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THE EFFECTS OF ORAL PHYSOSTIGMINE ON CONSTRUCTIONAL AND SPATIAL ABILITIES IN DEMENTIA OF THE ALZHEIMER'S TYPE

by

ALAN D. BLAU

A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, City University of New York.

1988

This manuscript has been read and accepted for the Graduate Faculty in Psychology in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

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ABSTRACT

THE EFFECTS OF ORAL PHYSOSTIGMINE ON CONSTRUCTIONAL AND SPATIAL ABILITIES IN DEMENTIA OF THE ALZHEIMER'S TYPE

by

Alan D. Blau

Adviser: Professor Gordon Barr

Recent scientific evidence has strongly implicated the cholinergic neurotransmitter system as a critical component in Alzheimer's disease. This dissertation was designed to investigate the role of the effects of physostigmine on certain cognitive functions in early Alzheimer's disease. Memory changes in patients with Alzheimer's disease is the most robust deficit. Nevertheless, there is a growing literature uncovering a variety of cognitive deficits which appear independent of changes in memory. Of these, visuo-spatial and constructional impairments are the most outstanding. The second major goal of this dissertation was to understand the nature of these cognitive deficits with the qualitative assessment of performance. Specifically designed battery of neuropsychological instruments shown to be sensitive to these types of abilities was administered. This battery included tests of spatial orientation, direct copy of simple and complex figures, and block and puzzle constructions. Subjects diagnosed

with early dementia of the Alzheimer's type (DAT) were studied. The subject's spouses, when possible, served as one comparison group, and subjects from a normal aged population comprised the other. DAT subjects were given the test battery on three separate occasions. The first (initial baseline) was prior to any drug treatment. The second (best dose level), was at the most responsive dose level to physostigmine as determined by performance on tests of memory when subjects were titrated over a 8.0 to 12.0 mg. dose range over a three week period. A final testing (final baseline) occurred following drug wash-out. Comparison subjects were tested on a single occasion. There was no significant difference on a test of egocentric spatial ability between the groups. DAT subjects were significantly impaired compared to the comparison groups on all complex copying and constructional tasks. Task complexity resulted in a decrement in the performance of DAT subjects. Qualitative sequential analysis of the subject's individual performance indicated a planning and monitoring deficit in the DAT population, suggestive of frontal lobe dysfunction in the early phase of the disease. Physostigmine failed to improve performance on any of the tasks from the experimental battery when drug treated subjects were compared to a placebo treated group.

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CHAPTER I. TYPES OF DEMENTIA AND THEIR PHYSIOLOGICAL BASIS

A. Diagnostic Criteria for Dementia

The Diagnostic and Statistical Manual of the American Psychiatric Association (1981) has defined dementia as a "loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning." Impairment of memory is the principle deficit and is an essential characteristic in the diagnosis of dementia. The memory impairment generally takes two forms: first, an inability to learn new material (short-term memory deficit) and second, a deficit in retrieving material from the past (long-term memory deficit) (Albert, 1981; Miller, 1981). Events in the remote past may often be recalled better than those of recent events. The diagnosis of dementia will often include one or more of the following cognitive deficits: (1) an impairment of abstract thinking, (2) an impairment of judgment, (3) disturbances in other higher cortical functions resulting in aphasia, apraxia or agnosia, and (4) personality changes.

The symptoms of a dementia can be caused by a variety of disorders; over 50 have been identified by Haase in 1977. Nevertheless, it has been reported that 50-60% of all cases of dementia are as a result of Dementia of the

Alzheimer's type (DAT) (Terry & Katzman, 1983).

The differential diagnosis of Alzheimer's type dementia from other dementing disorders is obtained by clinical criteria, based upon information derived from neurological (including an EEG and a CT-scan) and neuropsychological examinations. The definitive diagnosis of Alzheimer's disease can only be obtained by pathological verification of neurofibrillary tangles and neuritic plaques in the cerebral cortex. This can only be obtained at the time of autopsy or on the rare occasion of a brain biopsy. With this understanding, the diagnosis of DAT is one of exclusion when other more salient disease processes are effectively ruled out. Often pseudodementia, as the result of depression, can be ruled out by administering an adequate mental status examination (Katzman, 1981). An extensive medical examination may aid in ruling out reversible conditions that mimic dementia such as drug toxicity, metabolic and nutritional disorders, as well as infections (i.e. neurosyphilis) (Smith & Kiloh, 1981). Hydrocephalus and space-occupying lesions generally account for 4-6% of patients with dementia (Jellinger, 1976), but can be easily detected in computer tomographic scans. The absence of focal neurological signs and a history of insidious onset followed by a slowly progressive dementia can usually differentiate Alzheimer's type dementia from those caused

by multiple cerebral infarcts. The differential diagnosis of dementia is exceedingly difficult in patients who suffer from more than a single disorder -- usually referred to as a "mixed" dementia. These individuals often show a mixture of symptoms and history, making disease classification problematic.

B. The Neuropsychological Profile of DAT

In the early stages of DAT, a typical patient presents a number of neuropsychological deficits. General declines are noted in language functioning, visuo-spatial reasoning and most importantly in memory (Albert, 1981). Difficulties with abstract reasoning and a lack of mental flexibility are also evident early in the disease. Memory changes, along with difficulties pertaining to the job, are often the earliest indication to the family of a problem. At this stage, patients usually retain appropriate conversational and socialization skills, yet may appear withdrawn or depressed; they will often show self-denial or underestimate their impairments. In the more moderate stages of DAT, memory deficits become more pronounced with patients experiencing difficulties recalling both personal and non-personal events (Rosen,

1983). Patients are typically disoriented; they are unable to recall where they are, the time or the date. Non-verbal skills also show tremendous declines, with deficits in both perceptual and constructional skills. Language problems can become quite pronounced, with patients showing increased word-finding difficulties, and with disease progression, they become more and more dysfluent.

In the cases of severe dementia, cognitive abilities are devastated and are often impossible to measure; patients often have difficulty understanding the test instructions on many tests. As the disease progresses they will have problems with simple motor skills. The remaining language may be echolalic or palilalic. Personal hygiene are often neglected, and the patients can become incontinent.

A number of authors have summarized the neuropsychological patterns of early-to-moderate DAT patients (Fuld, 1983; 1984; Miller, 1981; Kaszniak, 1986), the neuropsychological picture is one of consistent strengths and weaknesses. The most widely used measure of intellectual functioning, the WAIS, has shown declines with DAT. The Verbal I.Q., although variable, shows modest declines, while the Performance I.Q. seems to be particularly vulnerable to this form of dementia. Memory impairment is usually the most striking deficit in all

dementias and can be profound in DAT. Impairments can occur in both verbal and non-verbal tasks and is particularly noticeable in tests that involve long-term memory storage and retrieval mechanisms. Patients with DAT have great difficulty on any neuropsychological test that involves visuospatial reasoning and constructions. The cognitive requirements of tests, such as the Block Designs and Object Assembly (from the Wechsler Adult Intelligence Scale -- WAIS), Raven's Matrices, and a large variety of copying and assembling tasks, can create difficulty for DAT patients. In addition to the spatial and constructional aspects to these tasks they also all have in common the manipulation of novel stimuli in new situations, with time limitation. DAT patients often have problems comprehending verbal instructions on these tests. Even when the task is understood the patients are easily distracted and fail to maintain their performance. At this stage of the disease, they do not have striking language impairments, nevertheless, they do display word finding difficulties and have problems with object naming and with verbal comprehension. In addition, there may be some loss of verbal abstracting ability with an increasing concreteness to their speech. Finally, Alzheimer patients seem to have normal sensory and motor functions, at least in the early-to-moderate stages of the disease.

A number of authors have attempted to specify

particular neuropsychological response patterns in early-to-moderate Alzheimer's patients. This would facilitate the use of neuropsychological findings as a tool in the differentiation of the dementias. It would also help to further understand brain changes as it relates to cognitive functioning in dementia. Fuld (1984) was able to identify a particular profile of WAIS performance which was specific for DAT when compared to other forms of dementia. This profile has the Information and Vocabulary subtests as having the highest age corrected scores; following this are scores on Similarities and the Digit Span tests. The most difficult subtests on the WAIS for this population -- and resulting in the lowest aged correct scores -- are the Digit Symbol and Block designs. Performance on the Object Assembly subtest was impaired, but is often better than that of the Digit Symbol or the Block Designs. This profile indicates that the Performance subtests cause greater difficulty for this population than the Verbal ones (often resulting in a greater than 15 point difference between the (VIQ) Verbal Intelligence Quotient and the (PIQ) Performance Intelligence Quotient). This profile has been verified by the clinical evaluation of 138 patients, resulting in only two false positive. This profile has also been confirmed by an independent research team (Brinkman & Braun, 1984). Although a similar pattern has

been suggested as the result of normal aging (Wechsler, 1958; Eisdorfer, Busse, & Cohen, 1959), a recent long-term aging project has found less than 1% (N=390) of non-demented (based upon a Blessed mental status score below 8) aged subjects, between the ages 75-85, to present this particular profile (Fuld, submitted for publication).

A team of workers at Washington University in St. Louis, involved in a long term aging project, have attempted to use neuropsychological test result patterns to predict DAT (Storandt, Botwinick, Danziger, Berg, & Hughes, 1983; Berg, Danziger, Storandt, Coben, Gado, Hughes, Knesevich, & Botwinick, 1984). The aim of the study was to devise a neuropsychological battery that could differentiate persons with early DAT from normal aging. An extensive 1.5 to 2.0 hour battery of neuropsychological tests were administered to a sample of both mild Alzhiemer's patients and a matched group of healthy older individuals. The data was then analyzed with a stepwise discriminant function analysis. This allowed the number of tests needed for accurate differential diagnosis to be reduced to four: the logical memory and the mental control subtests of the Wechsler Memory Scale (WMS), Form A of the Trailmaking Test, and word fluency for letters "S" and "P". This abbreviated battery has the advantage that it could be administered in

a short time span (ten-minutes). The study by Berg and his co-workers (1984) demonstrated that these psychometric tests (described above) could also serve as a predictor of the progression of the dementia, the severity, and also the survival of the individual. They suggest that scores on the digit symbol subtest of the WAIS seemed to be one of the best predictors of disease progression. This is in agreement with findings of Naguib and Levy (1982) who showed that patients who display dysphasic-dysgraphia and dyspraxia had the worse survival rate.

CHAPTER II. STRUCTURAL AND CELLULAR CHANGES ASSOCIATED WITH ALZHEIMER'S DISEASE

The neuropathological changes associated with Alzheimer's disease were derived by the comparison of brain tissue from demented patients, aged matched controls, and normal young subjects. This made it possible to distinguish changes in the human brain associated with normal aging and those believed to be a result of some process occurring in Alzheimer's disease (Terry, 1980).

Terry, Peck, DeTeresa, Schechter, & Horoupion in 1981, had reported a reduction in mean brain weight by 8% in patients diagnosed with Alzheimer's disease compared to age matched controls. The overall brain atrophy appeared different from controls only when DAT was in an advanced stage; the brain appeared smaller and the sulci looked wider with enlarged ventricles (Terry & Davies, 1980). The cortical thickness was not significantly different from aged matched controls (Terry & Davies, 1980; Terry et al., 1981). A reduction in the number of large size neurons (>90 Å) was reported, with a 40% reduction in the frontal region and up to a 46% loss in the temporal area in patients with Alzheimer's disease when compared to aged matched normals (Terry, 1980). Similar types of reduction, but not as great a percentage of loss, have been reported in normal aged subjects (Henderson,

Tomlinson, & Gibson, 1980).

The Scheibels (Scheibel & Scheibel, 1975; Scheibel, 1978) demonstrated with Golgi techniques that normal aging was characterized by an extreme and progressive loss of dendritic arbors, particularly from the base of the cortical pyramidal cells. These types of losses can severely limit synaptic interactions, and the authors suggest that this dendritic loss might be related to a choking off of the cytoplasmic space with abnormal tubular material. This dendritic atrophy has been shown, by a number of investigators, to be greater in Alzheimer's disease than in age matched controls (Scheibel & Scheibel, 1975; Buell & Coleman, 1979). Others have found similar reductions in the post-synaptic elements (Mehraein, Yamada, Tarowska, & Pziduszho, 1975).

Overall, there are four major histologic lesions of Alzheimer's disease. These lesions have been shown to occur to some extent with normal aging, but the frequency and distribution in the brain have been shown to be dissimilar to what has been shown in the brains of Alzheimer patients. The first are lipofuscin granules, which are pigmented subcellular organelles that seem to accumulate with age in the cytoplasm of neurons. They are thought to be an aggregation of large end stage lysosomes, or recycled membranes, that cannot be further catabolized by the neuron (Cote, 1981). Different parts

of the central nervous system seem to accumulate these granules at different rates, but the reason for this is unclear. Currently, there is no evidence that these granules are at all harmful to the cells in which they accumulate or that they are associated with dementia, but may have potential for cytotoxicity (Mann & Sinclair, 1978).

The second cellular landmark is the presence of granulovacuolar bodies, consisting of small clear vacuoles that are bound by a unit membrane and contain a cluster of dense, fine granular material (Terry & Wisniewski, 1971). They seem to accumulate in the cytoplasm and dendrites of degenerating nerve cells, particularly in the pyramidal neurons in the hippocampus region. The granulovacuolar bodies are strongly correlated with dementia (Woodard, 1962), since they appear more numerous in the brains of demented patients than aged-matched controls. The reason for the formation of these lesions is currently unknown, but Terry and Davies (1980) have suggested that they resemble abnormal endocytotic vesicles.

The neurofibrillary tangle is the third hallmark, and together with the senile plaque are the two major neuropathological markers of Alzheimer's disease. Both are found quite uniformly in the frontal, temporal and parietal lobes of the neocortex. Mainly tangles, but not plaques, are found in the basal nucleus of Meynert within

the substantia innominate. Both types of lesions are present in great numbers in the amygdala, hippocampus and the hypothalamus (Terry & Katzman, 1983). Although these cellular lesions are found predominantly throughout the brains of patients with Alzheimer's disease, they are also seen to some degree with normal aging, though rarely are they found in the neocortex (Terry & Katzman, 1983). Neurofibrillary tangles in mature neurons fall into two principal classes: neurotubules with diameters greater than 240 Å, and neurofilaments with diameters less than 100A. The tangle consists of an argentophilic mass of neurofibers that are paired and twisted into paired helical filaments (PHF). In some tangles, there is a mixture of normal appearing filaments and tubules within the PHF. The presence of tangles is strongly correlated with the degree of cognitive impairment (Tomlinson & Henderson, 1976). The number of tangles have also been shown to be correlated with choline acetyltransferase activity, an important biochemical marker of dementia (Perry, Tomlinson, Blessed, Bergmann, Gibson & Perry, 1978; Bowen, Smith, White & Davison, 1976; Davies & Maloney, 1976).

Deboni & Crapper, in 1978, using in vitro techniques, were able to demonstrate the formation of PHF in normal brain tissue cultures when incubated with extracts from brains derived from Alzheimer's disease patients. This

finding would indicate that some type of transmissible agent might be involved in Alzheimer's disease. Neurofibrillary tangles have not been found in the brains of aging non-human animals at the present time (Terry & Davies, 1980), but have been induced in the brains of primates following the intracerebral injection of aluminum salts (cited in Kandel & Schwartz, 1981). This may be an important finding since Crapper, Krisham, & Dalton (1975) reported an increased concentration of aluminum in the brains of Alzheimer's patients.

The neuritic plaque is the forth major morphologic marker of Alzheimer's disease, and is also found to a lesser extent in the brain tissue of normal aged subjects. Similar to tangles, plaques are highly correlated with the severity of dementia (Blessed, Tomlinson, & Roth, 1968).

Under the light microscope, the plaque appears to be a central core amyloid surrounded by argentophilic rods and granules. It is thought to be made up of 90 to 100Å filaments (possible lysosomal in nature) yet quite different in texture and density of PHF's seen in the tangle. Surrounding this core appears to be enlarged unmyelinated neuritis, thought to be gila in nature, containing many lamellar dense bodies as well as mitochondria in various stages of alteration and which appear contracted. Present around the plaque are numerous astrocytic processes and microglia (Terry, 1980; Terry &

Davies, 1980).

It is believed that much of the neuritis within the plaque are the remains of axonal boutons following some type of neuronal degeneration process; the synapse and the post-synaptic processes appear normal and intact (Terry & Davies, 1980). This plaque, as suggested by many investigative teams, is the result of degeneration of pre-synaptic mechanisms.

The neuritic plaque -- as opposed to the neurofibrillary tangle -- has been discovered in the cortex of aged dogs and primates (Wisniewski, Ghetti, & Terry, 1973; Wisniewski, Narany, & Terry, 1976); the plaque in these animals appear similar in both structure and in texture to those found in humans.

In summary, patients diagnosed as suffering from Alzheimer's disease may show some degree of symmetrical cortical atrophy and other gross brain changes, of which some may differ significantly from the normal processes of aging. Neuropathological examination of brains of Alzheimer's disease patients show significant number of neural abnormalities that are associated with dementia. These abnormalities may be indicative of some underlying neural degeneration which is characteristic of Alzheimer's disease.

CHAPTER III. BIOCHEMICAL CHANGES ASSOCIATED WITH ALZHEIMER'S DISEASE

There is a substantial body of evidence indicating dysfunction of the cholinergic neurotransmitter system in Alzheimer's disease. As far back as 1964, Pope, Hess and Levin reported a reduction in the cortical levels of acetylcholinesterase (Ache) in Alzheimer's patients (this discovery was confirmed in studies by Bowen, Smith, White & Davison, 1976; Davies & Maloney, 1976 and many others). Ache is an enzyme that is responsible for the degradation of acetylcholine into products of choline and acetate. It has however been shown to be an unreliable marker of cholinergic function, since this enzyme has been shown to appear in non-cholinergic neurons (see McGeer, Eccles & McGeer, 1978). The reported changes in this enzyme may be indicative of a general CNS change in Alzheimer's disease. A more reliable indicator of acetylcholine innervation is the enzyme -- choline acetyltransferase (CAT) -- which is responsible for the synthesis of acetylcholine. This enzyme has been shown to be present only in acetylcholine synthesizing neurons in the nervous system of mammals (Kuhar, 1976). Davies (1979) was able to demonstrate a reduction of the activity of CAT (ranging from 20% to 60%) in the hippocampus and cortical regions (midtemporal, parietal, convexity frontal and orbital frontal cortex) in

Alzheimer's disease patients when compared to aged matched controls. These reductions of enzymatic activity are thought to reflect a loss of acetylcholine neurons from these regions. The findings were confirmed by Bowen, Smith, White, Goodhardt, Spillane, Flack, & Davison (1977) and Perry, Perry, Blessed & Tomlinson (1977), except the changes of CAT activity in patients with Alzheimer's disease were not as pronounced as those reported by Davies & Maloney (1976). The difference in these studies may be accounted for first, by the different ages of the control groups and second, by the severity of the dementia in the patients with Alzheimer's disease. Since reductions in CAT activity have been reported with normal aging (Davies, 1979), a comparison with older control groups would make Alzheimer group reductions of CAT appear less drastic.

At least one type of acetylcholine post-synaptic receptor seems unaltered by Alzheimer's disease -- as shown by three independent research groups. Muscarinic receptor concentrations appear similar to those of control subjects in patients with Alzheimer's disease in all cortical regions and sub-cortical areas examined, including the hippocampus (Davies & Verth, 1977; White, Goodhardt, Keet, Hiley, Carrasso, Williams, & Bowen 1977; Perry, et al., 1977). The affinity constants of the receptors also appeared normal in patients with Alzheimer's disease (Davies & Verth, 1977). In contrast

to the above reports, Reisine, Yamamura, Bird, Spokes, & Enna (1978) and Reisine, Pedigo, Meiner, Iqbal & Yamamura (1980) reported a 50% loss of muscarinic receptors in the hippocampus in Alzheimer's disease patients. The discrepancies between these studies may be difficult to resolve as all research teams used similar biochemical techniques -- they all measured the binding of 3H-Quinuclidinyl benzilate (3H-QNB) to CNS muscarinic receptors in both demented and control subjects. They also all employed standard histologic techniques to demonstrate the presence of plaques and tangles in the demented group, while the control subjects were free of such markers. Nevertheless, other factors such as variability of the tissue dissection, disease severity and other confounding illness in the patient population can all contribute to the differences in the studies. The age of the patients may also be a significant factor, as Perry, Blessed, Perry & Tomlinson (1980) and White et al (1977) have shown declines in muscarinic receptors with normal aging.

Changes in the catecholamine (CA) neurotransmitter system in Alzheimer's disease has been the subject of a number of investigations over the past 20 years and, for a variety of reasons, the findings remain inconclusive. Gottfries, Gottfries & Roos 1969 and Gottries and Roos in 1973 have reported reductions in the metabolites of

dopamine (DA) in the cerebrospinal fluid of patients with Alzheimer's disease. Adolfsson, Gottfries, Oreland, Roos & Winblad in 1978 reported similar reduction of DA metabolites from brain tissue obtained at autopsy from patients with Alzheimer's disease. In contrast, an equal number of studies have failed to find these changes (Parkes, Marsden, Der, Curzon, Kentamaneni, Knill-Jones, Akbar, Das & Kataria, 1973; Mann, Stanley, Neophytides, DeLeon, Ferris & Gershon 1981; Yates, Allison, Sampson, Maloney & Gordon, 1979; and Davies, 1979). It should be noted that of the studies that reported reductions, all failed to report pathologic evidence that the patient population was suffered from "pure" Alzheimer's disease. Davies (1983) pointed out the importance of excluding patients with pathologic evidence of Parkinson disease, a disorder with known dopaminergic involvement. The DA deficits reported in some cases of Alzheimer's disease may actually be instances of Parkinson disease, which can also cause dementia with or without Alzheimer's disease. Most studies are in agreement regarding other CA changes, not finding differences in noradrenalin or 5-hydroxytryptamine in the Alzheimer's disease population.

Changes in the Gamma-amino-butyric acid (GABA) neurotransmitter system as the result of Alzheimer's disease are as unclear as that of the dopaminergic system. Studies by Bowen et al in 1976, were able to show a

reduction in the enzyme glutamic acid decarboxylase (GAD) -- an enzyme responsible for the synthesis of GABA -- in the cortex of Alzheimer's disease patients. This finding was not confirmed by White et al, in 1977 nor by Davies in 1979. The use of GAD as an indicator of GABA concentrations is unreliable since it is quite sensitive to factors operating just prior to death of the patient (e.g., the length of coma, type of illness, and cause of death). Better matched controls are needed before any conclusive statement can be made concerning the relationship between GABA and Alzheimer's disease.

To summarize, the data thus far presented suggest that only the cholinergic neurotransmitter system shows reliable alterations in patients diagnosed with Alzheimer's disease. This has led to the hypothesis that in Alzheimer's disease there is a selective loss of cholinergic neurons; this is supported by reductions in the acetylcholine-related enzymes CAT and Ache. Post-synaptic muscarinic receptors appear unaltered by the disease processes and the role of other neurotransmitter systems remains inconclusive at the present time.

Whitehouse, Price, Struble, Clark, Coyle, & DeLong in 1982, took the first steps to understanding the involvement of the cholinergic system and Alzheimer's disease by pinpointing the major source of cholinergic innervation to the cerebral cortex. They suggest that a

nucleus called the "Basalis of Meynert" (nbM) is the major source of cholinergic input to cortex, and in patients with Alzheimer's disease there is a progressive degeneration of the neurons of this nucleus. The denervation of this region has been shown to be correlated with reductions in CAT activity. Previous studies have verified the location of the nbM to be in the magnocellular basal forebrain region, specifically in the substantia innominata, and that the neurons in this nucleus are cholinergic in nature being rich in CAT activity (Kimura, McGeer, Peny, & McGeer, 1981; McKinney, Struble, Price & Coyle, 1982). Other investigators, using retrograde tracing techniques, have shown that neurons in the nbM project directly to cortex in the monkey (Divac, 1975; Kievit & Kuypers, 1975; Meserlan & Van Hoesen, 1976). In the rat, an analogous region to the nbM located in the ventral palladium is also rich in CAT activity and projects to cortex (Whitehouse et al, 1982; Hartgraves, Mensah & Kelly, 1982). When this region in the rat is lesioned, there is a reduction of cholinergic pre-synaptic markers in the cortex (Johnston, McKinney, & Coyle 1979; Lehmann, Nagy, Atmadja, Fibiger, 1980).

Whitehouse et al, (1982) examined the brains of patients with Alzheimer's disease and aged matched controls looking for changes in the basal forebrain region. The identification of patients with Alzheimer's

disease was based on two criteria: first, a progressive history of cognitive decline, and second, the presence of plaques and tangles in the autopsied brains. Cell counts were made in the brain regions that contained the nbM for both Alzheimer's disease and non-demented age matched controls. They were able to show up to a 73% loss of cells in the nbM region in patients diagnosed with Alzheimer's disease. This was nearly a four-fold difference with the controls. Under closer examination of the brain tissues, patients with Alzheimer's disease showed a significantly greater number of neurofibrillary tangles within the nbM region than the controls. Finally, this experiment was able to show a consistent relationship from the amount of cell loss in the nbM to reductions of pre-synaptic markers (CAT and Ache activity) for acetylcholine. Overall, this study supports both the cholinergic model of Alzheimer's disease, as well as the idea that pathological changes in the nbM is fundamental to the acetylcholine abnormalities in Alzheimer's disease.

In another paper by this same investigative team (Struble, Cork, Whitehouse, & Price, 1982), they were able to demonstrate that neuritic plaques -- one of the classic landmarks of Alzheimer's disease -- are made up of pre-synaptic cholinergic axons that arise from the basal forebrain. These plaques are formed, the authors suggest, when these cholinergic projections to the cortex

selectively degenerate. In their experiments, rhesus monkeys were killed at various ages, and the presence of plaques in the cortex were noted. It has already been demonstrated that primates develop neuritic plaques with age, similar to aged humans (Wisniewski, et al, 1973). Sections were taken from the frontal cortex and stained with congo red, which allowed visualization of the amyloid as well as Ache activity. Ache is synthesized in the cell bodies and then transported to the nerve endings via axoplasmic flow (McGeer et al., 1978). Using this method, they were able to classify plaques into three distinct categories: (1) an immature plaque, characterized by a small amyloid and a high level of Ache activity contained in neuritic-like form; (2) classical plaques, which contained a large amyloid and marked Ache activity; and (3) an end-stage plaque containing an abundant amyloid core, few neurites and very little Ache activity. Examination of the monkey brain at various ages revealed that in young animals (4 to 9 years of age) the cortical sections were free from plaques. In the older animals (26 to 31 years of age) there was a presence of plaques quite similar to normal aged human subjects. They were further able to demonstrate greater staining for Ache with the subjects that had the fewest number of plaques. The oldest animal in the experiment (31 years old) had the greatest number of plaques and also the greatest number of

end-stage plaques.

From these samples of cortical tissue taken from various age animals, the authors speculated about the evolution of plaque formation in the brain (see review article by Price, Whitehouse, Struble, Clark, Coyle, DeLong, & Hedren, 1982). The immature plaque first appears as an enlarged neurite that is rich in Ache. Due to some unknown process the neurite degenerates and the contents are released into the microenvironment. This released material is acted upon by glial cells and results in the formation of the amyloid core. The classical plaque contains this core center which still stains for Ache. In the end-stage plaque, the dystrophic axons die away, correlating with the loss of Ache activity. Thus, the neuritic plaque, one of the classic neuropathological landmarks of Alzheimer's disease, are degenerated axons nerve endings which remain behind in the cortex when cholinergic neurons projections from the basal forebrain (nbM) undergo some type of degenerative disease process.

The current knowledge regarding the biochemical and neuropathological changes that occur in Alzheimer's disease, when compared to age matched controls, indicate some degenerative process affecting the cholinergic neurotransmitter system. The development of the neuritic plaque, one of the classic neuropathological marker of the disease, has been linked to the degeneration of

cholinergic projection. The cell bodies of this system are located in the nbM and project wide spread across cortex and sub-cortical structures. Reductions in the principal enzymes of synthesis (CAT) and catabolism (Ache) in both the cortex and hippocampus are associated with cell loss in the nbM. Finally, post-synaptic muscarinic receptors appear unchanged despite disease progression.

CHAPTER IV. THE EXPERIMENTAL MANIPULATION OF THE CHOLINERGIC SYSTEM IN NORMAL YOUNG AND ELDERLY SUBJECTS

The neuropathological and neurochemical changes as described in the last two chapters must be functionally relevant and have led to the neuropsychological profiles as summarized in chapter one. These findings have also led to the "cholinergic hypothesis" of geriatric memory dysfunction (Bartus, Dean, Beer & Lippa, 1982) and to numerous attempts to pharmacologically compensate for the presumed cholinergic disturbance in both aged and DAT individuals.

A. Cholinergic Manipulation in Young Subjects

1. The Effects of Scopolamine

Studies in the 1960's (Ostfeld and Aruguete, 1962; Ostfeld, Machine, & Unna, 1960) and in the 1970's (Safer & Allen, 1971; Crow & Grove-White, 1971 & 1973; Hrbek, 1970 & 1971; Peterson, 1977) have all reported an impairment in the ability for young subjects to recall objects, digits or to repeat paragraphs following treatment with moderate doses of scopolamine. Scopolamine is a powerful muscarinic receptor blocking agent which is frequently used as a preanesthetic medication prior to surgery. Information learned prior to the administration of the

drug was unaffected. As a result this drug was thought to interfere with the acquisition of new information.

Drachman and his colleagues (Drachman & Leavitt, 1974; Drachman & Sahakian, 1979) investigated the effects of scopolamine on three phases of memory: immediate memory, memory storage and retrieval from old memory stores. Specific tasks were devised to test these different memory processes. Normal young subjects who were given 1.0 mg. of scopolamine showed marked memory impairments with the greatest difficulty occurring on the tasks that accessed the storage and retrieval of new information. Immediate memory was unaffected by the drug. Caine, Weingarter, Ludlaw, Cudahy, & Wehry (1981) found similar impairments with the drug when young subjects were tested on a variety of learning and memory paradigms, including a selective reminding test. These findings indicate that cholinergic blockade by the use of scopolamine produce a marked impairment on both the storage and retrieval from memory. The impairment of storage was clearly demonstrated in all these studies by the poor performance on all tests of recall. Retrieval deficits were demonstrated by the subjects inability to recall items under cued recall conditions (Caine, et al, 1980) and further by their poor ability to generate words from semantic categories, thought to come from old memory stores (Drachman & Leavitt, 1974). Non-memory related

cognitive functions were may also be affected by the drug. Drachman & Leavitt (1974) reported a decline in the Performance I.Q. (from the WAIS) following scopolamine treatment.

The specificity of the cholinergic system with regards to memory and cognitive functions was demonstrated in two ways. First was by showing that physostigmine, an acetylcholinesterase inhibitor, effectively reversed the memory impairments caused by scopolamine (Drachman & Sahakian, 1979), and second was that d-amphetamine, an catecholamine agonist, had no effect on the scopolamine induced dementia (Drachman & Sahakian, 1977). These findings suggest that the cognitive deficits produced by blockade of the cholinergic system was due to a specific, temporary "ablation" of cholinergic neurons.

2. The Effects of Physostigmine

The facilitory effects of physostigmine to enhance memory functions was tested by a number of investigators. Drachman & Leavitt in 1974 found only a trend towards improvement when low doses of physostigmine (1 mg.) was given subcutaneously. Davis, Mohs, Tinklenberg, Pfefferbaum, Hollister, & Kopell (1978) found significant effect for the drug (given in a slow I.V. infusion) to improve long-term storage and retrieval, with no effect on short-term memory. Both groups reported a worsening of

performance with high doses of the drug (> 3.0 mg.) and a significant amount of inter-subject variability. The route of drug administration and the time of testing may account for these study differences.

3. The Effects of Precursors

A number of authors have administered choline chloride, a long lasting cholinomimetic which has been shown to increase brain levels of acetylcholine in rats (Cohen & Wurtman, 1976). Davis, Mohs, Tinklenberg, Hollister, Pfefferbaum, & Kopell (1980) was unable to show improvements on any aspect of memory when subjects were treated with this drug (16mg./day over 12 days). In contrast, Sitaram, Weingartner & Gillin (1978) found subjects reached criterion significantly faster on a task of serial learning following drug administration. Methodological differences may account for this discrepancy in these studies. First, subjects in the Davis et al. (1980) study were given the drug chronically over a three day period (4 grams/4 times a day), while subjects in the Sitaram et al. (1978) study received a single dose of 10 grams and tested 90 minutes after, suggesting that these subjects may have had higher levels of the drug in their bodies during the time of testing. Secondly, the two studies used different measures of memory. The Davis et al. (1980) study used a standard

task of recall (15 words) and a selective reminding test. Subjects in the Sitarem et al. (1978) study were tested on an uncategorized serial learning task of 10 words. Improvement was measured by the number of times the list was repeated to reach criterion. These tasks differences suggest that the subjects in the Sitaram et al. (1978) study were tested on a simpler measure of memory in combination with a higher dose of the drug can account for significant differences between the studies.

A single study administered the drug arecoline, an cholinergic receptor agonist to young subjects. Sitaram et al. in 1978 found significant improvement to learn a list of related words when the subjects were administered 4.0 mg. of the drug subcutaneously. In addition, this drug was also successful in reversing scopolamine induced cognitive deficits.

B. Cholinergic Manipulation in Elderly Subjects

An important comparison was made in the 1974 Drachman and Leavitt paper between young subjects treated with scopolamine and normal aged subjects. They were able to demonstrate that the memory and cognitive deficits, produced in young normal subjects by the drug scopolamine, was strikingly similar to that seen in normal aged subjects. Specifically, deficits were found in memory

storage and retrieval, as well as a disruption of non-memory cognitive functions. These deficits mimicked declines usually seen with aging (Drachman & Leavitt, 1972; 1974). This suggests that the cognitive declines as the result of aging may be directly related to cholinergic changes in the central nervous system. It has been hypothesized that the transient interference of neural transmission at the cholinergic synapse by scopolamine may parallel neural degeneration of the same system as the result of the aging process. This hypothesis has been substantiated by evidence from both biochemical and neuropathological investigations. With this in mind, it is not surprising that a number of investigations have attempted to facilitate declines in cognition as the result of aging with drugs which enhance cholinergic functioning.

1. The Effects of Physostigmine

There is conflicting evidence with regards to the effects of physostigmine when given to normal elderly. Davis, Mohs, & Tinlenberg (1979) showed positive effects of the drug on a 24-word free recall task when given to a group of normal aged subjects. Drachman & Sahakian (1980) and Drachman, Glosser, Fleming, & Longenecker (1982) failed to demonstrate a significant effect with physostigmine, or when physostigmine was given in

combination with lecithin (a dietary source of choline).

Once again procedural differences may account for discrepancies in these studies. In the Drachman studies all subjects received a single dose of the drug (0.5 or 0.8 mg. subcutaneously) in contrast, the subjects in the Davis et al. (1979) study were individually titrated over six different infusions of physostigmine (.125 to 0.5 mg. I.V.). All these studies report considerable individual variability to the drug. The Drachman studies, using a single dose, may have missed the narrow therapeutic dose on his subjects, but Davis et al. by individually titrating over a range of doses found each individuals best dose response. Five of the six subjects showed improvements in their study with a dose response function in the form of a inverted "U", which further supports the narrow therapeutic window of this drug.

2. The Effects of Precursors

The administration of cholinergic precursors in an attempt to increase acetylcholine levels in the brain generally was unsuccessful in facilitating cognition in aged subjects. For example, Mohs, Davis, Tinklenberg, Hollister, Yesarage, & Kopell (1979) failed to show improvements in normal aged subjects when given 2 or 4 grams of choline chloride on tests of either learning or retrieval.

Overall, there is agreement that precursor loading by the administration of either choline (choline chloride) or lecithin has little positive effects on memory functions in normal young or normal aged subjects. This is despite a rise in the levels of choline found in the blood. There are a number of plausible explanations to account for these negative findings. First, is that peripherally administered precursors have not been shown to effectively stimulate central cholinergic activity such that as an increase in synthesis or release of the transmitter (Bartus, et al., 1982). Secondly, is that the neurochemical changes that occur as a result of the precursors are insufficient to produce measurable behavioral effects, particularly with regards to standardized memory tests. Finally, greater plasma choline levels may be needed to cause central acetylcholine levels to rise, but the use of choline or lecithin to do this appears unlikely. Thal, Rosen, Sharpless, & Crystal (1981) demonstrated that intestinal absorption mechanisms may be saturated at 100mg/kg. The development of different types of precursors might be more effective. Another important consideration is that the cholinergic system may not be the only transmitter system involved in cognition.

The cholinergic system appears distinctly different than the dopaminergic system in its response to precursor

loading. Many patients who suffer from Parkinsonism respond positively to L-DOPA treatment. Some have attributed this in part to the high rate of activity of the remaining nigrostriatal fibers as the system attempts to compensate for the cell loss (Hornykiewicz, 1974). The cholinergic system may be biologically unable to regulate transmitter release as the DA system and as a result not benefit from an increase supply of precursor. Other pharmacological approaches have shown facilitory effects. Physostigmine appears to be an active compound when administered under controlled and titrated conditions in both normal young and elderly subjects. In addition, muscarinic receptor agonists such as arecholine, show facilitory effects as well, since central muscarinic receptors appear unchanged with aging as well as dementia.

In summary, a link between the cholinergic neurotransmitter system and cognition is supported by a number of factors: (1) a correlation between cholinergic pathological and biochemical markers of aging and DAT with the severity of the cognitive impairments, (2) The transient cognitive impairment caused by the receptor antagonist, scopolamine, and the subsequent reversal by both physostigmine and arecholine, and finally (3) the positive, yet limited facilitory effects of physostigmine. When these factors are considered it was not surprising

that a number of investigators have administered cholinergic drugs to facilitate cognitive functioning in patients with a known cholinergic dysfunction -- Alzheimer's disease.

CHAPTER V. TREATMENT OF DAT WITH CHOLINERGIC DRUGS

A. The Effects of Cholinergic Precursors on DAT

The treatment of patients with mild-to-moderate Alzheimer's disease with acetylcholine precursors, such as choline or lecithin, has been for the most part disappointing. For example, Peters and Levin (1979) gave DAT patients 1200 mg. of lecithin three times daily and then tested memory function by the use of a selective reminding test. All five patients in the study failed to improve either in the number of words that entered long term storage or in the number of words retrieved from storage. In fact, most patients did significantly worse on lecithin when compared to their performance at baseline. Thal et al. (1981) treated mild-to-moderate DAT patients with three different levels of choline chloride (50,100 or 200 mg/kg per day) or placebo, and then tested them on an extensive cognitive battery, including a variety of memory and non-memory tests. Despite a rise in plasma choline that indicated maximal intestinal absorption, the patients did not show significant improvement on any cognitive test, yet there were trends towards an increased recall and better performance on a construction test. This study, and by far the majority of the studies that have administered cholinergic precursors, have failed to improve cognitive deficits in patients with

Alzheimer's disease (Boyd, Grahman-White, Blackwood, Glen, McQueen, 1977; Signoret, Whitely, & Lhermittee, 1978; Smith, Swash, & Exton-Smith, 1978; Peters & Levin, 1978; Renvoize & Jerram, 1979; Christie, Blackburn, Glen, Zeisel, Shering, & Yates, 1979; Fovall, Dysken, & Lazarus, 1980).

Two studies have shown positive results with precursors. Etinne, Gauthier, Johnsen, Collier, Mendis, Dastoor, Cole, & Muller in 1978, reported a small improvement when DAT patients were given choline, but were unable to replicate this when similar patients were given lecithin. Vroulis, Smith, Brinkman, Schoolar, & Gordon in 1981, were the only investigator that reported an improvement with lecithin, showing facilitation of short term and long term memory as well as increasing storage. The significant findings in this study and the trends towards improvement in other studies, at best may indicate a response by a sub-population of demented subjects.

The failure of the large majority of studies with precursors to improve performance in patients with DAT can be explained by many of the reasons as discussed earlier. In addition, some of these factors are particularly relevant with regards to patients with DAT, where there is already a significant loss of cholinergic neurons to incorporate the precursor and a reduction of CAT which would convert choline to acetylcholine (Thal et al.,

1981).

One investigation attempted to increase cholinergic neurotransmission by the use of the muscarinic receptor agonist arecholine. Christie, Shering, Ferguson, & Glen in 1981, administered 2 to 4 mg. of arecholine intravenously to DAT patients. Improvement on a picture-recognition test was demonstrated in a dose response fashion, with significant improvement occurring at 4 mg. The use of arecholine as a treatment for Alzhiemer's disease has not been extensively tested in the United States (Growdon & Wurtman, 1983), but its short half-life and systemic cholinergic side effects will limit its potential as an effective treatment.

B. The Effects of Physostigmine on DAT

The inhibition of the hydrolytic enzyme ACHE is another way to enhance acetylcholine neurotransmisson. The most popular cholinomimetic drug to do this has been the anticholinesterase physostigmine.

Peters & Levin (1979) subcutaneously administered titrated doses (.005 to 0.015 mg/kg; approximately 0.34 to 1.02 mg) of physostigmine to DAT patients who were also maintained on 3600 mg/day of lecithin. All patients were tested on selective reminding tests. Comparisons were made to placebo conditions or baseline levels. No improvement occurred when either lecithin or

physostigmine was given alone. But when lecithin was given in combination with physostigmine, an improvement in long-term storage and long-term retrieval was obtained. Christie (et al., 1981) reported an improvement in a picture-matching task in moderate DAT patients when titrated doses of physostigmine (0.25 to 0.375) were administered intravenously. Some patients demonstrated a clear dose-response function, with a narrow therapeutic window. Low doses of the drug (below 0.375) were ineffective, while high doses (greater than 0.5mg) resulted in nausea and other side effects that interfered with performance.

In a series of articles, K. Davis and his co-workers investigated the effectiveness of physostigmine to improve cognitive functioning in DAT patients (Davis, et al., 1979; Davis, Mohs, Rosen, Greenwald, Levy, & Horvath, 1983; Mohs & Davis 1982; Johns, Levy, Greenwald, Rosen, Horvath, Davis, Mohs, & Davis, 1983). In the studies that used intravenous infusion of physostigmine, the procedure involved two phases. First was the dose response phase; subjects were given, double blind 0, .125, or 0.5mg of physostigmine over a 30 minute period. The second phase was a double blind replication study in which the dose of physostigmine associated with the subject's best scores was administered and compared to performance on placebo infusions. Cognitive tests consisted of the Famous Faces

test, a digit span task and a recognition memory task (either words or pictures). Physostigmine failed to improve performance on either the digit span or Famous Faces test, but all patients performed better at some dose of the drug on the recognition memory test when compared to placebo conditions. These findings were substantiated during the replication phase of the study. Of note was the discovery that each patient generated individual dose response functions, usually in the shape of an inverted U. The dose resulting in the most improvement varied considerably between the patients, which suggested that sensitivity to physostigmine at an individual patient's level is a critical factor in the evaluation of the drugs effectiveness.

The Mohs and Davis (1982) paper was unique in that it applied a signal detection technique to evaluate patients performance following physostigmine administration. Their aim was to determine whether physostigmine-improved performance as a result of an increase in the amount of information stored (changes in sensitivity) or, due to a change in the patient's willingness to say they recognized the stimuli (change in criteria). The analysis demonstrated that, in fact, both were altered by the drug. Physostigmine significantly improved the patient's ability to discriminate old from new stimuli, indicating an increase in the amount of information stored pertaining to

the stimuli. The drug also caused patients to adopt a stricter criteria (noted by a reduction in the false alarm rate), such that they were less willing to make inappropriate responses. This is a particularly interesting finding in light of neuropsychological data that has consistently shown that inappropriate verbal responding is a specific characteristic of Alzheimer's dementia. Fuld (1983) in particular has made reference to this phenomenon and has labelled them intrusions.

Oral physostigmine seems as effective as the intravenously administered drug when levels are carefully titrated for the individual patients (Davis, et al., 1983; Thal & Fuld, 1983; Thal, Fuld, Masur, & Sharpless, 1983). In the Thal studies patients were titrated with doses of oral physostigmine over a 10 day period (from 0.5 to 4.0 mg per. dose; total daily dosage from 3.0 to 16mg). During the drug treatment period, the patient's diet was supplemented with lecithin, with daily dosages of 10.8 gm (equivalent to 536 mg of choline). Twice each day, patients were tested on a 12 trial, 12 word selective reminding task (see Buschke & Fuld, 1974). All responding patients were re-challenged in a double-blind, cross-over replication study at the optimal dose. Eight out of twelve patients showed significant improvements, which is noted by an increase in total recall, long term retrieval, and a reduction in the number of intrusions. The peak

performance by most of the responders occurred between 2.0 and 2.5 mg. Doses greater than 2.5mg. often resulted in side effects such as nausea, cramps and diarrhea. All eight patients who showed improvements during the titration study, again demonstrated a drug effect during the replication phase of the study.

Nine patients in this study underwent lumber puncture and their CSF underwent biochemical analysis. Inhibition of CSF cholinesterase was negatively correlated with the number of intrusion made by the patients and positively correlated with long-term retrieval. The reductions in intrusions as the result of physostigmine/lecithin treatment may be related to the reduced false alarm rate reported by Mohs and Davis (1982). Thus, the drug's ability to inhibit the occurrence of inappropriate responding has been shown by two independent research teams. The correlation between intrusion reduction with cholinesterase inhibition suggests that intrusion errors may be a specific indicator of cholinergic dysfunction. No changes in CSF MHPG, 5-HIAA, HVA, VIP or somatostatin concentrations were found in the CSF following the physostigmine/lecithin treatment. This further supports the specificity of cholinergic dysfunction system in DAT.

In a recent paper Thal and his associates (Thal, Masur, Sharpless, Fuld, & Davies, 1986) were successful in replicating their earlier findings, which found a positive

effect of physostigmine/lecithin treatment. Ten of sixteen DAT patients showed an improvement in memory following the combined drug treatments in this present study. Several patients, during the replication phase of these projects, were treated with physostigmine alone. Under these conditions, the patients maintained their drug facilitated improvements. Five patients in the study continued on drug treatment for extended periods (4 to 20 months); most of these patients continued to demonstrate a positive drug response initially, but lost responsiveness to physostigmine as their dementia progressed.

There have been some attempts to facilitate non-memory cognitive functions in patients with DAT with physostigmine. Muramato, Sugishita, Sugita, & Toyokura in 1979 and Muramoto, Sugishita, & Ando in 1984 measured performance on constructional and memory tasks following subcutaneous, intravenous, and orally administered physostigmine. Constructional abilities were assessed by the administration of the Bender-Gestalt (for the mildly impaired patients); a geometric copying task was used for the more impaired subjects; memory was measured with a selective reminding test. Both subcutaneous and intravenously administered physostigmine were successful in improving copying performance in three of six patients; memory enhancement was demonstrated in only a single patient. Of significance was that responding patients

showed a reduction in particular forms of drawing errors, most notably in the "closing-in" phenomenon (Mayer-Gross, 1935). This type of error refers to the extent in which the patient's drawings are placed close to, or overlap, the model to be copied. These studies were the first to demonstrate that drugs, that facilitate memory functioning by enhancing the cholinergic system in DAT patients, also affect constructional abilities.

Some investigations using physostigmine failed to show improvements in DAT patients. Ashford, Soldinger, Scheffer, Cochran, & Jarvik in 1981 administered 0.5mg of physostigmine to six DAT patients and than tested them on a selective reminding test and a copying task (BVRT). In this double-blind acute study, the drug failed to improve constructional skills or any aspect of memory. The main discrepancy between this report, and those with positive findings, is that they used a fixed dose of the drug without individual titration. This factor has been shown critical for demonstrating drug effectiveness.

Wettstein (1983), although using multiple doses of physostigmine, failed to show improvements in memory and other neuropsychological functions following the treatment. The patients used in this study may have been beyond the mild to moderate stages of the disease, since the authors reported that the selective reminding task seemed too difficult for their patient population. Their

failure to derive positive effects may be due to the poor patient sample, since, as suggested by Thal et al (1986), physostigmine becomes ineffective in the advanced stages of the disease.

It is clear from these investigations that the cholinomimetic agent, physostigmine, can improve memory and constructional abilities in patients with mild-to-moderate DAT. In the late stages of the disease, when there is profound reductions of cholinergic activity in the cortex, the drug becomes ineffective probably because it lacks the ability to halt the progressive neural degeneration resulting in further depletion of acetylcholine. Nevertheless, the positive findings are in support of a cholinergic role in DAT disease and provides functional correlates to the physiological changes known to occur with this form of dementia.

CHAPTER VI. SPATIAL AND CONSTRUCTIONAL ABILITIES: CHANGES ASSOCIATED WITH AGING AND DEMENTIA.

Spatial abilities refers to the appreciation of the position and extension in space of a stimulus. Two major spatial integrative factors have been suggested: visualization and orientation. Visualization is the ability to imagine the relative movement of parts of a stimulus with respect to each other. Orientation is the ability to comprehend the spatial arrangement of elements in a stimulus pattern, to perceive the whole and remain non-confused regardless of changes due to rotation or inversion of the pattern (Ratcliff, 1982).

Constructional abilities is truly an integrative cognitive function which involves perception, organization, planning and carrying out monitoring of appropriate actions. Spatial abilities are a vital component for success on constructional tasks. Distinct patterns of deficits on constructional tasks have been described for lesions of either hemisphere as well as anterior and posterior distinctions.

Declines in performance involving both spatial and constructional abilities have been reported following aging to some extent, and in DAT to a larger extent. These abilities will be the focus of this dissertation. Patients with the research diagnosis of mild-to-moderate

DAT will be compared to both aged matched controls and elderly subjects as they perform on a battery of neuropsychological tests designed to evaluate spatial and constructional abilities.

A. Disorders of Spatial Abilities

Some authors have suggested that disorders of spatial abilities can be broken down into a number of sub-classes of disorders. The first subdivision is the distinction between sensory analysis and complex integrative functions. The latter class can be further sub-divided into disorders of personal space and those that involve space external to the body. Disorders of personal space refers to a spatial disorientation with respect to parts of one's own body and the bodies of others. It also involves the designation of the two halves of space (Benton, 1969). Often this type of disturbance is referred to as a deficit in "body schema".

Disorders of extra-personal space has been given the clinical name "visual-spatial agnosia" and refers to a faulty appreciation of the spatial aspects of visual experience (Benton, 1979). This type of disorder effects a patient's orientation, either as he moves through the environment, or orientation within the environment of a static subject. This type of spatial disorder produces a general defect in perceptual integration such that

difficulties occur on tasks that require various types of operations upon perceptual stimuli.

1. Disorders of Personal Space (Body Schema).

The most frequently described syndromes associated with the general category of disorders of body schema are: anosognosia, bodily agnosia, and right-left confusion. Anosognosia is a loss of the ability to recognize or acknowledge bodily defects. It is often a term used to describe patients who deny their deficits. This is most frequently observed in patients who suffer left side paralysis; patients may rationalize their failure to use their limbs or have delusions that the limb does not belong to them (outside their body image). Within this category are patients with inattention (usually the left side) of their body, in absence of any neurological weakness or paralysis. This form of inattention is quite striking when seen in patients, particularly while they are observed when dressing or bathing (dressing apraxia). These types of deficits are usually associated with lesions to the right parietal region.

Bodily agnosia is a disturbance of body image where patients are unable to name or localize parts of their own body. One common deficit in this category has been called "finger agnosia". Which has been defined as a consistent "loss of ability to recognize, identify, differentiate, name, select, indicate, and orient as to the individual

fingers of either hand, the patient's own as well as those of other persons" (Gerstmann, 1958). Right-Left confusion is noted by an inability to discriminate the left and right parts of the body.

2. Visuospatial Agnosia. Visuospatial agnosia involves a breakdown in the analysis of complex perceptual stimuli into integrated units. Dysfunction of this sort can result in deficits in the effective comprehension and manipulation of stimuli in the environment. Specifically, patients may have difficulty in describing, negotiating and remembering how to get from one place to another; they will have problems estimating the distance between objects or locations, in describing and recalling spatial relationships of familiar surroundings, and have difficulty orienting to geography. One good illustration of this type of deficit is on a task which requires patients to draw a floor plan of their home. McFie, Piercy and Zangwill in 1950 examined the plans of patients with frontal-parietal lesions and discovered that the drawings gave no information about the layout of the house. The plans consisted of a disorganized array of landmarks which were scattered piecemeal with no regards to their relative position. Their performance was not simply an inability to draw, nor was it primarily a memory deficit, since specific verbal information concerning their house was retained (see also: Benton, 1969; DeRenzi

and Faglioni, 1967; Lawson, 1969). If there is a memory loss, it is of the nature of loss of topographical information. These patients have been shown, experimentally, to rapidly lose information concerning spatial relationships following a time delay (DeRenzi & Faglioni, 1967); these patients will also have difficulty reading and following maps. Semmes, Weinstein, Ghent & Teuber in 1963, demonstrated that parietal injured patients failed to maintain proper body orientation when asked to follow a route on a map. Similarly, Butters and Barton (1970) and Butters, Soeldner and Fedio (1972) showed impaired performance on the Money road-map test of direction sense, a task requiring reversible mental spatial operations, following parietal lobe injury.

Patients who are spatially disoriented will have difficulty on any neuropsychological task that requires complex spatial analysis, rotational abilities or visuospatial matching such as The Raven's Matrices (1962); Hooper Visual Organization test (1958); The Benton Visual Retention Test (copy, memory and multiple choice versions, 1963) and all tests of construction such as Block Designs and Object Assembly subtest of the WAIS. All these tasks require subjects to mentally reorient, invert or rotate perceptual stimuli to solve visuospatial reasoning problems, with or without a motor component.

Patients with visuospatial deficits may also have

problems with reading and in calculating (dyscalculia). These patients may also be unable to make sense of printed material (dyslexia), although they would be able to recognize letters and words. In terms of mathematical operations, patients may remember the problem and even the rules, but are unable to carry out the operation due to what has been described as the "quasi-spatial" nature of the numbers. Luria (1966) suggested that all mathematical operations require, at some level, manipulation of the elements of calculation in an external spatial field (Luria, 1966 p 159), the significance of a number is altered according to its spatial relation to other numbers.

B. Constructional Apraxia

Constructional abilities were defined by Benton and Fogel in 1962 to involve a number of interrelated cognitive activities. Generally, constructional tasks all require the patients to assemble, join or articulate parts to form a simple unitary structure. To succeed on these types of tasks requires the combination of manipulative, executive spatial and perceptual skills. The standard tasks employed to uncover constructional difficulties are drawing (free style or copying from models), and building (e.g., Block Designs and puzzles (e.g., Object Assembly). Both two- and three-dimensional constructions are

valuable tools in the assessment of constructional apraxia (Benson and Barton, 1970; Benton and Fogel, 1962).

1. Drawings (direct copying and free hand).

Drawings are a essential instrument in neuropsychological assessment, and have been shown to be strongly correlated with organic impairment (Lezak, 1983). Drawing abilities can be studied by the use of a variety of copying and free drawing tasks. The most popular are (a) the Bender-Gestalt (Bender, 1938; Hutt, 1969); (b) the Minnesota Percepto-Diagnostic test (MPD) (Fuller, 1969; Fuller and Laird, 1963; (c) the Complex Figure Test (CFT) -- copy administration devised by Rey (1941) and standardized by Osterrieth (1944), and referred to as the Rey-Osterrieth figure; and (d) the Benton-Visual Retention Test (BVRT) --copy administration (Benton, 1963). The Benton test consists of a series of simple-to-complex geometric-shaped line drawings, in which subjects are required to reproduce them exactly. The tasks start with an easily copied figure, usually consisting of a central large figure containing a limited number of angles. As the test proceeds, the models get progressively more complex involving multiple and overlapping central figures with small accompanied peripheral figures. It should be noted that most neurologists, when testing mental status in patients suspected of a dementia, employ some limited copying in a non-formalized manner, often taking the form

of some simple geometric figure copying, such as circles, triangles or cubes.

Patients are often asked to spontaneously draw from a "picture in their mind" (freehand drawing). There are a number of tests of this type such as: draw-a-person, the house-tree-person or star-cube-house tests (see Lubin, Wallis & Paine, 1971; Lezak, 1983), the Bicycle drawing of Taylor (1959). The drawing of a clock, and setting the hands to a specified time, is another common test employed by neuropsychologists (see Fuld, 1983; Luria, 1966) and is also part of the Parietal Lobe Battery (Goodglass and Kaplan, 1972; Borod, Goodglass, & Kaplan, 1980).

Specific types of drawing defects have been described by a number of authors (Paterson & Zangwill, 1944; Piercy, Hecaen & Ajuriaguerra, 1960; Benton, 1973; Hecaen, 1981) and include: distortions and simplification; omissions or additions of parts; rotations, reversals and disruptions of vertical and horizontal axes; misplacement and size errors; and errors of spatial orientation. Errors or neglect to a particular side of the patient's reproductions may be an indication of a lateralized brain injury. A number of elaborate scoring systems have been devised for the purpose of quantifying the patient's performance on drawing tests: (a) the Bender-Gestalt scoring system revised by Hain, 1964; Pascal and Suttell, 1951; (b) the Rey-Osterrieth figure scoring systems by

Taylor, 1959; and (c) the BVRT scoring system (see Benton, 1963). Often these systems assign point valves to the various drawing errors in terms of the there severity and frequency. These scores are then used in conjunction with other cognitive indicators to aid in the differential diagnosis of a variety of CNS diseases affecting cognitive functioning.

2. Building and Assembling. There are a number of standardized neuropsychological tests that require subjects to build from models. The most frequently administered is a block design type of task -- Kohs blocks (Arthur, 1947; Goldstein and Scheerer, 1947; 1953); WAIS Block Designs (Wechsler, 1955). The WAIS Block Designs require subjects to construct replicas from either experimenter's models or from pictures. The complexity and degree of difficulty was thought to increase with the order of design presentation, but Ben-Yishay, Diller, Mendleberg, Gordon and Gerstman (1971) were able to demonstrate, in a group of brain damaged subjects, success on some of the later designs, while failing earlier ones. One explanation for this finding was suggested by Kierman (1982) who states that Block Design complexity is based upon the natural block-face segmentation (tectonic cues). Designs with clearly distinct boundaries between the colors and blocks provide greater cues for construction than those designs in which patterns run across multiple

blocks. For example, design #6 from the WAIS Block Designs appears more difficult to construct than design #7 (the first nine block design). In design #7 each individual block is distinguishable, while in #6 the four blocks have a continuous pattern across the face of the blocks and the borders of the individual blocks are difficult to make out.

The subject's score on this task is based on the correct number of designs with extra points awarded for rapid completion. Kaplan (1982) has suggested a correlation with the types of errors and the sequence of assembling by subjects on constructional tasks with specific lesions sites in the brain. For example, patients with right frontal brain damage will often begin their design in the corner of the right quadrant and predominantly make errors on the side contralateral to their lesion. Their performance is characterized by self-correction. Patients with right hemisphere damage often violate the 2X2 matrix, while left hemisphere lesioned patients often make errors of perseveration.

The Object Assembly subtest of the WAIS requires subjects to put things together into a familiar configuration when presented with form board cut-outs (Wechsler, 1958). At best, it requires immediate perception of the whole, with a critical understanding of the relationship of the individual parts. Failing that,

the subject's approach to the test can be revealed (i.e., trial and error or edge matching strategy) as he attempts to make sense of the puzzle. Similar to the Block Designs, the assemblies become more complex, with less salient cues as the test proceeds (4 puzzles in the object assembly test of the WAIS).

Other popular building and assembling tests include: (1) stick constructions (Goldstein & Scherrer, 1953 a & b; Fogel, 1962; Benson & Barton, 1970; Butters & Barton, 1970); (2) the block rotation test of Satz (1966a), (3) the paper-folding test (see 1960 revision of the Stanford-Binet); and finally, (4) tests of three-dimensional construction (Critchley, 1966; Benton & Fogel, 1962) have also been employed to study constructional apraxia.

C. Spatial and Constructional Abilities: Changes due to Aging

Despite the inherent problems of longitudinal and cross-sectional studies both support a tendency for intellectual functions to decline with age (Birren & Schaie, 1977; Hulicka, 1978). Studies by Wechsler (1958) and Eisdorfer et al. (1959) have shown that not all cognitive functions decline at a uniform rate, some decline rapidly while others are well preserved. Both these studies have described a WAIS pattern of scores that reflect normal aging. The verbal subtests of the WAIS

appear the most stable with increasing age, while scores on the performance subtests decline.

This type of pattern has become known as the "classical" aging pattern (Doppelt & Wallace, 1955). A similar pattern has also been described by the use of the Halstead-Reitan neuropsychological battery (Overall & Gorham, 1972; Goldstein & Shelly, 1981). Both batteries, particularly the Halstead-Reitan, have been criticized for inadequate norms for the elderly, nevertheless, the pattern may reflect the different cognitive requirements of the verbal and performance tasks. The verbal tasks rely on the use of previously stored information (general information and vocabulary sub-tests are a prime example). The non-verbal performance sub-tests rely heavily on visuospatial and visuoperceptual skills, and require the manipulation of novel material in unfamiliar and complex ways (Block Designs and Object Assembly are the best examples). (Birren, Botwinick, Weiss, & Morrison, 1963; or Schonfield & Robertson, 1966). A decline over a wide range of visuospatial tasks has been shown with aging: (1) the Bender-Gestalt test (Gilbert and Levee, 1965); (2) the Embedded figure test (Axelrod & Cohen, 1961); (3) spatial rotation tests (Cerella, Poon, & Flozard, 1981); and (4) figure drawings (Plutckik, Conte, Weiner, & Teresi, 1978). Recently, Eslinger and Benton (1983) have shown that both spatial and non-spatial visuoperceptual

abilities decline with age.

Some authors have suggested that the classical aging pattern as described above resembles that of patients with acute or chronic right hemispheric brain damage (Goldstein & Shelly, 1981; Benton, Eslinger, & Damasio, 1981), which would indicate that aging affects the right hemisphere more than the left (Levy-Agresti & Sperry, 1968). This hypothesis has been supported by a number of investigations that have shown declines on a wide range of cognitive tests believed to be heavily loaded for the right hemisphere. These tasks involve non-verbal memory, visuoperception, visuospatial, attention and constructional abilities (Benton, et al., 1981; Goldstein & Shelly, 1981; Bak & Greene, 1980).

Others have interpreted these findings, not so much as differential decline of the right hemisphere, but as verbal versus non-verbal cognitive strategies (Bak & Greene, 1980) or due to psychomotor slowing with age (Bigler, Steinman, & Newton., 1981). Nevertheless, all these studies have demonstrated declines in certain cognitive abilities, usually on non-verbal visuospatial tasks with aging. This pattern has also been described for depression in the elderly (Caine, 1986).

The emphasis of all these studies have been in terms of success or failure of the test items. Kaplan (1982) and Hochandel & Kaplan (1984) believes that this approach

can be misleading. A better method to uncover cognitive impairments is by investigating the strategies that individuals employed to produce their final outcome, regardless of success or failure. A number of authors have employed qualitative methods to analyze test performance in the elderly.

For example, Ben-Yishay, Diller, Mandelberg, Gordon & Gerstman (1971) showed that normal aged subjects made a significant number of constructional deviations (violation of the matrix) on the Block Designs. This type of error is seen typically with patients with right hemisphere damage. Albert & Kaplan (1980) found many instances of perseveration and segmentation (focus upon individual parts and an inability to form integrative wholes), on tasks from the Boston-Parietal lobe battery when given to elderly subjects. These types of errors have been interpreted as indicative of frontal dysfunction in normal aging.

Declines in problem-solving abilities and concept formation have also been reported with aging (Bigler et al., 1981; Grambra & Arenberg, 1980; Rabbitt, 1977; Arenberg, 1968). Elderly subjects also have difficulties with tasks that involve the maintenance of attention, hypothesis generation and planning, as well as the ability to alter responses as a result of feedback, including response shifting. All these deficits are in support of

frontal lobe changes with aging.

D. Spatial and Constructional Abilities: Impairment Following DAT

As discussed in earlier sections of this review there is ample evidence that patients given the diagnosis of DAT are impaired with regards to spatial orientation and constructional skills. Presently the literature is lacking in documenting these deficits quantitatively. At a clinical level, patients with DAT demonstrate a WAIS profile similar in many respects to normal aged subjects (Fuld, 1984) except it reflects severe impairments as compared to moderate declines. As predicted from the WAIS profile, and uncovered by Fuld (1984), the Block Designs and the Digit Symbol sub-tests are the most severely effected by the disease. The differential declines of these two sub-tests has also been reported by other investigators (Sim, Turner, & Smith., 1966; Crookes, 1974; Brinkman & Brain, 1984). The poor performance on these two subtests is an indication that constructional apraxia and spatial disorientation are major cognitive deficits in DAT, independent of a memory problem.

The few studies that have looked at drawing and copying in DAT patients have shown their performance to be impaired (Muramoto et al, 1979; 1984; Rosen, 1983 A & B). In the Muramoto studies the drawings of geometric outline

figures were very difficult for DAT patients. One of the most common errors occurred when the patients placed their own drawing close to, or directly upon, the model (closing in). In the Muramoto's 1984 study, early to moderately impaired DAT patients were administered the Bender-Gestalt test (scored by the Pascal-Suttel method). Again, "closing in" seemed to be a general characteristic of this disease. Photographs and analysis of the patient's performance seemed to indicate that the difficulties in this population were related to constructional, spatial, and perceptual problems.

Rosen (1983 A & B) administered an extensive neuropsychological battery to a group of patients with DAT and normal aged controls. The demented group was further subdivided into a mild and severe group. Patients were tested for visual memory, visual copying and a multiple choice recognition. All groups did better on direct copying than on recall. There was a significant decline in performance on the copy task from normal aged to mild DAT to severe DAT. Normal aged were equal to the mild group on the matching task, but both were significantly better than the severe group; only the severe group was impaired on the visual memory test.

In contrast to normal aging, patients even in the early stages of dementia have a significant defect in their ability to copy geometric forms. This finding is in

support of a constructional disturbance. Rosen (1983B) suggested that one reason for this constructional deficit was a defect in visuoperceptual abilities. This is supported by evidence in the recognition task where demented patients chose forms with spatial displacements twice as often as the normal aged. The most common error type in the aged group was a tendency to select simplified forms, an indication of a failure to analyze all parts of the form properly.

Normal aging seems to be characterized by a decline in certain cognitive abilities, most notably in tasks that require visuospatial or visuoconstructional abilities and attention. There is a marginal decline in memory functions. Dementia, particularly of the Alzheimer's type may show similar patterns of decline with regards to perceptual and constructional skills, but to a significantly greater degree. They also have a marked memory impairment, and changes in language abilities. When a direct comparison of qualitative performance between normal aged and patients with Alzheimer's type dementia are made, the latter group demonstrates significantly greater visuospatial errors. This discovery may have fundamental implications for both the differential diagnosis of the disease as well as its underlying mechanisms.

CHAPTER VII. HYPOTHESES

Chapters II and III described the physiological changes known to occur in the brains of DAT patients. Senile plaques and neurofibrillary tangles are the neuropathological hallmarks of the disease, while reductions of cholinergic activity is the major neurochemical finding. These changes in the brain are thought to be the direct result of a degeneration process of a pre-synaptic cholinergic pathway. This pathway has its origin in the nucleus Basalis of Meynert (nbM) of the basal forebrain and projects diffusely to the frontal, temporal and parietal lobes, as well as to sub-cortical structures. The presence of these physiological markers has been shown to be strongly correlated with functional declines of intellectual abilities (as outlined in Chapter I).

The specificity of the cholinergic system with regards to memory and other cognitive functions was summarized in chapters IV and V. In brief, pharmacological interference or enhancement of the cholinergic system in young, aged, or patient population can result in behavioral changes that support the role of this transmitter in cognitive functioning.

Non-memory cognitive declines have been shown to

occur due to aging and dementia, with constructional and spatial abilities showing the greatest changes. Links between these abilities and the cholinergic system have been suggested.

In this study a battery of spatial and constructional tasks has been adninistered to a group of early-to-moderate DAT subjects and their performance is compared to that of the same aged and a normal aged comparison groups.

HYPOTHESIS 1: Constructional and spatial abilities in subjects with early-to-moderate DAT will be both quantitatively and qualitatively different than that of an Aged and same aged (Spouse) comparison subjects.

a) It is expected that a significant difference will occur between a group of subjects who have been diagnosed with DAT and a group of appropriate matched subjects without dementia. The subjects in the matched comparison group (spouse) are expected to perform at appropriate levels for their age on the battery of spatial and constructional tasks, making few errors and demonstrating effective constructional strategies. Based upon the limited reports in the literature and clinical assessments the DAT subjects will be impaired on tests of spatial and constructional tasks when compared to the same aged

comparison group. This would suggest that constructional abilities show significant cognitive decline in DAT, similar to memory and language changes.

b) It is hypothesized that significant differences will occur between subjects with DAT and normal-aged individuals. These differences will be both qualitative and quantitative in nature. This would indicate that the underlying disease process associated with DAT is independent of the normal aging process.

HYPOTHESIS 2: The administration of optimal doses of oral physostigmine to DAT subjects will improve their performance on constructional and spatial tasks.

Physostigmine has been shown to improve memory performance when given to mild-to-moderately impaired DAT subjects when an individual optimal dose were titrated for. It is expected that the drug will similarly improve performance on the spatial and constructional tasks administered in this study. This would suggest that the wide range of cognitive deficits in this population are as a result of a common physiological changes in the cholinergic system known to occur in DAT.

CHAPTER VIII. METHODS

This study was conducted simultaneously with an ongoing project that tested the ability of oral physostigmine to improve memory in patients with dementia of the Alzheimer type. In addition to memory tests, all patients were administered an experimental battery of spatial and constructional tests at specific times, and their performance was compared to a Spouse and normal Aged comparison group.

A. Subjects

1. Patient Population. This included 11 patients with a diagnosis of DAT; six were treated with physostigmine, the remaining five were given a placebo. Clinical characteristics for inclusion into the study was based upon a history and examination (as shown on Table 1), demonstrating a progressive cognitive impairment with memory loss (confirmed by psychometric testing), and possible simultaneous and progressive deficits of cognition, apraxias, and agnosias.

Findings on examination including prefrontal release signs, hypertonia, extensor plantar response and myoclonia may also be present. All patients showed a normal level of consciousness. All the following were within normal limits: (1) EEG (or diffusely slow); (2) blood

TABLE 1

Entering Screening battery

A. Complete history

B. Complete medical and neurological examination

C. Psychometric testing to include:

1. Blessed mental status test
2. Wide Range Acheivement Test (WRAT)
3. Wechsler Adult Intelligence Scale (WAIS)
4. Raven's Progressive Matrices (Color version)
5. Language screening examination
6. Orientation testing
7. Fuld-Object Memory Test
8. Sensory-cortical and motor tests
9. Purdue pegboard
10. Mattis Dementia Rating Scale

D. Hachishi Ischemic Score

E. Visual field testing

F. Chest X-ray

G. EEG

H. EKG

I. Blood screening

J. CT-scan

chemistries, B12 and T4; (3) EKG and rhythm; and (4) CT scan (or showing cortical atrophy). Entering criteria on the Blessed Mental Status (BMS) test was the following (based upon a 33 point maximum): (1) 2-12 errors for patients in their fifties; (2) 4-14 errors in their sixties; (3) 5-18 errors in their seventies and (4) 10-20 errors in their eighties. These cutoffs were based upon ranges described for normal aging and early-to moderate dementia from Fuld (1978).

Exclusionary criteria were history, examination and laboratory tests of primary affective disorder; chronic schizophrenia or other psychiatric illness; alcoholism or drug abuse; traumatic or space-occupying CNS lesions; thyroid dysfunction; Vitamin B12 or folate deficiency; exogenous toxins; malnutrition; infections (including syphilis); endocrine disease and significant cardiovascular disease, history of prostatism, urinary retention, glaucoma, syncope, malignancy, significant cardiac renal or hepatic disease. All individuals who used psychotropic medications, including tranquilizers and sedatives, were excluded. The study included both English-speaking male and female patients.

All patients were english-speaking and selected from those requesting treatment at Albert Einstein College of Medicine under investigator L. Thal, M.D., Associate Professor of Neurology.

2. Spouse Comparison Group. Each patient that was enrolled in the study had a responsible individual available to administer the medication and to report from week to week on patient's progress. When possible, the individuals (often the spouse), who could be matched (N=9) in terms of age and education level, served as control subjects. They were administered the experimental battery on a single occasion.

3. Normal Aged Comparison Group. Eleven individuals were obtained from the ongoing long-term aging project being conducted in the Department of Neurology, Albert Einstein College of Medicine. All were non-demented, community dwelling volunteers. This population consists of 400 (75 to 85 year old) who receive medical as well as neuropsychological testing on a yearly basis. An expanded neuropsychological examination (to include the experimental battery) were administered to a selected sample from this population. This sample consisted of both male and female individuals whose mental status rating (based upon scores on the Fuld adaptation of the Blessed Mental Status Examination) was well within normal limits (less than 3 errors) and has remained unchanged over the last three years. The Experimental battery was administered on a single occasion.

B. Experimental Design and Drug Procedure

The design of this study was a double blind, parallel study comparing physostigmine and placebo. Oral physostigmine was supplied in 1 mg tablets by O'neal, Jones and Feldmen Pharmaceutical. Following evaluation and baseline testing, each patient began with 2 mg of drug/placebo q1d x 1 week (4 times per day), then increase to 3 mg p.o. q1d x 1 week, then 4 mg p.o. q1d x 1 week. If gastrointestinal symptoms developed, the spouse of the patient automatically lowered the dose by 1 mg/dose. Patients were seen weekly after each increment for evaluation. At the end of the initial three weeks of treatment, the medication dose producing the best response on the selective reminding test (showing improvement on both sum of recall, long-term retrieval and a reduction in intrusions) or the highest dose tolerated was chosen for continued testing. Patients were then seen after 2, 4 and 6 weeks of therapy for repeated evaluation. The medication was stopped and a final baseline was collected after two weeks of wash-out.

C. Test Administration Schedule

The following tests were administered 8 times for each patient:

1) Two 12 item/12 trial selective reminding test (See Buschke and Fuld, 1974).
2) Retrieval from semantic categories (fruits, animals, flowers, vegetables and same sex names).
3) The Rosen Drawing Test (Rosen, 1981).
4) Nurses Observation Scale for in Patient Evaluation (NOSIE) (Honingfeld, Gillis and Klett , 1966).
5) Activities of Living (ADL) (Linn & Linn, 1983).
6) Raskin and Crook Depression Scale (1976).
7) Instrumental Activities of Daily Living Scale (IADL) (Lanton & Brody, 1969).

The following tests were administered at the initial baseline, at a best dose, and at the final baseline:

1) The Fuld adaptation of the Blessed Mental Status Examination (Fuld, 1978).
2) The Mattis Dementia Scale (1976).
3) Performance of Activities of Daily Living (PADL) (Kuriansky & Gurland, 1976).

The experimental battery (see Table 2) was administered at the initial baseline, at best dose and at the final baseline (washout).

TABLE 2

THE EXPERIMENTAL BATTERY

A. The Money Road Map Test of Spatial Orientation

B. The Rey-Osterrieth Complex Figure Drawing Test

C. The Benton Visual Retention Test: Copy (Administration)

D. The Benton Visual Retention Test:
Delayed Match-to-Sample

E. The Benton Visual Retention Test:
Direct Match-to-Sample

F. Block Design subtest from the WAIS

G. Object Assembly subtest from the WAIS

D. The Experimental Battery Procedure

The Road Map Test of Direction Sense (Money, 1976): The instructions were followed exactly as specified in the manual (Money, 1976), with the exception that the route (along the dotted line, see appendix I) was drawn as the direction was asked from the subject. The examiner made sure the subject had full understanding of the task by going over the sample turns and, as needed, made reference to real environmental stimuli. Time to complete the entire route was recorded.

The Rey-Osterrieth Complex Figure Drawing (Rey, 1941; Osterrieth, 1944): Subjects were handed a blank piece of 8"X 10" paper and instructed to copy in all details the Complex Figure (refer to appendix IIa). The figure was set out so that its length ran along the subject's horizontal plane. At one minute intervals, the examiner handed the subjects a different colored pencil and the order of the colors was noted. The time to completion was recorded.

Benton Visual Retention Test (BVRT) - Copy form C (Benton, 1963): Subjects were supplied with single sheets of paper, identical in size to the model, and a black felt tip marker. The subjects were instructed to copy the

entire design presented to them from a series of 4x8 inch cards. The subjects were directed to "try to make yours look just like this, don't leave anything out, and tell me when you have finished". Unlimited time was allowed to complete the designs, but the time to completion was recorded by the experimenter. A total of 10 models were presented in order from the booklet.

Benton Visual Retention Test - delayed Match-to Sample (Benton, 1956): Following completion of each drawing from the direct copy test, the subject's drawing and the model were removed. They were then presented with a plate consisting of four separate drawings -- three slightly resembling the model and, one a true match. The three foils varied in the spatial arrangements of the original stimulus. Subjects were asked to "tell me which one of the four match the model you have just seen". The subjects' choice was recorded by the experimenter as was the length of time needed for the decision.

Benton Visual Retention Test - Direct match to sample (Benton, 1956): Following the completion of tests of copying and the delayed match to sample, the subjects were presented with seven cards from form E from the BVRT and ask to visually match it to one from a large plate containing four drawings. One of the drawings was a correct match, while the remaining three were either geometric variations, rotations or have omitted parts.

The first seven of the ten forms from form E were used.

Block Designs: Test instructions conformed to those specified by the WAIS manual (Wechsler,1955). With the following exceptions: the awarding of points for a correct construction only occurred if subjects completed the design within the time limit, but all subjects were allowed an extended period to complete a design if significant progress was being made. In the standard procedure, three consecutive failures resulted in discontinuance of the subtest. For the purpose of this battery, subjects were encouraged to attempt designs even after three failures, or at least until design number 6 was administered (the first 9 block design).

Object Assembly: Instructions conformed to the WAIS manual in all details (Wechsler, 1955). Subjects were encouraged to continue working beyond the time limits as specified by the manual, but points were only awarded for those correctly assembled within the time limit.

E. Data Collection and Analysis

The performance on all components of the Experimental battery were first analyzed by quantitative methods. Scores were derived in terms of number of items correct within the time limit; for the Block Designs, for the Object Assembly, the number of correctly placed pieces.

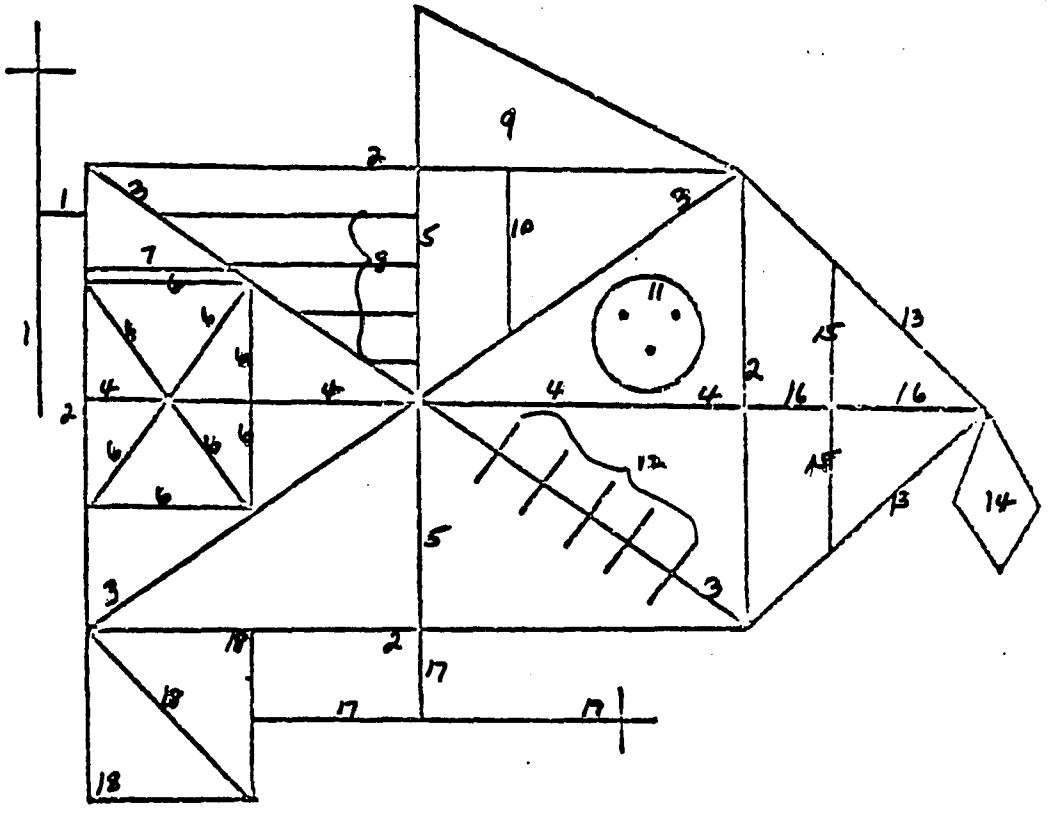
Raw scores from these sub-tests from the WAIS were derived and then converted to scaled scores and age-corrected scores based upon tables supplied in the test manual. For The BVRT-Copy, BVRT-immediate recognition, and BVRT direct match-to-sample, each drawing or choice was assessed in terms of correct (0 point) or incorrect (1 point). The maximum score was 10 for the copying task, and 7 each for the matching tasks.

The Complex Figure Drawing was scored by two scoring systems. The first was described by Lezak (1976) and will be referred to here as the accuracy score, the other system was developed by Binder (1982). The accuracy scoring system broke the figure into 18 discrete units (see figure 1) each was assessed separately for their accuracy and position within the whole design. Two points were awarded for a correctly drawn unit that was also properly placed. A single point was awarded to a unit that was drawn correctly but poorly placed, or drawn incorrectly (minor distortion or incomplete, but recognizable) but placed properly. One half a point (0.5) was given to a unit judged incorrect and placed poorly but, recognizable. Finally, zero points were given when a unit was considered not recognizable or missing. A maximum of 36 points was possible.

The validity of this scoring system was assessed by comparing the results of the accuracy score with ratings

FIGURE 1

SCORING UNITS OF THE REY-OSTERRIETH COMPLEX
FIGURE DRAWING TEST



of each drawing by five independent judges. Each rater was asked to arrange in a sequence -- from best to worst -- two sets of drawings. The first set (N=30) consisted of all the Complex Figures Drawings of the DAT (initial baseline) and the two comparison groups (Aged and Spouse). The second set (N=32) contained all the drawings made by the DAT patients over the three treatment sessions. The sequence the rater placed the drawings were converted to a hierarchical ranking. The drawing rated "best" was assigned the numerical value of 1; the drawing judged the "worst" was given the number equal to the total number of drawings to be rated in the set. The accuracy score was ranked into a similar hierarchy; the drawing with the highest score was given the rank of 1; the drawing with the lowest accuracy score was given the lowest rank in the set of drawings. Interrater reliability was assessed by correlations between the five raters. A correlation between the raters and the accuracy score hierarchy addressed the issue of validity of the accuracy scoring system as a true indicator of copying competency.

An additional way to analyze the performance on the Complex Figure Drawing was by breaking the 18 components into four major subdivisions (see figure 1): (1) the outer framework (units 2 & 13; with a maximum of 4 points), (2) internal details (units 6,7,8,10,11 & 12; with a maximum of 12 points), (3) internal subdivisions

(units 3,4,5,15 & 16; with a maximum of 10 points, and (4) external details (units 1,9,14,17 & 18; with a maximum of 10 points).

The use of the Binder scoring system (1982) allowed the assessment of the configuration of the design and how the subjects drew five of the structural elements of the figure (horizontal midline, vertical midline, two diagonals and the vertices of the pentagon). Three scores were obtained: (1) configural units, which were the number of the five elements that were drawn as one unit, (2) fragmented units, which were the number of elements not drawn as a unit, and finally, (3) missing units, which were the number of units incomplete or omitted. Comparison of these different units were made across the groups as well as across the treatment sessions for the DAT patients.

The Standardized Road Map Test was scored in terms of the total number correct orientations made by the subjects (maximum 32) and the time it took to complete the route. The turns on the test were further divided into turns that pointed in the "away" direction (N=17) and those in which the orientation was "towards" the subjects (N=15).

A sequential analysis of test performance was made for a number of sub-tests from the experimental battery. Two techniques were applied to assess qualitative performance. First, by assessing performance at various

times during the testing and second, by the analyzing of the types of errors that the subjects made.

On the Road Map Test of Spatial Orientation the pattern of subject's response were determined and the number of errors, when the patient was moving "away" from himself, was compared to the number of errors made when the subject was moving "toward" himself.

On the Rey-Osterrieth Complex Figure Drawing the changing of pencil colors at one-minute intervals as well as the detailed notes taken by the examiner, made it possible to chart the sequence and the direction of the lines that were drawn. The process the subject went through could either be orderly or piecemeal, even though the final product may resemble the model. The sequential mapping of the subject's performance allowed the determination of the subject's approach and strategies. In addition, the types of errors, such as: rotations, reversals, and omissions, helped in determining the kinds of difficulties the subjects were having with this complex figure drawing.

Qualitative assessment of the Benton Visual Retention Test (copy only) was accomplished by the scoring system described by Benton (1963). Several of error types were noted: omissions, distortions, perseverations, rotations, misplacement, and size errors.

CHAPTER IX. RESULTS

This chapter is organized into three main sections. The first is the group comparisons (DAT, Aged and Spouse) across the tests on the experimental battery. The second is the treatment comparisons (Drug or placebo) on each individual task, and the third is comparisons of the different groups as their performance interrelates across the different tasks of the experimental battery and other neuropsychological indices. In the first two sections the results on each task from the experimental battery will be presented in the following order: The Roadmap Test of Spatial Orientation; the Complex Figure Drawing; the Benton Visual Retention test (to include the two matching tasks); and finally the Block Designs and Object Assembly subtests from the WAIS.

The first section (section 1: Group comparisons) begins with demographic comparisons among the three groups. Quantitative findings from each task on the experimental battery task are then be presented. In all cases the initial baseline (BL1) performance from the DAT group will be compared to the single testing occasion of the comparison groups (Aged & Spouse). This will be followed (on some tasks) with qualitative assessment. On all tasks a main between-subject factor of "group"

(DAT/Aged/Spouse) will be entered into an analysis of variance (ANOVA). A number of within-subject factors will also be entered into the analysis and will be specified prior to the summary of the findings. When the data from the Spouse and Aged comparison groups were not found to be significantly different, they were combined to form a single comparison group. ANOVA's were then carried out for the between subjects factors with two groups.

The effects of physostigmine on performance on the tasks from experimental battery (section 2: Treatment comparison) will be assessed by comparing the drug treated trials (the "B" in the "ABA" design) in relation to the two non-drug treated trials. In addition, comparisons between drug-treated and placebo-treated groups will also be made. All analysis will have a main between-subject factor: Treatment (drug group vs. placebo group), and a number of within-subject factors of which one will be trials (BL1 vs BD vs BL2). Other within-subject factors will be specified when the individual task results are summarized.

The final section of the results (section 3: Cross Task Comparisons) will look at the correlations of test scores from the different tasks of the experimental battery. In addition correlations with a number of tasks not administered as part of this experimental battery was also made in the DAT group. This will make it possible to

make some general statements about cognitive strengths and weakness in the groups studied.

Section 1: Group Comparisons

a) Demographic Comparisons

The number of subjects within each group were unequal, the DAT and Aged groups both had 11 subjects and the spouse comparison group had 9. The groups were unevenly distributed with regards to gender. As shown on Table 3 there were a greater number of males in the DAT group, and greater number of females in the Aged and Spouse comparison groups.

The Aged comparison group (mean age = 82.7) was significantly older than the DAT (mean age = 67.7) and the Spouse (mean age = 65.7) comparison group ($F(2,30) = 25.9$, $p < 0.01$).

The three groups were not significantly different in terms of their mean number of years of formal education. The DAT averaged 12 years, or completion of high school, while the Aged group (mean years = 11.2) and the spouse comparison group (mean years = 10.6) had sightly less ($F(2,30) = 5.26$, n.s.).

TABLE 3

Demographic Comparisons

Group		DAT	Aged	Spouse
N		11	11	9
Sex	Male	7	4	3
	Female	4	7	6
Mean Age (Yrs.)		67.7 (1.91)	82.7 (1.04)	65.9 (0.70)
Mean Education (Years in School)		12.0 (1.27)	11.2 (0.88)	10.6 (0.96)

1) Aged > DAT = Spouse ($F(2,30) = 25.90$, $P < .01$)
2) DAT = Aged = Spouse ($F(2,30) = 5.26$, N.S.)

b) The Roadmap Test of Spatial Orientation

The mean number of errors (maximum = 32) and the mean duration to complete the route, were analyzed across groups with a one-way analysis of variance (ANOVA) for independent groups (see Table 4A). No significant difference existed between groups with regards to the mean number of errors ($F(2,30) = 1.56$, n.s.). The Aged group made 6.9 errors, the Spouse group made 10.5 errors and the DAT group made 11.2 errors during their initial baseline testing. The combined comparison group data (Mean = 8.6 SEM = 1.4) was also not significantly different than that of the DAT subjects. No findings emerged between groups with regard to the time to complete the route in seconds (Aged = 187.8, Spouse = 129.7; DAT = 206.5).

The 32 turns on the roadmap were divided into two major types of turns, those that pointed in the "away" direction (N = 17), and those in which the orientation was "towards" the subjects (N = 15). Due to this inequality of turn types, the number of errors were converted into percentage of errors within each turn type. The results were analyzed using a two-factor mixed design ANOVA with Groups (Aged/Spouse/DAT) as the main between-subject factor and direction (away/towards) as the main within-

TABLE 4

Roadmap Test of Spatial Orientation: Group Comparisons
Total Number of Errors and Duration: Means and SEM

[A]

Measure	Aged (N=11)	Spouse (N=9)	Dat. (N=11)	
Mean Errors	6.9 (1.59)	10.6 (2.36)	11.2 (1.59)	(1)
Mean Duration	187.7 (29.17)	129.7 (17.56)	206.5 (19.71)	

[B]

Drug Treatment (N=6) (2)

Measure	BL1	B.D.	BL2	(3)
Mean Errors (1)	7.8 (2.42)	8.2 (3.07)	10.8 (3.20)	
Mean Duration	205.0 (33.75)	153.8 (18.67)	162.5 (23.63)	

[C]

Placebo Treatment (N=5) (2)

Measure	BL1	B.D.	BL2	(3)
Mean Errors	15.2 (1.20)	16.4 (0.93)	17.6 (1.36)	
Mean Duration	208.2 (20.60)	208.8 (37.57)	216.4 (34.09	

(1) Aged = Spouse = DAT ($F(2,30) = 1.56$, n.s.)
(2) Mean Errors: Drug Treatment group > Placebo Treatment group ($F(1,10)$ 6.17, $p < 0.03$)
(3) Mean Errors: BL1 = B.D. = BL2 (2,22) = 1.75, n.s.)

subject factor. No significant difference existed between the three groups ($F = (2,30)\ 1.74$, n.s.). There was, however, a significant effect of direction across all three groups ($F\ (1,31) = 36.9$; $P < 0.01$) A greater number of errors were made on turns in which the direction was "towards" the subjects when compared to turns "away". As can be seen on Table 5(A) and Figure 2, on the average, twice the percentage of errors were made in the "towards" direction then compared to the "away" direction. No significant Group x Direction interaction was obtained ($F\ (2,31) = 0.21$, n.s.). Comparison to the data obtained from the combined comparison groups (Aged and Spouse together) showed similar results. The combined comparison group had a mean 0.22 (SEM = 0.04) percent error in the "away" direction and a mean 0.39 (SEM = 0.06) percent error in the towards direction. No significant difference occurred between the two groups ($F\ (1,30) = 1.41$, n.s.). There was once again a significant difference between turn orientation ($F\ (1,31) = 38.17$, $p < 0.01$) with a greater percentage of errors made in the "towards" direction. There was no significant interaction between groups and direction ($F\ (1,31) = 0.41$, n.s.).

A three-factor mixed ANOVA was performed with Group (Aged/Spouse/DAT) and sex (male/female) as between subject factors and direction ("away/towards") as a within-subject factor. There was an overall main effect of sex (F (1;30)

TABLE 5

Roadmap Test of Spatial Orientation

[A] Group Comparisons: Direction

Direction (2)	Aged N	Aged Mean	Aged SEM	Spouse N	Spouse Mean	Spouse SEM	DAT (1) N	DAT (1) Mean	DAT (1) SEM
Percent Errors "Away" (N=17)	11	0.10	.04	9	0.23	.07	11	0.22	.07
Percent Errors "Towards" (N=15)	11	0.34	.07	9	0.45	.10	11	0.50	.07

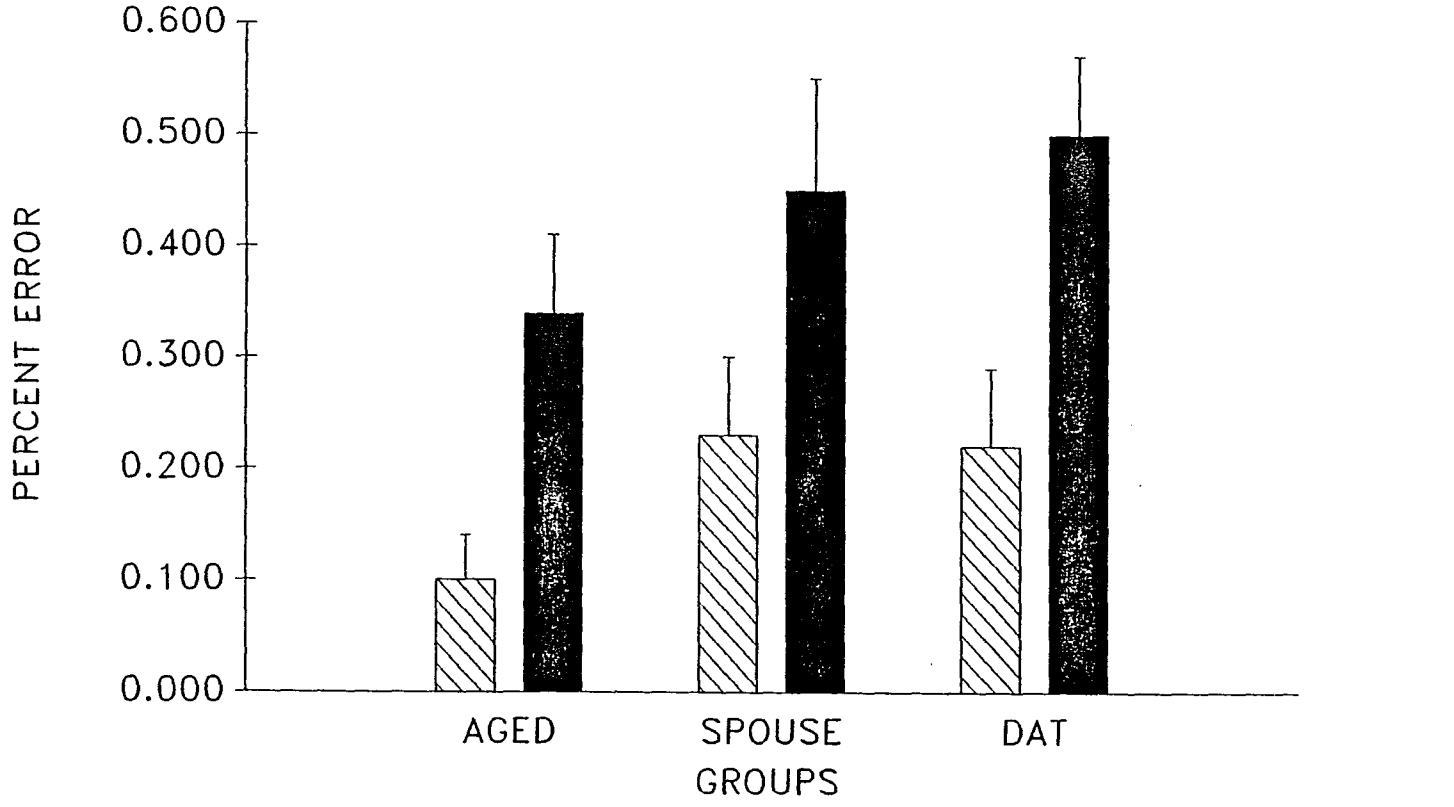
(1) Aged = Spouse = DAT ($F(2,30) = 1.74$, n.s.)
(2) Towards > Away ($F(1,31) = 36.90$ $P < 0.01$)

[B] Group Comparisons: Sex Differences

Sex (1)	Aged N	Aged Mean	Aged SEM	Spouse N	Spouse Mean	Spouse SEM	DAT N	DAT Mean	DAT SEM
Percent Errors Males	4	0.17	.09	3	0.10	.08	7	0.32	.06
Percent Errors Females	7	0.24	.06	6	0.44	.06	4	0.41	.12

(1) Females > Males ($F(1,30) = 5.28$, $P < 0.03$)

FIGURE 2
SPATIAL ORIENTATION TEST
GROUP COMPARISONS



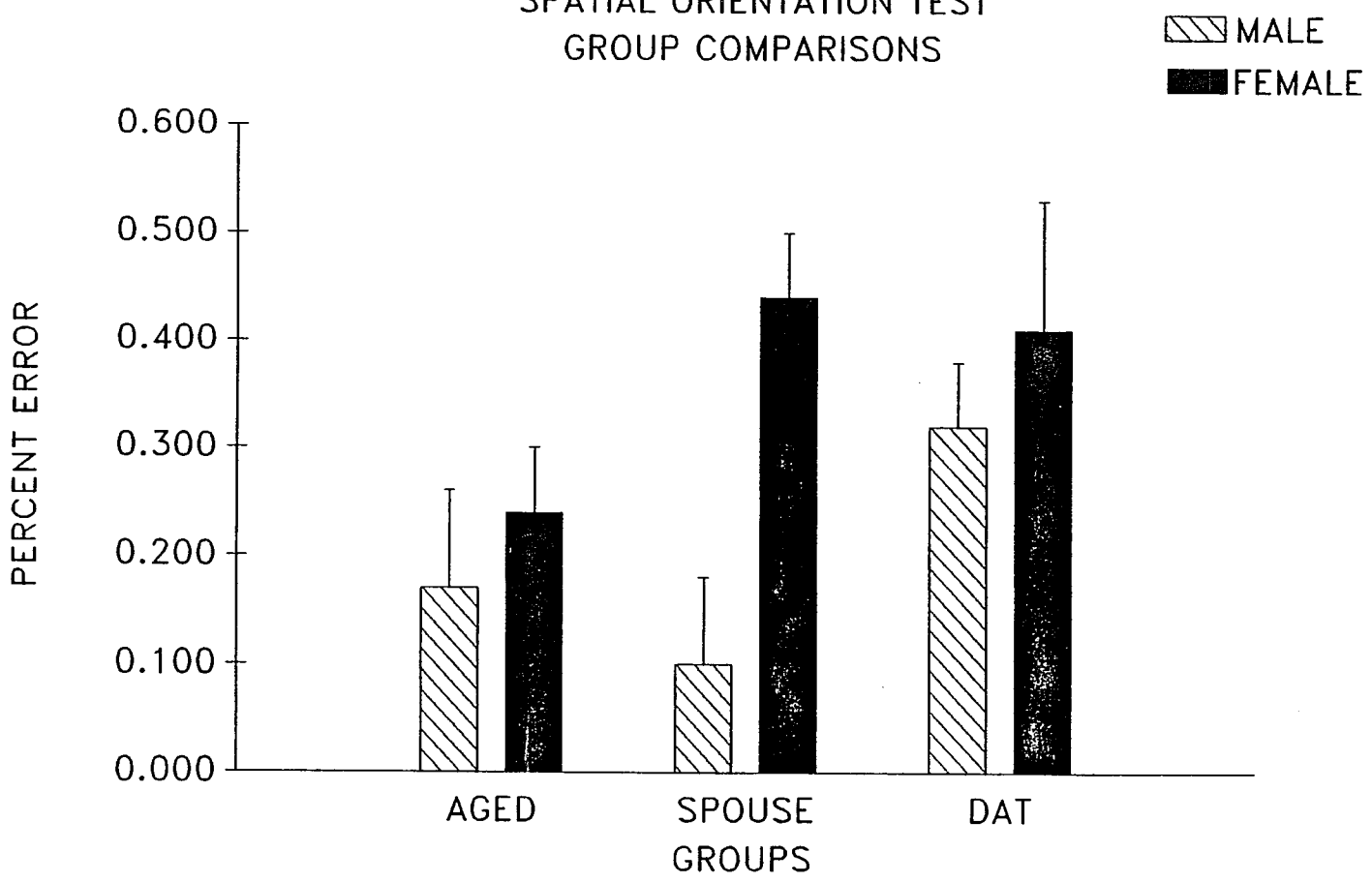
= 5.28), $p < 0.03$), females made a greater percentage of errors than males (collapsed across direction, females made 0.36 errors, while males made 0.24 errors). Although not statistically significant the Spouse comparison group showed the greatest disparity between males and females (see table 5(B) and Figure 3).

Similar to the above analysis there was a significant effect of direction ($F(1,31) = 36.13$, $p < 0.01$), but no significant difference across the three groups ($F(2,30) = 2.08$, n.s.). There was no significant interaction between any of the factors.

c) The Complex Figure Drawing

A number of different measures were analyzed with regard to the Complex Figure and are presented in the following order: (1) comparisons of the overall accuracy scores obtained with the scoring system described by Lezak (1976) as well as the fragmentation scoring system as described by Binder (1982), (2) the reliability of the accuracy scoring system, (3) a comparison across and within the three groups on the actual number of the different types of points (2,1,0.5 or 0) awarded for the 18 units, (4) a comparison across and within the groups on the percentage of points awarded for the four defined subdivisions of the drawing (outer framework, internal details, internal subdivisions and the outer details --

FIGURE 3
SPATIAL ORIENTATION TEST
GROUP COMPARISONS



see method section for the definition of the subdivisions and Figure 1 and 5 qualitative comparisons across the three groups.

1) Total Accuracy Score and Configuration Comparisons

The findings are presented on Table 6 and show that the subjects in the DAT group obtained significantly lower accuracy scores derived from the scoring system, as described by Lezak, than either the Aged or Spouse comparison groups ($F < 2,29) = 10.25$; $P < 0.01$). The DAT group showed a range from 3.0 to 32.0 with a mean of 16.7 (SEM = 3.5). The two comparison groups obtained ranges from 18.5 to 36.0 with a mean for the Aged of 31.0 (SEM = 1.6) while the Spouse group had a range of 19.5 to 36.0 and a mean of 28.3 (SEM = 1.7). The combined comparison group had a mean accuracy score of 29.8 (SEM = 1.16) and was significantly greater than that of the DAT subjects ($F (1,29) = 20.21$, $p < 0.01$).

The Spouse comparison group took significantly less time to complete the copying of the Complex Figure than both the DAT and Aged subjects. ($F (1,29) = 6.68$, $p < 0.01$). The Spouse group averaged 3.5 minutes (208.0 seconds) while the DAT subjects took 6.2 minutes (371.2 seconds) and the Aged subjects averaged 5.4 minutes (324.7 seconds).

Two categories as defined by Binder (1982) in the

TABLE 6

Complex Figure Drawing: Group Comparisons
Accuracy and Configuration Scoring systems: Means and SEM

Measure	Aged (N=11)	Spouse (N=9)	DAT. (N=10)	
Accuracy	31.00 (1.60)	28.39 (1.66)	16.70 (3.46)	(1
Fragmented Units	1.73 (0.38)	0.89 (0.35)	0.70 (0.22)	(n.
Missing Units	0.09 (0.09)	0.67 (0.29)	2.30 (0.53)	(2)
Configuration Units	3.18 (0.42)	3.44 (0.41)	2.00 (0.36)	(n.

(1) DAT < Aged = Spouse F (2,29) = 10.25; P < 0.01
(2) DAT < Aged = Spouse F (2,29) = 11.75; P < 0.01

configuration scoring system were non-significant across the groups (Fragmentation and Configuration). However, the number of missing units were significantly greater in the DAT group ($F(2,29) = 11.75$; $P < 0.01$) then either Spouse or Aged group.

2) Accuracy Scoring System Reliability

The total accuracy score and the hierarchical ranking position obtained from the independent raters (see method section) were highly correlated. Interrater reliability with a Kendall Rank-Order correlation (tau) exceeded 0.65 between all raters (see Table 7), as well as the hierarchy derived from the accuracy scoring system (all were significant at $P < 0.01$). This was true for both group drawing comparisons and treatment comparisons. These correlations suggest that the accuracy scoring system is a reliable indicator of copying competency of the Complex Figure Drawing.

3) Point-Type Distribution Comparisons

The reliability of the accuracy scoring system allowed the use of the points awarded to each component of the drawing as a source of analysis. Tabulation of the actual point distribution (2, 1, 0.5. or 0 points) for each of the 18 components of the figure were compared across and within the groups. The DAT group obtained

TABLE 7

Complex Figure Drawing
Kendall Rank-Order Correlation of Independent Ratings and Accuracy Score

[A] Group Comparisons (N=30)

Raters	AB	JH	PA	KD	KB	Accuracy
AB	---	.81	.71	.69	.69	.81
JH	.81	---	.75	.74	.89	.84
PA	.71	.75	---	.69	.75	.77
KD	.69	.74	.67	---	.78	.75
KB	.82	.89	.75	.78	---	.84
Accuracy	.81	.84	.77	.75	.84	---

[B] Treatment Comparisons (N=32)

Raters	AB	JH	PA	KD	KB	Accuracy
AB	---	.79	.72	.80	.78	.71
JH	.79	---	.80	.89	.77	.77
PA	.72	.80	---	.79	.79	.76
KD	.80	.89	.79	---	.80	.76
KB	.78	.77	.79	.80	---	.77
Accuracy	.71	.77	.78	.76	.77	---

All Correlation P <.001

significantly fewer numbers of two-point rated components than either the Aged or Spouse comparison groups ($F(2,29) = 8.64$, $P < 0.01$), while obtaining a significantly greater number of zero-point rated responses ($F(2,29) = 7.04$; $P < 0.01$). Table 8 displays the actual number of the different types of points awarded for each of the 18 units that make up the total accuracy score. On the average 5.7 units were given 2-points in the DAT group, in contrast 13.8 for the Aged group and 11.9 units for the Spouse group received 2-points. In terms of zero-point responses, the DAT subjects had 5.4 units given "zero" points. The Aged and Spouse groups both received less than 1 unit with a "zero" point response. Thus, as a group, about 1/3 of the components were judged missing or not recognizable in the DAT group. The number of 1 and 0.5 point responses were not significantly different between the groups. This suggests that the number of components drawn distorted or misplaced, though recognizable, were not different across the groups.

An identical pattern emerged when the Aged and Spouse subjects were merged into a single comparison group. There was a significant main effect of point type ($F(3,89) = 37.55$, $p < 0.01$) with a significant interaction between the groups and the point type ($F(3,29) = 12.34$, $p < 0.01$).

Comparison within each group were made across the

TABLE 8

Complex Figure Drawing: Group Comparisons

Point Types from the Accuracy Scoring System: Means and SEM

Point Type	Aged (N=11) (5)	Spouse (N=9) (6)	DAT (N=10) (7)
2	13.8 (1.3)	11.9 (1.3)	5.7 (1.8) (1)
1	3.1 (0.1)	4.3 (0.1)	4.4 (0.9) (2)
0.5	0.6 (0.5)	1.3 (0.5)	1.8 (0.5) (3)
0	0.5 (0.2)	0.4 (0.2)	5.4 (1.8) (4)

---

(1) DAT < Aged = Spouse (F (2,29) = 8.64, P < 0.01)
(2) DAT = Aged = Spouse (F (2,29) = 0.70, n.s.)
(3) DAT = Aged = Spouse (F (2,29) = 1.84. n.s.)
(4) DAT > Aged = Spouse (F (2,29) = 7.04, P < 0.01)
(5) (2-pt.) > (1-pt.) = (0.5-pt.) = (0-pt.) (F (3,30) = 45.86, P < 0.01)
(6) (2-pt.) > (1-pt.) = (0.5-pt.) = (0-pt.) (F (3,27) = 27.15 P < 0.01)
(7) (2-pt.) = (1-pt.) = (0.5-pt.) = (0-pt.) (F (3,30) = 1.29. n.s.)

different point-types (2,1,0.5 or 0). For the DAT group point-types were not significantly different ($F(3,30) = 1.29$, n.s.). The comparison groups both showed significant differential point-type distribution (Aged: $F(3,33) = 45.86$, $p < 0.01$); Spouse: $F(3,27) = 27.15$, $p < 0.01$). Post-hoc comparisons for both of these groups showed that 2-point responses significantly exceeded all remaining point-types. This indicates that the subjects in the comparison groups were receiving the maximum point totals more often then the subjects in the DAT group.

4) Subdivision Comparisons

The 18 units derived from the accuracy scoring system were used to create 4 subdivisions: outer framework (OF), internal details (ID), internal subdivisions (IS) and outer details (OD) (see method section for description and figure 1). As there was an unequal number of units that made up the different subdivisions the accumulated points were converted into percentage of the total points possible within each division. This made it possible to compare the different subdivisions directly. A two-factor mixed ANOVA was carried out with groups (DAT/Aged/Spouse) as the between-subject factor and percentage of point total within each subdivision (OF/ID/IS/OD) as the within-subject factor. There was a significant effect of both group and subdivision without a group x subdivision

interaction. As shown on Table 9 the DAT group was significantly different from both comparison groups ($F(2,29) = 10.17$, $p < 0.01$) when the data was collapsed over the different subdivisions. All groups demonstrated a similar pattern with the "outer detail" subdivision receiving significantly greater percentage of the maximum score allowed when compared to the three other subdivisions ($F(3,90) = 7.70$, $p < 0.01$). The remaining three subdivisions were non-significantly different. The same pattern emerged when a combined comparison group was used in the analysis. There was a significant difference between the groups ($F(3,29) = 20.34$, $p < 0.01$) and subdivision types ($F(3,90) = 7.39$, $p < 0.05$) without a significant interaction ($F(3,29) = 0.71$, n.s.).

Both the Aged and Spouse comparison groups received approximately 90% of the maximum total of the possible 10 points. The DAT group received approximately 60% of the total, but this was still significantly greater than that of the remaining subdivisions.

5) Qualitative Assessment of the Complex Figure Drawing

Careful inspection of individual drawings yielded some interesting differences between the DAT and the comparison groups. The two comparison groups received their greatest number of "zero-point" responses with item #7 (refer to Figure 1) the small horizontal segment above

TABLE 9

Complex Figure Drawing: Group Comparisons

Percent of the Maximum Point Total from
Four Subdivisions from the Accuracy Scoring System: Means and SEM

Subdivison (2)		Aged (N=11)	Spouse (N=9)	DAT (N=10) (1)
Outer Framework (Max. = 4.0)	(OF)	0.86 (0.06)	0.81 (0.03)	0.43 (0.12)
Internal Details (Max. = 12.0)	(ID)	0.84 (0.05)	0.65 (0.07)	0.38 (0.09)
Internal Subdivide (Max. = 10.0)	(IS)	0.82 (0.05)	0.84 (0.06)	0.43 (0.10)
Outer Details (Max. = 10.0)	(OD)	0.91 (0.04)	0.89 (0.04)	0.59 (0.09)

(1) DAT < Aged = Spouse ($F(2,29) = 10.17$, $P < 0.01$)
(2) OD > OF = ID = IS ($F(3,90) = 7.70$, $P < 0.01$)

the rectangle within the large rectangle but, only the DAT group obtained an equal number of "zero-point" responses with a similar vertical going segment (unit #10).

Both these items are unique in that they consist of a single line segment (most of the 18 scored components are made up of multiple segments), and so these units are a good indication of a pure detail. The fact that both small segments were left out by the DAT group suggests a lack of attention to small details. The item that received the least number of "2-point" responses for both the Aged and Spouse groups was the small rectangle at the extreme left within the large outer framework rectangle (unit #6), for the DAT group the item that received the least two-point scores were the diagonal cross that subdivided the main rectangle (unit #3). The bisecting diagonals are critical components to proper copying of the Complex Figure Drawing. Many of the internal details are drawn in relation to how the figure is divided. Poorly drawn diagonals can result in misplacement, distortions and leaving out of internal details.

Another interesting finding of the DAT subjects' drawings was discovered by examining the sequence of the first 8 lines drawn by the subjects. This information was gathered by two methods: (1) by the administration of different colored pencils after each minute, and (2) by

the detailed notes taken by the examiner in which each line segment drawn by the subject was recorded and labeled in proper sequence. Two interesting trends emerged from this investigation. First, more than 5 of the first 8 lines drawn by subjects in the Aged and Spouse groups were taken from the external framework or from the internal subdivisions of the figure -- the DAT group only averaged 3.5 lines from the first 8 of these subdivisions. The second major distinction between the groups was that only 1 of the 10 DAT subjects had completed the outer rectangle (unit #2) after drawing the first 8 lines, while 6 of the 11 from the Aged group and 5 of 11 from the Spouse group had the rectangle completed at this point. When the Aged and Spouse subjects were combined into a single comparison group, 12 of the 20 comparison subjects had unit #2 (the inner rectangle) completed after the first 8 line segments, compared to 2 of 10 of the DAT subjects. This difference was significant ($X^2 = 4.29$, $p < 0.05$). Finally, 5 of the 10 DAT subjects drew internal details (ID) from the figure in the first 8 line segments while only 4 of the 20 combined comparison subjects drew internal details at this point. Although this was a non-significant difference ($X^2 = 2,86$, n.s.), the trend was clear.

d) Benton Visual Retention Test (BVRT)

The BVRT copying task was analyzed in terms of the number of correct reproductions from the ten stimulus cards, as well as the total number of errors that occurred over the 10 drawings. A reproduction was judged incorrect when a single error occurred. A one-way ANOVA for between group comparisons (DAT/Aged/Spouse) was carried out for the number of designs drawn correctly (maximum = 10), the number of errors and for the mean duration for completing each drawing. Table 10 shows the two comparison groups successfully drew a greater number of drawings (Aged = 7.9; Spouse = 9.0) and made less errors (Aged = 2.2; Spouse = 1.0) than the DAT group (number correct = 6.5, number of errors = 6.3) but neither of these two variables were statistically different across the groups (number of correct drawings ($F(2,30) = 2.87$, n.s.; total number of errors ($F(2,30) = 3.04$, n.s.). Subjects in the DAT group took significantly greater time to complete their drawings ($F(2,29) = 7.03$, $p < 0.01$) (mean = 38.6 seconds) than the two comparisons groups (Aged = 25.2 sec. and the Spouse = 19.9 sec.).

A significant difference over the three groups

TABLE 10

Benton Visual Retention Test (BVRT): Group Comparisons

	Aged			Spouse			DAT			
Measure	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	
Del. Match.	11	5.36	0.41	7	6.43	0.43	8	2.38	0.60	(1)
Dir. Match.	11	6.64	0.28	7	6.86	0.14	8	5.50	0.42	(2)
# Correct	11	7.91	0.56	9	9.00	0.43	11	6.45	1.00	
# Errors	11	2.18	0.66	9	1.00	0.44	11	6.27	2.48	
Duration	11	25.22	2.30	9	19.99	2.23	10	38.67	5.29	(3)
BVRT Number of Error Types										
Omissions	11	0	0	9	0	0	11	0.73	0.41	
Distortions	11	0.18	0.12	9	0.56	0.29	11	3.18	1.35	(4)
Perservation	11	0	0	9	0	0	11	0	0	
Rotation	11	0.27	0.15	9	0.11	0.11	11	0.09	0.09	
Misplacement	11	1.27	0.38	9	0.33	0.50	11	1.36	0.36	
Size	11	0.46	0.16	9	0	0	11	0.91	0.72	

(1) DAT < Aged = Spouse ($F(2,25) = 17.19$, $P < 0.01$)
(2) DAT < Aged = Spouse ($F(2,25) = 5.03$, $P < 0.02$)
(3) DAT > Aged = Spouse ($F(2,29) = 7.03$, $P < 0.01$)
(4) Aged < DAT = Spouse ($F(2,30) = 3.85$; $P < 0.03$)

occurred on both the delayed match-to-sample ($F(2,25) = 17.19$; $P < 0.01$) and the direct match-to-sample ($F(2,25) = 5.03$; $P < 0.02$) the DAT group made significantly more errors on both tests than the two comparison groups. On the delayed match-to-sample, the Aged and Spouse group choose 5.4 and 6.4 correct from the seven stimulus cards. The DAT group only had, on the average, 2.5 correct. On the direct match-to-sample task, the DAT group chose 5.6 correct compared to 6.6 and 6.9 correct choices for the Aged and Spouse groups. The DAT subjects did significantly better on the direct match-to-sample then on the delayed match-to-sample ($t = 1.95$, $p < 0.01$). There was no significant difference between these two tasks in the comparison groups.

The types of errors that occurred on the drawings were classified by the scoring system described by Benton (1963). A two-factor mixed ANOVA was carried out with groups (DAT/Aged/Spouse) as the main between-subject factor and number of errors within the various types of error categories (omissions/distortions/preservation /rotation/ misplacement/size) as the main within-subject factor. There was a trend for DAT subjects to make more errors than the two comparison groups ($F(2,30) = 3.04$, $p < 0.06$) without reaching significance. However, there was a significant main effect of error type ($F(5,55) = 8.83$, $p < 0.01$) as well as a significant group x error type

interaction ($F(10,55) = 3.15$, $p < 0.01$). Post-hoc analysis of these findings showed the error type of "distortion" occurred more frequently in the DAT group then compared to the two comparison groups. The category of distortion was used as a catch-all and encompassed all forms of inaccurate reproductions including: simple substitution, fragmentation and multiple reproductions, but did not include rotations and displacements. Errors of omissions, perseveration, rotations, misplacement and size were not significant across or within the groups.

The two comparison groups were combined together to form a single comparison group and then the analysis was repeated. Under these comparison conditions, significant differences emerged on many key variables on this task.

Table 10A shows the combined comparison data and the findings from the DAT subjects. Significant differences occurred with regard to the number of drawings judged correct ($F(1,30) = 4.71$, $p < 0.05$) and the number of errors ($F(1,30) = 5.97$, $p < 0.05$). On both variables, the DAT subjects performed significantly worse than the comparison group.

Similar to the previous comparisons, the DAT subjects were less able to perceptually match stimuli in either a direct copy paradigm ($F(1,25) = 30.19$, $P < 0.01$) or when a delay was imposed ($F(1,25) = 10.13$, $p < 0.01$).

The pattern of error types made on the BVRT drawings

TABLE 10A

Benton Visual Retention Test (BVRT): Group Comparisons

Measure	Combined Comparison Group N	Mean	SEM	DAT N	Mean	SEM	
Del. Match.	18	5.78	0.32	8	2.38	0.60	(1)
Dir. Match.	18	6.72	0.18	8	5.50	0.42	(2)
# Correct	20	8.40	0.38	11	6.45	1.00	(3)
# Errors	20	1.65	0.41	11	6.27	2.48	(4)
Duration	20	22.87	1.68	10	38.67	5.29	
BVRT Number of Error Types							
Omissions	20	0	0	11	0.73	0.41	(5)
Distortions	20	0.35	0.15	11	3.18	1.35	(6)
Perservation	20	0	0	11	0	0	
Rotation	20	0.20	0.09	11	0.09	0.09	
Misplacement	20	0.85	0.24	11	1.36	0.36	
Size	20	0.25	0.10	11	0.91	0.72	

(1) Comparison group > DAT ($F(1,25) = 30.19$, $P < 0.01$)
(2) Comparison Group > DAT ($F(1,25) = 10.13$, $P < 0.01$)
(3) Comparison Group > DAT ($F(1,30) = 4.71$, $P < 0.05$)
(4) Comparison Group > DAT ($F(1,30) = 5.97$; $P < 0.05$)
(5) Comparison Group > DAT ($F(1,30) = 5.99$, $P < 0.05$)
(6) Comparison Group > DAT ($F(1,30) = 7.85$; $P < 0.01$)

were similar to the three group comparison. Distortions and misplacement errors occurred significantly more often than the remaining types ($F (5,30) = 6.17$, $p < 0.05$). With regard to particular error types across the two groups, both omissions ($F (1,30) = 5.99$, $p < 0.05$) and distortions ($F (1,30) = 7.85$), $p < 0.01$) occurred significantly more frequently in the DAT group.

e) Block Designs and Object Assembly

Table number 11 shows the raw, scaled and age-corrected scaled scores on both the Block Design and Object Assembly for the three comparison groups. The age-corrected scores were entered into a one-way ANOVA for independent groups. Significant differences were found when comparing the DAT, Spouse and Aged groups on both of these tasks. On the Block Designs, the DAT group had significantly lower age-corrected scores than the two comparison groups ($F (2,30) = 13.77$, $p < 0.01$), and this finding held up when the two comparison groups were combined into a single group ($F (1,30) = 19.18$, $p < 0.01$).

A slightly different pattern emerged on the Object Assembly task. The Aged comparison group received significantly greater age-corrected scores than both the DAT group and the Spouse comparison group, the DAT group and the Spouse comparison group were not significantly

TABLE 11

Block Design and Object Assembly: Group Comparisons

	Aged			Spouse			DAT			
Measure	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	
Block Designs										
Raw Score	11	24.00	2.27	9	21.22	2.63	11	11.27	2.40	
Scaled Score	11	7.55	0.69	9	6.56	0.75	11	3.82	0.74	
Aged Score	11	12.27	0.75	9	9.33	0.80	11	6.10	1.01	(1)
Object Assembly										
Raw Score	11	22.09	2.66	9	19.00	1.82	11	13.64	2.70	
Scaled Score	11	7.09	0.95	9	6.11	0.56	11	4.27	0.81	
Aged Score	11	11.36	0.94	9	8.56	0.50	11	6.73	0.79	(2)

(1) DAT < Aged = Spouse ($F_{(2,30)} = 13.77$, $P < 0.01$)
(2) Aged > DAT = Spouse ($F_{(2,30)} = 9.33$, $P < 0.01$)

different. ($F(2,30) = 9.33$, $p < 0.01$).

Section 2. Treatment Comparisons

a) The Roadmap Test of Spatial Orientation

The effect of physostigmine on performance on the Roadmap Test was first analyzed by examining at the total number of errors made over the three testing sessions (Baseline 1 (BL1)/Best Dose (BD)/Baseline 2 (BL2)) across the two treatment groups (Drug/Placebo). A two-factor ANOVA on the total number of errors had treatment conditions (Drug/Placebo) as the between-subject factor and sessions (BL1/BD/BL2) as the within-subject factor. The Placebo group made significantly more errors (16.3) when the data was collapsed across sessions then the drug group (8.9) ($F(1,10) = 6.17$, $p < 0.05$) (see Table 4 A & B) There was no significant effect of sessions ($F(2,22) = 1.75$, n.s.) nor a significant treatment x session interaction ($F(2,22) = 0.20$, n.s.).

A three factor mixed design ANOVA was performed with treatment (Drug/Placebo) as the main between subject factor and session (BL1/BD/BL2) and direction (converted to percentage of errors in the "away" and "towards" direction) as the main within-subject factors. The findings are presented on Table number 12 which show a significant main effect of group ($F(1,10) = 6.25$, $p < 0.05$) and direction ($F(1,55) = 60.11$, $p < 0.01$).

TABLE 12

Roadmap Test of Spatial Orientation: Treatment Comparisons
Total Number of Errors by Direction: Means and SEM

Drug Treatment (N=6) (2)

	BL1		B.D.		BL2	(3)
Percent Errors "Away" (N=17) (1)	0.14	(0.08)	0.15	(0.08)	0.19	(0.11)
Percent Errors "Towards" (N=15)	0.37	(0.08)	0.38	(0.12)	0.50	(0.11)

Placebo Treatment (N=5) (2)

	BL1		B.D.		BL2	(3)
Percent Errors "Away" (N=17) (1)	0.31	(0.09)	0.35	(0.04)	0.41	(0.08)
Percent Errors "Towards" (N=15)	0.67	(0.06)	0.70	(0.04)	0.68	(0.01)

(1) Towards > Away (F (1,18) = 60.11, P < 0.01)
(2) Placebo > Drug (F (1,10) = 6.25, P < 0.03)
(3) BL1 = BD = BL2 (F (2,55) = 1.82, n.s.)

Subjects in the drug treatment group made a significantly smaller percentage of errors than the placebo treated subjects when the data was collapsed over sessions and direction. The drug treated group made 0.29 percent errors (S.D. = 0.26), while the placebo treated group made 0.52 percent errors (S.D. = 0.21). As shown on Figures 4 and 5 both types of treatment, significantly more errors were made in the "toward" direction (mean percent errors = 0.25, S.D. =0.21) than the "away" direction (mean percent errors = 0.54, S.D. = 0.24). The effect of session was non-significant (F (2,55) = 1.82, n.s.), nor were there any significant interaction between the factors.

b) The Complex Figure Drawing

A number of different measures were analyzed with regards to the Complex Figure and compared across and within treatment groups and the findings will be presented in the following order: (1) comparisons of the overall accuracy scores obtained with the system described by Lezak (1976) as well as the fragmentation scoring system as described by Binder (1982), (2) a comparison of the actual number of different types of points (2,1,0.5 or 0) awarded for the 18 units. (3) a comparison of the percentage of the maximum points allowed for 4 defined

FIGURE 4
SPATIAL ORIENTATION TEST
DRUG TREATMENT COMPARISONS

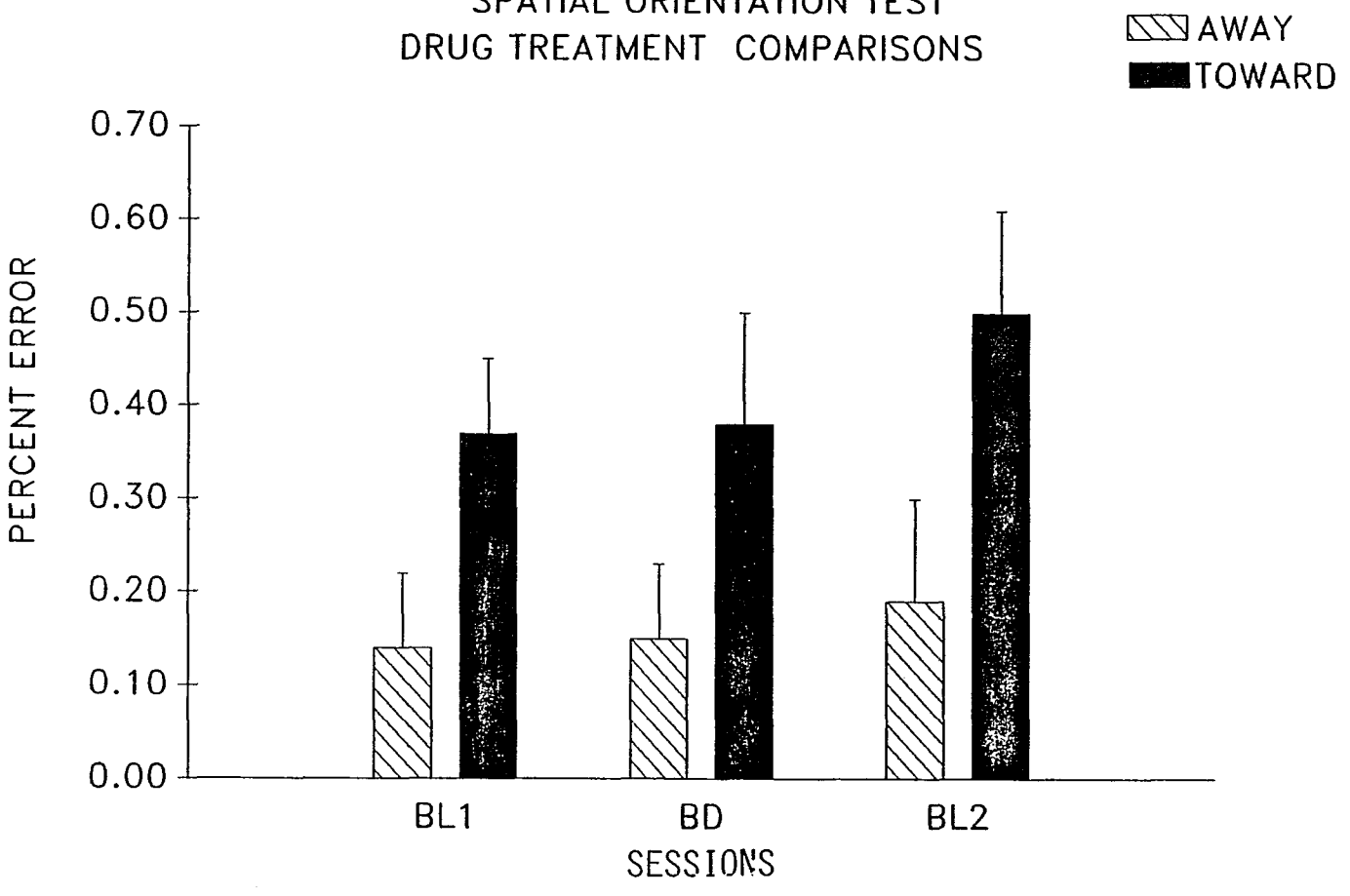
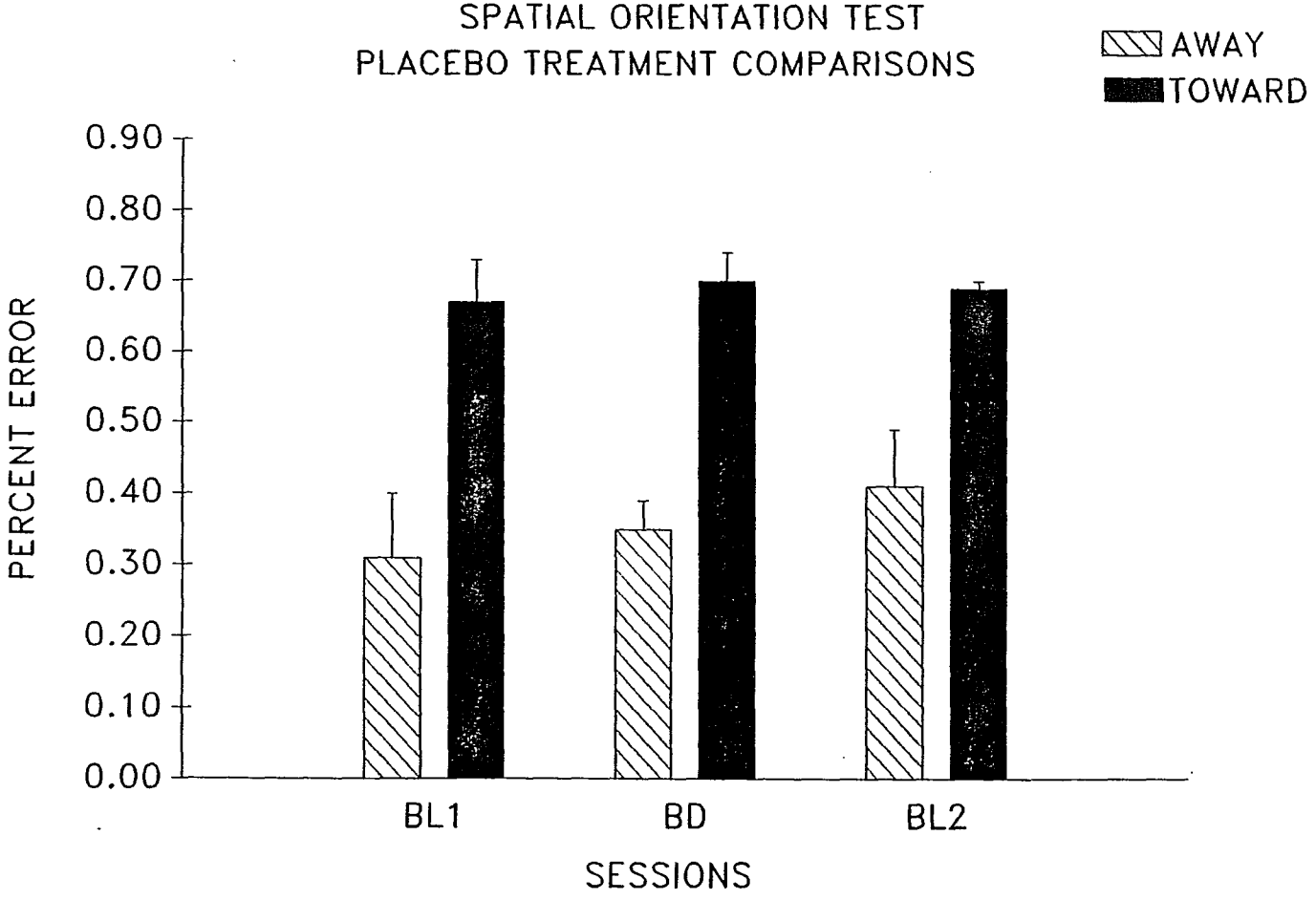


FIGURE 5
SPATIAL ORIENTATION TEST
PLACEBO TREATMENT COMPARISONS



subdivisions of the drawing (outer framework (OF), internal details (ID), internal subdivisions (IS) and the outer details (OD) - see method section for the units that make up each of these subdivision and figure number 1).

1) Total Accuracy and Configuration Comparisons

A two-way ANOVA was carried out with the total accuracy score as the dependent measure. Treatment groups (Drug/Placebo) were the between-subject factor and sessions (BL1/BD/BL2) were the within-subject factor. Table 13 shows the mean and standard error of the means for the accuracy score, as well as the configuration measures defined by Binder (1982). There was a significant main effect of sessions with the "best Dose" (BD) testing session exceeding the initial baseline ($F(2,20) = 4.40$, $p < 0.05$). There was no main effect of group ($F(1,9) = 0.77$, n.s.), nor was there an significant group x session interaction ($F(2,20) = 1.44$, n.s.). These findings indicate that the improved performance under "best dose" occurred in both drug and placebo treated groups. When the data was collapsed over the two treatment groups the "best dose" sessions averaged 22 points (S.D. = 9.0), while the initial baseline averaged 16.7 (S.D. = 10.9) and the final baseline averaged 17.6 (S.D. = 11.2).

TABLE 13

Complex Figure Drawing: Treatment Comparisons
Accuracy and Configuration Scoring Systems: Means and SEM

Drug Treatment (N=5) (1)

Measure	BL1	B.D.	BL2 (2)
Accuracy	20.3 (3.14)	25.8 (2.29)	18.5 (4.34)
Fragmented Units	1.00 (0.45)	1.33 (0.54)	1.00 (0.30)
Missing Units	1.60 (0.51)	1.50 (0.84)	2.17 (0.87)
Configuration Units	2.40 (0.51)	2.17 (0.59)	1.83 (0.77)

Placebo Treatment (N=5) (1)

Measure	BL1	B.D.	BL2 (2)
Accuracy	13.10 (6.13)	18.20 (4.92)	16.70 (6.15)
Fragmented Units	0.40 (0.40)	1.00 (0.32)	0.20 (0.20)
Missing Units	3.00 (0.84)	2.20 (0.73)	2.80 (0.97)
Configuration Units	1.60 (0.51)	1.80 (0.58)	2.00 (1.05)

(1) Drug Treatment = Placebo Treatment ($F(1,9) = 0.77$, n.s.)
(2) BL1 < BD = BL2 ($F(2,20) = 4.40$, $P < 0.03$)

When looking at the three sessions graphically for the individual subjects (Figure 6 A & b) 3 of the 6 drug treated subjects showed improvement during the "best dose" phase (DAT subjects #6, #8 & #10). Another DAT subject entered the study performing at a high level and may have demonstrated a ceiling effect (DAT subject #4). Under "best dose" conditions DAT subject #2 maintained his entry level performance, while subject #1 was only tested on two occasions (a best dose and a final baseline) without a significant difference. Two subjects of five placebo-treated subjects had their best performance under "best dose" conditions (DAT subjects #3 & #11). DAT subject #7 maintained his entry level performance under "best dose", while DAT subject #5 obtained his worst score during this session. Finally, DAT subject #9 showed steady improvement over the three testing sessions.

The initial and final baseline sessions were averaged together to determine a single baseline. This single baseline was then compared to the single best dose session. Five of the six drug treated subjects showed improvement in the best dose session when compared to the mean baseline session. But two of the five placebo treated subjects also showed improvement during their "best dose" session. Thus, the ability for physostigmine to improve performance was not significant (Fisher Exact

FIGURE 6 (A)
COMPLEX FIGURE DRAWING TEST
DRUG TREATMENT COMPARISONS

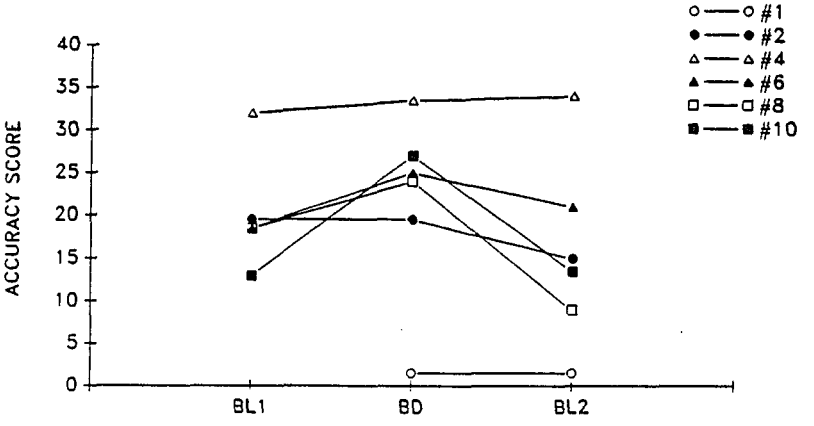
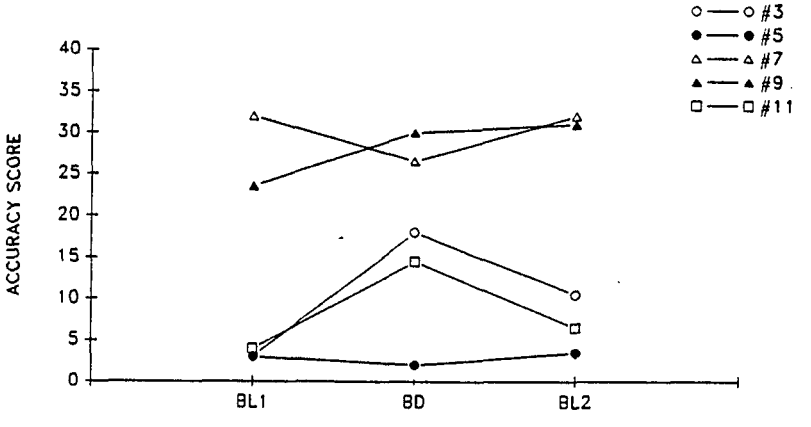


FIGURE 6 (B)
COMPLEX FIGURE DRAWING TEST
PLACEBO TREATMENT GROUP



Probability = 0.42, n.s.).

The configuration scoring measures of Binder (1982) showed no significant changes over the three testing sessions in either group.

2) Point-Type Distribution Comparisons

A three-factor mixed design ANOVA was performed with treatment groups (Drug/Placebo) as the between-subject factor and session (BL1/BD/BL2) and the number of different point-types distributed over the 18 units (2,1,0.5 or 0) as the two within-subject factors. The data is presented in Table 14. There was no significant difference between the two treatment groups ($F(1,9) = 0.80$, n.s.) or over the three testing sessions ($F(2,110) = 1.07$, n.s.). There was also no significant difference between the four different point-types ($F(3,16) = 2.68$, n.s.). However there was a significant session x point-type interaction ($F(6,24) = 2.91$, $p < 0.02$). indicating a significant trend for an increase in the number of 2-point responses and a reduction of the number of 0-point responses under "best dose" conditions across both treatment groups.

TABLE 14

Complex Figure Drawing: Treatment Comparisons
Point Types from the Accuracy Scoring System: Means and SEM

Drug Treatment (1)

Point Type (3)	BL1 (N=5)	B.D. (N=6)	BL2 (N=6) (2)
2	6.6 (1.9)	10.6 (1.4) (4)	6.4 (4.3)
1	6.2 (2.7)	3.8 (2.2)	4.6 (1.2)
0.5	1.8 (1.6)	1.6 (0.5)	2.2 (1.2)
0	3.4 (2.6)	1.8 (1.6)	4.8 (1.4)

Placebo Treatment (1)

Point Type (3)	BL1 (N=5)	B.D. (N=5)	BL2 (N=5) (2)
2	4.8 (3.1)	6.2 (2.2) (4)	6.6 (3.3)
1	2.6 (0.4)	5.0 (1.3)	2.6 (0.4)
0.5	1.8 (0.8)	1.6 (0.8)	1.8 (1.0)
0	8.6 (3.0)	4.8 (2.1)	7.0 (2.5)

(1) Drug Treatment = Placebo Treatment ($F(1,9) = 0.8$, n.s.)
(2) BL1 = BD = BL2 ($F(2,110) = 1.07$, n.s.)
(3) 2-pts. = 1-pts. = 0.5-pts. = 0-pts. ($F(3,116) = 2.7$, n.s.)
(4) Session x Point Type ($F(6,110) = 2.9$, $P < 0.02$)

3) Subdivision Comparisons

Another three-factor mixed design ANOVA was performed with treatment groups (Drug/Placebo) as the between-factor and sessions (BL1/BD/BL2) and percentage of the maximum point total within each subdivision (OF/ID/IS/OD) as the within subject factors. The data breakdown is shown on Table 15. There was no significant difference between the two treatment groups ($F(1,9) = 0.86$, n.s.). There was a significant main effect for sessions ($F(2,110) = 6.65$, $p < 0.01$). Post-hoc analysis revealed "best dose" performance exceeded the initial baseline performance across both treatment groups. When the data was collapsed over the two treatment groups 62% of the maximum point total was obtained under "best dose" conditions compared to 40% of the maximum point total during the initial baseline. There was a also a significant difference between the subdivision ($F(3,16) = 9.87$, $p < 0.01$). Across both treatment groups, the "outer details" of the figure received a greater percentage of the maximum point totals (67%, S.D. = 0.23) than the remaining three created subdivisions (OF = 50%, S.D. = 0.33; ID = 44%, S.D. = 0.27; IS = 54%, S.D. = 0.37). There was no significant interaction between any of the factors.

TABLE 15

Complex Figure Drawing: Treatment Comparisons

Percent of the Maximum Point Total from
Four Subdivisions from the Accuracy Scoring System: Means and SEM

Drug Treatment (N=5) (1)

Subdivison (3)		BL1	B.D.	BL2 (2)
Outer Framework (Max. = 4.0)	(OF)	0.53 (0.15)	0.70 (0.10)	0.48 (0.16)
Internal Details (Max. = 12.0)	(ID)	0.48 (0.10)	0.60 (0.08)	0.39 (0.13)
Internal Subdivide (Max. = 10.0)	(IS)	0.53 (0.15)	0.80 (0.11)	0.64 (0.16)
Outer Details (Max. = 10.0)	(OD)	0.71 (0.09)	0.78 (0.08)	0.73 (0.08)

Placebo Treatment (N=5) (1)

Subdivison (3)		BL1	B.D.	BL2 (2)
Outer Framework (Max. = 4.0)	(OF)	0.33 (0.19)	0.53 (0.14)	0.45 (0.15)
Internal Details (Max. = 12.0)	(ID)	0.28 (0.15)	0.49 (0.14)	0.39 (0.13)
Internal Subdivide (Max. = 10.0)	(IS)	0.37 (0.18)	0.49 (0.15)	0.42 (0.24)
Outer Details (Max. = 10.0)	(OD)	0.46 (0.18)	0.71 (0.10)	0.60 (0.17)

(1) Drug Treatment = Placebo Treatment ($F(1,9) = 0.86$, n.s.)
(2) BD > BL1 = BL2 ($F(2,110) = 6.65$, $P < 0.01$)
(3) OD > OF = ID = IS ($F(3,16) = 9.87$, $P < 0.01$)

c) Benton Visual Retention Test (BVRT)

Table 16 shows the mean and SEM for the results of the BVRT for the drug and placebo treatment conditions. All BVRT variables were entered into a two-factor mixed ANOVA with treatment groups (drug/placebo) as the between-subject factor and sessions (BL1/BD/BL2) as the within-subject factor. There was no significant group differences ($F(1,10) = 0.069$, n.s.) nor was there an effect of sessions ($F(2,29) = 0.38$, n.s.) when the number of correct drawings was looked at. Similarly, the number of total errors did not show significant differences across the two treatment groups ($F(1,10) = .017$, n.s.) or across the testing sessions ($F(2,22) = 0.89$, n.s.).

The mean duration to complete each drawing was entered into a similar ANOVA. The drug treatment subjects were significantly faster in their copying than the placebo treated subjects ($F(1,9) = 6.22$, $p < 0.05$). When the data was collapsed across the testing sessions the DAT subjects averaged 27.1 second (S.D. = 7.5) to complete each drawing, while the placebo group averaged 44.9 seconds (S.D. = 14.9). There was no significant effect of sessions ($F(2,20) = 1.39$, n.s.) nor a significant treatment group x sessions interaction.

A three factor-mixed ANOVA was carried out with the

TABLE 16

Benton Visual Retention Test (BVRT): Treatment Comparisons

Drug Treatment

	BL1			B.D.			BL2			
Measure	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	
Del. Match.	4	3.00	0.92	4	4.25	0.25	4	3.75	0.95	(1)
Dir. Match.	4	5.75	0.48	4	5.75	0.95	4	6.00	0.41	
# Correct	6	6.50	1.41	6	6.33	1.26	6	7.33	1.28	
# Errors	6	5.50	3.00	6	6.00	3.47	6	5.17	3.58	
Duration	5	30.82	3.38	6	24.35	2.60	6	28.23	2.98	
BVRT Number of Error Types										
Omissions	6	0.67	0.42	6	0.83	0.83	6	1.17	1.17	
Distortions	6	3.17	2.18	6	3.17	1.99	6	2.83	2.06	(2)
Perservation	6	0	0	6	0	0	6	0	0	
Rotation	6	0	0	6	0.17	0.17	6	0	0	
Misplacement	6	1.50	0.56	6	1.67	0.56	6	1.00	0.51	
Size	6	0.17	0.17	6	0.33	0.21	6	0.17	0.17	

Placebo Treatment

	BL1			B.D.			BL2			
Measure	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	
Del. Match.	4	1.75	0.75	5	1.40	0.60	5	3.00	0.89	(1)
Dir. Match.	4	5.25	0.75	5	4.80	0.80	5	5.00	0.71	
# Correct	5	6.40	1.60	5	6.00	1.58	5	6.20	1.65	
# Errors	5	7.20	4.46	5	5.80	3.34	5	5.60	3.19	
Duration	5	46.52	9.15	5	46.38	6.66	5	41.90	4.86	
BVRT Number of Error Types										
Omissions	5	0.80	0.80	5	0.80	0.58	5	0.60	0.40	
Distortions	5	3.20	1.61	5	3.60	2.16	5	3.40	2.18	(2)
Perservation	5	0	0	5	0	0	5	0	0	
Rotation	5	0.20	0.20	5	0.20	0.20	5	0.20	0.20	
Misplacement	5	1.20	0.49	5	1.00	0.32	5	1.20	0.49	
Size	5	1.80	1.56	5	0.20	0.20	5	0.20	0.20	

(1) Direct Match-to-Sample > Delayed Match-to-Sample ($F(1,12) = 28.9$, $P < 0.01$)

(2) Distortion > All other error types ($F(5,18) = 4.57$, $P < 0.01$)

match-to sample data (both delayed and direct). The main between-subject factor was treatment group (drug/placebo) and two within-subject factors where sessions (BL1/BD/BL2) and task (Delay match-to-sample/direct match-to-sample). There was no significant effect between the treatment groups ($F(1,7) = 3.77$, n.s.) or over the testing sessions ($F(2,40) = 0.55$, n.s.). However a significant greater number of correct matches (mean correct matched = 5.4, S.D. = 1.4) were made under the direct matching task ($F(1,12) = 28.91$, $p < 0.01$), when compared to the delayed matching task (mean correct matched = 2.7, S.D. =1.7).

A final three-factor ANOVA with treatment groups (Drug/Placebo) as the between-subject factor and sessions and Benton's errors types (omissions/distortions/ perseverations/rotations/misplacement and size errors) as the within-subject factors. There was no significant difference between the two treatment groups ($F(1,10) = .014$, n.s.) or differences over the three testing sessions ($F(2,187) = 0.95$, n.s.). There was however a significant difference between the different error types ($F(5,18) = 4.57$, $p < 0.01$). Post-hoc analysis indicated that the error type of "distortion" occurred significantly more often then the other types of drawing errors.

d) Block Designs and Object Assembly

Table 17 presents the results from the Block Designs and Object Assembly for the drug and placebo treatment groups. The comparisons over the groups (Drug/Placebo) and over the sessions (BL1/BD/BL2) were based upon the aged-corrected scores. On the Block Designs there was no significant difference between the treatment groups $F = (1,10) = 0.00$, n.s.) or significant changes over the three testing sessions ($F (2,22) = 0.12$, n.s.). A similar pattern emerged with the aged correct scores on the Object Assembly. There was no significant difference between the two treatment groups ($F (1,10) = 0.15$, n.s.) or over the three testing sessions ($F (2,22) = 1.71$, n.s.).

Section 3: Cross-Task Comparisons

a) Across Group Comparisons

From the different tasks from the experimental battery a number of the key variables were compared by Pearson r correlations (See table 18). These correlations were carried out within each group (DAT/Aged/Spouse) separately and for the comparison groups added together. The initial baseline data (BL1) from the DAT group and

TABLE 17

Block Design and Object Assembly: Treatment Comparisons

Drug Treatment

Block Designs	BL1 N	BL1 Mean	BL1 SEM	B.D. N	B.D. Mean	B.D. SEM	BL2 N	BL2 Mean	BL2 SEM
Raw Score	6	13.33	3.17	6	11.00	2.62	6	12.33	4.20
Scaled Score	6	4.33	0.99	6	3.67	0.80	6	4.17	1.30
Aged Score	6	6.33	1.42	6	5.67	1.18	6	6.17	1.56
Obj. Assembly									
Raw Score	6	15.67	3.48	6	13.17	4.91	6	17.67	4.47
Scaled Score	6	4.83	1.08	6	4.17	1.49	6	5.50	1.43
Aged Score	6	7.17	1.11	6	6.17	1.74	6	7.67	1.60

Placebo Treatment

Block Designs	BL1 N	BL1 Mean	BL1 SEM	B.D. N	B.D. Mean	B.D. SEM	BL2 N	BL2 Mean	BL2 SEM
Raw Score	5	8.80	3.72	5	11.60	3.37	5	10.80	3.20
Scaled Score	5	2.60	1.16	5	3.80	1.02	5	3.60	1.03
Aged Score	5	3.20	1.69	5	6.40	1.81	5	6.20	1.69
Obj. Assembly									
Raw Score	5	11.20	4.36	5	11.60	3.97	5	10.80	3.46
Scaled Score	5	3.80	1.36	5	3.80	1.16	5	3.60	0.93
Aged Score	5	6.20	1.20	5	7.00	1.41	5	6.40	1.03

Table 18

Cross-Correlation of Key Variables from the Experimental Battery

Variable 1	Variable 2	Aged r	Spoused r	DAT r
Complex Figure Tot. Acc. Score	Roadmap Test Tot. Errors	-0.40	-0.34	-0.28
Complex Figure Tot. Acc. Score	BVRT Number Corect	0.26	0.41	0.23
Complex Figure Tot. Acc. Score	Aged-Corrected Block Design	0.73**	0.62*	0.61
Complex Figure Tot. Acc. Score	Age-Correct Object Assembly	0.57	0.43	0.50
Roadmap Test Tot. Errors	BVRT Number Correct	0.15	-0.12	-0.25
Roadmap Test Tot. Errors	Age-Corrected Block Designs	-0.09	-0.64*	-0.34
Roadmap Test Tot. Errors	Age-Corrected Object Assembly	-0.15	-0.21	-0.01
BVRT Number Correct	Age-Corrected Block Designs	0.81**	0.44	0.00
BVRT Number Correct	Age-Corrected Object Assembly	0.57	0.40	0.19
Age-Corrected Block Designs	Age-Corrected Object Assembly	0.72**	0.44	0.25

* P < 0.05
** P < 0.01

the data from the single testing session of the comparison groups was used in the analysis. Few of the task variables were significantly correlated (see Table 18). There was a significant correlation between the age-corrected scores on the WAIS Block Designs and the total accuracy score derived from the scoring system used on the Complex figure in the DAT and Aged comparison group (DAT: $r = 0.73$, $p < 0.01$); Aged: $r = 0.62$, $p < 0.05$); Total group $r = 0.65$ $p < 0.05$). The correlation in the Spouse comparison group ($r = 0.61$) was in the right direction but failed to reach significance ($P < 0.08$). The accuracy score demonstrated significant correlations with the Age-corrected scores from the Object Assembly ($r = 0.66$, $p < 0.05$) for the combined group data.

There were some group differences with regards to some of the cross-task correlations. In the Aged comparison group a significant negative correlation was found between the total number of errors on the Roadmap test with the Aged-corrected score of the Block Designs ($r = - 0.64$, $p < 0.05$). There were non-significant correlations in the DAT and Spouse groups with these same two variables. In addition, there was a significant correlation in the DAT group only between the BVRT number of drawings correct, with the Aged-corrected score on the Block Designs ($r = 0.81$, $p < 0.01$) and a significant correlation between the Aged-corrected scores on the

Block Design and the Object Assembly in the DAT group.

In the combined group correlations there were significant correlations between the Benton Visual Retention Test (number of correct drawings) and the Age-corrected score on the Object Assembly ($r = 0.44$, $p < 0.05$). In addition, there was a significant positive correlation between the Age-corrected score on the Block Design and the Age-corrected score on the Object Assembly ($r = 0.52$, $p < 0.05$).

b) Within DAT Group Comparisons

As an indicator of disease severity the Fuld adaptation of the Blessed mental status examination (Fuld, 1978) was administered to all individuals in the DAT and Aged comparison groups. The DAT subjects had a mean of 10.3 errors (SEM = 1.05) with a range of 4 to 16 points (a maximum of 33 points were possible with the higher the point total the more severe the impairment). All subjects in the Aged group had less than 2 Blessed errors (Mean = 0.82, SEM = 0.18).

As shown on Table 19 there was no significant correlation with the scores on the Blessed mental status

test with any of the key variables from the experimental battery (total accuracy score derived from the complex figure, total errors on the Roadmap test, the number of BVRT drawings correct or the Aged-corrected scores on the Block Designs and the Object Assembly).

The Mattis Dementia Rating Scale (MDRS, 1976) is another scale used to assess severity of dementia. The group of 11 DAT subjects received a mean of 116.5 points (SEM = 3.7) on this scale (range: 101 to 139). The MDRS failed to correlate with any of the key variables from the experimental battery.

All DAT subjects in the study were administered on a number of occasions a 12 trial/12 word selective reminding test (Buschke & Fuld, 1974). This was the principal instrument used to assess verbal memory improvement following physostigmine treatment. Comparisons were made between some of the key variables from the experimental battery and some of the measures obtained from the selective reminding test when administrated upon the subjects initial screening visit. As shown on Table 19 the total accuracy score from the Complex Figure was significantly correlated with a number of the important verbal memory variables (long-term retrieval (LTR) and consistent retrieval (CR), both had correlations greater than 0.60 ($P < 0.05$). All other key variables (Total errors on the Roadmap test, number of drawings correct on

Table 19

Correlation Between Key Variables from the Experimental with Mental Status and Memory

	Blessed Mental Status Exam	Mattis Dementia Rating Scale	Sel. Remind. LTR	Sel. Remind. Consist.Ret.
Complex Figure Tot. Acc. Score	-0.20	0.39	0.73 *	0.63 *
Roadmap Test Tot. Errors	0.04	-0.27	-0.34	-0.48
BVRT Number Correct	-0.22	0.44	0.06	0.03
Age-Corrected BD	-0.30	0.32	0.23	0.15
Age-Corrected OA	-0.23	0.46	0.33	0.53

P > 0.05

the BVRT, or the Aged-corrected scores on the Block Designs or the Object Assembly) failed to significantly correlate with the measures of memory.

CHAPTER X. DISCUSSION

A. Constructional and Spatial Abilities in Early DAT

1. The Roadmap Test and Egocentric Spatial Abilities in DAT

The results of this investigation indicate that spatial orientation as measured by the Roadmap Test did not appear significantly impaired in early DAT as compared with Aged and Spouse groups. In addition, all three comparison groups showed similar patterns of errors. Few errors occurred with regards to right/left discrimination alone, (turns that went 'away' from the subject). Rather, the large proportion of the errors occurred when the subjects were required to right/left discriminate as well as mentally rotate in space to achieve proper orientation (turns that went 'towards' the subject). Clearly, the mental rotation dimension adds to the complexity of the task. This increase in complexity may explain the poor performance of all groups. These findings are corroborated by Brouwers, Cox, Martin, Chase, & Fedio (1984). They also found DAT subjects were not significantly different from an appropriately matched intact comparison group and more errors were made by each group in the toward direction.

Aging, independent of dementia, appears to impair spatial orientation abilities. All three groups used in this investigation made a greater number of errors on the Roadmap Test then what has been reported for a younger sample of subjects (Butters, Soelder & Fedio, 1972; Tapley & Breyer, 1977).

There was a significant sex difference associated with performance on this task. Females made a significantly greater number of errors than males. These differences support the accumulating evidence of male superiority in spatial abilities (Maccoby & Jacklin, 1974). A similar pattern of sex differences in DAT subjects on the Roadmap test has been reported (Brouwers, Cox, Martin, Chase, & Fedio, 1984). Furthermore, significant sex differences have also been found in a normal subject population. Undergraduate male college students made approximately 0.5 errors on this task, while females made, on the average, 3.5 errors. (Tapley & Bryer, 1977).

An unusually large number of errors (10.5) occurred in the Spouse comparison group. Since this group had more females (9) than males (3), the most obvious explanation is that the sex differences account for the unexpected number of errors. As noted earlier, females as a group have greater difficulties on spatial tasks than males. In addition, this group may have performed more poorly than

the Aged group because they are in a highly stressed situation. This situation has been called the "caregiver burden", referring to the physical, psychological, social and financial problems experienced by caregivers of impaired adults (George & Gwyther, 1986). The DAT group were all out-patients, whose care and maintenance was the responsibility of their spouses (the Spouse control group). Many studies have reported on the mental and physical efforts that such 24 hour care-giving can take. George and Gwyther (1986) have shown that caregivers have a significantly greater number of mental health problems than comparison groups. Under these circumstances, it was not surprising that the Spouse-comparison group performed at less than optimal level.

Looking at the results of the present investigation with the few studies that had administered this task to various populations a number of conclusions can be drawn. First, aging alone results in a decline in the ability to properly orient in a rotated environment. Second, females make significantly more errors than males. Third, DAT does not, at least early in the course of the disease, significantly impair performance on this task relative to age and sex cohorts.

2. Simple and Complex Drawing

The findings of this study indicate that DAT patients, early in the course, remain competent in the copying of simple geometric arrays even though there was a significant difference compared to a combined comparison group of Spouse and Aged subjects. The DAT subjects successfully copied an average of 6.5 of the 10 plates from the BVRT while the combined comparison group averaged 8.5 out of 10. Two of the 11 DAT subjects made a far greater number of errors then the rest of the group and demonstrated severe copying problems (Subject #1 made 20 errors and Subject #5 made 25 errors). When these two subjects were removed from the analysis the remaining 9 individuals made on the average 2.7 errors. This is comparable to that demonstrated in the Aged (mean errors = 2.2) and Spouse (mean errors = 1.0) groups.

The majority of errors across all groups were distortions or misplacements. The most common example of distortions were incomplete figures or simple substitution (i.e. squares drawn as a rectangles). Errors of misplacement usually occurred when the small peripheral figure was drawn lower or higher on the copy than on the model.

The DAT group took significantly more time to

complete their drawings than the comparison groups (on the average the DAT took slightly over 15 seconds longer to complete their drawings). This suggests that a greater processing time was needed to analyze the stimuli or in executing the copying.

The relative success on this task for the majority of DAT subjects indicate that (1) the DAT subjects in this study were able to comprehend and carry out the instructions of the copying task, (2) they were capable of perceiving and analyzing fairly simple geometric line drawings, and (3) were able to execute the proper motor programs to reproduce the figures in a way not different from the comparison groups.

Significant group differences emerged on the Rey Osterrieth Complex Figure Drawing. The DAT subjects demonstrated significant copying difficulties on this more complex task.

The drawing accuracy was measured by the scoring system described by Lezak (1983). Maximum possible accuracy points was 36. The accuracy of the drawings of the DAT subjects in their initial baseline, averaged 16.7 points. This accuracy score differed significantly from the two comparison groups averaging 31.0 points for the Spouse group and 28.4 points for the Aged group.

The group of DAT subjects tested by Brouwers et al. (1984) averaged approximately 17.0 points (based upon

estimations from their published figure), while their controls scored on the average 31.0 points. These findings show a remarkable consistency across the studies, and supports the use of the scoring system as a good measure of constructional praxis. The significant correlations found in the present study between the scoring system scores and subjective judgments of accuracy made by raters lend further support to the Lezak accuracy scoring system.

There may be two interrelated factors that can help account for the poor drawing accuracy of the DAT group on the Rey figure: task complexity and poor or inefficient copying strategy.

Clearly, as the copying task becomes perceptually more complex, the DAT subject's performance deteriorates. The comparative success on the BVRT suggests that simple geometric figures pose less copying problems for this group. However, when simple geometric figures are arranged within complex perceptual arrays and overlapping stimuli, the DAT group failed to integrate the components and could not properly reproduce them. One strategy the DAT subjects apparently used to deal with this complex drawing was to simplify it by reducing the number of elements. As a result their drawings had an overall sparse appearance as noted by the significant number of omissions.

This observation was supported when the distribution of point types awarded over the 18 components (as defined by the accuracy scoring system) was examined. A significantly greater number of "zero" point responses (missing units) were awarded to the DAT subjects when compared to same aged and elderly subjects, while the number of units drawn distorted or misplaced was not significantly different. Using the Binder configuration scoring system (1982) missing units were also the only significantly different measure between the three groups.

Another indication that task complexity contributed to the poor drawing accuracy of the DAT subjects was evident when the success of copying specific parts of the figure was examined. This was accomplished by breaking up the figure into 4 subdivisions: outer framework, internal details, internal subdivisions and the external details. A distinct pattern emerged. The greatest percentage of accuracy points was obtained from the external details subdivision, while the least percentage of total accuracy points was obtained from the internal details. This pattern held for all three groups but was most dramatic with the DAT subjects.

The potential significance of this pattern is that the internal aspects of the drawing, which contained the most perceptually complex stimuli, received the least number of points from the accuracy scoring systems. The

outside details of the figure, which contained the most salient and perceptually isolated stimuli, received the highest number of accuracy points. The cognitive demands in copying the external details of the figure may be similar to that needed for successful performance on the simple geometric copying on the BVRT copying task.

The second factor, inefficient copying strategy, also appears to contribute to the poor performance of the DAT subjects on the complex drawing task. The strategy normal adults employ in copying the Rey figure is to draw the outer framework of the figure first, and then usually follow by filling in the internal details (Osterrieth, 1944). This is the most efficient approach. In contrast, patients with brain damage use a disorganized and ineffective approach: they tend to copy the discrete parts of the figure without an organized structure. Visser (1980) noted that for these subjects, the large rectangle does not appear to exist, and the main organizing lines and details are mixed. The DAT group seemed to adopt a similar strategy.

Performance of the DAT, Aged and Spouse groups was compared by tracking the sequential performance during the early course of copying the Complex figure (noting the order and placement of the first 8 lines drawn). One significant difference was that more than half of the subjects in the comparison groups had the inner rectangle

completed after the first 8 line segments, whereas this pattern was observed in only two of the 10 DAT subjects. Similarly, five of the first 8 line segments made by the Aged and Spouse groups were used to draw the inner rectangle, while only 3.5 of the first 8 lines drawn were from the inner rectangle for the DAT group. These findings suggest that the copying strategy used by the DAT subjects was indeed different from that employed by the comparison groups.

Specifically, DAT subjects tended to copy the external details of the figure before the framework was completed. This type of copying approach is similar to what has been called an analytic strategy (Semenza, Denes, D'Urso, Romano, & Motorsi, 1978). In this strategy, constructions proceed segment-by-segment, usually from left-to-right or from top-to-bottom. Preference is not given to the main framework, but rather there is a focus upon the details.

The comparison groups in the present study, on the other hand, appear to employ a global strategy, similar to that employed by normal adults. The external outline or the full internal framework of the design is constructed first. This is then followed by filling in the details.

The analytic approach to copying is thought to be the result of an inability to plan and execute sequential activities. This strategy has been shown to occur more

frequently in patients with left hemisphere lesions than in those with right hemisphere damage (Semenza et al., 1978). This impairment in planning maybe characteristic of left hemisphere damage. Hecaen & Assal (1970) demonstrated improvements in drawing abilities when patients with left hemisphere damage were provided with reference points to aid them in their copying. These cues seemed to compensate for the deficit in global organization.

In this study, DAT subjects did not employ a strict analytic approach in their reproductions. Although they did copy details prior to the completion of the outer framework, they rarely worked in a systematic pattern from left-to-right or top-to-bottom (only 3 of the 10 subjects in the DAT group worked from left-to-right). The pattern that appeared most frequently in this group was one in which no clear strategy was employed. Both analytic and global approaches seem to be mixed in their copying style, resulting in an inability to stick to any effective approach in completing the drawing. This may account for finding errors in the DAT group that are characteristic of both constructional strategies: missing units and incomplete framework. The DAT subjects do not resemble patients with either right- or left-hemisphere lesions. Rather, their constructional style presented deficits indicative of both groups. This finding is consistent

with the fact that DAT is a disease affecting both hemispheres of the brain simultaneously resulting in diffuse cerebral dysfunction (Katzman, 1986).

3. Constructions of Blocks and Puzzles

The present investigation found the two construction tasks of the WAIS, the Block Designs (BD) and the Object Assembly (OA), exceedingly difficult for the DAT sample. The Age-corrected scores on the BD for these subjects were significantly inferior to those of both comparison groups: greater than one standard deviation below the mean. The performance of the DAT subjects on the OA was better, although not significantly, than that on the BD. However, their scores on the OA test were not significantly different from the Spouse comparison group. As previously discussed, the sex bias, as well as the emotional strain on these caregivers may have contributed to their poor performance. The Aged comparison group was significantly superior to both these groups on the OA.

The fact that the DAT group had greater difficulty with these sub-tests of the WAIS and performed somewhat better on the OA than the BD is consistent with the WAIS profile of DAT described by Fuld (1984) and supported by Brinkman and Braum (1984). Based upon a large clinical

sample of DAT patients, Fuld showed the BD to be one of the most difficult WAIS sub-tests for this population. Further, Age-corrected performance on the OA is generally found to be better than that on the BD.

Qualitatively, DAT subjects all showed they could understand the BD task, and were all able to successfully construct one or two of the early designs (8 of 11 DAT patients received full or partial credit for the first design). However, when design complexity increased their performance deteriorated (only one DAT subject was able to construct design #6, and none were able to complete any of the nine block designs). Similar to findings on the Complex Figure, task complexity appears to have contributed to poor performance.

The BD task is generally thought to be a good measure of visuospatial, perceptual and organizational abilities (Lezak, 1983). The nature of the DAT groups impaired performance on the BD is difficult to quantify. The constraints of the standardized test administration made it impossible to decipher the relative contributions of the three components of cognitive function measured by the BD. Nevertheless, one can speculate that perceptual abilities in this group appears to be the most intact of the three. This was suggested by the DAT subject's good performance on the match-to-sample task from the BVRT and their relative success with the OA task.

A specific spatial impairment in the DAT group was also not supported. The DAT subjects failed to make systematic errors on the BD thought to be spatial in nature (i.e. rotations, disorientation and misplacements). These types of spatial problems appear more frequently with patients with localized posterior lesions (Mcfie, 1975). In addition, as reviewed earlier, at least one type of spatial ability (egocentric) did not show declines as the result of DAT in the early stages.

It would not be unreasonable to suggest that organizational problems, similar to what has been described for the copying tasks, is the major contributor to the constructional problems demonstrated on the BD in the DAT population.

4. Speculation on Frontal Lobe Dysfunction in Early DAT

Across all tasks one consistent finding in the performance of individuals with DAT was poor organization in carrying out the task. This was particularly evident in the copying of the Complex Figure. The sequential analysis of the DAT performance, particularly on the Complex Figure, showed a failure to either plan an efficient approach or to maintain an effective copying strategy to successfully complete the task. The ability to properly plan, initiate, and maintain a course of

action is believed to involve the frontal region and one could speculate that disturbance of the frontal region of the brain may be characteristic of early DAT.

In general, the neuropsychological deficits found in patients with frontal lobe lesions involve the highest of intellectual functions as well as cognitive synthesis. Among the most prominent neuropsychological deficits of localized frontal lesions are a breakdown in motor programming, a failure of response inhibition and behavioral inflexibility. In addition there are problems in temporal ordering and in self-ordering behavior (Stuss & Benson, 1984). Self-ordering behavior refers to an inability to generate, organize and carry out effective plans in problem solving. Specifically, this type of deficit may be particularly relevant to the cognitive demands on the DAT subject group in this study.

Buttters, Soelder, & Fedio (1972) have suggested that the left-frontal region involves egocentric spatial abilities. They found that patients with this type of discrete lesion do poorly on the Money Roadmap test. A direct comparison of subjects in the Butter et al study with the group of DAT subjects in the present investigation is not legitimate. The subjects in the Butter et al study were all middle-aged males (mean = 49.0 years) with localized brain injuries. In addition, the total number of errors was the only reported data; turn

orientation was not specified. The orientation of the turns ("away" or "towards") appears to be a critical distinction in the separation of a true egocentric spatial problem from a right/left discrimination problem.

Other studies show supporting evidence for the hypothesis that DAT interferes with cognitive abilities thought to be controlled by the frontal region of the brain. First, patients with known frontal lobe lesions demonstrate a pattern of deficits on constructional tasks which were remarkably similar to the pattern described for the DAT subjects in this study. Lhermitte, Deroussne, & Signoret, (1972) demonstrated deficits on the block designs and on the Complex Figure Drawing in patients with frontal lobe injury. Further, when the patients were presented with additional visual cues (block-outlined models) for each design, or if they were taught to copy the Complex Figure Drawing in a structured and sequential fashion, they did better on these tasks. In other words, when planning and execution were improved, so was performance. This suggests that spatial and perceptual deficits may not be the primary cause of the observed poor performance. Rather, this data supports the role of the executive functioning of the frontal lobes in the ability to perform this task, and implies that the frontal lobes are impaired in DAT.

Second, the results of other neuropsychological

investigations of DAT may be interpreted as supportive of frontal lobe dysfunction. The phenomenon of inappropriate responding on verbal tests, described as intrusions by Fuld, Katzman, Davies, and Terry, (1982) may indicate mental inflexibility or perseveration (Luria, 1976). In addition, the high number of false alarms noted in the study by Mohs & Davis (1982) on a perceptual task may be interpreted as a failure to inhibit responses. Both behavioral inflexibility and failure of response inhibition are symptoms of frontal lobe dysfunction.

Finally, there are physiological correlates of frontal lobe dysfunction in DAT. Neurofibrillary tangles and senile plaques are present in the frontal region as they are in the parietal, temporal and sub-cortical structures in patients with DAT (Adams, 1980). In addition, C-T scans of demented patients have shown lower tissue densities in both frontal and temporal lobes. This may reflect greater cell loss in the brain regions compared with other lobes (Bondaroff, Baldy, & Levy, 1981). Katzman (1986) reported a high correlation between mental status, memory and CHAT levels in parietal, temporal and frontal regions of the brain in DAT patients. Lower CHAT levels in the frontal lobes were correlated with higher Blessed errors and lower recall on the Fuld Object-memory test.

5. DAT and Normal Aging

The inclusion of a 'normal' aged control group in this study (Blessed mental status score below 2) made it possible to investigate the effects of aging, independent of dementia.

The qualitative and quantitative performance on the non-verbal constructional tasks from the experimental battery can now be described for this 'normal' elderly population. As previously discussed, many cognitive functions have been shown to decline with age. The greatest difficulties for this population arise on tasks that involve visuo-spatial processing, learning and memory (Wechsler, 1958; Arenberg, 1968). Tasks which rely on well-established skills and knowledge tend to be preserved.

The results of the present study showedthat the aged subjects did not demonstrate the expected age-related declines. In fact the performance of this group equalled (or at times exceeded) that of the Spouse comparison group (an average of 16.8 years younger than the aged group).

It may be that this group of aged subjects were not representative of the normal aged. The subjects were obtained from a self-selected sample of elderly (N > 500) who were participating in a long term research project.

The group was made up predominantly of white middle class elderly in the Bronx, N.Y. The Aged comparison group consisted of 11 individuals who were selected on the basis of intact mental status. The data obtained for this present battery was collected 3 to 4 years into the longitudinal study. As a result, the data may have been biased by a common problem to longitudinal studies: age differences may be minimized due to selective subject attrition (Botwinick, 1977). In retrospect, the aged subjects in this study may best be viewed as 'super-normal' and this may account for the failure to demonstrate the expected age-related cognitive declines.

Qualitative aspects of the Aged groups performance, such as general approach to the tasks, was similar to that of the Spouse comparison group. This was particularly evident on the Complex Drawing task where the elderly subjects copied the figure in global style. Both groups constructed the external outline first and followed by filling in the details.

Some have reported that the cognitive decline observed in normal aging is remarkably similar to that seen in DAT subjects, although the level of performance by the DAT subjects was significantly inferior (Jolles & Hijman, 1983). Comparison between the DAT subjects and the `super-normal` aged group in this study indicate that the two groups were both qualitatively and quantitatively

different on this particular experimental battery. Therefore, this study can not support the findings of Jolles and Hijman.

Although the pathological processes associated with DAT may be quite distinct from the normal biological processes of aging, this can not be confirmed by the findings of the present study. A more representative sample of non-demented elderly may reveal performance patterns similar to that found in this super-normal aged group or conversely, reveal cognitive declines similar to that found in early DAT.

6. Constructional and Spatial Abilities - Cross Task Comparisons and the Relationship to the Severity of Dementia

In order to achieve some understanding of how the tasks from the experimental battery were related, correlations were made using the key independent variables from the various tasks (refer to tables 17 & 18). These correlations must be interpreted with some degree of skepticism due to the small sample size and the high number of correlations carried out. Nevertheless, some of the significant correlations, as well as the non-correlations between certain variables, appear theoretically meaningful.

The best demonstration of the relationship between

the tasks was found by looking at the correlations when all groups were placed together This increased the sample size to 30 and resulted in a broader distribution of performance. Two general trends emerged. First, the performance on the Roadmap test failed to correlate with performance from any other task. Second, the remaining tasks (Complex figure, BVRT, Block Designs and the Objects Assembly) all showed some degree of relationship.

In both the Aged and Spouse groups, a significant correlation was obtained between the total accuracy score on the Complex Drawing and the Age-corrected score from the BD task for the Aged and Spouse comparison groups (Aged group $r = 0.73$; $p < 0.01$); Spouse group ($r = 0.62$; $p < 0.04$). In the DAT group a strong trend emerged ($r = 0.61$; $p < 0.08$). There was also a significant overall group correlation (0.46; $p < 0.05$). As indicated earlier, both these tasks involve the highest level of constructional abilities related to complex visuo-spatial analysis, integration, planning and graphomotor execution. One could speculate that the cognitive demands of these tasks were equivalent. Essentially, they were the most complex and difficult tasks from the experimental battery and resulted in the strongest correlations. Further, these two tasks caused the greatest difficulties for the DAT subjects.

The Roadmap Test generally failed to correlate with

the other tasks from the battery. As noted earlier, this task appears to be unidimensional with regard to its cognitive demands; only egocentric spatial abilities are required. It appears that performance on this task in no way predicts performance on tasks that require a more complex form of spatial analysis (i.e. The Complex Figure or the BD). Similarly, simple geometric copying (BVRT) failed to correlate with complex copying, suggesting the greater cognitive demands made by the latter.

A second series of correlations were made in the DAT group between published indices of dementia severity and key variables from the tasks of experimental battery. Once again, the small sample size (N=10) and the large number of correlations make the interpretation of these analyses problematic. A significant correlation with one or more of the tasks would support its usefulness as an measure of dementia severity. The number of errors obtained on the Blessed Mental Status exam failed to correlate with any measure from the experimental battery. This test has been shown to be positively correlated with the number of plaques and tangles, the pathological indices of DAT (Blessed et al., 1968). However, it has recently been suggested that the Blessed test may not be the best indicator of dementia as the Blessed scores did not change much, particulary in young patients (Fuld, Blau, Aronson & Dickson 1987; Fuld, Dickson, Crystal &

Aronson, 1987).

Similarly, no correlation were found between tasks from the experimental battery and the scores obtained on the Mattis Dementia Rating Scale (MDRS). The mean score for the DAT group on this screening instrument was 116.5 (S.D. 12.3). Normal elderly score on the average 140 and above on this test and patients with a greater than 3 year history of DAT had a mean of 81 points on the scale (Mattis, 1976). Overall there was a rather narrow range of variation over the DAT group and therefore, the MDRS doesn't seem to be a sensitive enough indication dementia severity in the early stages of the disease.

The only positive correlations obtained were between the total accuracy score on the Complex Figure and two indices of long-term memory function from the selective reminding memory test. This suggests that the DAT subjects were performing at similar levels of impairment. A number of interpretations are possible. Performance on the Complex Figure may invoke a memory component. Although the Block Designs and the Complex Figure may measure essentially the same cognitive abilities (r ranges from 0.61 to 0.73) the latter was correlated with the selective reminding variables ($r = 0.73$ and 0.63) while the former was not ($r = 0.23$ and 0.15). On the other hand, the rather narrow range of scores on the Block Designs for the DAT subjects limit its usefulness in the

correlational analysis. Nevertheless, within the constraints of the limited value of these correlations, the performance on the Complex Figure appears to be as sensitive an estimate of non-verbal/constructional abilities as the selective reminding test is of verbal memory functioning (at least in the early stages of DAT). Since impairment of non-verbal/constructional abilities appear to be as important a component of DAT as verbal memory deficits, the Complex Figure may be an invaluable addition to DAT neuropsychological assessment.

7. Implications and Limitations of Clinical Research: Ideas for Future Studies

Anecdotal reports of deficits in spatial and constructional abilities are abundant in the clinical literature. However, few systematic investigations can be found over the past 20 years. This dissertation provides a first step in the systematic assessment and qualification of non-verbal visuospatial and constructional abilities in mild DAT subjects in comparison to a matched and normal aged sample.

The approach taken in this dissertation was to administer a battery of objective and standardized tests that are typically used in a clinical neuropsychological evaluation. The battery was devised to assess a variety

of subject attribute variables particularly pertaining to spatial and constructional tasks. Comparisons were then made between two matched groups of individuals: one physically healthy, one affected by a disease process (DAT). This methodology is usually referred to as clinically based research and differs from experimental or laboratory research where there is systematic control and manipulation of defined independent and dependent variables. Each approach has associated strengths and weaknesses.

The advantage of experimentally based research is that a single independent factor can be systematically varied while holding other possibly influencing factors constant. This variable control provides a high degree of internal validity, but may often be weak in the area of external validity. Thus, this approach may produce results which lack meaningfulness for clinical (real world) populations.

Clinically based research, often examines a broad spectrum of variables from which individuals differences can be elucidated between subject groups in a less artificial situation. A greater degree of external validity is then afforded by this approach, but often at the expense of precise variable control. For example, in this study, systematic control of stimulus (e.g. level of difficulty) and response (e.g. reaction time) parameters,

was considered less important than clinical applicability.

Results from clinically based studies give direction into what important variables should be investigated in a laboratory situation. For example, from the results of this study, the systematic presentation of increasing complex drawings can be administrated experimentally with precise control of the exposure (stimulus) variables. In addition, the presentation of drawings varying in information with regard to spatial, perceptual, and organizational elements can also be experimentally investigated. These types of studies would further add to our knowledge about constructional abilities in DAT and normal aging.

Small sample size (11 DAT subjects) and lack of subject homogeneity have limited generalizability of the findings of this dissertation. Small sample sizes tend to reduce the power of any statistical effect, and a heterogeneous subject sample has been shown to increase error variance (West, 1985). In this study, two subjects in the DAT group (#1 & #5) were more constructionally apraxic then the remaining subjects. Including these two individuals may have exaggerated the reported differences between the DAT and comparison groups. Furthermore, these two subjects might be representative of a select subgroup of DAT subjects who manifest visuoconstructional

disturbances as their major deficit early in the course of the disease (Crystal, Horoupian & Katzman, 1981; McDonald, 1969; Becker, Huff, Holland & Boller, 1988). Both these issues have been recently addressed in a paper by Masur, Blau, Thal and Fuld (1988) who describe the difficulties in obtaining a large and homogenous sample of early DAT subjects who meet the rigid diagnostic and psychometric criteria for entry into a drug treatment study.

8. Conclusions

A number of significant conclusion can be drawn from this study. Some give insight into the non-verbal cognitive abilities in early DAT. Other results have a practical application and allow for better diagnosis and follow-up of DAT population.

In the early course of the disease, DAT patients retain specific forms of spatial abilities with respect to egocentric space: they make few errors involving right/left discrimination. While their ability to orient when the environment is rotated is impaired in comparison to younger subjects, it is no greater than that found in elderly control groups. This type of spatial ability appears to be affected more by age and gender than DAT.

DAT subjects have demonstrated some difficulty in

copying even simple geometric figures, but demonstrate severe impairment when they are required to copy a complex perceptual array. Other complex forms of constructions (BD and OA) are also significantly impaired. The nature of the deficits in DAT as suggested by this study, are related to both task complexity and an inability to form or maintain effective constructional strategies to complete the task. Perceptual, spatial, memory processes, and executive factors all appear to be impaired by DAT. The underlining physiological disease process in DAT resulting in diffuse dysfunction of non-sensory regions of the brain is unlikely to result in specific perceptual, visuo-spatial or graphomotor deficits. Rather, the dysfunction may be manifested in the integration of these complex components. Future studies should be designed to clarify the individual roles of these cognitive processes in the constructional abilities of DAT.

The Complex Figure Drawing task has been shown to be a useful neuropsychological instrument in the study of early to moderate DAT. Further, the accuracy scoring system described by Lezak (1983) has been shown to be a reliable measure of constructional deficits in the DAT population. This scoring system generally estimates drawing accuracy in a way similar to subjective ratings. Based on the significant correlations found between performance scores on the Complex Figure and the

selective reminding memory test the sensitivity of these tasks to measure level of impairment in DAT may be equivalent.

The accuracy scoring system provided a wide range of scores which correlated with the severity of dementia as measured by memory functioning. In addition, performance on the Complex Figure task can be followed sequentially and allowing for both qualitative and quantitative assessment of constructional performance. Overall, the task can be administered in a short time period (generally less than 15 minutes) and may prove to be a useful instrument to monitor non-verbal cognitive decline with advancing dementia.

The performance on the BD and OA by DAT subjects in this study was similar to what has been reported (Fuld, 1978). Both tasks were very difficult for DAT subjects even in the early stages. Therefore, these tasks were subject to floor effects in moderate and advanced DAT patients. The usefulness of these two tasks for the study of dementia would improve with the development of structured qualitative assessment techniques.

B. The Effects of Physostigmine on Constructional and Spatial Abilities in DAT

Physostigmine failed to significantly improve performance on all subtests of the experimental battery when compared to placebo treated subjects. The performance of the drug group exceeded that of the placebo treated subjects on the Roadmap Test of Spatial Orientation, but neither group showed a 'drug' enhancement. Examination of the percentage of errors on the Roadmap Test over the three sessions generally showed a decline in performance for both groups.

The findings on the Complex Figure drawing test indicate some facilitatory effects occurred during the best dose treatment phase of the study. The accuracy scores during this session were significantly greater than that on initial baseline performance, although not significantly different from the final baseline performance. Since this pattern emerged in both groups (drug and placebo) it is not possible to make any statements about the positive effects of physostigmine on the complex drawing without a group by task interaction.

Placebo facilitated improvements may have effected the results of this study. Dementia of the Alzheimer's type -- at least in the early phase -- can present as a combination of cognitive impairment with a superimposed

depression (Katzman, 1981). The placement of DAT subjects into a therapeutic situation with the possibility of an effective treatment can result in some cognitive improvement either due to the elevation of depression and/or due to a placebo effect. Placebo effects have been reported for a wide variety of pharmacological treatments for numerous disorders and these effects may be both psychological and physical (Feldman & Quenzer, 1984). While the use of double blind procedures may have helped to lower the incidence of placebo responders in the present study the effect can not be eliminated (Feldman & Quenzer, 1984).

The possibility of a practice effect in this population should also be considered since testing occurred over three sessions. However, these sessions spanned a three month period, and any practice effects are unlikely to have influenced testing performance of the DAT subjects. The type of dementia that these subjects are afflicted with would make it difficult for them to remember information over such a period of delay.

One investigator has reported positive effects of physostigmine on constructional tasks (Muramoto et al., 1979 & 1984). In these related studies, six subjects in the early stages of DAT were given the drug in an acute paradigm. Half the subjects were reported to statistically improve in their copying of geometric

figures under treatment. Only one subject showed improvement on a test of memory (six-item Selective Reminding Test). In contrast, the present study found all DAT subjects (N=6) administered physostigmine to be positive responders with respect to improvement in their memory, while none of the placebo treated subjects were considered responders (x^2 =2.2, $p < 0.01$). A positive responder was defined as having improvement in consistent retrieval and a reduction in intrusions on Selective Reminding memory tests (Thal, Masur, Blau, & Fuld, submitted for publication). Yet, the same DAT subjects were not positive responders to the drug on constructional task performance. One possible explanation for this discrepancy is that individuals were titrated to a best dose level. This level was determined as that which produced the greatest improvement in memory. This titrated dose level may be inadequate to properly stimulate cholinergic functioning for non-memory cognitive tasks. Future studies might benefit by titrating to a dose based upon facilitation on tests other than those that include memory.

A number of investigations have shown the positive effects of physostigmine in improvement of memory in subjects with DAT. This included studies that have administered the drug on a single occasion (Christie et al., 1979; Smith & Swash, 1979; Mohs & Davies, 1982;

Muramoto et al., 1979; 1984; Peters & Levin, 1979), as well as studies that have given the drug over extended periods (usually in the oral form) (Peters & Levin, 1982; Davis et al., 1983; Thal et al., 1986; Thal et al., submitted for publication).

Studies that have failed to find positive effects on memory with the drug either used a fixed dose without titration (Ashford et al., 1981; Delwaide, Devoitille, & Ylieff, 1980), or have used subjects who were moderate-to-severely impaired (Wettstein, 1983).

One study showed that while overall DAT subjects improve with physostigmine a number of DAT subjects fail to show facilitatory effects of physostigmine to improve their memory (Thal, et al, 1986). This may be due in part to the amount of cholinesterase inhibition, which can vary due to a number of factors such as variation in gastrointestinal absorption, the rate of peripheral metabolism, or competition with other compounds for the blood brain barrier (Thal, et al., 1986). Non-responsiveness to the drug may also be the result of misdiagnosis of DAT.

The half-life of physostigmine is an inherent problem of the drug. Effectiveness was thought to be only 2 to 2.5 hours following a single dose (2 - 2.5mg.). Recent findings of Thal et al. (1986) demonstrated that when multiple doses of oral physostigmine were administered,

improvement of memory can last as long as 15 - 17 hours. This suggests that with multiple doses there might be an accumulation of the drug enhancing effectiveness.

Finally, it should be kept in mind that physostigmine does not halt the progression of the neural degeneration in DAT. In a recent paper (Thal, et al., 1986), positively responding subjects were maintained on the medication for as long as 18 months. Although the treatment initially produced facilitatory effects, DAT subjects eventually became refractory to the therapy and failed to maintain improvements in their memory. This gradual decline in drug responsiveness has not been documented for non-memory cognitive tasks.

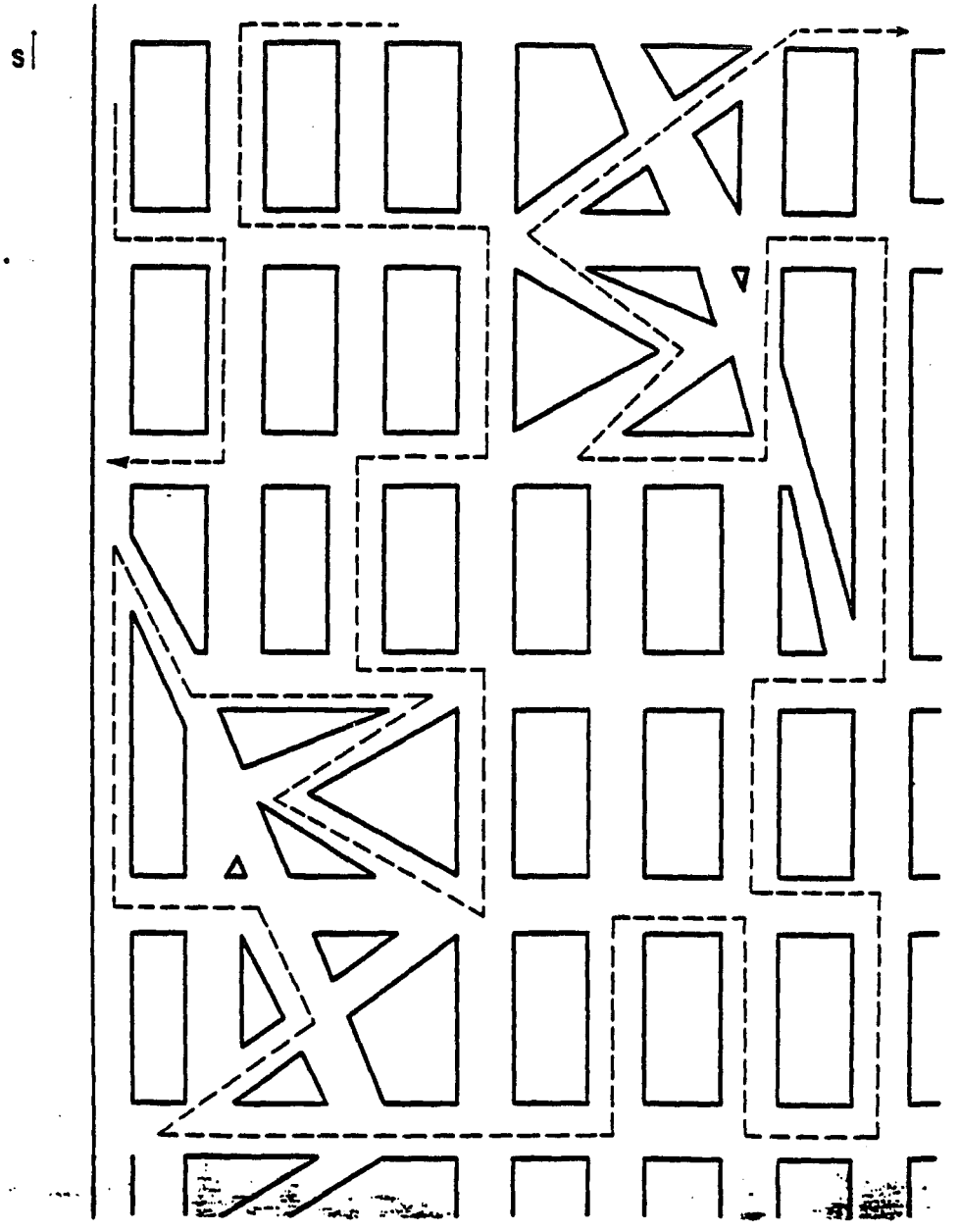
In conclusion, the cholinesterase inhibitor physostigmine did not appear more effective than placebo treatment in improving performance on the battery of non-verbal constructional and spatial tests. These findings might indicate that (1) these abilities are not dependent on an intact cholinergic neurotransmitter system, and the impaired performance by subjects with DAT is the result of as of yet unexplained neurophysiological dysfunction or, (2) physostigmine either under-or overstimulates the cholinergic system for non-verbal cognitive enhancement, since the drug was titrated for maximum verbal-memory enhancement.

Constructional abilities are a complex integrative

cognitive process involving a wide range of perceptual, spatial, manipulative and executive functions. It would seem unlikely that the manipulation of a single neurotransmitter system would effectively enhance performance on these complex tasks. It might be more fruitful to examine the effects of physostigmine on more specific non-verbal cognitive functions (such as perceptual and spatial abilities) in isolation.

APPENDIX

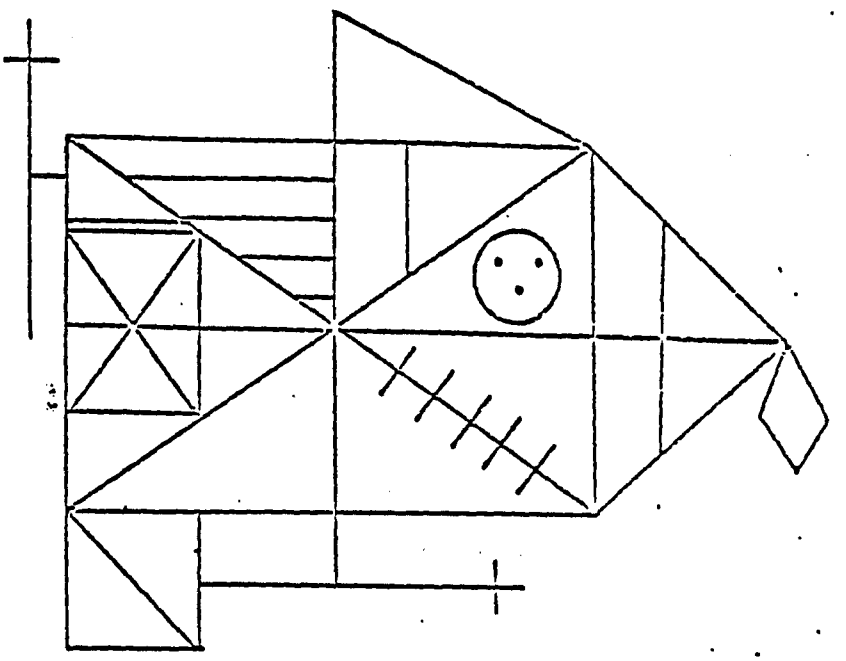
The Roadmap Test of Spatial Orientation



Appendix 1

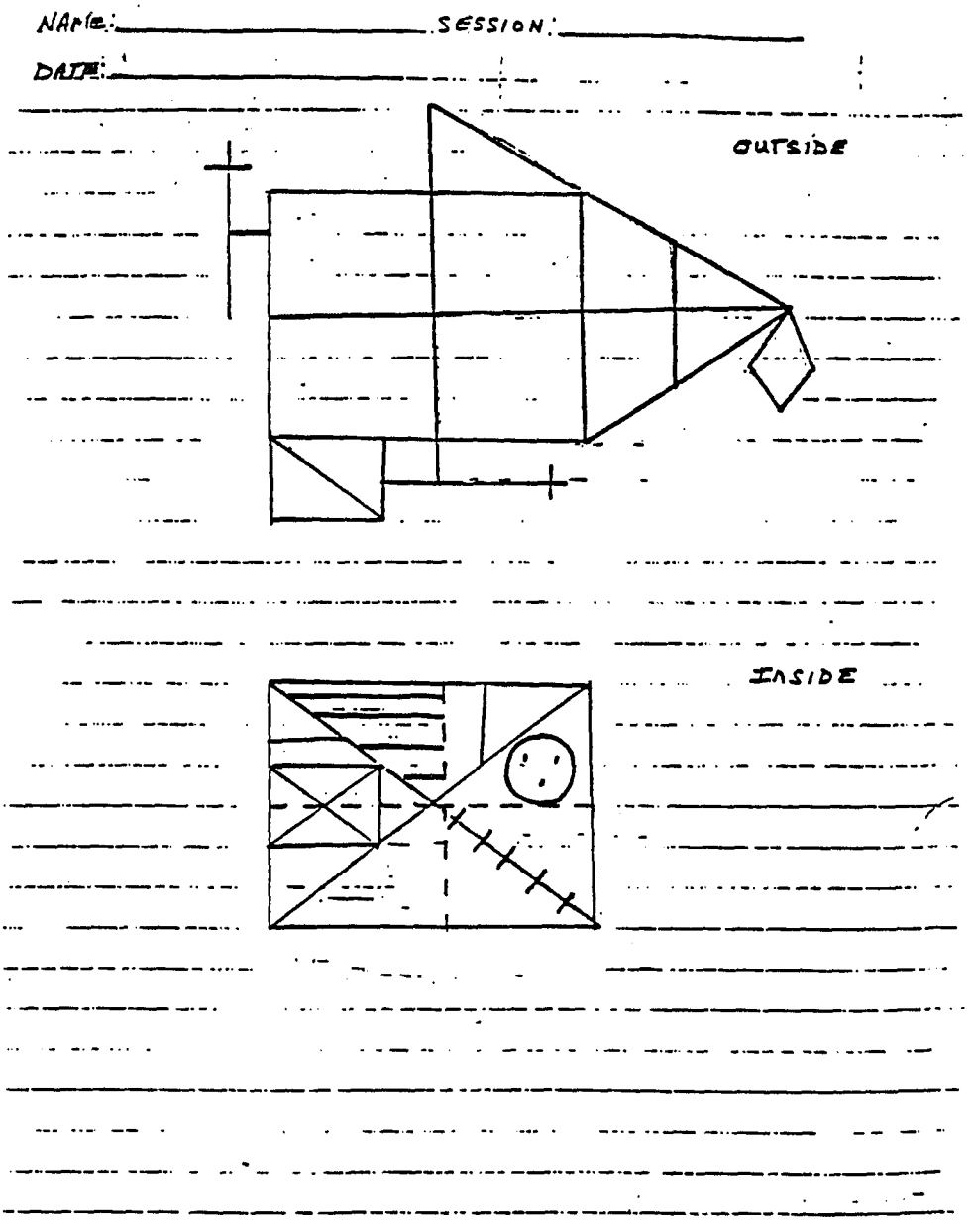
The Rey-Osterrieth Complex Figure

Rey - Osterrieth Design



Appendix 2A

The Rey-Osterrieth Complex Figure - Observation Sheet



Appendix 2B

The Benton Visual Retention Test: Record Form

VISUAL RETENTION TEST

NO. _____

Arthur L. Benton

RECORD FORM

NAME _____ AGE _____ SEX _____

PLACE OF TESTING _____ EXAMINER _____

FIRST TESTING DATE _____

FORM _____ ADMINISTRATION _____

Design	Score (0 or 1)	Errors*	Number of Errors
I			
II			
III			
IV			
V			
VI			
VII			
VIII			
IX			
X			
Number Correct Score		Error Score	

*Use symbols: see Chapter 2 of manual.

ERROR CATEGORIES:

Omissions _____

Distortions _____

Perseverations _____

Rotations _____

Misplacements _____

Size Errors _____

Left Errors _____

Right Errors _____

SECOND TESTING DATE _____

FORM _____ ADMINISTRATION _____

Design	Score (0 or 1)	Errors*	Number of Errors
I			
II			
III			
IV			
V			
VI			
VII			
VIII			
IX			
X			
Number Correct Score		Error Score	

*Use symbols: see Chapter 2 of manual.

ERROR CATEGORIES:

Omissions _____

Distortions _____

Perseverations _____

Rotations _____

Misplacements _____

Size Errors _____

Left Errors _____

Right Errors _____

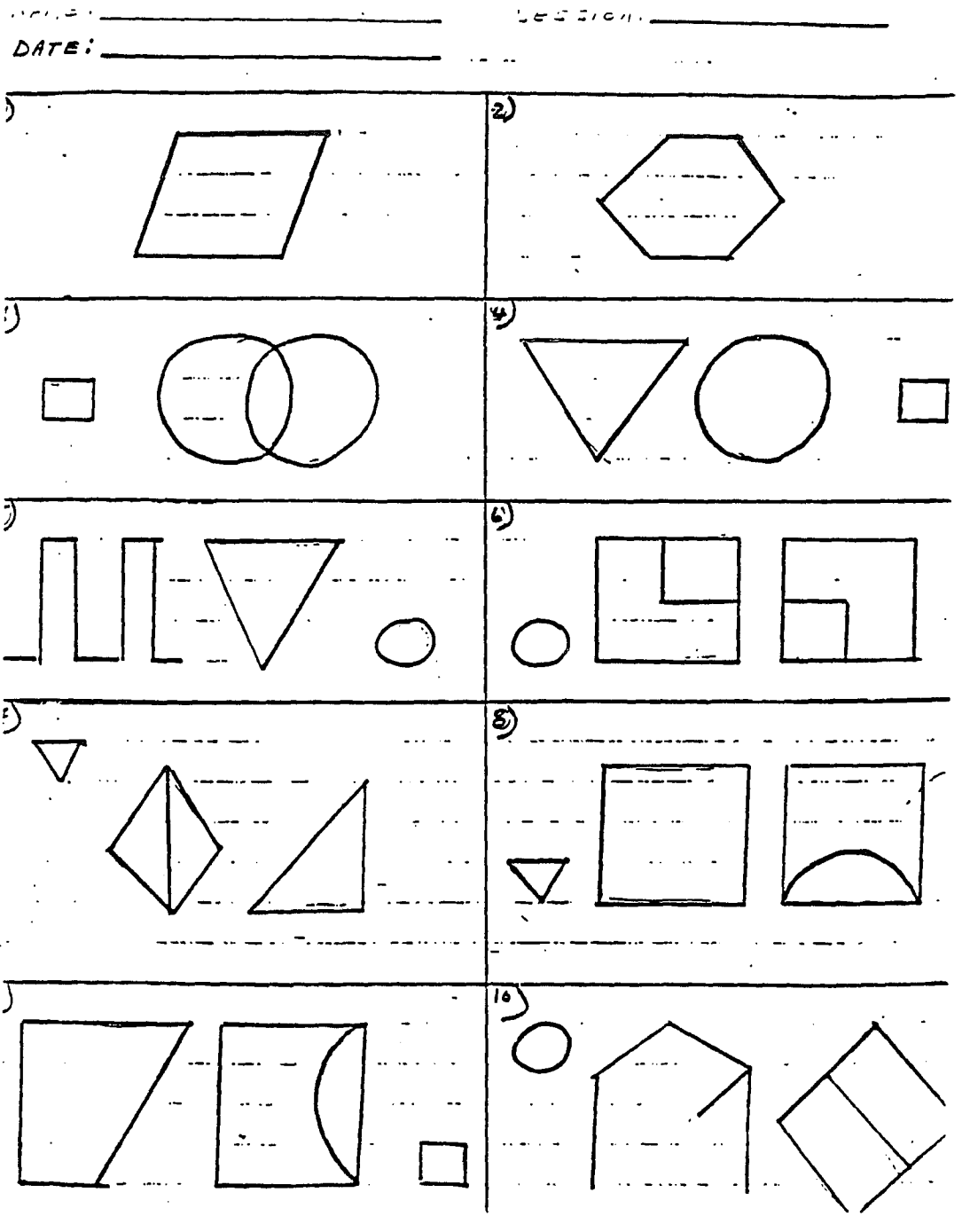
REMARKS _____

INTERPRETATION _____

79-133AS 9-027428

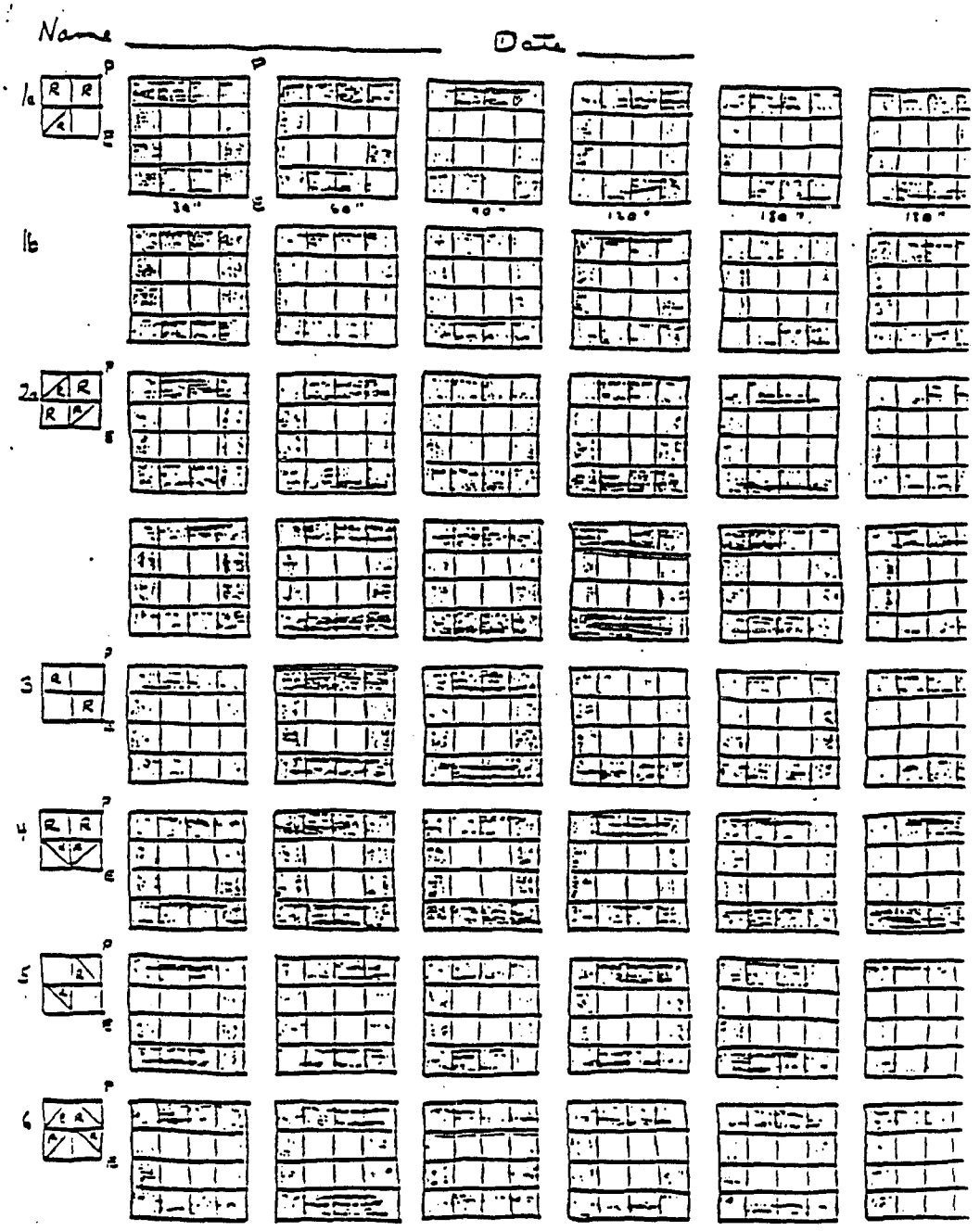
Appendix 3A

The Benton Visual Retention Test: Observation Sheet



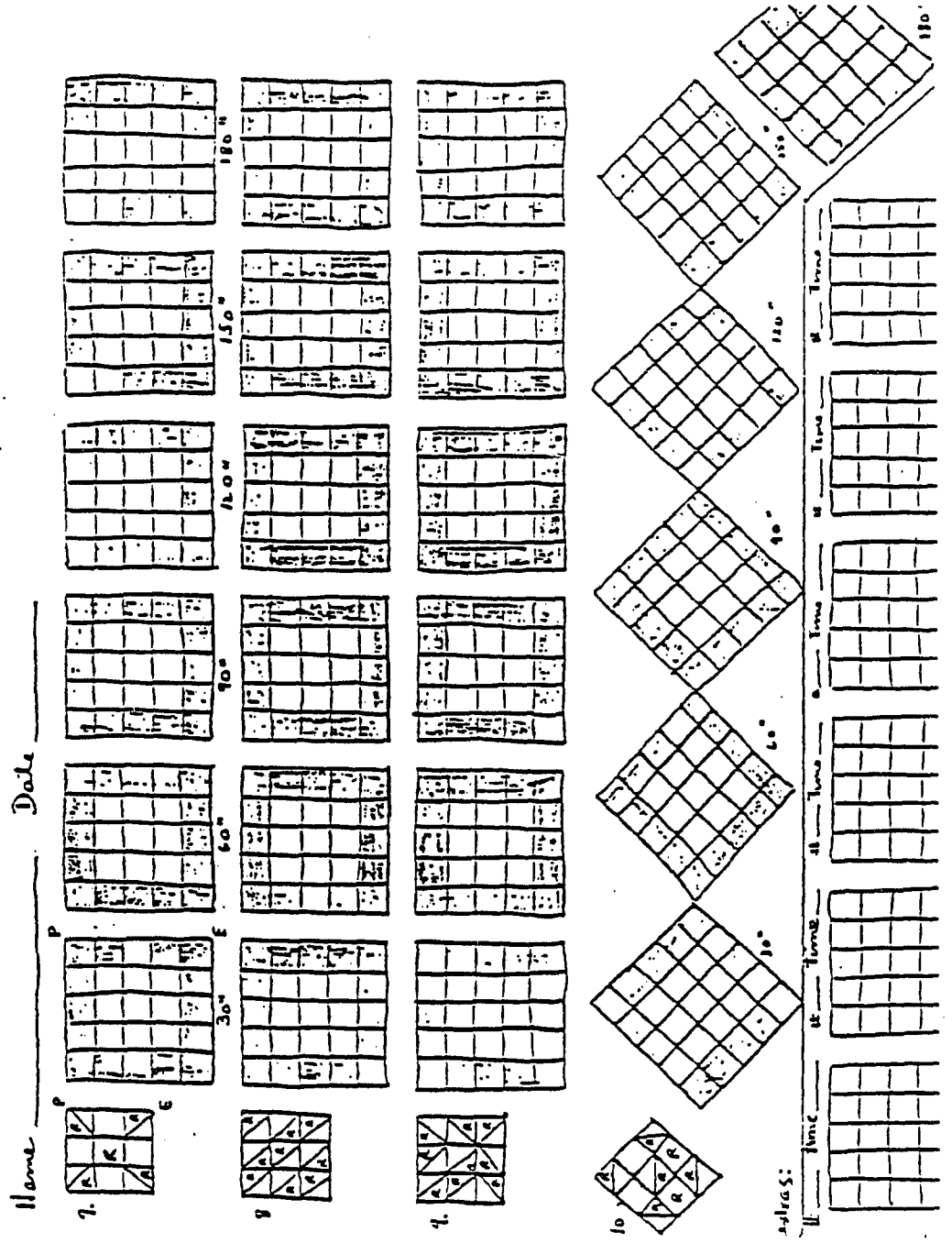
Appendix 3B

Block Design Observation Sheet (Items 1-6)



Appendix 4A

Block Design Observation Sheet (Items 7-10)

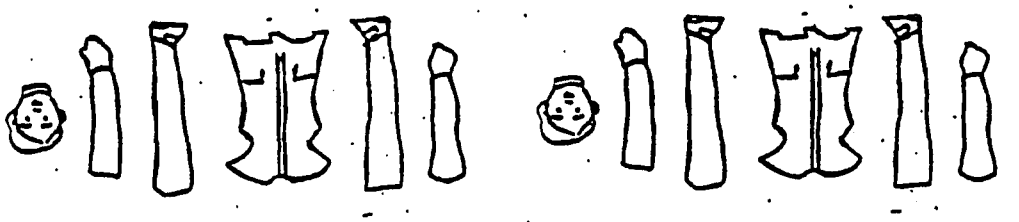


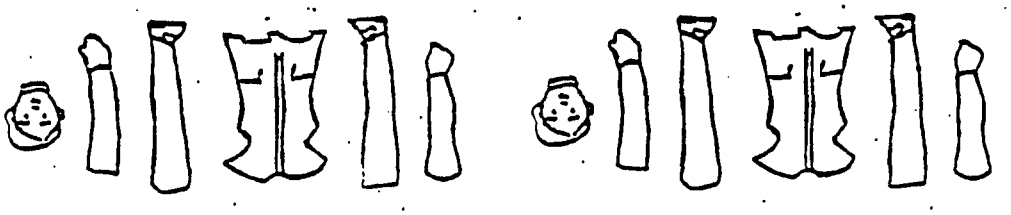
Appendix 4B

Object Assembly Observation Sheet: Manikin

MANIKIN

SECTION	ORDER	TIME	REMOVE	REPLACE
HEAD				
RD. ARM				
SD. ARM				
RD. LEG				
SD. LEG				



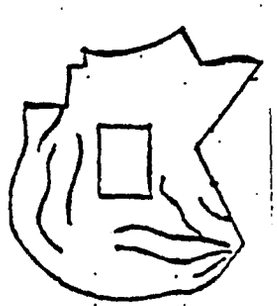


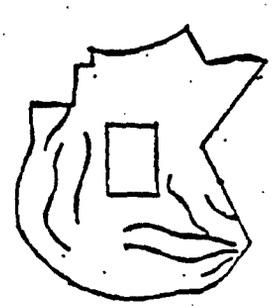
Appendix 5A

Object Assembly Observation Sheet: Profile

PROFILE

SECTION	ORDER	TIME	REMOVE	REPLACE
EYE				
NOSE				
LIP				
HAIR				
TOP EAR				
BOT. EAR				
EAR CORR.				

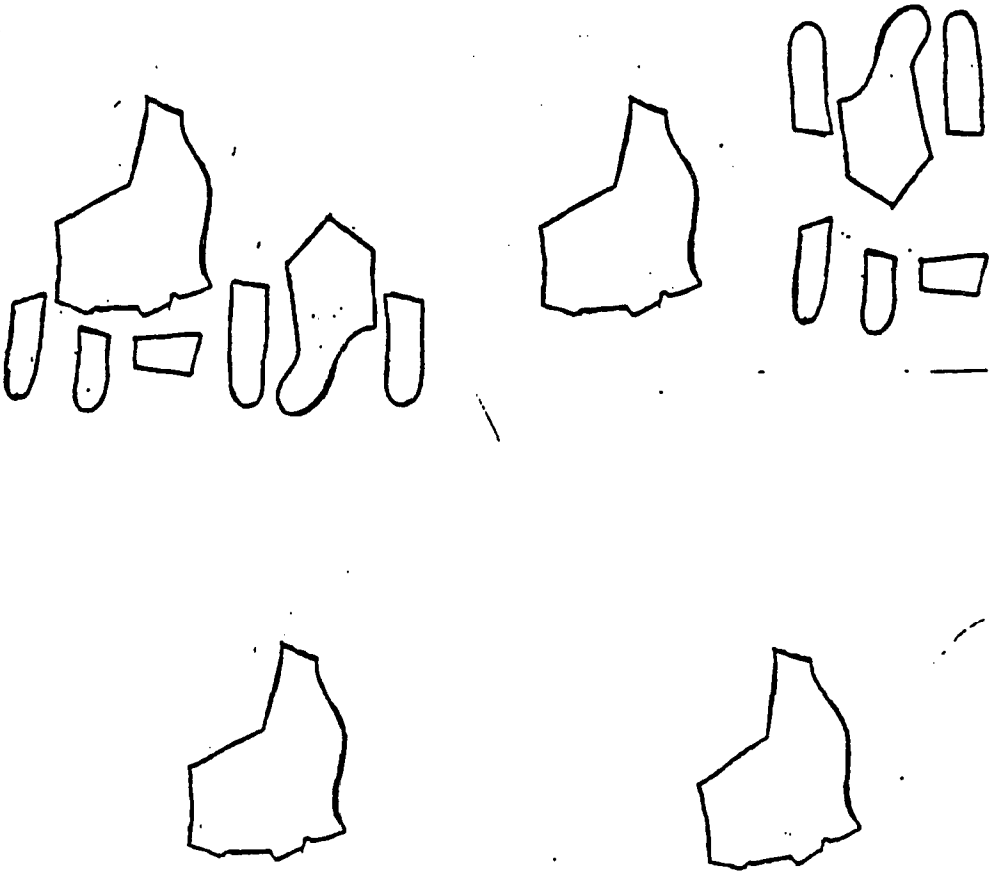




Appendix 5B

Object Assembly Observation Sheet: Hand

SECTION	ORDER	TIME	REMOVE	REPLACE
THUMB				
WRIST				
INDEX				
MIDDLE				
RING				
PINKY				

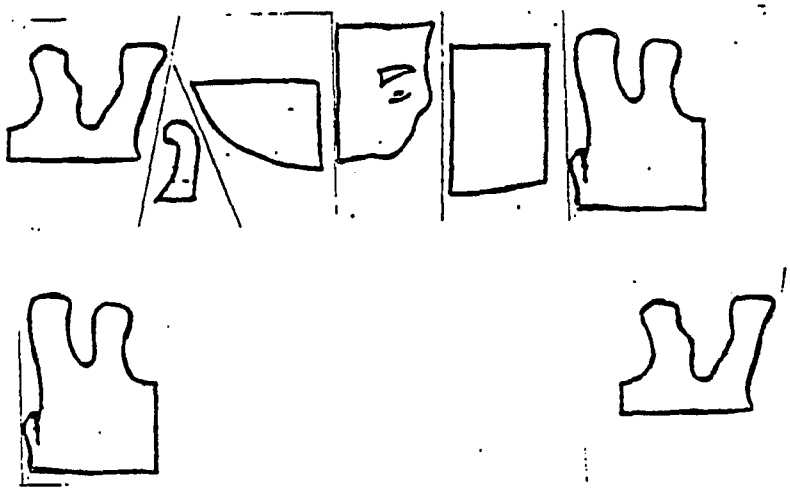


Appendix 5C

Object Assembly Observation Sheet: Elephant

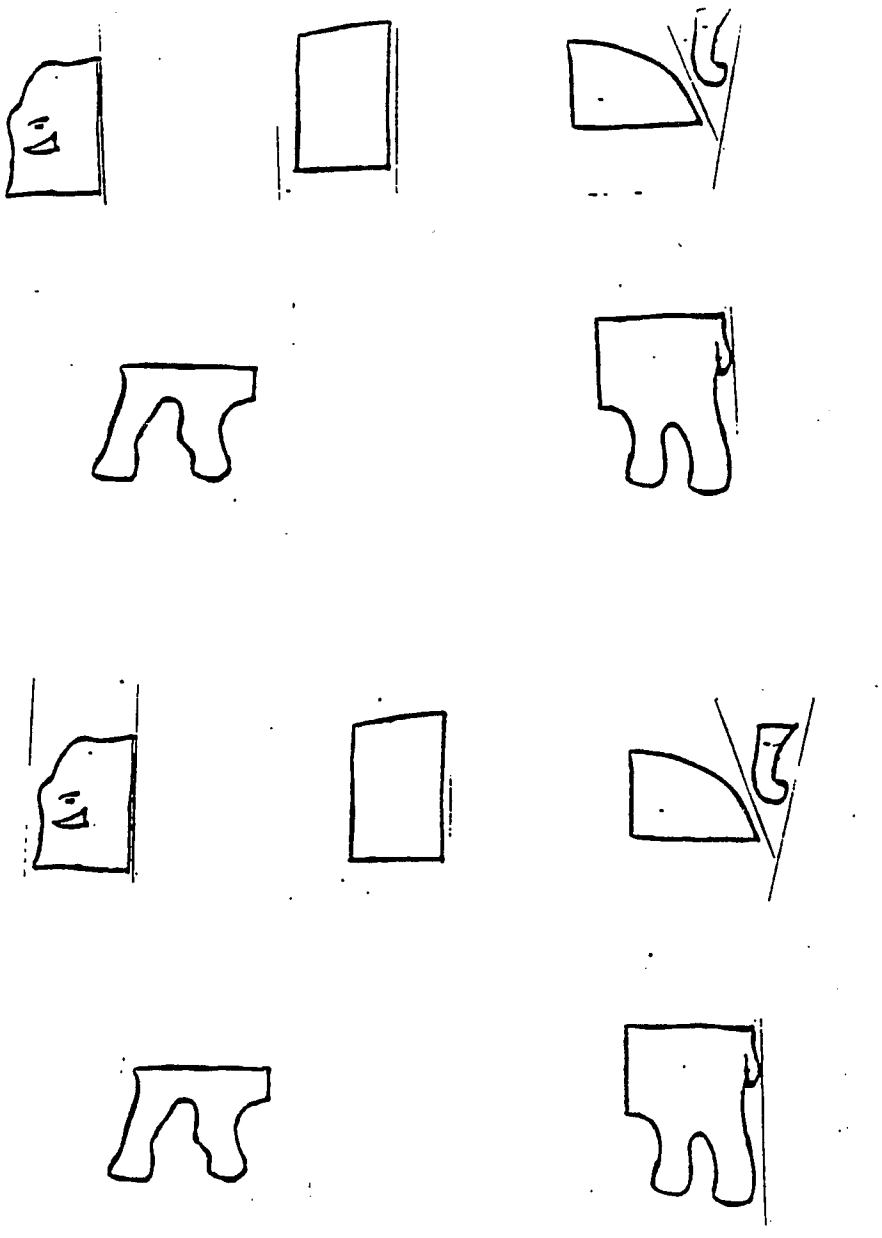
ELEPHANT

SECTION	ORDER	TIME	REMOVE	REPLACE
HEAD-CENTER				
REAR-CENTER				
REAR-BACK				
BACK-FRONT				
FRONT-HEAD				
HEAD-TRUNK				
CENTER-FRONT				
CENTER-BACK				



Appendix 6A

Object Assembly Observation Sheet: Elephant



Appendix 6B

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