The CLOSED DROP PK/WID CV, back pair also correlated with Object Assembly scores. The ranks of scores for the Similarities subtest correlated with the ranks of both the mean and SD measures for OPEN DROP WID, back pair. Finally, the CLOSED MDN PK/WID CV correlated with the Digit Symbol subtest.

See Figures 22, 23, and 24, a selection of scatterplots of chosen for significant correlations with the normal control data. SDAT data points are included on the plots for comparison.

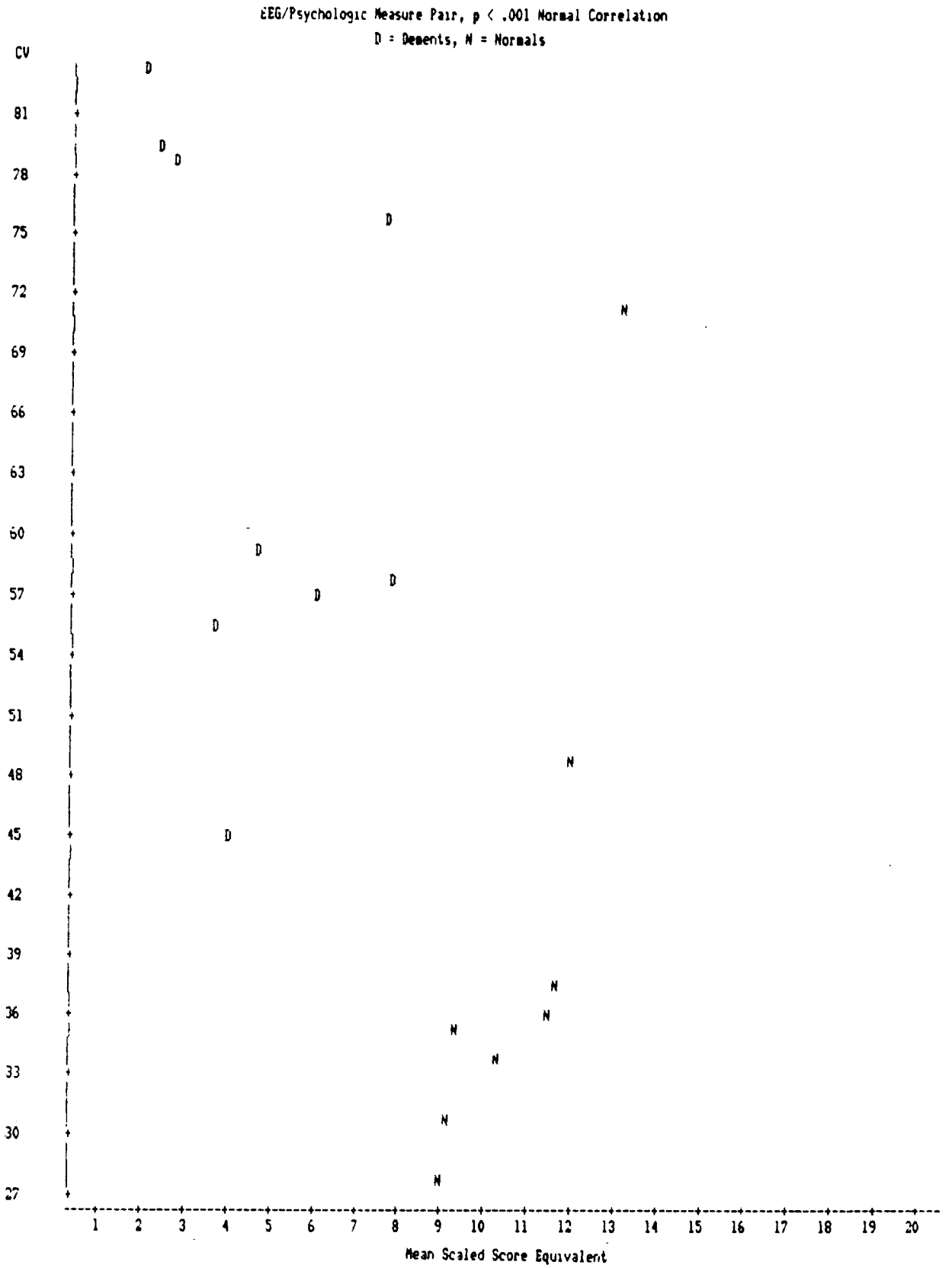


Figure 22. CLOSED PRE PWR/PT CV, back channel pair vs. mean WAIS scores.

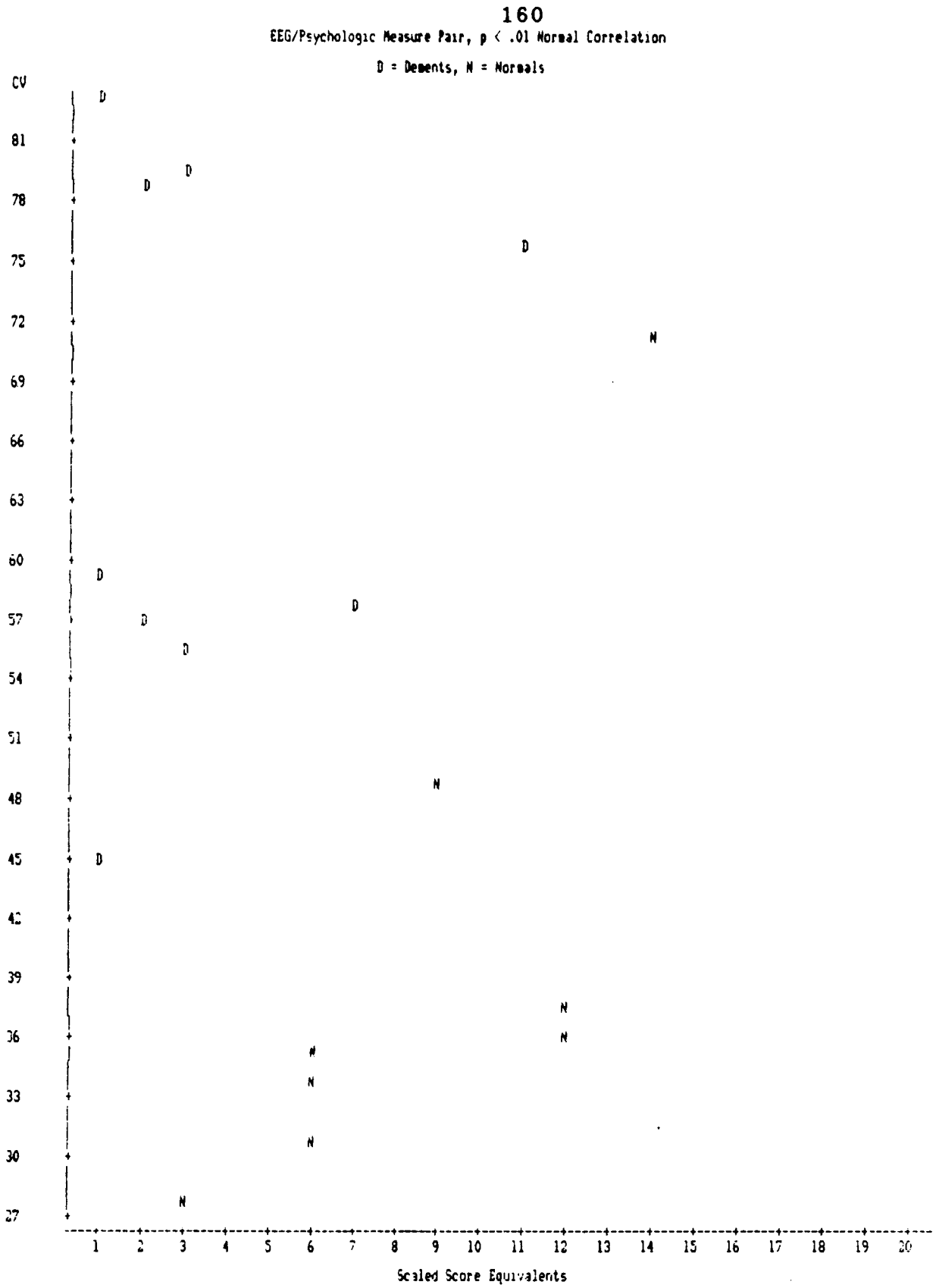


Figure 23. CLOSED PRE PWR/PT CV, back channel pair vs. WAIS object assembly scores.

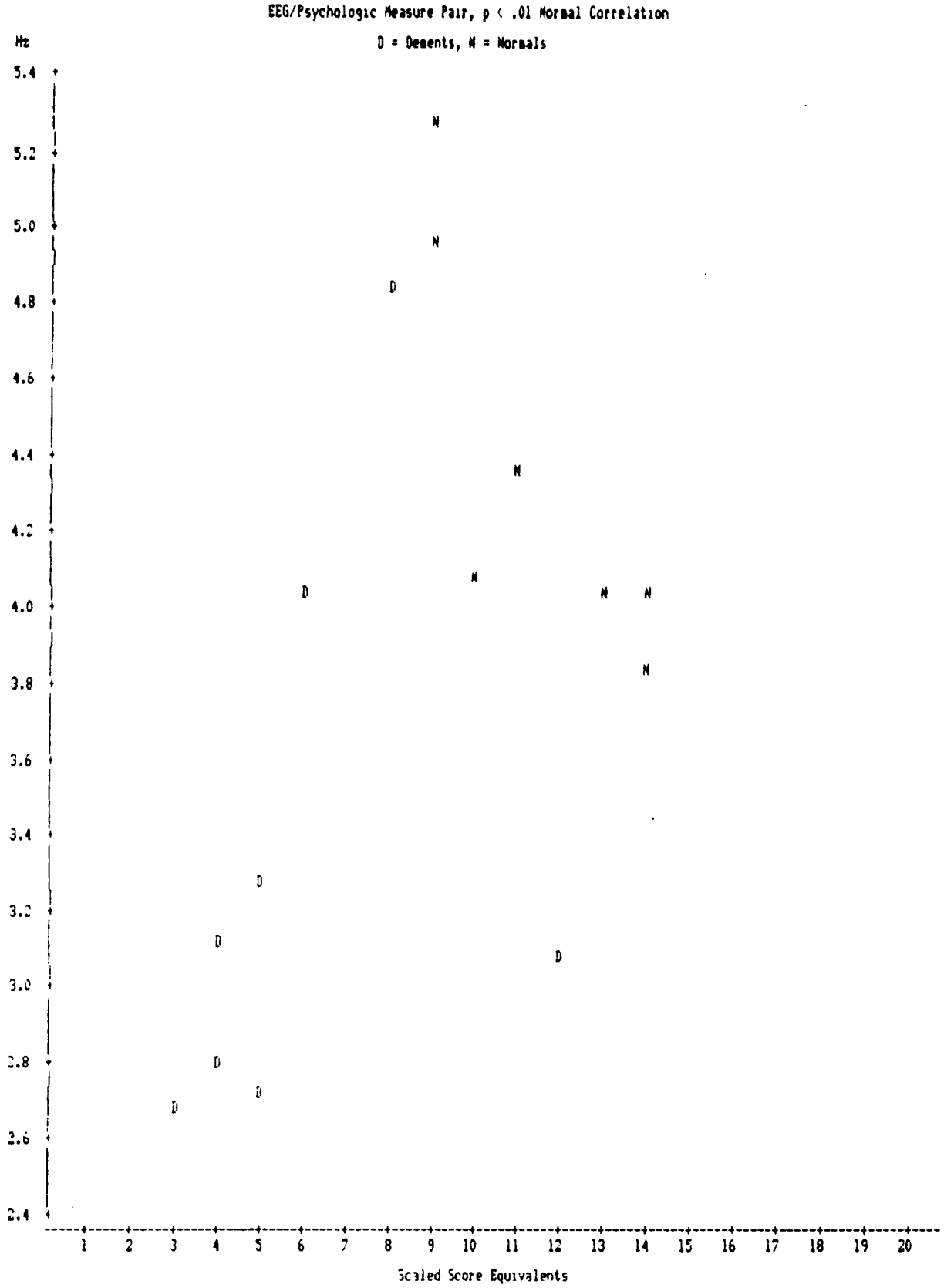


Figure 24. OPEN DROP WID, back channel pair vs. WAIS Similiarities scores.

SDAT Subjects

A much larger number of correlations at the $p < .01$ level were seen between ranks of EEG and ranks of non-EEG variables in the SDAT group. Four significant pairs were found with members of the demographic and medical history data sets. The LISTEN DROP WID CV, back channel pair correlated with years of education. The Cardiovascular medical history category correlated with both CLOSED and LISTEN PRE PWR/PT mean, front pair. The OPEN POST PWR/PT SD, right pair correlated with the Metabolic medical history data.

Three CBRS subscale correlations were seen. These were: CLOSED MDN PK/WID CV, front pair with Orientation; CLOSED DROP PK/WID CV, back pair with Ischemia; and LISTEN MDN PK/WID CV, front pair with Need for Routine.

More numerous and interesting findings were seen for MSQ, Aphasia, Trails B, mean WAIS-R, and several of the WAIS-R subtests. These correlations at the $p < .01$ level are summarized in Table 16. This is an admittedly complicated table, but it allows the several clusters of significant findings to be seen. The table is

Table 16

Correlations of EEG Measures to Psychologic Measures

EEG Measure (type/condition)		Psychologic Tests							
		MMS	APH	TRA	WAIS	DSP	SIM	OBJ	BLK
WMF	MN OP	F							
MAX AMP	CV LS						f		
MAX FRQ	MN CL								B
	MN OP							B	FB
	MN LS				FB	F	B		
	SD OP	B			B				
	CV OP						B		
MDN	MN OP	F			B	FB			B
	MN LS						F*B*		
	SD OP						F*B		
DROP WID	MN OP	F*				B			
	SD OP	B				B			
	CV OP				B	B			
DROP PK/WID	MN OP	F							
	CV OP				F				
PRE PWR/PT	MN OP							b	
	MN LS						b		
	CV OP		F						
	CV LS		F	F					

* p<.001
NOTE: See NOTE on following page

Table 16

(Continued)

NOTE: F/f--Front channel pair (T3-T5, T4-T6), +/- correlations at $p < .01$
B/b--Back channel pair (T5-O1, T6-O2), +/- correlations at $p < .01$

EEG Measure types:

MN--mean of measure
SD--mean of standard deviations
CV--mean of coefficients of variation

EEG stimulus conditions:

OP--OPEN condition
CL--CLOSED condition
LS--LISTEN condition

Psychologic tests:

MMS -- Mini Mental Status Questionaire
APH -- Halstead-Reitan Aphasia Screen
TRA -- Halstead-Reitan Trails A
WAIS -- Mean score of all WAIS-R subscales applied
DSP -- Digit Span subscale of WAIS-R
SIM -- Similarities subscale of WAIS-R
OBJ -- Object Assembly subscale of WAIS-R
BLK -- Block Design subscale of WAIS-R

arranged by measure, measure statistic type (group mean, SD, or CV) and stimulus condition (CLOSED, OPEN, and LISTEN). An "F" or a "B" is entered in the table under the appropriate test if a significant positive correlation exists for the respective front or back channel pair. The small letters "f" or "b" are used similarly for negative correlations. Note that the Aphasia and Trails A scores are negatively valued, so higher scores mean poorer performance.

Figures 25 through 36 are plots of the significantly correlated pairs from the MMS and WAIS columns. Figures 37, 38, and 39 are plots of the three EEG/Similarities subtest pairs whose significance reached $p < .001$. Figures 40, 41, 42 and 43 are plots of these latter three variables vs. age. The corresponding data points from the normal control group are included on each plot, though none of the normal group data were significantly correlated on those variables.

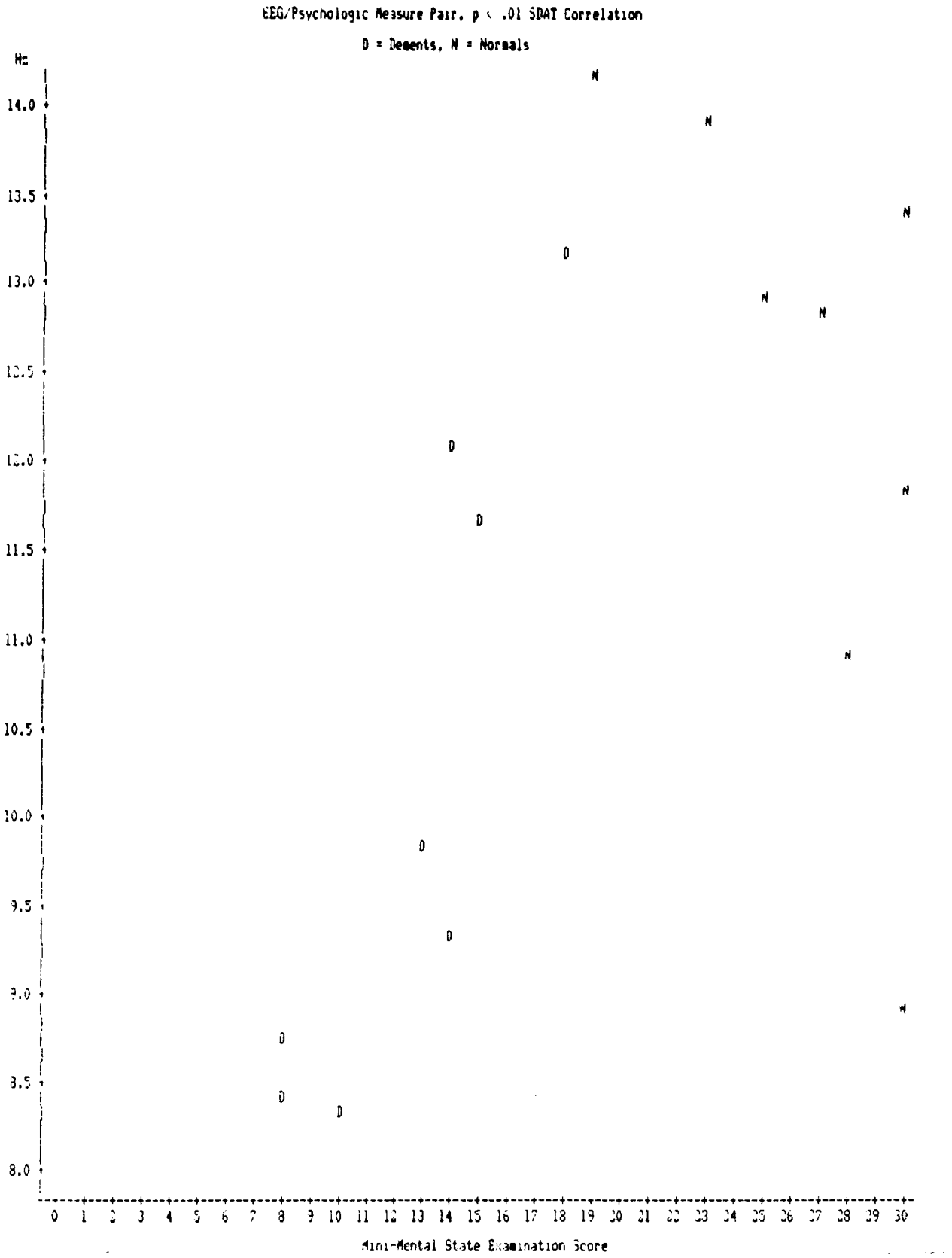


Figure 25. OPEN WMF mean, front channel pair vs. MMS scores.

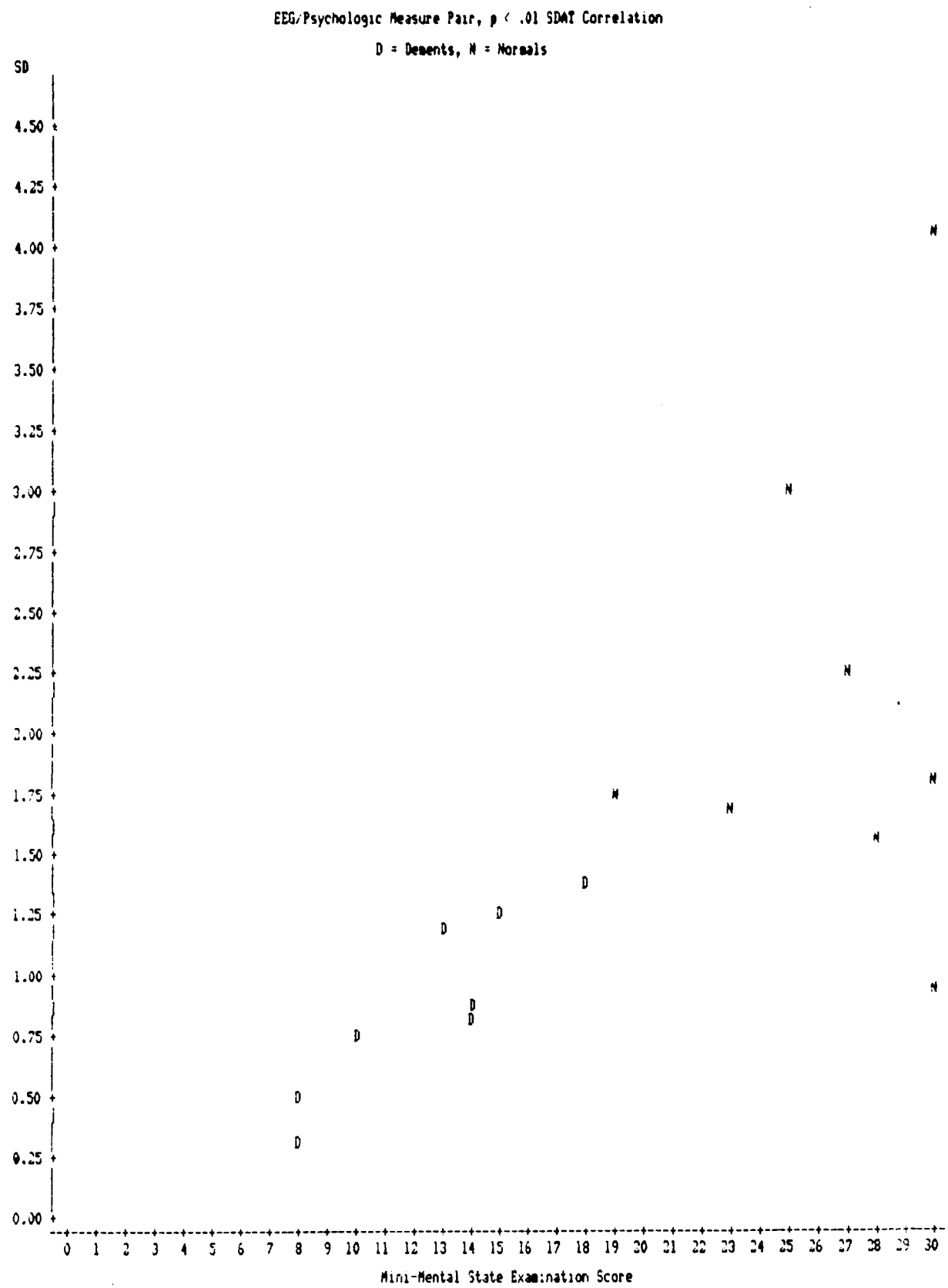


Figure 26. OPEN MAX FRQ SD, back channel pair vs. MMS scores.

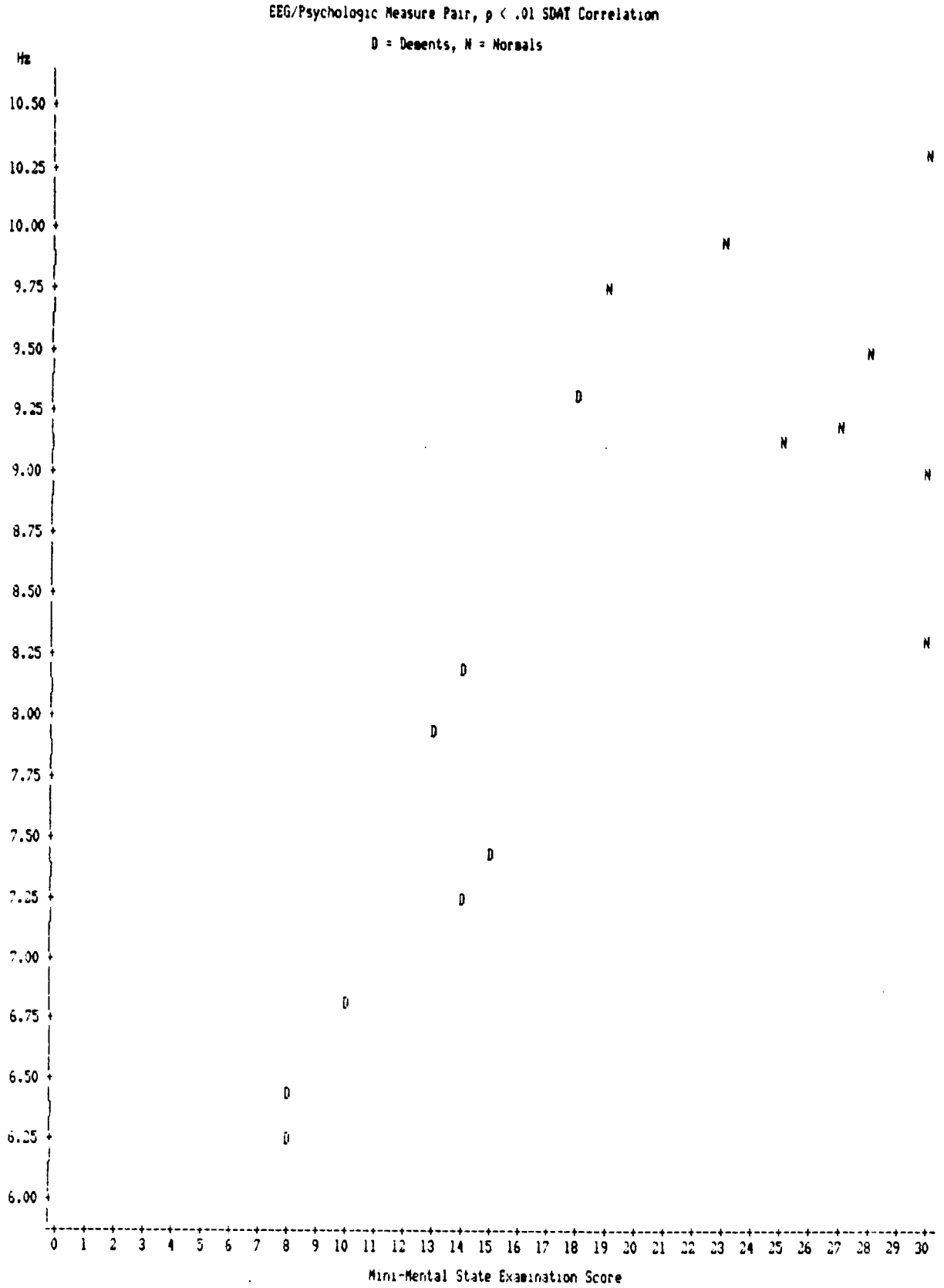


Figure 27. OPEN MDN mean, front channel pair vs. MMS scores.

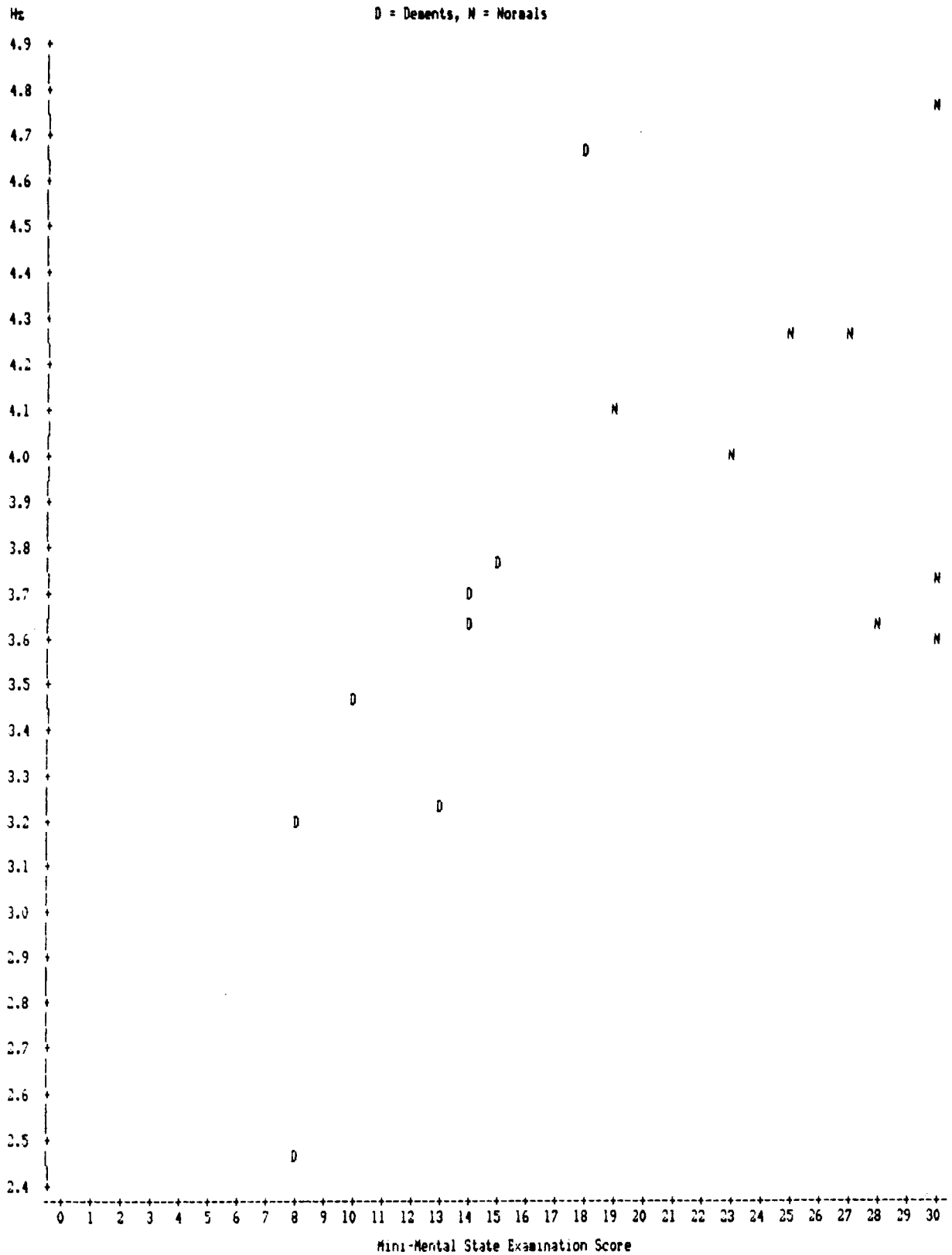


Figure 28. OPEN DROP WID mean, front channel pair vs. MMS scores.

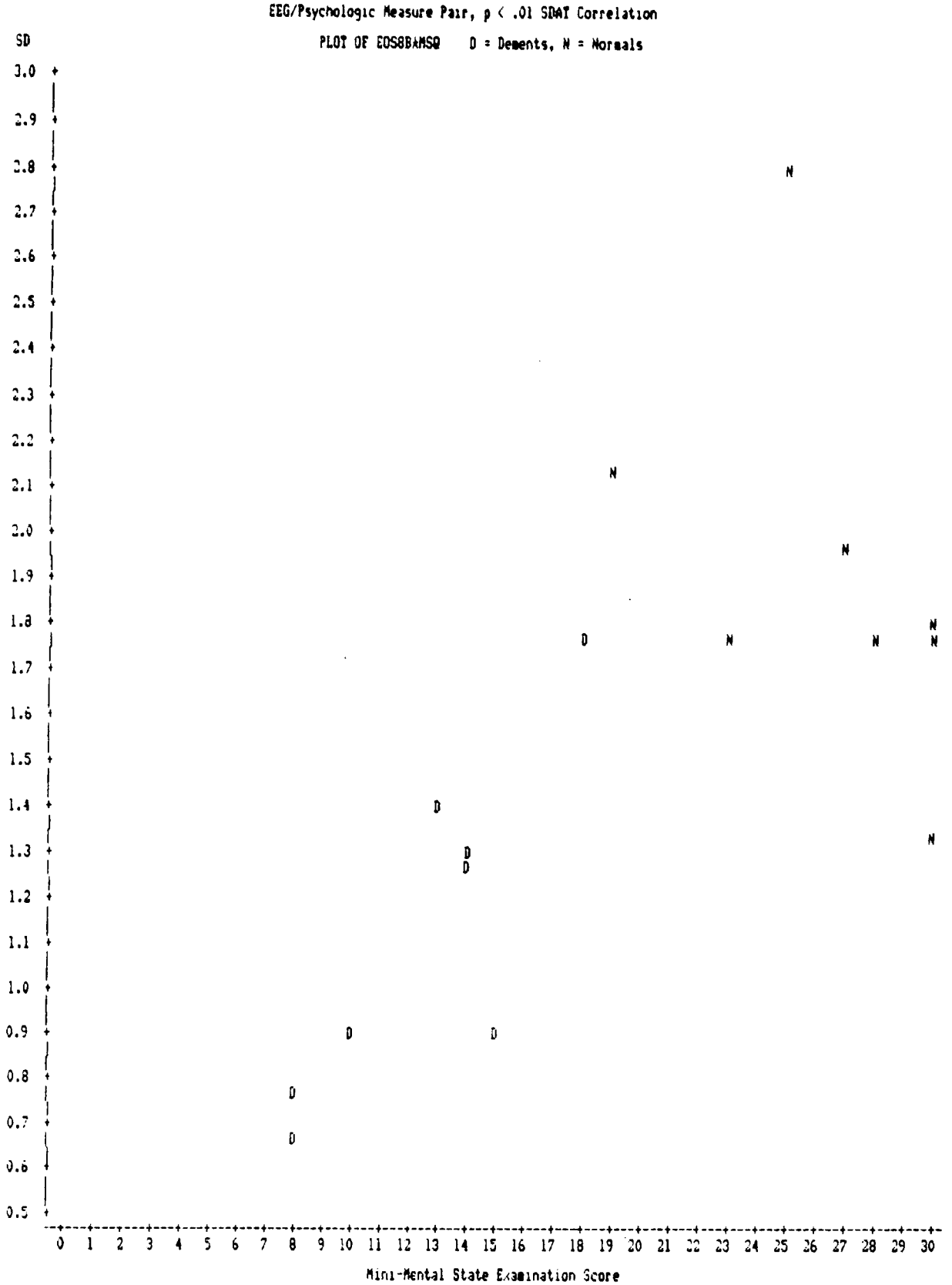


Figure 29. OPEN DROP WID SD, back channel pair vs. MMS scores.

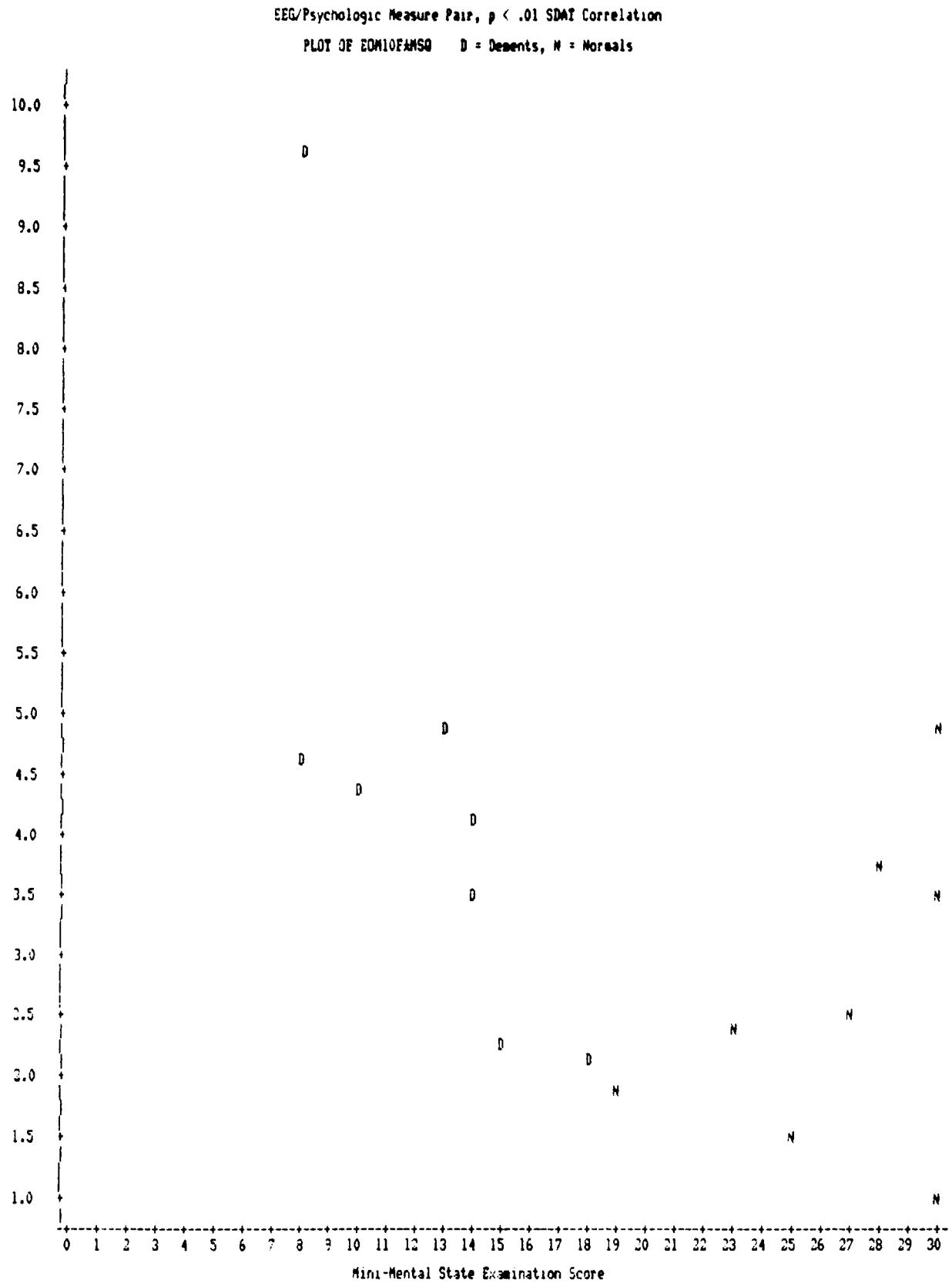


Figure 30. OPEN DROP PK/WID mean, front channel pair vs. MMS scores.

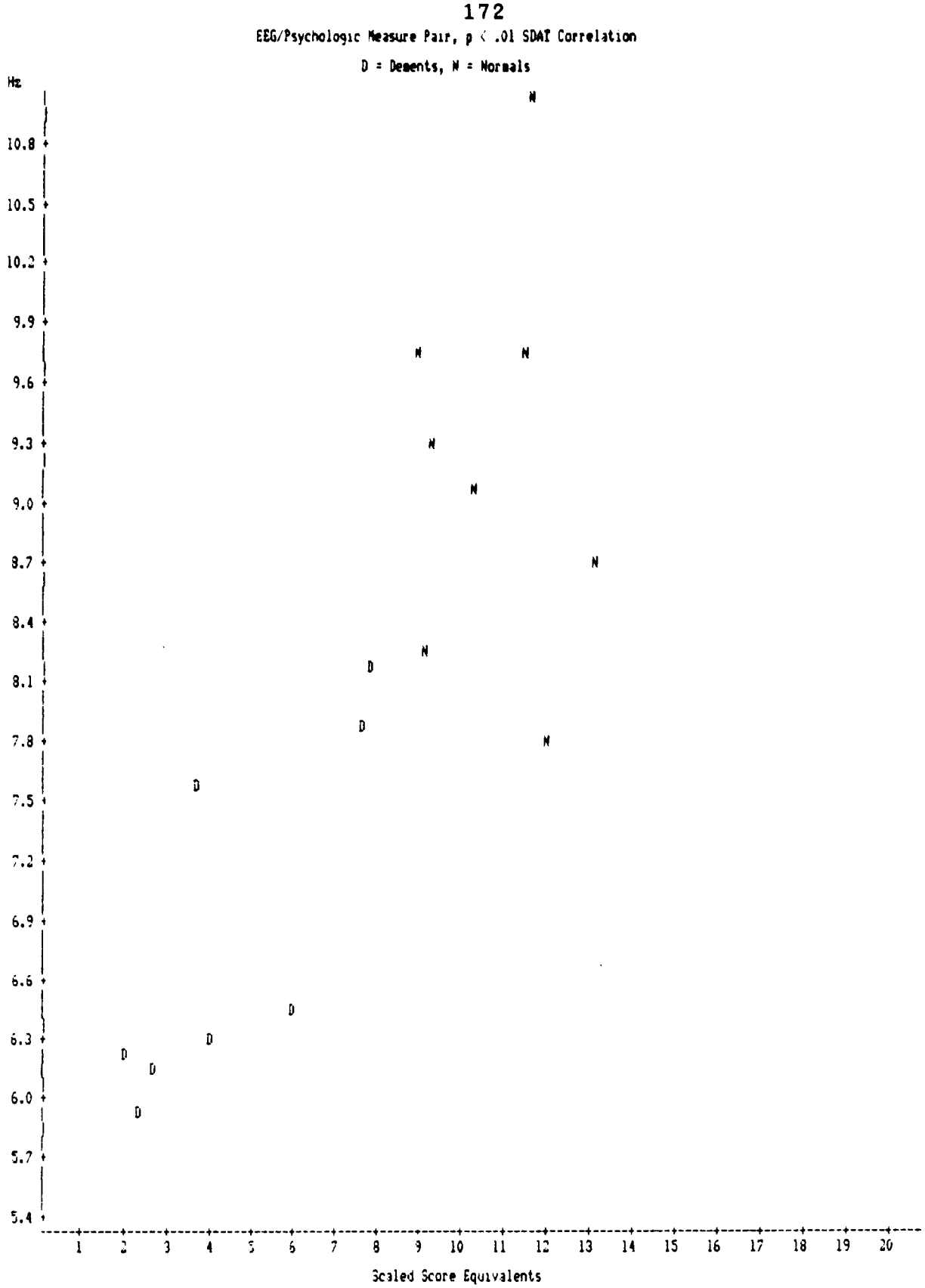


Figure 31. LISTEN MAX FRQ mean, front channel pair vs. mean of WAIS scores.

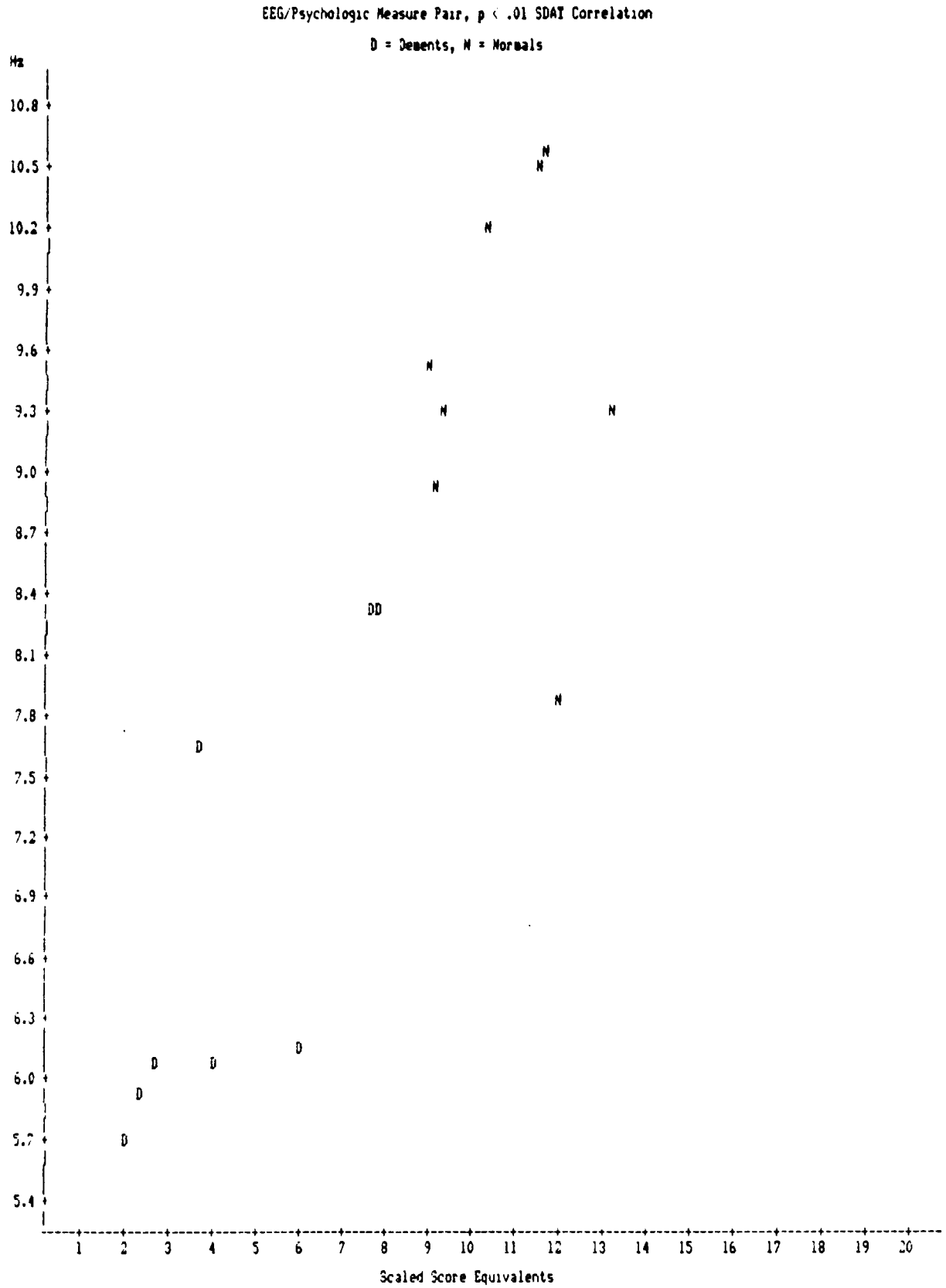


Figure 32. LISTEN MAX FRQ mean, back channel pair vs. mean of WAIS scores.

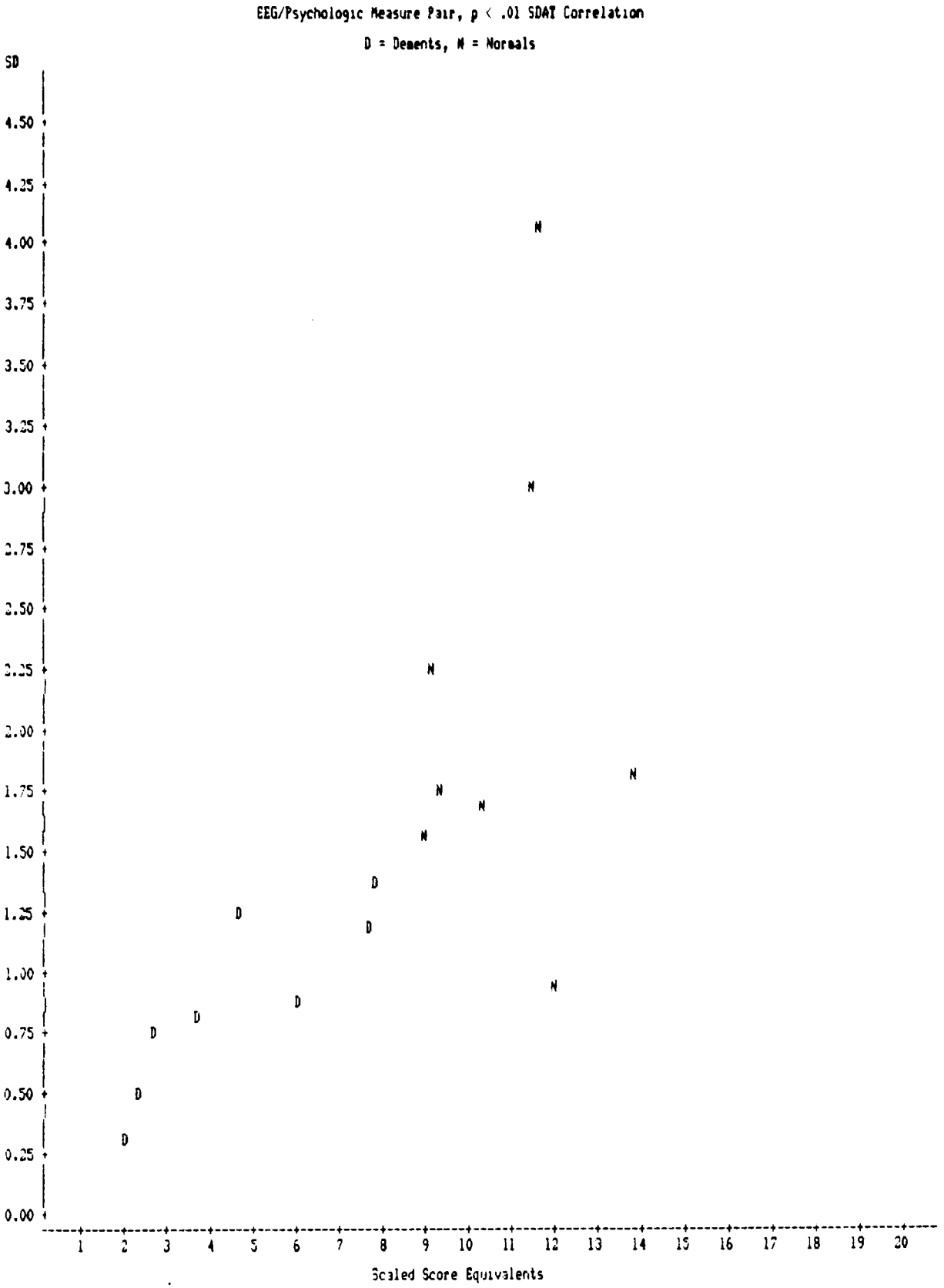


Figure 33. OPEN MAX FRQ SD, back channel pair vs. mean of WAIS scores.

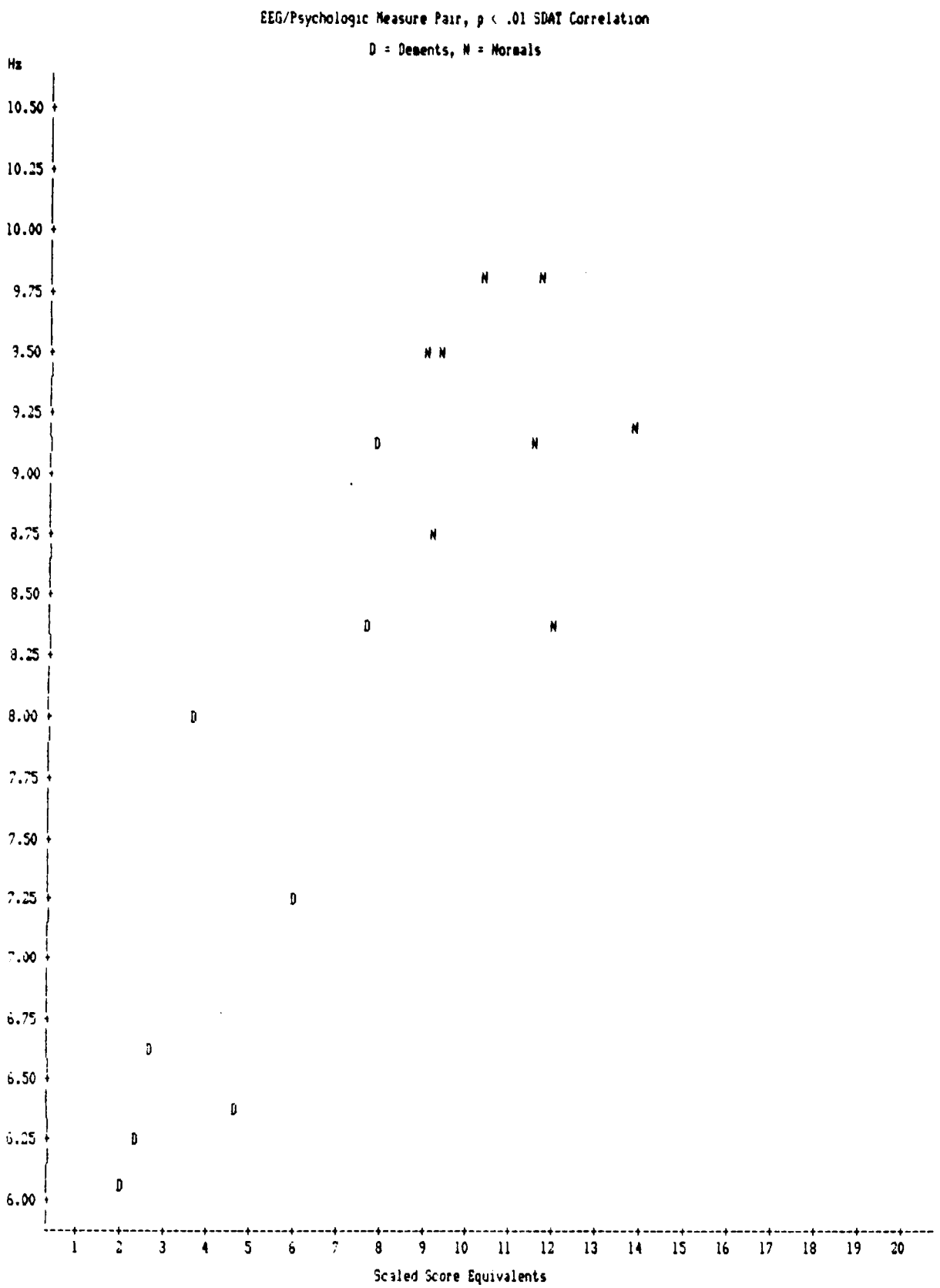


Figure 34. OPEN MDN mean, back channel pair vs. mean of WAIS scores.

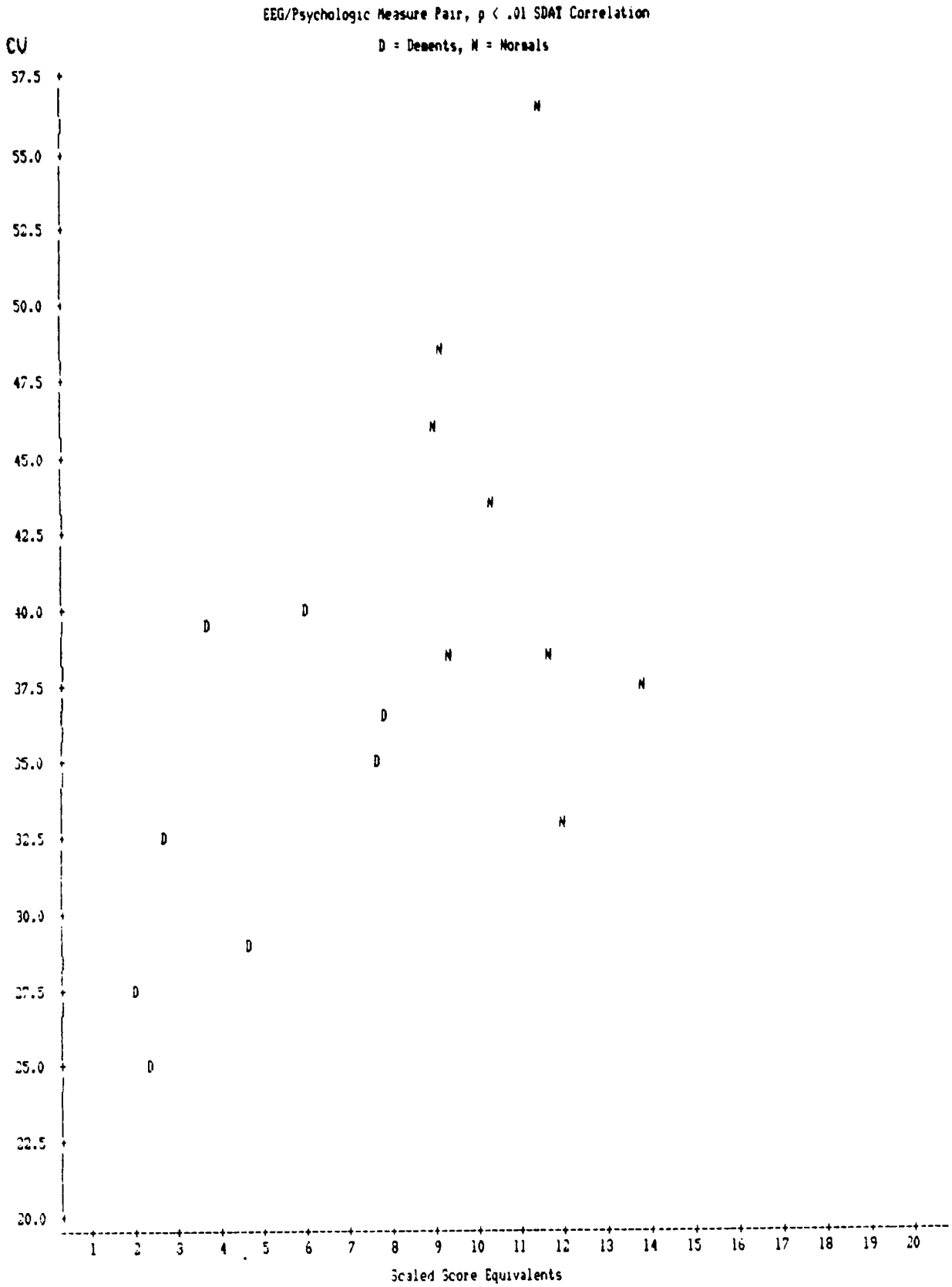


Figure 35. OPEN DROP WID CV, back channel pair vs. mean of WAIS scores.

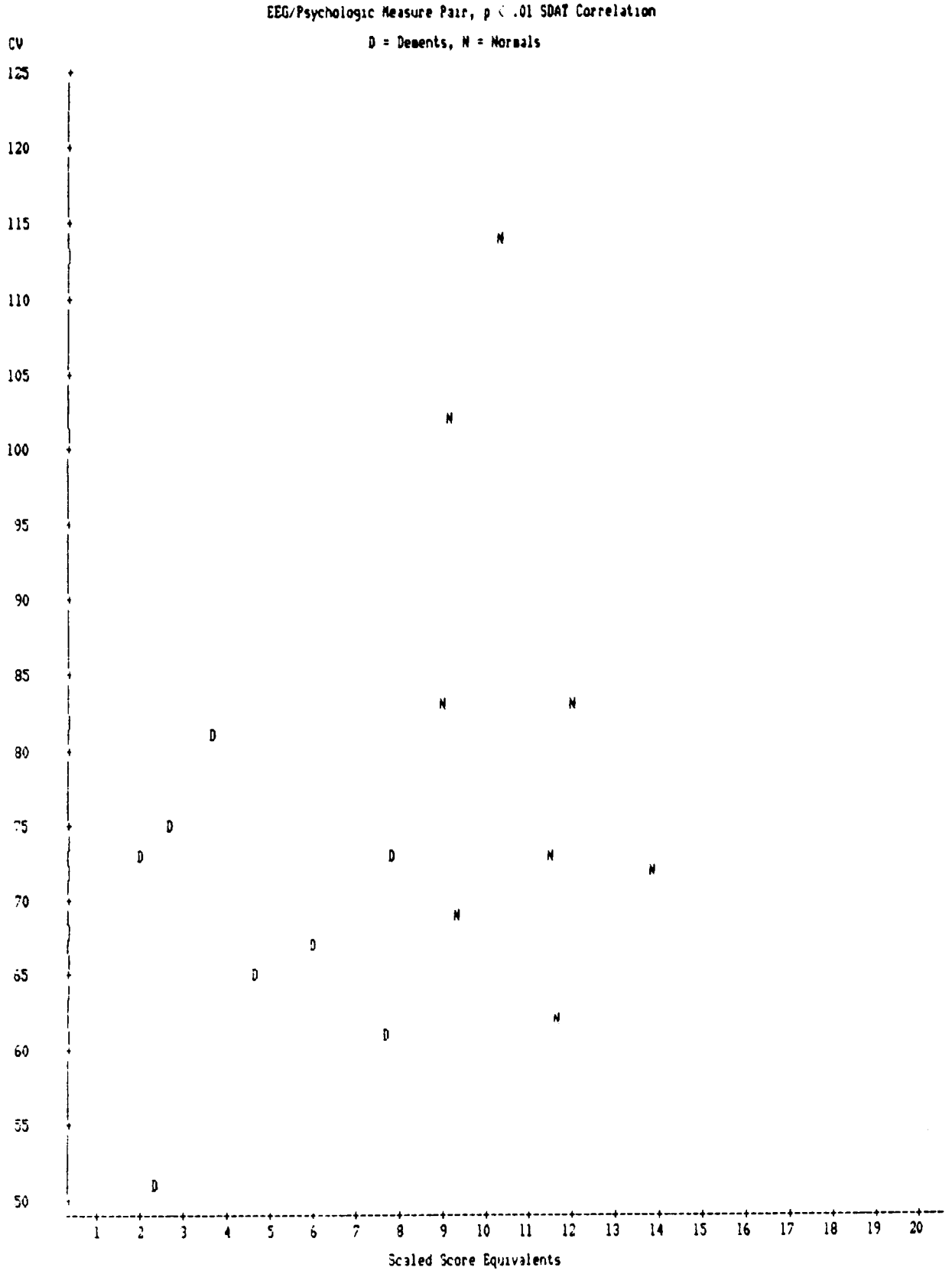


Figure 36. OPEN DROP PK/WID CV, front channel pair vs. mean of WAIS scores.

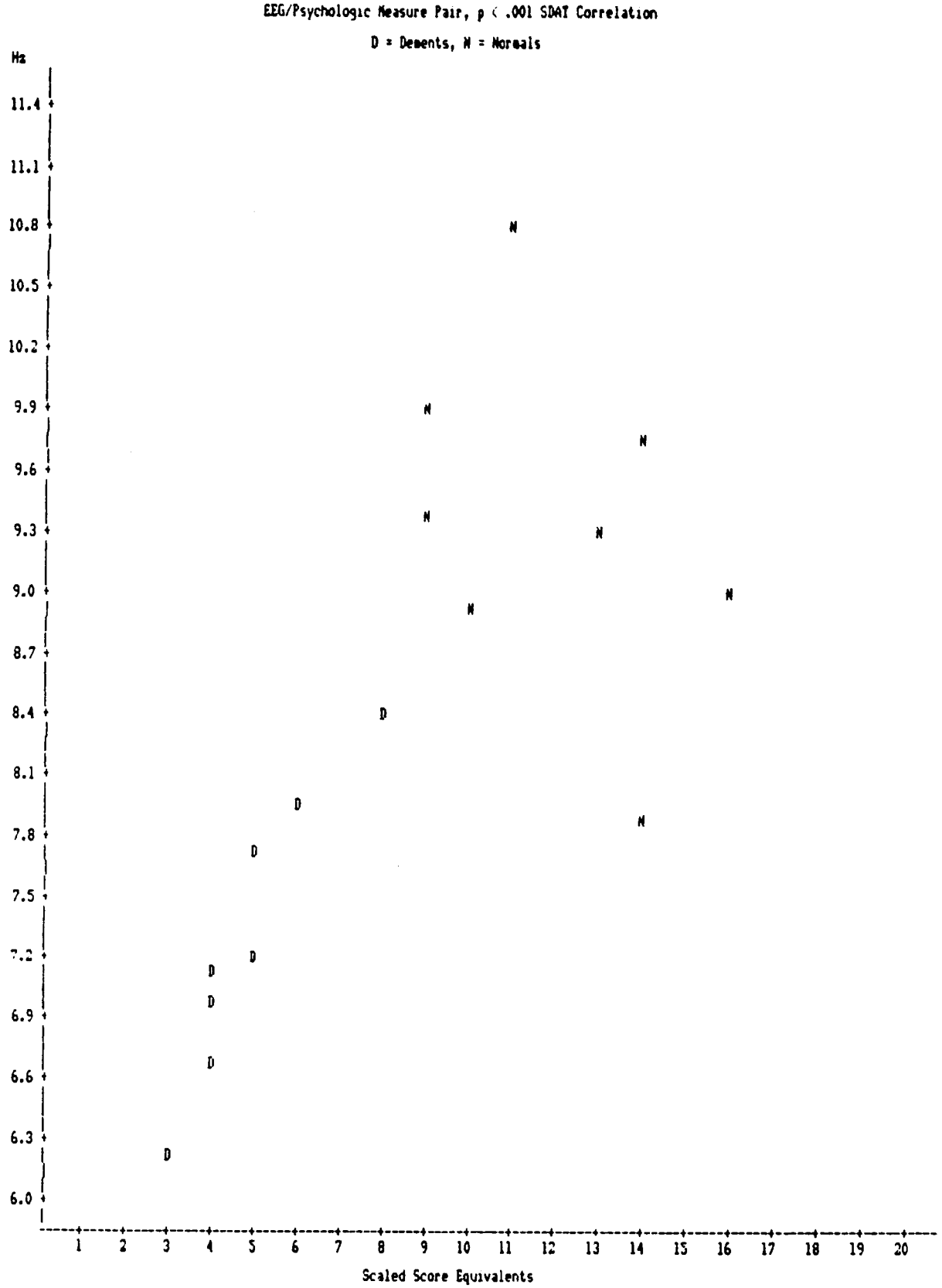


Figure 37. LISTEN MDN mean, front channel pair vs. WAIS Similarities scores.

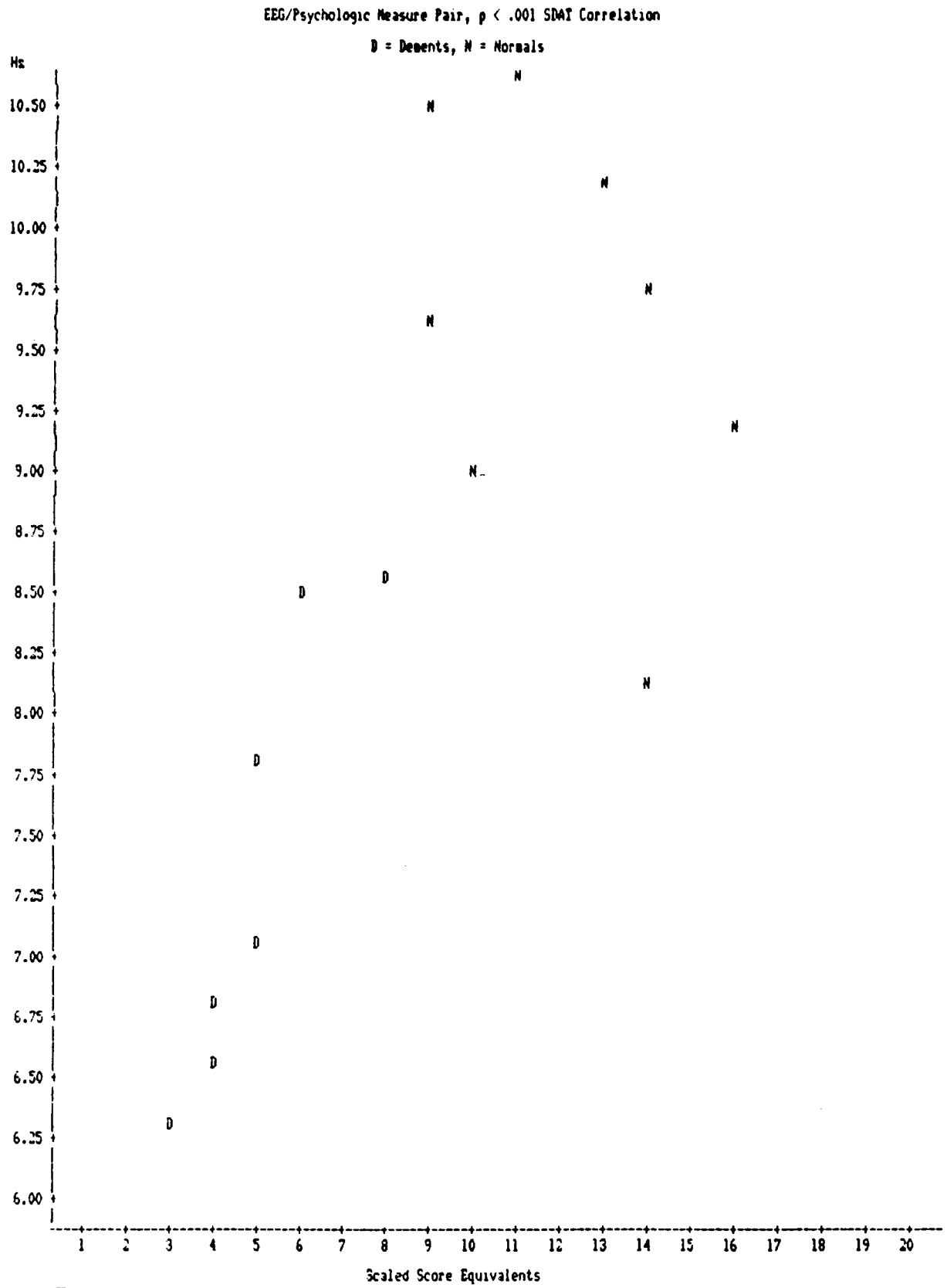


Figure 38. LISTEN MDN mean, back channel pair vs. WAIS Similarities scores.

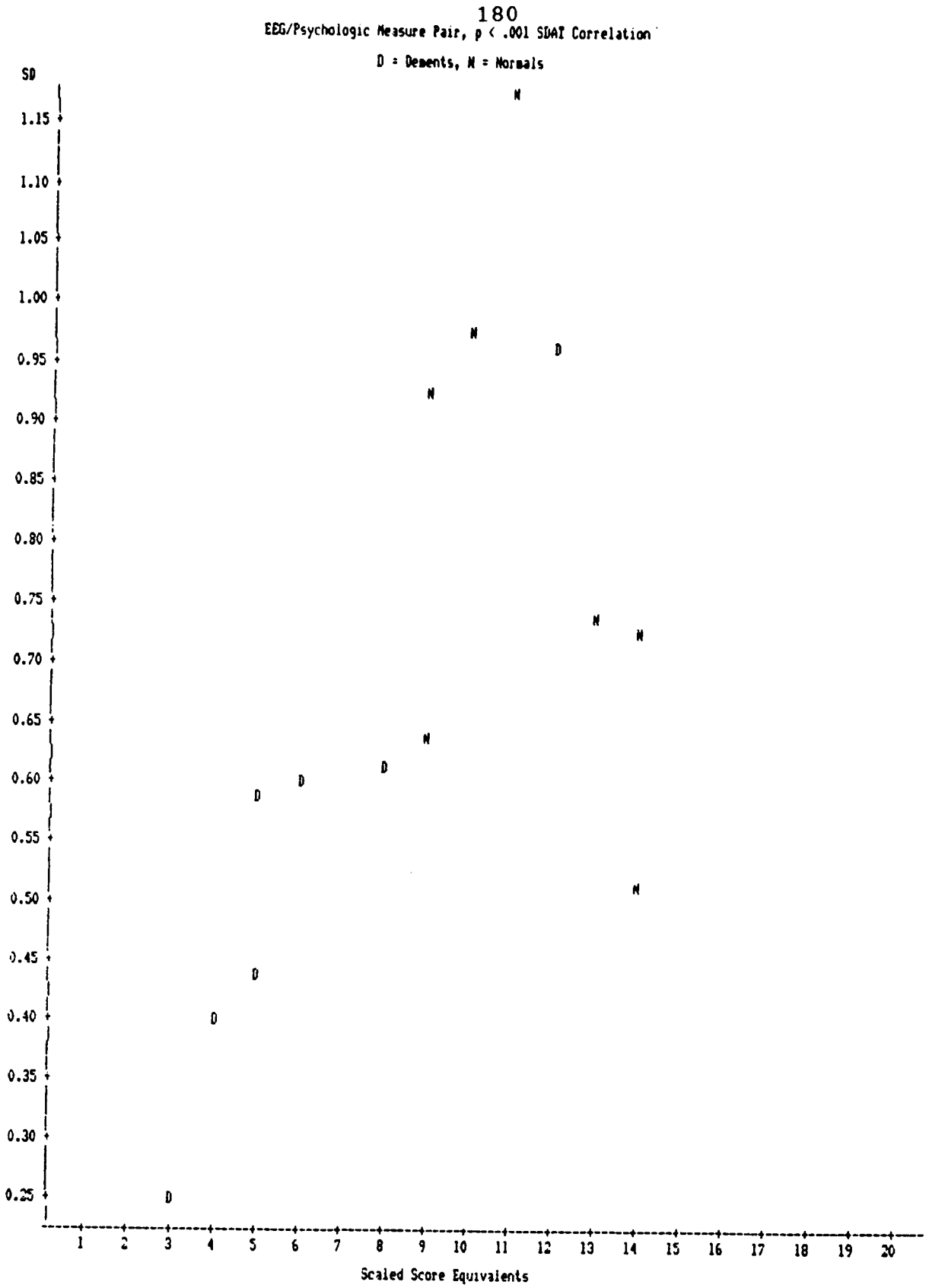


Figure 39. OPEN MDN SD, front channel pair vs. WAIS Similarities scores.

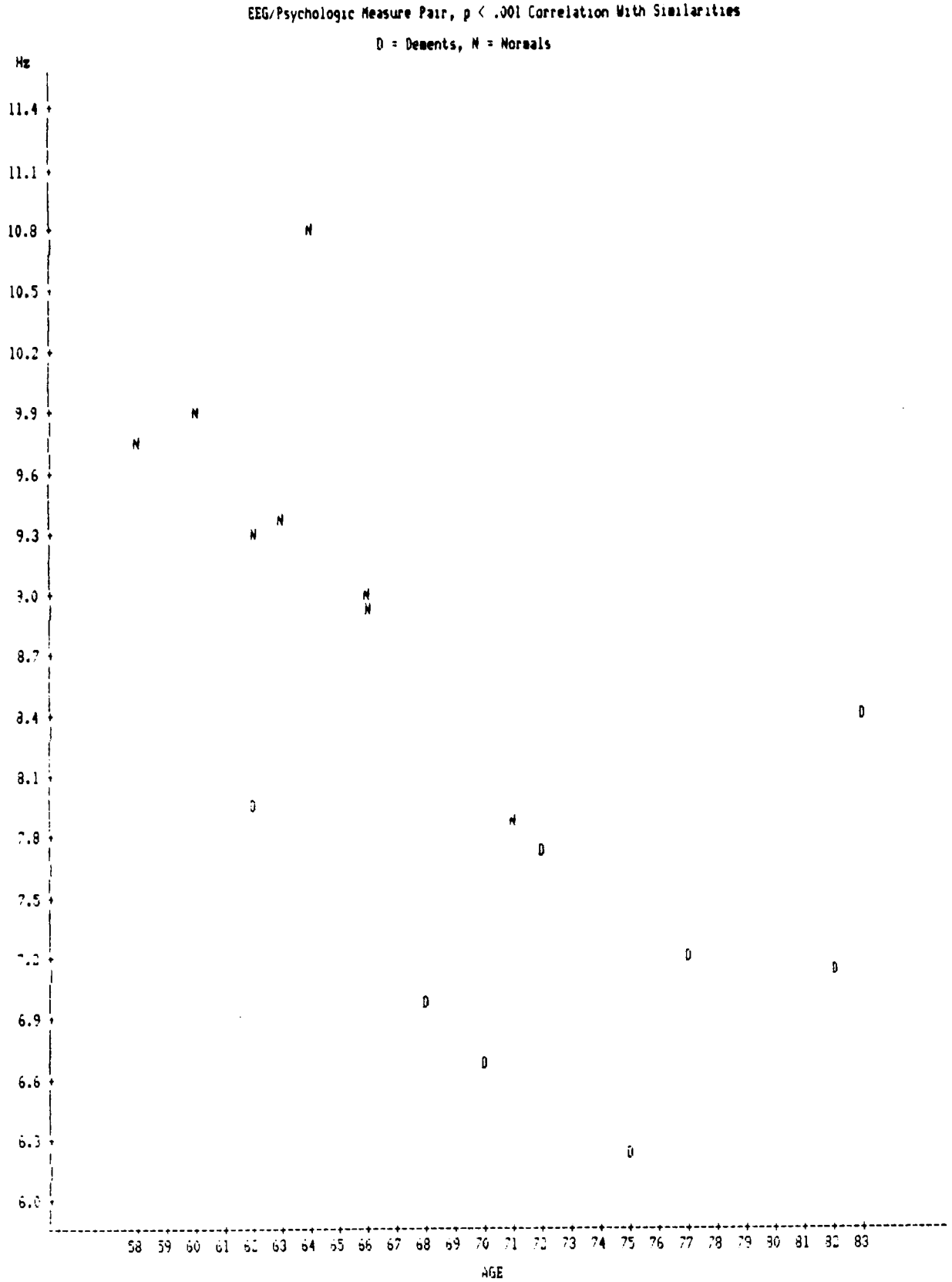


Figure 40. LISTEN MDN mean, front channel pair vs. age.

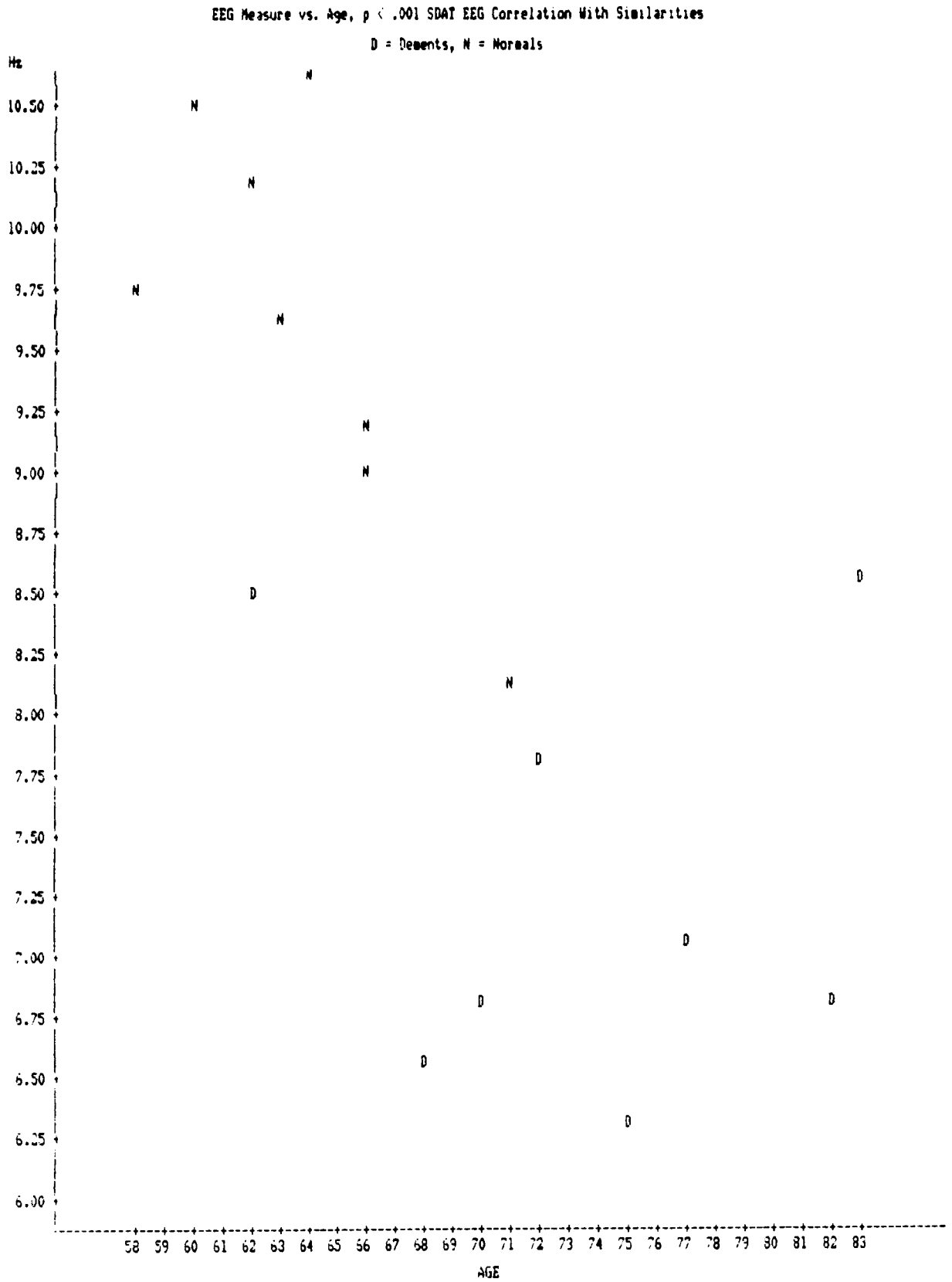


Figure 41. LISTEN MDN mean, back channel pair vs. age.

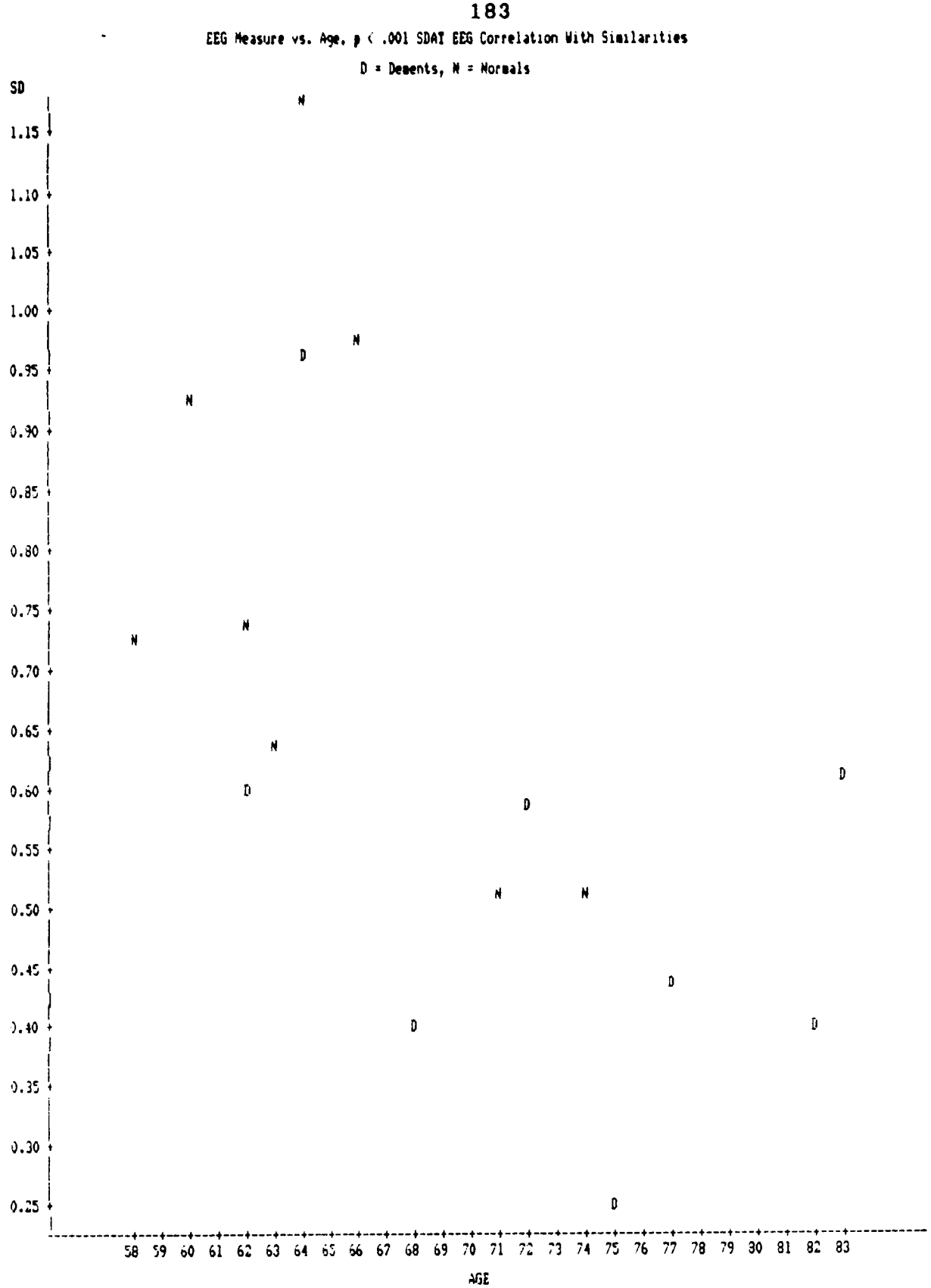


Figure 42. OPEN MDN SD, front channel pair vs. age.

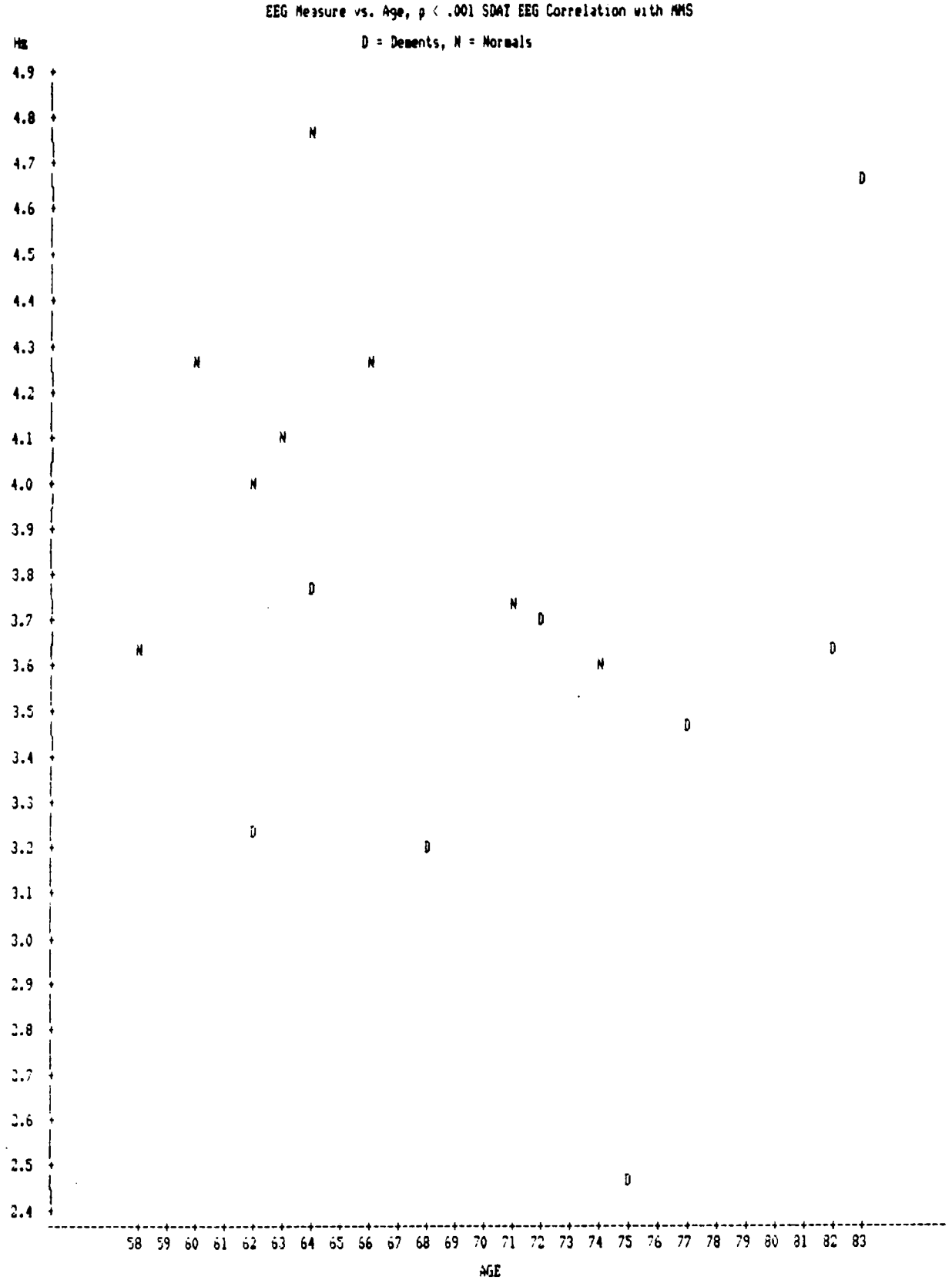


Figure 43. OPEN DROP WID mean, front channel pair vs. age.

IV. DISCUSSION

The final presentation of the hypotheses in the Introduction divided this study into five parts. First, the SDAT group needed to be confirmed as true probable AD patients. Second, the basic concepts about the DOR needed to be confirmed as present in the data. Third, the baseline values of the EEG measures, and the within-groups effects of stimulus condition activation on them, needed to be delineated. Fourth, across-groups comparisons of the measures needed to be done to evaluate the main hypotheses and the sensitivity of the various measures to group differences. Finally, correlations between EEG-based and psychologically-based measures were to be sought, based on the group rankings by these measures.

The findings of the study support the hypotheses of the first two parts, to the limits allowed by the techniques applied. The findings of the third and fourth parts, the core of the study, tended to replicate known findings and offered mixed support for the main hypotheses. The correlational analysis did successfully find a number of EEG/psychologic variable

correlation pairs, which cannot be taken as definitive due to the high number of correlations tested and a relatively low yield of significant pairs. Those pairs found do, however, tend to replicate previous findings or correspond to a remarkable degree in type and direction with the expectations of this study.

Validation of SDAT Group

The psychometric/neuropsychologic data as well as the DOR EEG measures in the baseline condition support the conclusion that the SDAT subjects were indeed probable AD patients. All of the members of the SDAT group had very poor scores on the psychometric measures. On the neuropsychologic measures for which five-point scales had to be created, the SDAT group consistently scored near the top of the scales, while the normal control group scored near the bottom.

The SDAT group had, as one would expect from previous findings, lower weighted mean frequency, lower mean and median DOR frequency.

Thus, on the measures applied in this study, all findings are consistent with the conclusion that the SDAT group genuinely consisted of moderately demented, probable AD patients. The followup information gathered on seven of the subjects supported this conclusion as well.

Validation of SDAT DOR as Slowed Alpha

The basic DOR mean parameters from the CLOSED baseline condition do not differ significantly between the two groups, save in frequency. This includes the measures of DOR amplitude, bandwidth, and amplitude/bandwidth ratios. This tends to confirm the notion that, insofar as the FFT technique is capable of describing it, the slow DOR of the SDATs is very similar to the faster DOR of the normal controls. It should also be noted that on all nine of the measures which change significantly on eye opening in the normal group, the SDAT group demonstrates a change in the same direction, though not to a statistically significant degree.

Admittedly, the FFT "window", especially as applied here with few channels, provides a limited view of all aspects of the underlying DOR activity evident in a multichannel EEG tracing. Such details as the topographic distribution, waveform morphology, and waveform variation certainly affect the FFT power spectrum, but in potentially subtle and nonspecific ways. The long-held view of many that increase in theta rhythm is a feature of AD cannot be rejected on the basis of the FFT data presented here. Visual inspection of the EEG tracings of these subjects, along with the above mentioned FFT findings, leads to the conclusion that for this SDAT subject group, the DOR seen is much more alpha-like than theta-like.

FFT Measures of EEG Findings

Individual Subject Percent Power Spectra

Before beginning the discussion of the EEG findings, I would like to present a brief discussion of the characteristics of the EEG as seen by FFT spectra. I think this will both help the reader understand the

data described below and might also offer insight into the intriguing, frustrating business of interpreting such data and designing measures to quantify the effects seen. To this end, I refer your attention to the individual subject grand average epoch spectra curves (Figures 5 through 21, pages 117 through 133).

These data, along with the accompanying individual epoch CSA plots (not shown), were the starting point for the development of my analysis method. As mentioned earlier, these grand average epoch spectra may obscure some of the interepoch effects the FFT measures quantify, but good indications of many of the individual and group differences to be discussed can be seen in those spectra.

As examples, compare the spectra of normal control subject number one (Figure 5, page 117) and SDAT subject number one (Figure 13, page 125). Looking at the middle set of plots for each of these subjects, the CLOSED condition data, visual inspection clearly shows the slower DOR hump of SDAT1. The DOR peak of SDAT1 centers at about 7 Hz, while that of NC1 centers at about 10 Hz. Referring to the lower of the pair of curves plotted for each channel, the actual grand

average epoch (the mean percent power across epochs, point-by-point), it would appear that the DOR peak bandwidth is about 4 Hz in each channel for both subjects. More difficult to determine visually is whether or not the DOR peak of NC1 is sharper than that of SDAT1. It would appear that this is probably the case to a mild degree. The two-standard deviation curves (the upper curve for each channel, plotted right atop the average percent power curve) definitely show a sharpness difference. That of NC1 is narrower and higher, indicating a sharper increase in amplitude variance surrounding the DOR peak as compared to SDAT1. It would appear that the "bandwidth" of the standard deviation variance peak is about the same as the grand average epoch DOR bandwidth for NC1, while that of SDAT1 extends a bit beyond the upper and lower DOR bandwidth boundaries. This could be an indication that the grand average epoch of SDAT1 represents DOR peak broadened through averaging of individual epoch DOR peaks which wander in frequency a bit. It seems that there is a good deal of potentially useful information present in the standard deviation curves, as it clearly highlights amplitude-active sections of the spectra.

DOR blocking on eye opening is clearly evident in the NC1 spectra, and the absence of blocking in SDAT1's data.

It so happens that the spectra of these two subjects, as well as several others, show patterns which fuel the speculations about the DOR alpha/theta issue. I have not explicitly stated a corollary of that issue, that is, If DOR slows into the theta frequency range in AD, what has become of genuine theta? There is a range of possible answers to this question, which were not directly studied here, and indeed, would be difficult to answer definitively. These possibilities include: genuine theta is virtually absent as in the normal alert adult, theta and DOR merge, theta slows in a fashion similar to DOR slowing, and of course the reverse of the postulation is possible, alpha-based DOR disappears and theta-based DOR takes over. Inspection of the OPEN and CLOSED spectra from NC1 presumably show the spectral pattern of genuine theta as a separate peak around 4 Hz. The value of the standard deviation curves is shown here, as the variance peak is much more noticeable than the underlying average peak. There is a hint of a similar peak in SDAT1's spectra centering

just below 4 Hz. This is perhaps best seen in the LISTEN condition. Complicating clear declaration of this little peak as theta is a rather bimodal appearance for the DOR peak in channels 5 and 6. I suspect that this indicates DOR activity with two major frequency components, but on these data alone it would be difficult to exclude definitively the possibility that the lower frequency component is the genuine theta, nearly merged with DOR. Interestingly, this lower frequency component seems to disappear in the LISTEN condition. There are several other subjects which show potential theta peaks separate from DOR and also several subjects, mostly SDATs, with bimodal DOR peaks. Perhaps all of the above possibilities are operative in different individuals.

Other patterns worth noting in the individual subject spectra include: several of the normal subjects, particularly NC4 and NC5, show a maximum DOR sharpness in channel 7 and a relative DOR broadening in channel 8; though the CLOSED vs. LISTEN comparison in both groups produced little effect on the study measures, visual comparison of the spectra often shows subtle differences in the curve shapes--often in

bandwidth differences or in the loss or gain of a frequency component producing a bimodal DOR appearance.

To conclude this examination of the individual spectra, I would invite the reader to peruse these plots a bit. I believe it is quite possible to form a gestalt perception of the SDAT-type of spectrum and the normal-type of spectrum, as well as to learn something about the dispersion of subtypes within these groups. It was through such examination of the spectra that I formed the conviction that, properly measured, sensitive FFT-based differentiation of the groups could be done. It was this conviction which saw me through the long process of developing such a set of measures. Finally, the reader's own impression of these spectra will allow for evaluation of the ultimate success and meaning of the results discussed below.

Effects of Activation Conditions

CLOSED vs. OPEN findings, normal subjects.

Activation by eye opening produced many significant

effects, as expected, on measures sensitive to DOR blocking. Referring to the individual spectra it can be seen that DOR blocking on eye opening in the normal group often virtually amounted to the complete cessation of DOR activity, as shown by the near-disappearance of the DOR spectral peak. As seen by the DOR MAX AMP and PWR/PT measures of the mean amplitude of the DOR peak point and the average percent power of all spectral data points within the DOR bandwidth, the effect of DOR blocking on percent power amplitude was to almost exactly halve the amplitude (14.78 percent vs. 7.37 percent for MAX AMP; 4.28 percent vs. 2.13 percent for DOR PWR/PT). One might also note that the total raw power fell to almost half its CLOSED value, but due to the across-subjects variance in total power this change was not statistically significant. This is an indication, though, of the difficulty of working with raw power measures, and also of how much DOR activity dominates the overall power spectrum.

The reduced level of DOR activity in the OPEN condition, which could be thought of as a state of "less organized" DOR, had been thought likely to be

accompanied by an increase in DOR amplitude and frequency variance. Such effects could be weakly seen only in frequency. The SD measures for MAX AMP and DOR PWR/PT showed significant drops on eye opening, but referring to the corresponding nonsignificant CV changes shows that the SD changes are nothing more than a byproduct of the amplitude/SD correlation--lower mean amplitude produced lower SDs, but there was actually no difference in terms of SD as a percent of the mean. The three frequency measures, WMF, MAX FRQ, and MDN all showed increases in SD and CV variance measures, but none significant at the .01 level (all were at the $p < .05$ level, however, with WMF and MAX FRQ nearly at .01--.0144 and .0101 respectively). The median-based bandwidth measure did increase on eye opening, which was probably due to intraepoch frequency distribution fluctuations. The drop-from-peak bandwidth change was not quite significant. Thus, when one accounts for known overall effects of reduced mean amplitude, there were no changes in amplitude variance measures, while weak signs of increased frequency variance could be seen.

With a much lower peak and average DOR percent power per point, as well as larger DOR bandwidths, one would expect the sharpness measures to fall, as indeed the mean DROP PK/WID measure did. The SDs for this measure also showed a decrease, but once again as for the other strongly amplitude-influenced measures, this variance effect disappeared in the CV measures.

The one not clearly expected effect was the increase in PRE PWR/PT, the average percent power per point of the spectral data points lower in frequency than the DOR. To the extent that this measure corresponds to a measure of theta activity, one would probably expect this measure to fall on eye opening if only because eye opening might reduce any drowsiness present. One might also expect it to fall as it is slightly contaminated with a residual amount of DOR, due to the fact that the DOR drop-based bandwidth measure is designed to cut off when 10 percent of the DOR base to peak distance is reached, leaving a bit of DOR "tail" in the pre-DOR measure. However, on a percent power measure, there may be a purely mathematical effect due to the big reduction in the amount of percent power taken up by the DOR. I suspect

that something like this is the case; it certainly does not represent the appearance of any significant amount of genuine rhythmic theta activity, as that would produce a large effect due to the huge amount of power in a theta waveform. This is probably an example of a spectral analysis measure effect which would be very difficult to relate to visual changes in the underlying EEG. Such measures may be of great value in distinguishing groups and conditions, but it is difficult to predict their behavior.

The overall DOR picture on eye opening in normals is that much lower and somewhat broader DOR peaks are seen in the FFT spectra, which nonetheless vary in amplitude about as much as eyes closed DOR peaks do, and probably vary a bit more in frequency than eyes closed DOR peaks do.

CLOSED vs. LISTEN findings, normal subjects.

The LISTEN condition was not very successful in altering the CLOSED EEG pattern. No main effects were seen on the thirteen measures, their SD, or CVs. Some suggestive interaction effects occurred at the channel

or channel pair level, which were seen to be in the direction of producing left/right asymmetries on median-based DOR bandwidth and average percent power per point above the DOR band. It is difficult to determine the meaning of these results. Presumably, a difference produced by listening to speech would be due to the activation of the receptive speech centers of the brain, that is, a left-sided activation primarily. However, the asymmetries produced in the data usually criss-crossed sides when going from the front channel pair to the back channel pair. Further study with more subjects and more channels would be needed to delineate fully potential speech reception effects on these measures, effects which are evidently quite subtle. For the purposes of this study, the pattern of interactions can only be of value in the comparison of the pattern displayed by the normal controls to that of the SDAT subjects. These two patterns did indeed differ, indicating that the LISTEN activation affected the two groups differently.

Across-conditions Findings, SDAT Subjects

The SDAT group did indeed demonstrate much less DOR reactivity across stimulus conditions. None of the effects of DOR blocking on eye opening evident in the normal control data occurred in the SDAT group to a significant degree. As noted above, the measures did change nonsignificantly in the proper directions, confirming that the SDATs' DOR is alpha-like. The SDAT response to listening to speech was even weaker than that of the normals, with no main effects and fewer interactions. Thus, the data show that the SDAT DOR is less subject to blocking or desynchronization than that of normals.

Across-groups Within Conditions Analyses

The results of comparing the two groups on the different stimulus conditions offered mixed support and disconfirmation of the hypotheses of DOR variance. In general, the hypotheses concerning reduced power amplitude variance in AD found support, while those proposing an increase in frequency variance did not.

The specific pattern of findings depended on stimulus condition as well. There were, however, a number of group differences on the variance measures, though sometimes in the direction opposite of prediction.

Findings in Support of Reduced Amplitude Variance

The strongest evidence of reduced moment-to-moment DOR amplitude variance was seen in the across-groups CLOSED and LISTEN comparisons of the two direct measures of DOR amplitude, MAX AMP and DOR PWR/PT. Indeed, these measures showed nothing but an amplitude variance difference, as the two groups did not differ on mean or SD measures; while the normal group had a significantly higher average CV in the LISTEN condition, the same effect was strong enough to also be seen in the total power measure. The significant differences on most of the sharpness CV measures was another aspect of this effect, as the corresponding width measures did not change. Thus, it was the amplitude component of the amplitude/width ratio sharpness measures which produced the difference.

These amplitude variance group differences disappeared in the OPEN condition comparison, though the percent power per point DOR CV values were very similar to those in the other two conditions. Presumably the slightly smaller groups used in the OPEN comparison resulted in a lower statistical significance level.

Frequency, Bandwidth, and Sharpness Measures Findings

The three frequency measures, weighted mean frequency, frequency of the DOR peak, and median DOR frequency all showed the expected group difference of a lower frequency in the SDAT group. This difference was maintained across all conditions. There were significant group differences in the frequency variance measures in only one case, and that difference opposed the prediction of increased variance in the SDAT group. The SD and CV measures of OPEN DOR MAX FRQ were significantly higher in the normal group. This is apparently an aspect of the strong DOR blocking effects of opening eyes in normals.

The mean bandwidth measures differed only in the OPEN comparison, and in that case the difference was opposite to the direction predicted in the main bandwidth hypothesis. Normals had a wider bandwidth than SDATs. This effect was, however, a consequence of the success of the DOR reactivity difference prediction--i.e., an aspect of the DOR blocking in normals was broadened DOR bandwidth, which did not occur in the SDAT group. In each of the across-groups condition comparisons at least one bandwidth SD measure showed a significantly higher value for the normal group, indicating that this was a genuine effect which had not been predicted.

As hypothesized, the sharpness measures always showed higher variance values in the normal group, with at least one CV measure reaching the .01 significance level in each of the comparisons. This is the strongest result indicating that the DOR of normals is more modulated than that of SDATs.

PRE PWR/PT and POST PWR/PT Findings

The PRE PWR/PT measures of the average percent power per point of points less than DOR in frequency

and greater than 4.00 Hz were always higher in mean value for the SDAT group, significantly so in the LISTEN condition. In the OPEN and LISTEN comparisons, the mean CV values were higher in SDATs at the $p < .001$ level, and the SD values were also higher. Nonsignificant differences in the same direction occurred in the OPEN condition. As mentioned in the discussion of the CLOSED vs. OPEN comparison, this measure can be thought of as a measure of theta, though if genuine runs of rhythmic theta were occurring very much, one would expect the mean values to be much higher. Nevertheless, considered purely as a spectral measure of slow activity, it seems to be higher in mean and variance in the SDAT group. Although this measure does not exactly match any other researcher's in definition, this finding would correspond to the often stated fact that slow activity increases in AD.

In a like manner, the POST PWR/PT measure can be thought of as a measure of low frequency beta activity (from the high end of DOR to 16.00 Hz). Several of the normal subjects had genuine beta peaks, though often centered above 16.00 Hz. For the rest, this measure is another spectrally-based measure of uncertain

relationship to the underlying EEG tracing. The normals had a higher SD value in the OPEN condition, but no other POST PWR/PT measure differed significantly between groups. The normal mean was always higher than the SDAT mean, though, which is what one would expect from the literature.

EEG/Psychologic Measures Correlations

The correlational data must be approached very cautiously with such small groups and such a large number of attempted correlations. An added problem is the known high correlations between many of the EEG measures and between a number of the psychologic measures. This latter situation makes it difficult to determine how meaningful it is that the SDAT group had many more correlated pairs than the normal control group. One correlation which in some way represents a genuine electrophysiologic/psychologic relationship may be picked up on several other pairs of similar measures. An assessment of the likely value of these correlations must fall back on some secondary criteria,

such as if at least some of them match expectations from other studies, if there is an overall theoretically reasonable pattern, and judgments from visual inspection of the scatterplots. Finally, I believe that such considerations, as well as the data itself, argue that a large portion of the correlated pairs found in the SDAT group represent genuine, meaningful relationships, and can at least be considered good candidates for further study.

The first feature to note in the SDAT data set is that the major cluster of correlations found are between the EEG and psychologic variables already shown to be most affected by AD. These were the mean DOR frequency variables with the MMS and WAIS measures. Coben, et. al. (1985) and others have found similar correlations before, though usually with a weighted mean frequency measure (which did occur here as well in one case). Another general feature worth noting is that the division by front and back channel pairs was worthwhile, since few correlations on both the front and the back pair were found. It must also be noted that, though SD and CV measures were well represented, only two appeared alone in the table without their

corresponding mean variables. While it is gratifying that some of the variance measures this study focussed on did appear, it seems that they were highly correlated rank-wise with their mean measure, and offered little extra power to this analysis.

The direction of every SDAT correlation matches what one would expect. Examples would be the DOR frequency measures, which were all in the direction of increased frequency correlating with better psychologic scores. Less obvious, but strengthened by the appearance of correlations for both OPEN and LISTEN conditions were the negative correlations, or positive correlations with negatively-valued measures, with PRE PWR/PT. One would expect this measure of slow activity to increase with decreased cognitive status.

Referring to the selected scatterplots it can be seen that many of the distributions of SDAT points had easily believable linear regressions. Figure number 37, page 178, is an extreme example of this. The normal data points are included in order to assess the likelihood that the SDAT trends were continued in the normal group. Actual regression tests were not done with such small groups, but as one would expect with

plots selected for SDAT significance, the SDAT group usually clearly shows a more organized pattern, and often a separation from the normal control pattern.

The normal control data did seem to differ in kind from the SDAT data. The pattern made less sense and the plots showed less clustering or ordering of the data points. This, along with the far fewer correlations, at least within the WAIS measures where true grading of the normal group by cognitive abilities was best assessed, makes it appear that the normal control correlations may indeed represent the random significant correlations one would expect to find in such an analysis.

The demographic and medical history correlations are another mixed bag. Several of these would be startling findings if true (such as the one measure in each group which correlates with years of education). More likely, particularly in the normal group where most of these variables were at the very low end of the scale with little variance, these are random, Type I error outcome, showing how modest must the conclusions be from this data set.

As a constant concern in this study was the age difference between groups, Figures 40 through 43, pages 181-184, are shown to demonstrate visually that the failure to find significant correlations with age was reasonable, even on the EEG component of the most significant pairs.

Conclusions

Limitations and Strengths of the Study

There are clearly several factors in this study which place limits on how firmly conclusions can be drawn. Chief among these is the small number of subjects in each group, which was further reduced in analysis by artifactual data. Secondly, the two groups differed in age by a statistically significant amount. The first factor would tend to reduce the chances of finding significant group differences, while the second might enhance group differences on some EEG variables which covary with age. The EEG variables known to be most affected by aging are the very DOR frequency variables of interest. That is, DOR frequency is known

to decline with age. The more recent studies using extremely healthy aged individuals tend to show this as a minor effect. As the subjects used in this study were all that were available to me at the time of data-gathering, there was little choice but to accept this group difference and check as best I could for age effects in the data.

This was difficult to do rigorously, as any measure showing a large group difference was also likely to show an age effect, since the age difference was a genuine group difference as well. An earlier set of analyses of variance were done with age as a covariate. In those analyses, the between-groups significance values for most measures was reduced approximately an order of magnitude. Covariance tests with age were done with the CLOSED and OPEN EEG data and showed very few significances, and then only on the variables known to separate the groups strongly. Visual inspection of a number of variables plotted against age rarely showed convincing age-related patterns.

This study clearly demonstrated that moderately demented SDAT patients differ from normals in their amount of DOR amplitude reactivity and variability.

There was little to distinguish SDAT EEG data across all three stimulus conditions, while the normal's patterns changed dramatically. The hypothesized higher variability in DOR frequency in SDAT did not occur.

A number of plausible rank correlations were found between SDAT EEG measures and psychologic measures. Beyond the previously known correlations of mean frequency and psychologic measures of dementia, there were several correlation pairs which included EEG measures of DOR variability, bandwidth, and peak sharpness. These measures would be likely candidates for further study.

The ultimate goal of this line of research would be to find out if the variance measures of FFT-measured EEG activity add to the sensitivity and specificity of EEG evaluation in AD. The findings of this study show that the FFT amplitude CV measures can distinguish between the groups nearly as well as the mean frequency measures can. This would make them good candidates for application in further studies to investigate whether or not these differences occur in milder AD, and whether or not these differences can be used to distinguish AD from other dementing conditions with more specificity than current techniques allow.

LIST OF REFERENCES

REFERENCES

Agnoli, A., Martucci, N., Manna, V., Conti, L., & Fioravanti, M. (1983). Effect of cholinergic and anticholinergic drugs on short-term memory in Alzheimer's disease: a neuropsychological and computerized electroencephalographic study. Clinical Neuropharmacology, 6(4), 311-323.

American Psychiatric Association. (1978). Diagnostic and Statistical Manual of Mental Disorders (3rd Edition). Washington, D.C. American Psychiatric Association.

Andersen, P., & Andersen, S.A. (1968). Physiological Basis of the Alpha Rhythm. New York: Meredith Corporation.

Basar, E. (1980). EEG-Brain Dynamics. Amsterdam, the Netherlands: Elsevier/North Holland Biomedical Press.

Berg, L. (1985). Does Alzheimer's disease represent an exaggeration of normal aging? Archives of Neurology, 42, 737-739.

Berg, L., Danziger, W.L., Storandt, M., Coben, L.A., Gado, M., Hughes, C.P., Knesevich, J.W., & Botwinick, J. (1984). Predictive features in mild senile dementia of the Alzheimer's type. Neurology, 34, 563-569.

Bickford, R.G., Fleming, N.I., & Bellinger, T.W. (1971). Compression of EEG data by isometric power spectral plots. EEG and Clinical Neurophysiology, 31, 632.

Blessed, G., Tomlinson, B.E., & Roth, M. (1968). The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. British Journal of Psychiatry, 114, 797-811.

Brenner, R.P., Reynolds, C.F., & Ulrich, R.F. (1988). Diagnostic efficacy of computerized spectral versus visual EEG analysis in elderly normal, demented and depressed subjects. Electroencephalography and Clinical Neurophysiology, 69, 110-117

Brenner, R.P., Ulrich, R.F., Spiker, D.G., Sclabassi, R.J., Reynolds, C.F., Marin, R.S., & Boller, F. (1986). Computerized EEG spectral analysis in elderly normal, demented and depressed subjects. Electroencephalography and Clinical Neurophysiology, 64, 483-492.

Breslau, J., Starr, A., Sicotte, N., Higa, J., & Buchsbaum, M.S. (1989). Topographic EEG changes with normal aging and SDAT. Electroencephalography and Clinical Neurophysiology, 72, 281-289.

Burke, W.J., Miler, J.P., Rubin, E.H., Morri, J.C., Coben, L.A., Duchek, J., Wittes, I.G., & Berg, L. (1988). Reliability of the Washington University clinical dementia ratng. Archives of Neurology, 45, 31-32.

Busse, E.W. (1983). Electroencephalography. In Reisberg, B. (Ed.), Alzheimer's Disease. New York: The Free Press.

Busse, E.W., & Obrist, W.D. (1965). Pre-senescent electroencephalographic changes in normal subjects. Journal of Gerontology, 20, 315-320.

Chui, H.C., Teng, E.L., Henderson, V.W., & Moy, A.C. (1985). Clinical subtypes of dementia of the Alzheimer's type. Neurology, 35, 1544-1550.

Coben, L.A., Danziger, W.L., & Berg, L. (1983). Frequency analysis of the resting awake EEG in mild senile dementia of Alzheimer's type. Electroencephalography and Clinical Neurophysiology, 55, 372-380.

Coben, L.A., Danzinger, W., & Storandt, M. (1985). A longitudinal EEG study of mild senile dementia of Alzheimer type: changes at 1 year and 2.5 years. Electroencephalography and Clinical Neurophysiology, 61, 101-112.

Consensus Conference. (1987). Differential diagnosis of dementing diseases. Journal of the American Medical Association, 258(23), 3411-3416.

Cooley, W.J. & Tukey, J.W. (1965) An algorithm for the machine calculation of complex Fourier series. Mathematical Computing, 19, 297-301.

Coolidge, F.L., Peters, B.M., Brown, R.E., Harsch, T.L., & Crookes, T.G. (1985). Validation of a WAIS algorithm for the early onset of dementia. Psychological Reports, 57(3 pt.2), 1299-1302.

Davies, P., & Maloney, A.J.F. (1976). Selective loss of central cholinergic neurons in Alzheimer's disease. Lancet, 2, 1403.

Davison, A.N. (1987). Pathophysiology of the ageing brain. Gerontology, 33, 129-135.

Diagnostic and Statistical Manual of Mental Disorders. (3rd Edition, 1980). Washington, D.C.: American Psychiatric Association.

Duffy, F.H., Albert, M.S., & McAnulty, G. (1984). Brain electrical activity in patients with presenile and senile dementia of the Alzheimer type. Annals of Neurology, 16, 439-448.

Dumermuth, G., & Molinari, L. (1987). Spectral analysis of EEG background activity. In Gevins, A.S. & Remond, A. (Eds.), Methods of Analysis of Brain Electrical and Magnetic Signals. EEG Handbook (revised series, Volume 1). Amsterdam, the Netherlands: Elsevier Science Publishers (Biomedical Division).

Ebersole, J.S. (1987). Physiological substrates of normal and abnormal EEG activity. In American Electroencephalographic Society (Ed.), 22nd Annual Course in Clinical EEG and Electrophysiology: Day 1 (pp. JSE-1 to JSE-14). Atlanta, Georgia: American Electroencephalographic Society.

Empson, J. (1986). Human Brainwaves. New York: Stockton Press.

Fenton, G. W. (1986). Electrophysiology of Alzheimer's disease. British Medical Bulletin, 42(1), 29-33.

Folstein, M.F., Folstein, S.E., & McHugh, P.R. (1975). "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research, 12, 189.

Friedland,, R.P., moderator. (1988). Alzheimer disease: clinical and biologic heterogeneity. Annals of Internal Medicine, 109, 298-311.

Gabor, A.J. (1978). Physiological Basis of Electrical Activity of Cerebral Origin. Quincy, Massachusetts: Grass Instrument Company.

Gandolfo, C., Vecchia, R., Moretti, C., Brusa, G., & Scotto, P.A. (1986). WAIS testing in degenerative and multi-infarct dementia. Clinica Neurologica, 8(1), 45-50.

Garcia, C.A., Reding, M.J., & Blass, J.P. (1981). Overdiagnosis of dementia. Journal of American Geriatrics Society, 29, 407-410.

Gevins, A.S. (1987). Introducton. In Gevins, A.S. & Remond, A. (Eds.), Methods of Analysis of Brain Electrical and Magnetic Signals. EEG Handbook (revised series, Volume 1). Amsterdam, the Netherlands: Elsevier Science Publishers.

Gevins, A.S. (1987). Overview of computer analysis. In Gevins, A.S. & Remond, A. (Eds.), Methods of Analysis of Brain Electrical and Magnetic Signals. EEG Handbook (revised series, Volume 1). Amsterdam, the Netherlands: Elsevier Science Publishers.

Gevins, A.S., Zeitlin, G.M., Doyle, J.C., Schaffer, R.E., & Callaway, E. (1979). EEG patterns during "cognitive" tasks. II. Analysis of controlled tasks. Electroencephalography and Clinical Neurophysiology, 47, 704-710.

Giaquinto, S., & Nolfe, G. (1986). The EEG in the normal elderly: a contribution to the interpretation of aging and dementia. Electroencephalography and Clinical Neurophysiology, 63, 540-546.

Gibbs, F.A, & Gibbs, E.L. (1958). Atlas of Electroencephalography (Volume 1). Reading, Massachusetts: Addison-Wesley.

Gibbs, F.A., Lennox, W.G., & Gibbs, E.L. (1941). The cortical frequency spectrum in epilepsy. Archives of Neurology and Psychiatry, 46, 613-620.

Goodin, D.S., Squires, K.C., & Starr, A. (1978). Long-latency event-related components of the auditory evoked potential in dementia. Brain, 101, 635-648.

Gordon, E.B. (1968). Serial EEG studies in presenile dementia. British Journal of Psychiatry, 114, 779-780.

Gordon, E.B., & Sim, M. (1967). The EEG in presenile dementia. Journal of Neurology, Neurosurgery, & Psychiatry, 30, 285-291.

Grabow, J.D., Aronson, A.E., Greene, K.L., & Offord, K.P. (1979). A comparison of EEG activity in the left and right cerebral hemispheres by power-spectrum anaylsis during language and non-language tasks. Electroencephalography and Clinical Neurophysiology, 47, 460-472.

Grass, A.M. (1984). The Encephalographic Heritage. Quincy, Massachusetts: Grass Instrument Company.

Grass, A.M., & Gibbs, F.A. (1938). A Fourier transform of the electroencephalogram. Journal of Neurophysiology, 1, 521-526.

Gubrium, J.F. (1986). Oldtimers and Alzheimer's: The Descriptive Organization of Senility. Greenwich: JAI Press.

Harner, R.N. (1975). EEG evaluation of the patient with dementia. In Benson, D.R. & Blumer, D. (Eds.), Psychiatric Aspects of Neurological Disease. New York: Grunne & Stratton.

Hart, R.P., Kwentus, J.A., Wade, J.B., & Hamer, R.M. (1987). Digit symbol performance in mild dementia and depression. Journal of Consulting and Clinical Psychology, 55(2), 236-238.

Henderson, V.W., & Finch, C.E. (1989). The neurobiology of Alzheimer's disease. Journal of Neurosurgery, 70, 335-353.

Huff, F.J., Becker, J.T., Belle, S.H., Nebes, R.D., Holland, A.L., & Boller, F. (1987). Cognitive deficits and clinical diagnosis of Alzheimer's disease. Neurology, 37, 1119-1124.

Huff, F.J., Growdon, J.H., Corkin, S., & Rosen, J. (1987). Age at onset and rate of progression of Alzheimer's disease. Journal of the American Geriatrics Society, 35(1),27-30.

Hughes, J.R., 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.

Hughes, J.R., & Cayaffa, J.J. (1977). The EEG in patients at different ages without organic cerebral disease. Electroencephalography and Clinical Neurophysiology, 42, 776-784.

Huppet, F.A., & Tym, E. (1986). Clinical and Neurophysiological assessment of dementia. British Medical Bulletin, 42(1), 11-18.

Johannesson, G., Brun, A., Gustafson, I., & Ingvar, D.H. (1977). EEG in presenile dementia related to cerebral blood flow and autopsy findings. Acta Neurologica Scandinavica, 56, 89-103.

Johannesson, G., Hagberg, B., Gustafson, L., & Ingvar, D.H. (1979). EEG and cognitive impairment in presenile dementia. Acta Neurologica Scandinavica, 59, 225-240.

Kaszniak, A.W., Garron, D.C., Fox, J.H., Bergen, D., & Huckman, M. (1979). Cerebral atrophy, EEG slowing, age, education, and cognitive functioning in suspected dementia. Neurology, 29, 1273-1279.

Katz, R.I., & Harner, R.N. (1987). Electroencephalography in aging. In American Electroencephalographic Society (Ed.), 22nd Annual Course in Clinical EEG and Electrophysiology: Day 2 (pp. 114-138). Atlanta, Georgia: American Electroencephalographic Society.

Katz, R.I. & Horowitz, G.R. (1982). EEG in the septuagenarian: studies in a normal geriatric population. Journal of the American Geriatrics Society, 3(4), 273-275.

Katzman, R. (1986). Medical progress: Alzheimer's disease. The New England Journal of Medicine, 314(15), 964-973.

Khachaturian, Z.S. (1985). Diagnosis of Alzheimer's disease. Archives of Neurology, 42, 1097-1105.

Kidd, M. (1963). Paired helical filaments in electron microscopy of Alzheimer's disease. Nature, 197, 192-193.

Knott, J.R., Gibbs, F.A., & Henry, C.E. (1942). Fourier transforms of the electroencephalogram during sleep. Journal of Experimental Psychology, 31(6), 465-477.

Kooi, K.A., Guvener, A.M., Tupper, C.J., & Bagchi, B.K. (1964). Electroencephalographic patterns in the temporal regions on normal adults. Neurology, 14, 1029-1035.

Kvale, J.N. (1986). Alzheimer's disease. Annals of Family Practice, 34(1), 103-110.

Larrabee, G.J., Large, J.W., & Levin, H.S. (1985). Sensitivity of age-decline resistant ("Hold") WAIS subtests to Alzheimer's disease. Journal of Clinical and Experimental Psychology, 7(5), 497-504.

Lazarus, L.W., Newton, N., Cohler, B., Lesser, J., & Schweon, C. (1987). Frequency and presentation of depressive symptoms in patients with primary degenerative dementia. American Journal of Psychiatry, 144(1), 41-45.

Letemendia, F., & Pampiglione, G. (1958). Clinical and electroencephalograpic observations in Alzheimer's disease. Journal of Neurology, Neurosurgery, & Psychiatry, 21, 167-172.

Leuchter, A.F., Spar, J.E., Walter, D.O., & Weiner, H. (1987). Electroencephalographic spectra and coherence in the diagnosis of Alzheimer's-type and multi-infarct dementia. Archives of General Psychiatry, 44, 993-998.

Mahendra, B. (1984). Dementia. Boston: MJP Press.

Mayeux, R., Stern, Y. & Spanton, S. (1985). Heterogeneity in dementia of the Alzheimer's type: evidence of subgroups. Neurology, 35(4), 453-461.

McAdam, W., & Robinson, R.A. (1956). Senile intellectual deterioration and the electroencephalogram: a quantitative correlation. Journal of Mental Science, 102, 819-825.

McGeer, P.I. (1986). Brain imaging in Alzheimer's disease. British Medical Bulletin, 42(1), 24-28.

McIntyre, H.D. (1985). The electroencephalogram in Alzheimer disease. Bulletin of Clinical Neurosciences, 50, 18-22.

McKhann, G., Folstein, M., Katzman, R., Price, D., & Stadlan, E.M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task force on Alzheimer's disease. Neurology, 34, 939-944.

Merskey, H., Ball, M.J., Blume, W.T., Fox, A.J., Fox, H., Hersch, E.L., Kral, V.A., & Palmer, R.B. (1980). Relationships between psychological measurements and cerebral organic changes in Alzheimer's disease. Canadian Journal of Neurological Science, 7(1), 45-49.

Mundy-Castle, A.C. (1951). Theta and beta rhythm in the electroencephalogram of normal adults. Electroencephalography and Clinical Neurophysiology, 3, 477-486.

Mundy-Castle, A.C., Hurst, L.A., Beerstecher, D.M., & Prinsloo, T. (1954). The electroencephalogram in the senile psychoses. Electroencephalography and Clinical Neurophysiology, 6, 245-252.

Nunez, P.L. (1981). Electric Fields of the Brain. New York: Oxford University Press.

Obrist, W.D. (1953). The electroencephalogram of normal aged adults. Electroencephalography and Clinical Neurophysiology, 6, 235-244.

Obrist, W.D. & Bissell, L.F. (1955). The electroencephalogram of aged patients with cardiac and cerebrovascular disease. Journal of Gerontology, 10, 315-330.

Obrist, W.D., Busse, E.W., Eisdorfer, C., & Kleemeier, R.W. (1962). Relation of the electroencephalogram to intellectual function in senescence. Journal of Gerontology, 17, 197-206.

O'Conner, K.P., Shaw, J.C., & Ongley, C.O. (1979). The EEG and differential diagnosis in psychogeriatrics. British Journal of Psychiatry, 135, 156-162.

Osorio, I. (1987). Organization and function of diffuse afferent cortical projection systems. In American Electroencephalographic Society (Ed.), 22nd Annual Course in Clinical EEG and Electrophysiology: Day 1 (pp. IO-1 to IO-13). Atlanta, Georgia: American Electroencephalographic Society.

Ottomo, E. (1966). Electroencephalography in old age: Dominant alpha pattern. Electroencephalography and Clinical Neurophysiology, 21, 489-491.

Ottomo, E., & Tsubaki, T. (1966) Electroencephalography in subjects sixty years and older. Electroencephalography and Clinical Neurophysiology, 20, 77-82.

Patterson, M.B., Gluck, H., & Mack, J.L. (1983). EEG activity in the 13-15 Hz band correlates with intelligence in healthy elderly women. International Journal of Neuroscience, 20, 161-172.

Pedley, T.A., & Miller, J.A. (1983). Clinical neurophysiology of aging and dementia. In R. Mayeux & W.G. Rosen (Eds.), The Dementias (pp. 31-49). New York: Raven Press.

Penttila, M., Partanen, J.V., Soininen, H., & Reikkinen. (1985). Quantitative analysis of occipital EEG in different stages of Alzheimer's disease. Electroencephalography and Clinical Neurophysiology, 60, 1-6.

Pepeu, G. (1988). Acetylcholine and brain aging. Pharmacological Research Communications, 20(2), 91-97.

Pomara, N., & Stanley, M. (1986). The cholinergic hypothesis of memory dysfunction in Alzheimer's disease--revisited. Psychopharmacology Bulletin, 22(1), 110-118.

Powers, L.B., & Dougherty, J.H. (1985). Dementia of the Alzheimer's type: clinical overview. Journal of the Tennessee Medical Association, (January), 13-15.

Prinz, P.N., Peskind, E.R., Vitaliano, P.P., Raskind, M.A., Eisdorfer, C., Zemcuznikov, N., & Gerber, C.J. (1982). Changes in the sleep and waking EEGs of nondemented and demented elderly subjects. Journal of the American Geriatrics Society, 30(2), 86-93.

Reifler, B.V. (1988). Clinical problems in geriatric psychiatry: The relationship between dementia of the Alzheimer's type and depression. North Carolina Medical Journal, 49(10), 536-538.

Reisberg, B. (1983). An overview of current concepts of Alzheimer's disease, senile dementia, and age-associated cognitive decline. In B. Reisberg (Ed.), Alzheimer's Disease. New York: The Free Press.

Roberts, M.A., McGeorge, A.P., & Caird, F.I. (1978). Electroencephalography and computerized tomography in vascular and non-vascular dementia in old age. Journal of Neurology, Neurosurgery, & Psychiatry, 41, 903-906.

Ron, M.A., Tonney, B.K., Garralda, M.E., & Lishman, W.A. (1979). Diagnostic accuracy in presenile dementia. British Journal of Psychiatry, 134, 161-168.

Roubicek, J. (1977). The electroencephalogram in the middle-aged and the elderly. Journal of the American Geriatrics Society, 25(4), 145-152.

Rugg, M.D., & Dickens, A.M.J. (1982). Association of alpha and theta activity as a function of verbal and visuospatial tasks. Electroencephalography and Clinical Neurophysiology, 53, 201-207.

Rumsey, J.M., Coppola, R., Denckla, M., Hamburger, S.D., & Kruesi, M.J.P. (1989). EEG spectra in severely dyslexic men: rest and word and design recognition. Electroencephalography and Clinical Neurophysiology, 73, 30-40.

Silverman, J., Busse, E.W., & Barnes, R.H. (1955). Studies in the process of aging: electroencephalographic findings in 400 elderly subjects. Electroencephalography and Clinical Neurophysiology, 7, 67-72.

Soininen, H., Partanen, V.J., Helkala, E.L., & Reikkinen, P.J. (1982). EEG findings in senile dementia and normal aging. Acta Neurologica Scandinavica, 65, 59-70.

Soininen, H., Partanen, J., Laulumaa, V., Helkala, E.-L., Laakso, M., & Reikkinen, P.J. (1989). Longitudinal EEG spectral analysis in early stage of Alzheimer's disease. Electroencephalography and Clinical Neurophysiology, 72, 290-297

Soininen, H., Partanen, V.J., Puranen, M., & Reikkinen, P.J. (1982). EEG and computed tomography in the investigation of patients with senile dementia. Journal of Neurology, Neurosurgery, and Psychiatry, 45, 711-714.

Stefoski, D., Bergen, D., Fox. J., Morrell, F., Huckman, M., & Ramsey, R. (1976). Correlation between diffuse EEG abnormalities and cerebral atrophy in senile dementia. Journal of Neurology, Neurosurgery, and Psychiatry, 39, 751-755.

Stigsby, B., Johannesson, G., & Ingvar, D.H. (1981). Regional EEG analysis and regional cerebral blood flow in Alzheimer's and Pick's diseases. Electroencephalography and Clinical Neurophysiology, 51, 537-547.

Swain, J.M. (1959). Electroencephalographic abnormalities in presenile atrophy. Neurology, 9(11), 722-724.

Strub, R.L., & Black, F.W. (1985). The Mental Status Examination in Neurology. Philadelphia: F.A. Davis Company.

Terry, R.D., Gonatas, N.K., & Weiss, M. (1964). Ultra structural studies in Alzheimer's presenile dementia. American Journal of Pathology, 44, 269-297.

Terry, R.D., & Katzman, R. (1983). Senile dementia of the Alzheimer's type. Annals of Neurology, 14(4), 497-506.

Tierney, M.C., Snow, W.G., Reid, D.W., Zorzitto, M.L., & Fisher, R.H. (1987). Psychometric differentiation of dementia: replication and extension of the findings of Storandt and coworkers. Archives of Neurology, 44, 720-722.

Tomlinson, B.E. (1977). Morphological changes and dementia in old age. In Smith, W.L., & Kinsbourne, B.M. (Eds.), Aging and Dementia. New York: Spectrum Publications.

Verma, N.P., Greiffenstein, M.F., Verma, N., King, S.D., & Caldwell, D.L. (1987). Electrophysiologic validation of two categories of dementias--cortical and subcortical. Clinical Electroencephalography, 18(1), 26-33.

Wade, J.P., Mirsen, T.R., Hachinski, V.C., Fisman, M., Lau, C., & Merskey, H. (1987). The clinical diagnosis of Alzheimer's disease. Archives of Neurology, 44, 24-29.

Wang, H.S. (1977) Dementia of old age. In Smith, W.L. & Kinsbourne, B.M. (Eds.), Aging and Dementia. New York: Spectrum Publications.

Weiner, H., & Schuster, D.B. (1956). The electroencephalogram in dementia: some preliminary observations and correlations. Electroencephalography and Clinical Neurophysiology, 8, 479-488.

Whitehouse, P.J., Price, D.L., Struble, R.G., Clark, A.W., Coyle, J.T., & DeLong, M.R. (1982). Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain. Science, 215, 1237-1239.

Williams, J.M., Klein, K., Little, M., & Haban, G. (1986). Family observations of everyday impairment in dementia. Archives of Clinical Neuropsychology, 1, 103-109.

APPENDIXES

APPENDIX A

HARDWARE DETAILS

This study was carried out with the following hardware (supplier/manufacturer noted in parentheses):

EEG Machine (Nihon Kohden America):

Nihon Kohden model EEG 7209 eight-channel EEG machine.

PDP-11/73 Computer System (Trimarchi and Associates):

System Unit:

SA-H125 system enclosure (SIS)
KDJ-11AA cpu board (DEC)
QRAM-22 1 megabyte RAM board (Clearpoint Inc.)
20 megabyte Winchester disk drive (Rodime)
20 megabyte Winchester disk drive (Syquest)
SDC-RLV12 Winchester disk controller (SIS)
1 megabyte floppy disk drive (Mitsubishi)
SDC-RXV31 Floppy disk controller (SIS)
DLV11-J serial line unit board (DEC)
AXV11-C analog input/output board (DEC)
KWV11-C real-time clock board (DEC)
DR11 board (DEC)
QRGB-Graph video board (Matrox Electronic Systems)

Peripherals:

WY75 CRT terminal (Wyse)
LA100-ZA Letterprinter dot-matrix printer (DEC)
HP7470 X-Y plotter (Hewlett Packard)
4020 color ink jet printer (Xerox)
C-3419 high resolution color display monitor (Matrox)

Associated Equipment:

PM3217 oscilloscope (Philips)
Circuitmate FG2 function generator (Beckman Industrial)
Custom-built TTL-pulse generator
Custom-built response switch

APPENDIX B

Date:_____

RATING SCALE–RELATIVE REPORT FORM

J. Michael Williams, Ph.D., Marsha Little, and Glen Haban
Memphis State University

Name of relative or friend to be rated:_____

Name of rater:_____

Instructions: Below is a list of phrases used to describe someone. How well do each of these descriptions characterize the person you were asked to evaluate?

	Not at all like the person	A little bit	Moderately	Quite a bit	Extremely like the person
Cross out the number to the right of the statement which matches your rating, like this: Misplaces objects	1	X	3	4	5
Now, make such a rating for each of these phrases.					
1. Has difficulty remembering the name of friends	1	2	3	4	5
2. Is able to maintain a simple converation	1	2	3	4	5
3. Has difficulty remembering the names of objects	1	2	3	4	5
4. Can easily tolerate changes in routine	1	2	3	4	5
5. Misplaces objects	1	2	3	4	5
6. Loses the train of thought in conversation	1	2	3	4	5
7. Remembers well	1	2	3	4	5
8. Hides objects	1	2	3	4	5
9. Denies problems with memory or thinking	1	2	3	4	5
10. Unaware of surroundings	1	2	3	4	5
11. Loses track of time	1	2	3	4	5
12. Takes off clothes in public	1	2	3	4	5
13. Seems confused	1	2	3	4	5
14. Forgetful	1	2	3	4	5
15. Panics	1	2	3	4	5
16. Angers easily	1	2	3	4	5
17. Has difficulty starting actions	1	2	3	4	5
18. Has difficulty dressing	1	2	3	4	5
19. Restless at night	1	2	3	4	5
20. Gets lost in unfamiliar places	1	2	3	4	5
21. Gets lost in familiar places	1	2	3	4	5
22. Has tremors in arms or legs	1	2	3	4	5
23. Is apathetic, doesn't seem interested in events	1	2	3	4	5
24. Is listless or tired	1	2	3	4	5
25. Withdrawn	1	2	3	4	5
26. Irritable	1	2	3	4	5
27. Tolerates frustration well	1	2	3	4	5
28. Nervous	1	2	3	4	5
29. Has poor judgement	1	2	3	4	5
30. Has problems with sleep	1	2	3	4	5
31. Blames others for difficulties	1	2	3	4	5
32. Has poor coordination	1	2	3	4	5
33. Has become more aggressive	1	2	3	4	5
34. Passive	1	2	3	4	5
35. Has a temper	1	2	3	4	5
36. Frustrates easily	1	2	3	4	5
37. Is suspicious	1	2	3	4	5
38. Has poor personal habits	1	2	3	4	5
39. Accuses others of taking things	1	2	3	4	5

	Not at all like the pers	A little bit	Moderately	Quite a bit	Extremely like the pers
40. Has difficulty speaking coherently	1	2	3	4	5
41. Insults others	1	2	3	4	5
42. Has difficulty writing	1	2	3	4	5
43. Seems disoriented	1	2	3	4	5
44. Defensive	1	2	3	4	5
45. Has difficulty communicating thoughts	1	2	3	4	5
46. Wanders aimlessly	1	2	3	4	5
47. Is more demanding	1	2	3	4	5
48. Conversation rambles	1	2	3	4	5
49. Seems agitated	1	2	3	4	5
50. Repeats the same actions	1	2	3	4	5
51. Has difficulty managing money	1	2	3	4	5
52. Follows other people	1	2	3	4	5
53. Upset by changes	1	2	3	4	5
54. Over-reacts to problems	1	2	3	4	5
55. Complains	1	2	3	4	5
56. Mood changes quickly	1	2	3	4	5
57. Stubborn	1	2	3	4	5
58. Violent	1	2	3	4	5
59. Critical of others	1	2	3	4	5
60. Substitutes an incorrect word that sounds similar to the correct word	1	2	3	4	5
61. Has trouble reading	1	2	3	4	5
62. Has difficulty following instructions	1	2	3	4	5
63. Is uncooperative	1	2	3	4	5
64. Cannot clean, dress or care for self	1	2	3	4	5
65. Has difficulty driving	1	2	3	4	5
66. Forgets meals	1	2	3	4	5
67. Has messy eating habits	1	2	3	4	5
68. Drools	1	2	3	4	5
69. Falls often	1	2	3	4	5
70. Incontinent (Has bowel or bladder accidents)	1	2	3	4	5
71. Has seizures or "epileptic fits"	1	2	3	4	5
72. Does not recognize others	1	2	3	4	5
73. Acts as if in a "dream world"	1	2	3	4	5
74. Remembers events from day to day	1	2	3	4	5
75. Has dificulty concentrating	1	2	3	4	5
76. Seems bewildered	1	2	3	4	5
77. Has to double-check all work	1	2	3	4	5
78. Forgets where they are	1	2	3	4	5
79. Unconcerned about problems	1	2	3	4	5
80. Has memory gaps	1	2	3	4	5
81. Covers up memory problems	1	2	3	4	5
82. Uses written reminders to cope with memory problems	1	2	3	4	5
83. Changes the subject in conversation	1	2	3	4	5
84. Avoids certain conversations and social situations	1	2	3	4	5
85. Repeats the same thing over and over again	1	2	3	4	5
86. Has less confidence	1	2	3	4	5
87. Needs constant reminders from other people	1	2	3	4	5
88. Benefits from a constant routine	1	2	3	4	5
89. Must have objects in the same place all the time	1	2	3	4	5
90. Resists bathing	1	2	3	4	5
91. Has difficulty chaining together complex actions	1	2	3	4	5
92. Does not benefit from instructions	1	2	3	4	5
93. Has a short attention span	1	2	3	4	5

	Not at all like the person	A little bit	Moderately	Quite a bit	Extremely like the person
94. Has lost a sense of humor	1	2	3	4	5
95. Cannot engage in complex games	1	2	3	4	5
96. Does not return objects to their usual places	1	2	3	4	5
97. Desires ice cream or other inappropriate food several times per day	1	2	3	4	5
98. Is able to clean, dress and care for self	1	2	3	4	5
99. Has poor table manners	1	2	3	4	5
100. Wanders at night	1	2	3	4	5
101. Is more confused at night than during the day	1	2	3	4	5
102. Becomes anxious when a familiar person leaves	1	2	3	4	5
103. Physically strikes others	1	2	3	4	5
104. Inconsiderate of others	1	2	3	4	5
105. Talks loudly	1	2	3	4	5
106. Has more accidents	1	2	3	4	5
107. Has less social judgement	1	2	3	4	5
108. Talks only about events long past	1	2	3	4	5
109. Has problems finding the correct words to say in conversation	1	2	3	4	5
110. Has trouble talking on the phone	1	2	3	4	5
111. Repeats actions, as if the person did not remember doing them the first time	1	2	3	4	5
112. Others take on the person's responsibilities	1	2	3	4	5
113. Conversation is not meaningful	1	2	3	4	5
114. Abandons former hobbies and interests	1	2	3	4	5
115. Sleeps in clothes	1	2	3	4	5
116. Sits vacantly in front of the T.V.	1	2	3	4	5
117. Leaves the stove on more often	1	2	3	4	5
118. Has good memory for the remote past, but poor memory for recent events	1	2	3	4	5
119. Cannot sort out important from unimportant events	1	2	3	4	5
120. Becomes anxious when leaving familiar surroundings	1	2	3	4	5
121. Has coarse or vulgar humor	1	2	3	4	5
122. Has temper outbursts with no apparent target	1	2	3	4	5
123. Details of recent and past memories are missing	1	2	3	4	5
124. Muscles are more rigid	1	2	3	4	5
125. Has muscle cramps at night	1	2	3	4	5
126. Has lost weight	1	2	3	4	5
127. This person has had serious psychological problems in the past	1	2	3	4	5
128. Has difficulty remembering names of people introduced recently	1	2	3	4	5
129. Has difficulty performing previously well-learned tasks	1	2	3	4	5
130. Has trouble recalling familiar phone numbers	1	2	3	4	5
131. Easily distractable	1	2	3	4	5
132. Unable to perform usual daily tasks	1	2	3	4	5
133. Has high blood pressure	1	2	3	4	5
134. Can manage own medications	1	2	3	4	5
135. Has a history of strokes	1	2	3	4	5
136. Until recently, the family and friends were unaware of this person's problems and their severity	1	2	3	4	5
137. There was not a definite point in time when memory problems began	1	2	3	4	5
138. This person has had memory and/or thinking problems for a long time	1	2	3	4	5
139. This person is clearly aware of memory problems	1	2	3	4	5
140. The problems were slow to develop	1	2	3	4	5
141. This person tries to hide memory problems	1	2	3	4	5
142. Sometimes this person remembers well, and at other times has trouble with remembering	1	2	3	4	5
143. The person explains his/her memory problems in detail	1	2	3	4	5
144. This person emphasizes his/her thinking and memory problems	1	2	3	4	5
145. This person tries to overcome thinking and memory difficulties	1	2	3	4	5

	Not at all like the person	A little bit	Moderately	Quite a bit	Extremely
146. This person is distressed about thinking and memory problems out of proportion to how severe the problems really are	1	2	3	4	5
147. When asked to recall something or perform some mental task, this person is quick to say, "I don't know," rather than make up something	1	2	3	4	5
148. This person has lost memory for particular events and not others	1	2	3	4	5
149. Problems with memory came after this person became depressed	1	2	3	4	5
150. This person complains about memory problems	1	2	3	4	5
151. This person guesses or makes up something rather than say, "I don't know"	1	2	3	4	5
152. This person reports more difficulties with memory than he/she really has	1	2	3	4	5
153. This person's problems improve considerably when this person is not depressed	1	2	3	4	5
154. This person has had previous episodes of memory problems which improved with time	1	2	3	4	5

Please answer the following questions by filling in the blank or circling the answer you judge to be correct.

155. How long have you known this person?_____

156. What is your relationship to this person?_____
(ex. son, daughter, brother, etc.)

157. What is his/her age?_____

158. What is his/her education?_____

159. What is his/her occupation?_____

160. What is his/her sex?
Circle: MALE FEMALE

161. Has this person ever been diagnosed as having a medical condition which affects memory or thinking?
circle: YES NO
If yes, what was the diagnosis? circle all that apply:
1. Alzheimer's Disease
2. Stroke
3. Head Injury
4. Anoxia
5. Encephalitis
6. Depression
7. Other (please list)_____

162. What kind of professional made the diagnosis? Circle all that apply.
1. Neurosurgeon
2. Neurologist
3. Psychiatrist
4. Psychologist
5. Family Doctor/GP
6. Other (please list)_____

163. To your knowledge, was the person ever given intelligence tests or other psychological tests as part of the evaluation?
circle: YES NO

164. How certain do you feel about the diagnosis of your friend or relative? Please circle:
1. Extremely certain
2. Quite a bit certain
3. Moderately certain
4. A little bit certain
5. Not at all certain

165. Where does your relative or friend presently live? Please circle:
1. At home
2. On their own
3. Nursing home or other extended care facility
4. Supervised apartment
5. Other (please list)_____

166. Does your relative or friend have a history or any of these problems? Please circle:
1. Alcoholism
2. Drug Abuse/Addiction
3. Head Injury
4. Huntington's Disease
5. Epilepsy/Seizures
6. Brain Tumor
7. Stroke
8. Other brain injury or disease (please list)_____

167. How frequently do you visit or interact with this person? Please circle:
1. everyday
2. 3 to 5 days per week
3. 1 or 2 days per week
4. only or mostly on week-ends
5. once every 2 weeks
6. once every month
7. Other (please list)_____

168. What symptoms or behaviors are exceptionally hard to cope with?

_____

_____

169. What symptoms or behavior make you feel confident your family member has Alzheimer's Disease?_____

_____

170. How long ago did you notice your relative had serious memory or thinking problems?

_____

The Memphis Dementia Rating Scale - Initial Reliability & Validity Studies

J. Michael Williams, PhD, Memphis State University

MDRS Scoring Key

Subscales:	Items:
MEMORY	1 3 5 6 7 10 14 20 21 50 66 72 74 77 78 80 82 85 87 89 92 96 111 117 118 123 126 130
LANGUAGE	2 40 42 45 48 60 61 62 109 110 113
NEED ROUTINE	4 52 53 88 108 120
SUSPICIOUS	8 37 39
DENIAL	9 81 141
ORIENTATION	11 13 43 73 75 76 93 131
APRAXIA	17 18 69
AGITATION	15 16 19 26 27 28 30 31 33 34 35 36 41 44 47 49 54 55 56 57 58 59 63 103 104 105 122
NEUROLOGICAL	22 32 68 70 71 124 125
DEMENTIA	12 23 24 25 38 46 64 65 67 79 83 84 86 90 94 97 98 99 100 101 106 108 112 114 115 116 119 121 126 129 132 134 137 138 140 151
HIGHER COGNITIVE	29 51 91 95 107
DEPRESSION	127 139 142 143 144 145 146 147 148 149 150 152 153 154
ISCHEMIA	133 135

Table 1

DEMOGRAPHIC DATA

	NORMAL n= 20	DEMENTED n= 43
Age	61	70
Education	13.2	10.7
Sex	9M 11F	15M 28F

Table 2

RELIABILITY STUDIES

	ALPHA N= 63	INTERRATER N=10
MEMORY	.92	.73
LANGUAGE	.89	.54
ROUTINE	.72	.80
SUSPICIOUS	.90	.80
DENIAL	.89	
ORIENTATION	.86	.94
APRAXIA	.84	
AGITATION	.94	
NEUROLOGICAL	.80	.76
DEMENTIA	.85	.48
HIGHER COGNITIVE	.84	
DEPRESSION	.87	.70
ISCHEMIA		

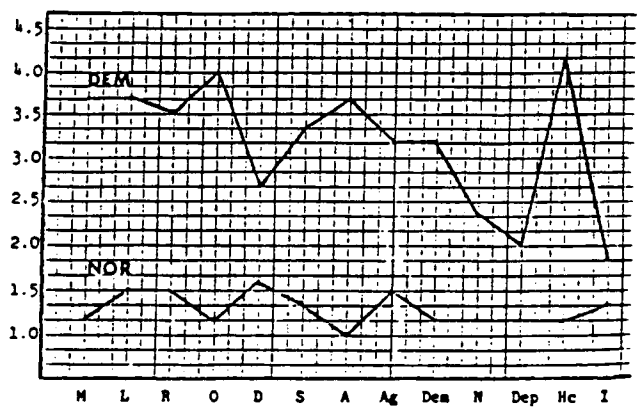
Table 3

Validity Studies

	NORMAL N=20	DEMENTED N=43
MEMORY	1.3	3.6
LANGUAGE	1.5	3.6
ROUTINE	1.5	3.5
ORIENTATION	1.1	4.0
DENIAL	1.6	2.8
SUSPICIOUS	1.4	3.4
APRAXIA	1.0	3.6
AGITATION	1.5	3.2
DEMENTIA	1.2	3.2
NEUROLOGICAL	1.1	2.4
DEPRESSION	1.2	2.0
HIGHER COGNITIVE	1.2	4.2
ISCHEMIA	1.4	1.7

Discriminant Function Canonical Correlation = .91

Classification Rate = 100%



VITA

Gary Scott Holder was born in Belleville, Illinois on July 29, 1953, son of Wilbur F. and Elva A. Holder. After beginning his schooling in that suburban St. Louis town, he moved at age nine with his family across the Mississippi River to St. Louis County, Missouri. He graduated from Hazelwood High School in June of 1971 and entered the University of Missouri at Rolla in August of that year.

While attending that institution as a physics major, he alternated school and work semesters as part of the Cooperative Education Program of the McDonnell Douglas Corporation, St. Louis, Missouri. Transferring to the University of Missouri at Columbia in January, 1975, he completed a Bachelor of Arts degree in Psychology there in August of 1976. That same month he entered graduate school at the University of Tennessee, Knoxville in the experimental psychology program.

After several years as a Graduate Assistant in the neuropsychology laboratory of Joel F. Lubar, Ph.D., Mr. Holder was employed in 1983 by the Neurodiagnostics Department of the University of Tennessee Medical Center, Knoxville. His work there in setting up and running the Alzheimer's Disease project funded by the Cole Neurosciences Foundation evolved into this dissertation project. Following graduation, he will continue in that position.