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The Relationship of Mental Status And Estrogen Use on Visual-Motor and Visual-Spatial Abilities in Elderly Women

By Christine Pezzanite Weber

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

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9/11/00
Date

Victoria Luine
Chair of Examining Committee

9/15/00
Date

Executive Officer

Victoria Luine, Ph.D.
Hunter College, CUNY

Steven Albert, Ph.D.
Columbia University

Jim Gordon, Ph.D.
Hunter College, CUNY

Diane Jacobs, Ph.D.
Columbia University

Vanya Quinones, Ph.D.
Hunter College, CUNY

Supervisory Committee

THE CITY UNIVERSITY OF NEW YORK

Abstract

The Relationship of Mental Status and Estrogen Use

On Visual-Motor and Visual-Spatial Abilities in Elderly Women

by

Christine Pezzanite Weber

Adviser: Professor Victoria Luine

The goal of this dissertation was to examine hand-eye movement deficits that manifest (visual-motor integration) in elderly individuals. Performance on visual-spatial tasks have been shown to involve parietal lobe function. Experiments investigated the relationship between cognitive status and visual motor performance tasks. A secondary study investigated the effects of estrogen replacement on visual-spatial abilities. In the primary study of 50 elderly women, participants were given a test of mental status and asked to perform a constructional ability task and a three-dimensional object placement task. They were compared on the basis of mental status scores, which were categorized into two groups: cognitively impaired versus cognitively normal. Age and education of each group was analyzed. Data demonstrated that woman who showed deficits on a test of mental status had difficulty performing tests of constructional ability and three-dimensional object placement as compared to normal elderly women ($p < .01$). The results suggest that tests which assess an

individual's ability to reach and grasp for objects are an indicator of visual-spatial deficits in elderly individuals and may provide an additional indicator of cognitive loss.

For the secondary study, women with a history of estrogen use were compared to women with no history of estrogen use to determine whether significant differences for visual-spatial abilities were present. Women were given tests of visual-spatial abilities (the Rosen Drawing test and the Benton Visual Retention Test). Analysis of the data demonstrated no significant differences for women with a prior history of estrogen use on tests of visual-spatial abilities compared to women with no history of estrogen use. The findings although not significant, show a trend between estrogen use and visual-spatial abilities, suggesting that further research would be useful in addressing this question.

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Chapter 1

Literature Review, Conceptual Framework, And Dissertation Hypotheses

Introduction

Research has found a relationship between errors in reaching and grasping for objects and mental status. This study examines mental status as a factor contributing to visual-motor (visual-spatial) impairment in older adults and object assembly tasks. This deficit in performance is associated with parietal lobe involvement. Independent age effects have also been found, with older individuals displaying greater deficits performing visual-motor tasks than younger individuals.

A secondary study was conducted to examine the effects of estrogen use on visual-motor abilities with a separate data set. Research has shown that estrogen affects cognitive abilities, including verbal and non-verbal memory. There is an extensive literature on the effects of estrogen on spatial abilities (Frick, 2000; Luine, 1994; Sherwin, 1994; Hampson, 1995). This study attempts to demonstrate an effect of estrogen on cognitively normal postmenopausal women and whether decline of visual spatial abilities is related to estrogen use.

In this chapter the study goals are presented, including the theoretical framework and hypotheses. Human and animal models are explored which investigate the relationship between cognitive/mental status and visual-motor integration. The relationship between mental status and performance on constructional ability tasks and three-dimensional object assembly tasks are also explored (Rosen, 1981, Stanford-Binet, 1986). Age and level of education are

variables that can influence individuals visual-motor performance and will be discussed.

Historical data is presented on lesion studies and the resulting deficits that manifest. We examine variables that relate to visual-motor deficits, such as individuals' mental status. Since a likely cause of memory loss and visual-spatial deficits in elderly individuals is Alzheimer's Disease, this disorder is explored and background literature presented.

The topic of estrogen and its relationship to visual-spatial abilities is explored. A discussion of the literature on estrogen and cognition is presented, which includes effects in animals and humans when levels fluctuate. These effects can be physical as well as cognitive. The relationship between verbal memory and visual-spatial tasks is also explored.

Primary Objective of the Dissertation

The primary objective of the dissertation is to examine the relationship between mental status and visual-motor performance of a three-dimensional object assembly task.

A secondary objective of this dissertation is to examine the relationship between estrogen use and visual-motor functioning in postmenopausal elderly women. Differences in cognitive abilities have been found when comparing women who have taken estrogen replacement therapy versus women who have not (Phillips, et al., 1992; Jacobs, et al., 1998).

Distinctive Features of This Study

For the primary study, performance of a two-dimensional constructional ability task and a three-dimensional object assembly task was examined by subjects exhibiting varying mental status scores. Both tasks require visual-motor integration and visual-spatial abilities (Benton, 1974; deRenzi, 1982). Customary tasks designed to measure visual-spatial ability have utilized two-dimensional constructions such as moving a cursor on a computer screen (Ghilardi, et al., 1999) or drawing figures (DiPellegrino, 1995; Carlesimo, 1993). While traditional methods detect visual-spatial deficits, they may not be as sensitive to tasks that require an individual to move in three-dimensional space. For example, drawing tasks detect deficits by scoring figures according to errors in angles and vertices. While they detect spatial components, the visual-motor act of drawing the figure is ignored. By designing a task in which the focus is on the arm and hand, movement becomes the center of attention. The movement can be broken down into component parts as one reaches or grasps in three-dimensional space.

The distinctive feature of this dissertation is that the object assembly task requires a three-dimensional arm/hand movement from subjects. Subjects are videotaped as they place beads on a stand. The Stanford Binet Bead Memory test (Stanford-Binet, 1986) has been adapted in this study to assess reaching and grasping deficits. This study examines three dimensional hand placement and grip in order to determine execution strategy deficits (difficulties placing the hand around the object); average number of errors for object placements (objects

that are to be placed on a small stick); and the ability to complete the three-dimensional task. Execution strategy deficits are defined as inappropriately placing the hand around an object so that readjustment of the object is needed, and overreaching or underreaching for the object. Another kind of execution strategy error involves use of tactile information from the fingers to locate the object (ex. groping for the object). The Rosen Drawing test (Rosen, 1981) is utilized as a secondary measure of visual-motor integration. It is an established test, which assesses integration, and is used to validate the three-dimensional object assembly task. Therefore, individuals who have difficulties completing the three-dimensional object assembly task should also score lower on the Rosen Drawing test.

The secondary study compared visual-spatial abilities of postmenopausal estrogen users and postmenopausal non-estrogen users. Performance tests were analyzed to determine whether there were significant differences based on estrogen use. Published data by Jacobs, et al., (1998) found that women with a history of estrogen use scored significantly higher on a test of verbal memory than women with no history of estrogen use. A question addressed in this study is whether estrogen users show enhanced visual-spatial performance compared to women with no history of estrogen use.

Performance and Visual-motor Integration

Theoretical models for visual-motor integration predict an anatomical relationship between visual processing and motor functioning. When this integration system is altered, problems occur whereby the individual experiences

particular types of cognitive deficits. Visual spatial impairment is a type of cognitive deficit that can manifest as a result of mental decline. Object assembly, drawing, visual search tasks and manipulations of objects require visual-spatial ability. Visual-motor skills fall under the category of visual-spatial abilities. These skills include tasks that require manipulation of objects.

In examining visual processes, two anatomical streams of processing have been found, which are associated with motor ability and skill. Mishkin, Lewis and Ungerleider (1982) identified two visual systems: a ventral stream of visual processing and a dorsal stream of visual processing. The ventral system of visual processing extends from the primary visual cortex (V1) to the inferotemporal cortex. The ventral stream is utilized when an individual attempts to identify an object in space, such as when a subject is asked to identify an item placed in front of him, for example, a cube (Mishkin, et al., 1982). A cube may be used because it has a particular shape and is three-dimensional. The sides of a cube are all square and equal in length. According to Mishkin, et al., (1982), asking the subject to view the cube and to name it is a ventral stream task. With respect to the dorsal stream of visual processing, which projects from V1 to the posterior parietal lobe, the individual views an object and attempts to localize that object in space, and then reaches for the object (Milner & Goodale, 1993). These processes has been referred to as the "what versus where" question by Mishkin, et al., (1982). It is thought, however, that there would need to be some communication between each stream of processing (Milner & Goodale, 1993). Clearly if one is asked to pick up an object and does so correctly, properties of

the object (form) must have been encoded in some way in order to properly adjust the fingers and grip around the object.

Milner & Goodale (1993) diagramed the visual system of the macaque brain and differentiate between the ventral and dorsal streams of processing (Diagram 1).

Diagram 1

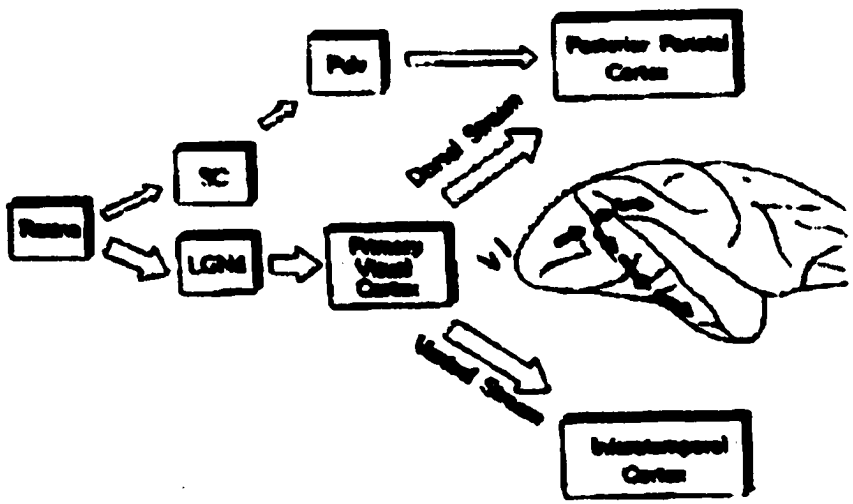


Diagram of visual input to dorsal and ventral streams in the right hemisphere of the macaque brain.

LGNd – lateral geniculate nucleus, pars dorsalis; pulv – pulvinar; SC – superior colliculus

From: Milner & Goodale 1993

The retina is the sensory organ that converts light into electrical signals. This signal is then sent to the superior colliculus and the lateral geniculate nucleus. The SC is the main subcortical center for visual reflexes and projects to the pulvinar, which receives afferents from the SC, and projects to the visual association cortex and parietal association cortex. The LGN is the principal thalamic nucleus for vision. M pathways are involved with the movement of visual

images while P pathways encode fine structure, form and color (Poggio, 1968). It receives retinal inputs from the eyes via the optic tract and projects to V1. According to the model, the dorsal stream contains two pathways for processing, one of which does not require primary visual cortex (Milner & Goodale, 1993). Structures involved in dorsal and ventral stream processing include the retina, lateral geniculate nucleus (LGN), primary visual cortex (VI), pulvinar, and superior colliculus (SC) (Jeannerod, 1997). If ventral stream processing were deficient, the individual would be able to grasp the object, but would not be able to identify what the object is. In contrast, if dorsal stream processing were defective, the individual would be able to identify the object, but would have difficulty grasping the object for manipulation (Mishkin, Lewis and Ungerleider, 1982). The grasp may be too small, too wide, or the extension of the arm may be in error.

The dorsomedial system has been implicated in visual and motor processing, which is important in reaching for objects in space (Milner & Goodale, 1993). The posterior parietal lobe is implicated in visual fixation, pursuit and saccadic eye movements, visually guided reaching and manipulation of objects. Reaching for an object in space (prehension) requires that an individual anticipate the appropriate position of the object, anticipate the distance the individual must extend in order to grasp the object, and anticipate the curvature of the fingers required in order to clasp the object appropriately. The term, "vision for action" is frequently used for movement (Jeannerod, 1986). This movement term is illustrated when observing an individual reaching, grasping or

clasping an object and in shaping the hand. Reaching involves visual processing prior to contacting the object, extending the reach of the arm, and positioning the hand appropriately around the object. Grasping or clasping the object is the end movement. In shaping the hand, it is the thumb in opposition to other fingers that allows an individual to grasp the object.

Literature Review – Lesion Studies

Movements that are visually guided are believed to be linked to dorsal stream processing and the parietal lobe. Visual deficits are produced when parietal lesions are present. Evidence to support this hypothesis has been examined studying non-humans and humans (Jeannerod, 1994; DeRenzi, 1982; Kaida, 1998).

With respect to dorsal stream processing, monkeys with posterior parietal lesions were shown to have deficits in perceiving spatial landmarks and deficits reaching for food objects (Mishkin, Lewis & Ungerleider, 1982; Bates & Ettinger, 1960; Milner & Goodale, 1993). In addition, Faugier-Grimaud, Frenois & Stein (1978) found that monkeys with inferior parietal lobe lesions are unable to shape the contralateral hand properly and produced awkward grasps. Monkeys with posterior parietal lesions demonstrate deficits in recognition and visual pattern discrimination.

Studies with humans indicate that subjects with parietal lobe damage have difficulties with spatial locations of objects, grasping, grip aperture deficits, and have longer reaction times in executing movements. Deficits seen in the dorsomedial system include such deficits as optic ataxia and constructional

apraxia (DeRenzi, 1982; Jeannerod, 1981; Milner & Goodale, 1993). Optic ataxia is the inability to use visual cues to reach out and grasp an object in the hemifield contralateral to the parietal lesion. Jeannerod & Biguer (1982), as well as Perenin & Vighetto (1988) found deficits in reaching and grasping objects following lesions. Deficits have been found in finger placement and hand orientation with individuals diagnosed with optic ataxia (Perenin & Vighetto, 1988). Individuals with this deficit are unable to localize objects in space. Slowed reaction times are also an indicator of parietal lobe deficits and optic ataxia (Petersen, et. al.1989). Because individuals cannot properly anticipate the position of the object for targets contralateral to the lesion, their movements are somewhat slowed and deliberate. Kaida (1998) found motor impairment in an individual with right-sided parietal lesions, as well as unskillful movements, left-handed myoclonus, a sudden twitching that occurs as a result of one or more muscle group contractions, and abnormal muscle tone.

Mishkin, Lewis and Ungerleider (1982) found that patients with damage to the posterior parietal cortex displayed optic ataxia. They were unable to use visual information to reach out and grasp objects in the hemifield contralateral to the lesion and made large directional errors. Patients with visual form agnosia, following damage to the occipitotemporal region were unable to recognize or describe common objects, faces, drawings, and abstract designs (Mishkin, Lewis and Ungerleider, 1982). These findings are consistent with prior literature, which found two streams of processing (Perenin & Vighetto, 1988; Petersen, 1989).

Likewise, Dijkerman, Milner and Carey (1998) have found deficits in reaching and grasping. Investigators presented transparent disks with circular finger holes to a patient with a ventral stream lesion. The patient was then asked to reach and grasp each object by inserting her fingers into transparent holes in each disk. Investigators varied the distance between the forefinger and thumbholes, as well as the orientation of the line of each hole. The patient was unable to adjust her grip aperture and hand orientation when presented with disks with three transparent holes. Investigators concluded that the ventral stream of processing is also important for providing individuals with appropriate spatial information in guiding motor responses.

Alternatively, constructional apraxia occurs when individuals are asked to assemble parts in order to produce a whole object and are unable to do so. This deficit is especially evident in an individual's attempt at drawing objects, including 3-dimensional objects. Depending upon which side of the brain is damaged, deficits manifest in unique ways (Rushworth, et al., 1997). Individuals with left parietal lobe involvement had deficits in motor attention and sequencing hand movements. Additional deficits may be experienced in word finding, reading and gesturing. Individuals with right side damage were unable to shift their eye movements from one saccadic target to another (Posner, 1984). Other right side deficits include impaired constructional ability, the inability to manipulate written numbers, integrating right to left, and the inability to localize an object in the left hemispace (Lezak, 1983). An example of this is putting a spoon to ones mouth and the movements the arm and hand must make in order to properly

execute the task. Similar to findings for subjects with optic ataxia, it has also been found that subjects displaying constructional apraxia have longer reaction times executing a task (Caselli, 1999, Ortiz, 1999).

Brain Changes Associated with Aging

There are characteristic changes in the brain for normal aging which includes decreases in brain weight and protein levels (Cote & Kremzner, 1983). There is a decrease in the number of neurons present and reduced levels of enzymes necessary to synthesize dopamine and neurepinephrine (Tomlinson, and Henderson, 1976). Receptors for dopamine, norepinephrine and acetylcholine are reduced (White, et al., 1977). These changes are thought to be a part of the normal aging process, and should not impact individuals daily activities significantly (Morris & McManus, 1991; Coleman and Flood, 1987).

A large literature supports an age effect on performance of three-dimensional tasks, with older human and non-human primates performing worse than young individuals (Greenwood, et al., 1993; Whitfield, 2000). Differences are found in reaction time, attention, visual fixation and stimulus selectivity (Greenwood, 1993; Whitfield, 2000). Whitfield (2000) compared young and old macaque's ability to manipulate objects and electrophysiological properties of neurons in the older macaque were less selective than the young monkeys, firing more frequently and at times without any external stimuli. Among the elderly, individuals who fall in the older age ranges (85 or above) tend to perform worse than individuals in the younger ranges (84 and below) on tests of cognitive functioning, such as the Folstein MMSE, digit span, and cube copying (Osterweil,

et al., 1994). While it is known that memory decline is a part of the aging process, age related memory loss becomes significant when impairment for an individual is worse than other individuals who are of the same age (Petersen, 2000). This kind of impairment is classified as mild cognitive impairment (MCI), which has been and is currently being investigated as a possible precursor to dementia (Celsis, 2000). Dementia is a deterioration of intellectual functioning caused by organic factors.

While aging itself is correlated with declines in visual-spatial abilities, a distinction is made between changes associated with the aging process and changes associated with disease processes and dementia. Addressing the issue of age on visual-spatial abilities, Greenwood (1993) examined cognitively normal individuals ranging from age 20 to late 70's on a target location task. Stimuli were presented at varied degrees from a fixation point and attention measured. Researchers attempted to compare these results to studies that examined demented individuals (Maruff, 1995; Buck, 1997). The results suggest a difference between normal aging and individuals with dementia. Demented individuals manifest deficits with voluntary and involuntary attentional shifting (Maruff, 1995). For normal aging, investigators found only a weak effect in voluntary and involuntary attentional shifting.

Education has been found to contribute to differences in cognition and memory. Overall, a survey of the literature has found a relationship between level of education and mental status scores (Ishizaki, 1998; Butler, 1996). Generally, individuals with fewer years of education have lower scores on tests of

mental status (Christensen, 1999). Osterweil (1994) found that elderly individuals with 0 to 4 years of education scored lower on tests of mental status than elderly individuals with greater than 4 years of education. Among the mental status tests administered were the Mini-mental status exam, cube copying and digit span. Mazaux et. al. (1995) found that women with low levels of education performed worse on tasks requiring focused attention and psychomotor ability as compared to women with higher levels of education. In a study examining elderly women, Butler, et al., (1996) found that the rate of cognitive decline in elderly Catholic nuns varied according to the level of education achieved. Scores on the MMSE for nuns with bachelor's degrees were higher than scores for nuns without bachelor's degrees. When stratifying by age, greater cognitive decline was found in nuns between 75 and 84 years of age with lower years of education. It might seem that education has a buffering effect on cognitive abilities, with less cognitive decline occurring for individuals with higher levels of education. It has been suggested that education and occupational attainment may produce a "cognitive reserve" resulting in a reduced risk of dementia or AD (Stern, et al., 1999; Alexander, et al., 1997). Stern, et al. (1999) demonstrated that individuals with higher education (>8 years) and occupational attainment had a delay in the onset of Alzheimer's Disease, although the clinical manifestations of dementia were more severe at diagnosis. Once the cognitive reserve was depleted in this population, they reported that the disease process was shorter with rapid memory decline. This "cognitive

reserve" may protect individuals from the symptoms of dementia and protect against Alzheimer's Disease (Stern, et al., 1992).

Alzheimer's Disease Physiological Changes

Alzheimer's Disease (AD) is a progressive disease that occurs most often in individuals over 65 years of age; approximately 50% of the population aged 85 and above are affected (Evans, et al., 1990). AD is associated with neuropathological changes of extracellular amyloid plaques and neurofibrillary tangles (Kandel, 1991). Amyloids are abnormal protein-polysaccharide complexes and different kinds of amyloids deposit extracellularly as a result of certain disease processes (Selkoe, 1991). Amyloid plaques are loose, irregular aggregates of glial and neuronal processes. In AD patients' plaques are found in the gray matter of the neocortex and hippocampus) and may also be present in the white matter, basal ganglia, thalamus and cerebellum (Pearson, et al., 1985). Neurofibrillary tangles are aggregates of paired helical filaments within a cell body and are found in the hippocampus, subiculum, entorhinal cortex, CA1 region and cerebellum (Pearson, et al., 1985).

Neuronal cell loss is found in the hippocampus, frontal lobe, anterior temporal lobe, parietal lobe, amygdala, olfactory system and basal forebrain of AD patients (Coleman, 1987; Tomlinson, 1976). Atrophy occurs in the frontal, anterior, temporal and parietal lobes of the brain. These differences in brain structure result in a decrease in brain weight and changes in neurotransmitter levels greater than those seen in normal aging (Tomlinson, 1976). In particular, cholinergic systems are affected and there is a 60-90% reduction of choline

acetyltransferase in the hippocampus and cerebral cortex of individuals affected with Alzheimer's Disease (Kandel, 1991). More specifically, severe neuronal loss is seen in the nucleus basalis, which is a major cholinergic system located at the base of the forebrain (Kandel, 1991). There is cell loss in the locus ceruleus, which may account for the decreased level of neurepinephrine in some patients (Mann, 1983). CT and MRI imaging have demonstrated that individuals with AD have enlarged ventricles and thin cortical gyri (Matsumae, 1996). Changes in cortical blood flow have been found with PET imaging (Rapoport, 1991). A definite diagnosis of AD is made upon autopsy of brain tissue when clinicians look for AD associated lesions, which include neuritic plaques, neurofibrillary tangles and neuropil threads. (Sclar, 1992; Markesbury, 1997). There are major cognitive changes that occur as a result of these changes. The accuracy rate for the clinical diagnosis of AD while an individual is alive is 80-90% (Growdon, 1999).

Alzheimer's Disease and Cognitive Changes

The major symptoms manifested in individuals with AD are diminished cognitive abilities, including impairment of memory, language, orientation and visual-spatial abilities; sleep disorders and personality/emotional changes, including paranoia (McKhann, et al., 1984). Diagnosis of AD is made using criteria established by McKhann, et al. (1984). Initially, symptoms begin with subtle memory loss with an individual forgetting recent events, the locations of objects or words (Reisberg, et al., 1982). An early indicator of Alzheimer's Disease may be deficits in verbal episodic memory (Celsis, 2000). According to

Reisberg, et al. (1986) AD progresses by stages (one to seven), with individuals become increasingly confused, memory loss increases and ultimately the individual may have difficulty recognizing friends or family members. Patients with AD may be disoriented to time and place, (not knowing what year it is) and not know where they are or reside. As the stage of the disease increases, language becomes severely affected, and the individual may be limited to speaking six words or less. Personality and emotional changes manifest, as individuals may become depressed, aggressive, or prone to verbal (as well as physical) outbursts. Individuals may become paranoid, and believe others are stealing from them. A delusional individual may believe that people are trying to hurt them (Reisberg, Borenstein, Franssen, Shulman, Steinberg, and Ferris, 1986). In the final stage (stage 7), cognitive and motor functioning are severely impaired. The individual may be unable to speak and may be unable to walk. It might seem as though the brain "cannot control the body" (Reisberg and Borenstein, 1986).

The individual with AD may experience difficulty in accessing both the visual system as well as the motor system. Activities affected may be walking, or performing daily activities such as using the telephone or lacing one's shoes. When the patient with AD is impaired in this way (with using visual-spatial and visual-motor components) the ability to maintain a visual image is disrupted and patients are unable to reproduce visual stimuli immediately after presentation (Quinn & Ralston, 1986; Grossi, Becker, Smith, and Trojano, 1993). This deficit

may be attributed to a defect in visual scanning and/or in fine motor manipulation tasks, which require assembling objects.

Cognitive impairment is seen when individuals with AD are asked to arrange blocks into a pattern, piece together a puzzle, draw particular objects such as a clock or draw a three-dimensional object (Grossi, et al., 1993; Esteban-Santillan, et al. 1998). Ghilardi, et al., (1998) found a relationship between the severity of dementia and movement control. Individuals were asked to move a cursor to a target on a computer screen without visual feedback (seeing the position of their hand/arm). During each movement, the position of the cursor was not displayed to the patient. The results indicated differences between AD patients and normal controls. AD patients were found to have an impaired feedforward motor system (Ghilardi, et al., 1998). This research demonstrated a relationship between mental status and visual-motor integration. However, the task being performed in this research was using two-dimensional space, (for example individuals guiding a computer image, a cursor, to locate a target) and not three-dimensional space. Individuals in this dissertation study were able to move their arm freely. The process when testing constructional ability is that the individual must be able to form a visual concept of an object and carry out the appropriate hand movements quickly. Speed of visual organization, as well as motor response, was being tested (Lezak, 1983). Another example of a visual-motor task is when individuals are asked to draw a clock. The clock drawing task has been designed to differentiate between normal elderly individuals and those with dementia and Alzheimer's disease

(Tuokko, 1992). Patients with mild AD made a greater number of errors in clock hand placement than normal controls (Esteban-Santillan, et al., 1998).

Additionally, Ross et al., (1996) found that patients diagnosed with Alzheimer's disease were unable to copy a complex figure and that patients drawing ability was poor. Furthermore, the ability to reproduce hand gestures and reaching for objects was impaired in these patients, and upon imaging, MRI scans revealed bilateral parietal lobe atrophy (Ross, et al., 1996).

Having individuals perform a task in three dimensions allows more freedom of movement and may relate more to tasks that individuals do on a daily basis in life than tasks which require individuals draw an object or move a cursor across a computer screen. Activities of daily living with visual-motor components include tying shoelaces, picking up objects such as eyeglasses or clothing, and washing dishes. Investigators explore many ways of illustrating visual-spatial and visual-motor deficits, including drawing, block design, and locating an object via computer mouse. In this dissertation, visual-motor functioning is being examined based on an individuals ability to reach for a target free of constraints and place four objects on a stand. This is an attempt to make the visual-spatial task more like everyday life or what an individual is required to do normally.

Literature Review - Estrogen Studies

Presently, there is an increased interest in determining the extent and the effects of estrogen on learning and memory. Estrogen is a female hormone and its principal function is development of female secondary sexual characteristics

during puberty, which include changes in the reproductive system, menstruation, and breast development. Receptors for estrogen are abundant in the hypothalamus where regulation of the hypothalamic-pituitary gonadal axis occurs (Handa, et al., 1994; Tierney & Luine, 1997). Receptors are also found in the developing cortex of rodents and nonhuman primates (Toran-Allerand, 1978; McEwen, 1976). In humans, estrogen receptors are found in the neocortex, hippocampus and nuclei of the basal forebrain (Osterlund, et al., 2000). At menarche estrogen levels increase due to stimulation by pituitary hormones transported through the blood stream. A mature ovarian follicle secretes estrogen. During a woman's reproductive life span, estrogen levels fluctuate due to monthly cycles and hormonal changes and at menopause, estrogen levels fall dramatically. Estrogen helps to prevent osteoporosis, osteopenia, and confers cardiovascular benefits during a woman's lifetime (Valverde, 1999; Palacios, 1999). There is evidence that estrogen is important in maintaining neural development, preventing neuronal cell loss, and increasing choline acetyltransferase activity (Simpkins, 1997; Tang, 1996; Luine, 1985). At menopause levels of estrogen drop and are associated with such symptoms as hot flashes, fatigue, sleep disturbances and irritability. Low levels of estrogen are associated with osteoporosis and there is an increased risk of cardiovascular disease (Vanin & MacLusky, 1997; Kirwan, 1997). That estrogens have a positive impact on the brain is supported by data that demonstrate an improvement in cognitive functioning in postmenopausal women on estrogen replacement therapy (Sherwin, 1998). It is also suggested that women on

estrogen have a reduced risk for Alzheimer's Disease (Pagannini & Henderson, 1996; Tang, et al., 1996; Kawas, et al., 1997).

Studies have examined the effects of estrogen on cognition in animals and humans. It has been demonstrated that individuals with AD have decreases in the level of acetylcholine in their brain and degeneration of cholinergic neurons (Giles, 1997). Addressing this issue, Luine (1985) examined the effects of estrogen on acetyltransferase activity. Acetyltransferase is the enzyme which synthesizes acetylcholine. She demonstrated that when gonadectomized female rats are given estradiol, there is an increase in choline acetyltransferase activity in the brain, particularly in the frontal cortex, the medial aspect of the horizontal diagonal band nucleus and the CA1 region of the dorsal hippocampus. In subsequent research, estradiol was found to have an enhancing effect on spatial memory in rats (Luine, 1994b). Likewise, estrogenic effects on the brain have been reported by Woolley et al., (1990) who measured effects of estrogen on dendritic spines during the female rats estrus cycle. Large differences were found between periods of high and low levels of estrogen. Dendritic spines on CA1 neurons were increased when estrogen levels were high (Woolley, et al., 1990). Gibbs (1994) has examined estrogen, and the role of choline acetyltransferase (ChAT) and nerve growth factor on memory and learning. Estrogen may enhance cognitive functioning by altering the expression of choline acetyltransferate and nerve growth factor, particularly in basal forebrain cholinergic neurons and in the hippocampus and cortex. Singh, et al., (1995) suggests that estrogen affects cholinergic systems by modulating levels of brain

derived nerve factor mRNA levels. Further supporting an enhancing effect of estrogen on spatial memory, Frick, et al., (2000) found age and gender effects for mice performing a visual-spatial task – the Morris water maze. In this paradigm animals were required to learn the location of a hidden, submerged platform in a small pool of water. The only cue given to the animal was its spatial relation to cues in the experimental room where the pool was placed. Researchers found female mice 25 months old displayed impaired visual-spatial reference memory when performing the Morris water maze. Mice 17 months old were less impaired than 25-month-old mice. All 25 month old mice had absent estrus cycles, while 80% of mice 17 months old displayed irregular estrus cycles, involvement of ovarian hormones is suggested. When comparing male and female mice 17 months old, a significant difference was found with females exhibiting more impaired spatial reference memory than males. No sex differences were found in mice 25 months of age.

When studying humans, researchers have demonstrated that postmenopausal women taking estrogen scored higher on tests of mental status than women who were not taking estrogen (Steffens, 1999; Sherwin, 1994). Sherwin (1997; 1998) has demonstrated that estrogen may help to maintain verbal memory in women, and enhance a woman's ability to learn new information. This research is supported by Jacobs, et al. (1998) who examined cognitive functioning in normal older women with a prior history of estrogen use. The findings of this study demonstrated an improved performance on verbal memory for prior estrogen users. In general, participants with a history of

estrogen use scored higher on tests of mental functioning than women with no history of estrogen use. Tang, et al., (1996) found a reduced risk for developing Alzheimer's Disease in women who reported taking estrogen for post-menopausal symptoms. Further, these researchers found that for individuals who developed Alzheimer's Disease the diagnostic age of onset was significantly later in women with prior estrogen use. Utilizing PET analysis, Resnick, et. al., (1998) found differences in cerebral blood flow activation between estrogen users and non-estrogen users. Cerebral blood flow was higher in estrogen users during figural memory tasks and women who received estrogen replacement scored better on neuropsychological tests than untreated women (Resnick, et al., 1998). During the figural memory tasks, interactions were found for the right parahippocampal and the inferior parietal regions of the brain. Increases were also seen in verbal and figural memory (Resnick, et al., 1998). Shaywitz, et al. (1999), also found increased activation of the inferior parietal lobe during a nonverbal task. Researchers concluded that estrogen had an effect on brain organization for postmenopausal women. In humans, estrogen may appear to be affecting parietal lobe functioning by acting as a neuromodulator (Berman, et al., 1997). It is suggested that it indirectly increases cerebral blood flow (Berman, et al., 1997). Brinton, et al. (1997), have found increases in the growth of neurons in the frontal, temporal, occipital and parietal region in vitro following addition of estrogens. Researchers hypothesized that it does this through an NMDA receptor-dependent mechanism. Supporting these findings, Diaz, et al., (2000) have found that women on estrogen replacement demonstrated

increased neuronal outgrowth in the hippocampus, basal forebrain, occipital, frontal, and parietal lobes.

Research on the relationship between estrogen and cognitive functioning is still in the early stages and its usefulness in preserving memory during aging is currently an active area of investigation. Thus far, the data suggests that women with decreased levels of estrogen are at greater risk for cognitive deficits and developing Alzheimer's Disease than men (Henderson, 1997). Sano (in progress) is currently attempting to determine whether giving estrogen to cognitively normal (postmenopausal) elderly women, with family histories of memory loss or Alzheimer's Disease, can delay the onset of memory loss or Alzheimer's Disease.

An area that is currently being investigated is the effect of estrogen on visual-motor integration and visual-spatial abilities. There is a large literature for the effects of estrogen on spatial memory on rats (Luine, 1998, 1994; Bimonte, 1997; Berry, 1997; O'Neal, 1996; Packard, 1996). An increase in spatial memory was found in male rats administered estrogen (Luine, 1994b) and enhanced acquisition of a spatial memory task found by Gibbs (1999). Luine (1998) found better spatial memory in estrogen treated ovariectomized rats compared to ovariectomized rats not administered estrogen on a radial arm maze performance task. Choice accuracy improved in estrogen treated rats after twelve (12) days of treatment. However with respect to human spatial memory, there is an ongoing debate as to whether estrogen enhances spatial performance or dampens it (Sherwin, 1994; Resnick, 1997). An additional question addresses

the role of progesterone in spatial memory. Sherwin (1994) has found evidence that estrogen may have a dampening effect on visual-spatial memory and progesterone an enhancing effect. Findings from a study by Resnick, et al., (1997) are contrary to Sherwin (1994) and suggest that estrogen may offer a protective effect on visual memory. Cognitively normal postmenopausal women treated with estrogen demonstrated better performance on a test of figures (BVRT) than non-treated women. Longitudinal analyses showed stable performance for women treated with estrogen (Resnick et al., 1997). Untreated women exhibited normal memory decline associated with age. Drake (2000) measured circulating levels of hormones and compared cognitive performance controlling for age, education and estrogen use. Results demonstrated increases in delayed verbal memory and retrieval when estradiol levels were high. Low levels of estrogen were related to improved immediate and delayed visual memory (Drake, 2000). No effects were found for progesterone, however the authors suggest that estrogen could affect cognition by enhancing some skills and depressing others (Drake, 2000). Frye, et al., (1995) have examined the effects of progesterone and results indicate that acquiring a spatial task took longer for female rats when GABA activated progesterone secretions were elevated.

Thus far, research in humans on the effects of estrogen and visual-spatial memory are contrary and inconclusive. The basis for estrogenic involvement and visual-spatial tasks in humans still needs to be addressed.

Verbal Memory and Visual-motor Performance

A secondary study of this dissertation is to examine the effects of estrogen replacement therapy among cognitively normal elderly women on tests requiring visual-motor skills. The data set used by Jacobs, et al. (1998), who reported a positive effect of estrogen use on tests of verbal memory, language and abstract reasoning abilities was used as a basis for these analyses.

Verbal memory and visual-spatial skill performance have been associated with parietal lobe functioning (Harmony, et al., 1999; Breier, 1998). Performance links to parietal lobe functioning have been found in the literature for verbal working memory and parietal-temporal areas of the brain (Harmony, et al., 1999). Harmony, et al., (1999) utilized EEG recordings and found frequency differences for arithmetic and controlled tasks. It is suggested that the parietal-temporal region may play a role in verbal working memory, which includes the rehearsal of information, storage, and production of speech. Breier et al., (1998) presented normal subjects with visually presented words while measuring magnetic flux of the scalp using magnetoencephalography (MEG). Researchers attempted to map out successive areas of cortical activation following the memory task with a whole head neuromagnetometer. The first area of activation was the occipital lobe, followed by the temporal area. Subsequently the temporal and parietal areas activated concurrently. Most of the activity measured was in the left cerebral hemisphere.

In the article by Jacobs, et al., (1998) significant effects of estrogen were found in the area of verbal memory for women with a prior history of estrogen

use during the postmenopausal period as compared to women who never used estrogen. Brain areas for verbal memory and language include the temporal lobe, parietal lobe and frontal lobe. Language and verbal areas of the brain are considered to be in the left hemisphere for the majority of the population. The parietal-temporal-occipital association cortex (Brodmann areas 39 and 40) also plays a role in the acquisition of language, as they are part of the pathway mediating language (Kandel, 1991). When portions of the pathway are damaged, comprehension, verbal output and retrieval are impaired (Kandel, 1991). Jonides et al. (1998) demonstrated a relationship between the parietal lobe and verbal memory. PET scan analyses were performed on normal subjects and subjects with lesions to assess regional blood flow (Jonides, et al., 1998). Conclusions suggested a possible link between the parietal lobe and brain areas which are involved in storage of short-term memory and retrieval of verbal information coded phonologically. There is evidence that individuals with Alzheimer's Disease who manifest inferior parietal lobe involvement have both impaired verbal memory as well as visual-spatial abilities (Keilp, et al., 1996).

Hagberg (1976) established a relationship between changes in cerebral blood flow to the brain and measures of cognitive ability. A battery of tests was administered to patients with presenile dementia. Results indicated that patients with impaired verbal abilities showed a reduction in blood flow to the occipital-temporal-parietal areas of the brain bilaterally (Hagberg, 1976).

It has also been suggested that individuals who have biparietal atrophy have a greater risk for developing Alzheimer's Disease (Fox, 1999). Since both

verbal memory and visual-spatial abilities have parietal lobe involvement, there may be a relationship between deficits in these areas. Individuals with impaired verbal memory may manifest some visual-spatial or visual-motor deficits.

Although both hemispheres of the brain have visual-spatial properties, performance is primarily associated with the right parietal lobe (Ratcliff, et al., 1973). Published results for this data set have found a relationship between estrogen use and verbal memory (Jacobs, et al., 1998). The analysis for this dissertation will attempt to determine whether performance on visual spatial tasks, associated with parietal lobe functioning, is enhanced in this sample of women by estrogen use.

Dissertation Hypotheses

The primary study hypotheses examined visual-motor performance differences in elderly women in relation to mental status score. We examined a constructional ability task (drawing) and a three-dimensional object assembly task (reaching for objects in space, grasping objects and object placement). A secondary study hypothesis examined the association between estrogen replacement and visual-motor performance in a population which exhibited significant differences in verbal memory based on estrogen replacement history. Hypotheses are as follows:

1. Individuals who score in the impaired range on a test of mental status have greater difficulty completing a constructional ability task and a three-dimensional object assembly task compared to individuals who score in the normal range, when age and level of education is controlled.

2. Individuals who score in the impaired range on a test of mental status make a greater number of object placements compared to individuals who score in the normal range, when age and level of education is controlled.

3. Individuals who score in the impaired range on a test of mental status display execution strategy errors when attempting an object placement task as compared to individuals who score in the normal range, when age and level of education is controlled.

4. Cognitively normal elderly women with a history of estrogen use will display significantly higher scores on tests of visual – spatial abilities as compared to cognitively normal elderly women with no history of estrogen use.

5. Cognitively normal elderly women with a history of estrogen use will have significantly less decline on tests of visual-spatial abilities longitudinally as compared to cognitively normal women with no history of estrogen use.

Summary

This chapter has presented introductory information about the dissertation, including the objectives, distinctive features, and background scientific information on visual-motor integration and hypotheses. Information has also been presented to support a relationship between mental status and estrogen use on the ability to perform visual-spatial tasks. The tasks have been shown to involve the parietal lobe function. There is evidence that visual-spatial tasks are affected by an individual's cognitive status, as measured by neuropsychological tests. One instrument widely used to assess mental status is the Mini Mental Status Examination (Folstein, 1975). The literature on estrogen replacement

therapy suggests a positive effect of estrogen use on cognition, particularly in the area of verbal memory.

Chapter II

Participant Sources, Evaluation Measures, And Dissertation Procedures

Methods Section

Overview

This chapter presents methodological approaches used to test the hypotheses of this dissertation. Topics addressed in this chapter fall into four sections: (1) sources of study participants, (2) subject screening and eligibility measures, (3) variables and operationalized definitions that support investigating the dissertation hypotheses, including procedures for measuring mental status and visual-motor integration, and (4) analytic design for distinguishing subjects tested. Information in this section is presented in two parts – methods and procedures for the primary study and methods and procedures for the secondary study.

Sources of Data

Data for this dissertation comes from two sources. For the primary study examining the relationship between mental status on visual-motor performance, data has been collected through New York Presbyterian Hospital and Hunter College by soliciting participants. For the secondary study of this dissertation examining estrogen use and its relationship to visual-motor performance, extant data from an on-going epidemiological study of aging and dementia in northern Manhattan, NY (P.I. Richard Mayeux, M.D; NIA P01AG07232), as reported by Jacobs, et al., (1998) of Columbia University College of Physicians and Surgeons, G.H. Sergievsky Center, New York, NY was used.

Primary Study

Study Participants

Subjects consisted of elderly women 65 years of age and older recruited from New York Presbyterian Hospital through existing clinical studies and from Hunter College solicited by flyers and personal contact. Sixty-seven subjects were screened; seventeen were excluded due to neurological/visual disorders leaving fifty subjects eligible to participate (Table 1). Subjects from New York Presbyterian Hospital (n=20) were from a sample of individuals receiving in-home health care in various regions of Brooklyn and the Bronx. In order to be eligible for in-home care, women had to have one or more deficits in activities of daily living. Activities of daily living consist of tasks such as the ability to dress oneself, groom or be able to feed oneself. This sample consisted of women who received in-home care due to either physical impairments or cognitive impairments. Physical impairment seen were individuals with one or two legs amputated, foot deformities, and paralysis below the waist. An elderly group of women, 65 years of age and older was recruited at various locations within Hunter College in Manhattan (n=30). The women were students pursuing college degrees. Educational levels for participants were between 8 and 19 years. Informed consent was obtained according to local IRB protocols.

Table 1

	Characteristics of Elderly Women in Primary Analyses Sample		
	Totals N (%)	Means	SD
Population (N)	50		
Age Distribution		78	8.3
65 - 74	19 (38%)		
75 – 85	18 (36%)		
86 +	13 (26%)		
Gender			
Female (%)	50 (100%)		
Race			
White	47 (94%)		
Hispanic	3 (6%)		
Education		13.4	2.6
8 to 12 years	25 (50%)		
13 plus	25 (50%)		
Handedness			
Right	49 (99%)		
Left	1 (1%)		

Subject Screening

A brief history was obtained from subjects to rule out visual defects/neurological impairments (APPENDIX 1). The subject's highest level of education was obtained.

Exclusion criteria consisted of patients with severe dementia (such that they could not comprehend instructions or perform screening tasks); hand or arm weakness; severe visual disorders such as cataracts or glaucoma; visual acuity less than 20/50; a diagnosis of neurological loss affecting nerves and muscles, such as amyotrophic lateral sclerosis (ALS) or Parkinson's Disease (PD); and education less than 8 years. Individuals were also excluded due to arthritis or hand/arm deformities.

A Snellen-like chart (MIS, 1997) was used to assess visual acuity of subjects. The chart is held 14 inches away from subjects, and subjects read lines of letters, from largest to smallest row possible. Each line is the equivalent of a specific visual acuity score. Visual acuity was recorded for each subject.

Individuals were given two motor tasks in order to rule out cerebellar deficits - opening and closing of the hand in a fist-like movement (20 times each); and finger dexterity - alternating movements of the thumb and opposition fingers opening and closing quickly (10 times) similar to Maeshima (1997).

A card containing drawings of four round objects was presented to subjects. The researcher presented to the participant a three-dimensional object of a particular size (a round ball) and asked subjects to select the drawing that best represented the size of the object. This task measures perception and

judgment, which should be intact. Subjects were excluded if they selected an incorrect representation of the object.

Mental Status Testing

The mMMSE (Stern, 1987, 1990) was used as a mental status-screening instrument (APPENDIX 2). The mMMSE is a modification of the MMSE (Folstein, 1975; Cockrell and Folstein, 1988) which is used as a dementia screening instrument (Richards, 1993). The Folstein mini-mental status examination (MMSE) is a 30-item test measuring various domains of cognitive ability. Individuals are asked a series of questions that assess attention, orientation, language, recall and memory. Subjects are given a specific number of points for correct answers. It is often used as a dementia-screening test for assessment of geriatric patients and has been used to document cognitive decline in dementia and delirium. Validity of the MMSE has been established by establishing correlations between electrophysiological, psychometric and neuroimaging methods (Cockrell and Folstein, 1988). Population based norms have been established for the MMSE by Cockrell and Folstein (1988) Crum, et al. (1993) and Ishizaki, et al., (1998). Interrater reliability has been established by Cockrell and Folstein (1998).

The mMMSE (Stern, et al., 1987) expands on the Folstein MMSE (1975), adding questions pertaining to digit span, language, memory and visual recognition. It measures language ability, orientation to time and place, calculation, recall, and language. Questions are asked such as the date, season, and the subject's location. For the mMMSE (Stern, 1993) additional items have

been added which require the subject to repeat a series of numbers forwards and backwards, repeat a sentence, and recall the current and four previous presidents of the United States. It also requires the subject to copy an additional figure, name ten items from the Boston Naming Test (Goodglass & Kaplan, 1972). Scores range from 0 to 57 with lower scores indicative of cognitive impairment. In a clinical diagnostic evaluation, the mMMSE is one measure that is used in conjunction with other screening measures, such as a neurological examination to assess current mental status. The mMMSE has demonstrated that it is a reliable and valid measure for assessing cognitive changes (Stern, et al., 1987). An individual would be considered impaired if he or she scored below 45. A score of 44 to 20 is considered mild to moderate impairment, 19 and under moderate to severe impairment. The mMMSE is administered according to the manual created by researchers at Columbia Presbyterian Medical Center (APPENDIX 3). As the mMMSE is sensitive to changes in cognition, it was used in this dissertation to assess global cognitive status for all participants. Two drawing items measuring constructional ability were subtracted from individual scores, leaving 55 as the highest possible score. This was done to avoid confounding the results for object assembly. A cutoff score of 44 or below was used to categorize individuals as impaired. This score was derived from a formula equating scores from the Columbia mMMSE (Stern, 1987) to the Folstein MMSE (1975). It is the equivalent of a score on the MMSE of 23 or below, which is the impaired range.

Normative scores for neuropsychological measures are listed in Table 2.

Table 2– Normative scores for neuropsychological measures

		Normal Score	Cutoff Score	Maximum
Mental Status	mMMSE	45-55	<45	55***
Construction	Rosen Drawing Test (5-item)	3-5	<3**	5
	Rosen Drawing Test (15 item)	12-15	<12**	15
	BVRT multiple choice Matching	8-10	<8**	10

** Median scores of the primary study sample
*** Two constructional items were omitted from the maximum score.

Visual-Motor Integration Testing

The Stanford-Binet Bead Memory test (1986), a subscale of the Stanford Binet Intelligence scales, was used as a three-dimensional visual-motor integration task. The test consists of four objects of varying shapes, sizes and colors that are to be placed on a six-inch stand. For this dissertation, only blue beads were used. Subjects were asked to grasp each bead and to place it on a stand. Variables examined were execution strategy errors, average number of object placements, and ability to complete the task. Execution strategy errors are the subjects' ability to properly grasp each object. Errors in execution strategy were assessed by observing whether the subject appropriately extended the arm to the proper location (i.e. did not over/under extend the arm), and grasped the object in such a way that readjustment of the hand upon the object was not necessary. Each bead has a hole in the center to be placed on the stand. If an individual grasps the object so as to obstruct the hole, it is counted as an error. The number of attempts at placing each bead on the stand was

obtained and analyzed (averaged between the four beads). Two individuals analyzed videotapes of subjects performing this task. One rater was blinded to individuals' mental status score. Inter-rater reliability was .938. Raters examined videotapes and measured object assembly categorized in three ways. The number of object placements were scored by counting the number of attempts a subject made placing each bead on a small stick with the dominant hand. Four attempts is a perfect score. Each bead has a small hole in the center in which to slide it down the stick. If a subject reached, picked up the bead, and did not properly slide the bead on the stick, it was counted as an object placement until a successful attempt was made. Once a successful attempt is made, the subject was asked to pause, then select the next bead. This procedure was done for all four beads with raters counting the number of attempts for all four beads individually. An example of an object placement error might be reaching and "missing" the stick with the hand. The number of object placements was complete when the bead slid down the stick through the hole. Once the subject has completed the task, the average number of attempts for all four beads was determined.

When coding for completion of the bead task, raters assessed whether the individual was able to complete placing all four beads on the stand. Individuals were categorized as either able to complete the task or unable to complete the task. The third way object assembly was scored was by examining execution strategy. Raters focused on the individuals hand and arm orientation to assess overreaching, underreaching, or deficits in picking up an object. If the object

needed to be readjusted in the hand, it was counted as an execution error. Individuals were categorized as either displaying execution strategy errors or having no execution strategy errors.

The Rosen Drawing Test (Rosen, 1981) is a drawing test of visual-motor integration (APPENDIX 4). Subjects are asked to draw fifteen progressively more difficult figures using their dominant hand with no time limit. Scoring ranges from 0 to 15. Abnormal drawings are those in which lines and vertices are inaccurate according to scoring criteria. Points of connection were analyzed in order to measure constructional ability quantitatively. The lower the score, the more impaired the subject. Instructions and scoring are based on a model formulated at Columbia University Sergievsky Center. (APPENDIX 5).

Design and Procedure

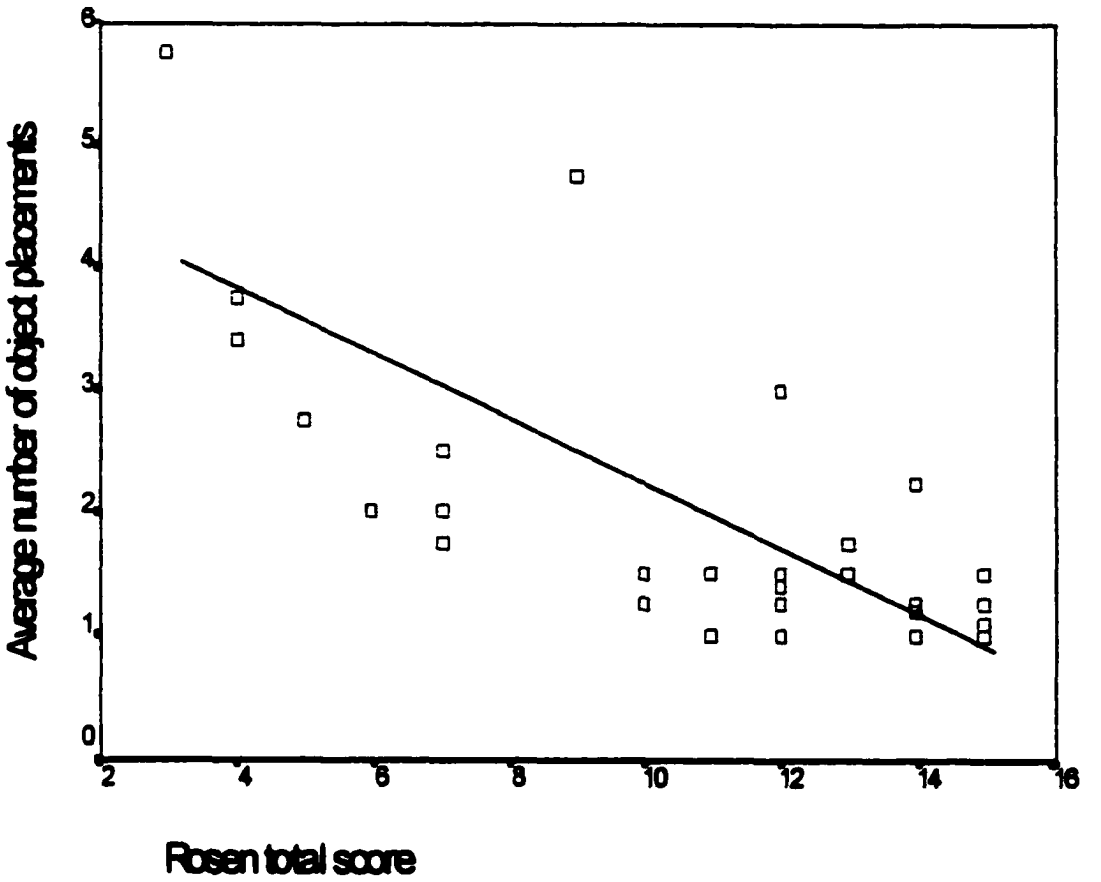
For each session, testing lasted from one – two hours, depending upon the subject's mental status. Once informed consent was read and signed (APPENDIX 6), a brief history was obtained and subjects were screened for visual acuity, motor functioning and perceptual ability. If patients were eligible to participate in the study, three tests were administered: a three-dimensional object assembly task, the Rosen Drawing test and the mMMSE. The three-dimensional object assembly task and the Rosen Drawing test assess visual-motor integration. Mental status was assessed by the mMMSE.

Subjects were seated at a table and a graph pad placed in front of them. The graph pad is 17" x 11" and has a white background with light blue squares measuring 4 per inch. The pad was placed directly in front of the subject,

approximately 20cm distance. The bead stand was placed at the midline of the subject. The stand height is approximately chin height. Four different shaped blue beads were placed on the graph pad in the following order - cone, ball, cylinder, and saucer. Horizontal distance between beads was 9 cm. The subject was asked to place each bead on the stand.

Subjects were videotaped performing the Stanford Binet Bead Memory Test with their dominant hand. The test was used as a means of detecting deficits in visual-motor integration, particularly in execution strategy, average number of object placements, and ability to complete the task. Scoring the subject's hand orientation and finger aperture was obtained by analyzing each subject's videotape. To determine whether the object assembly task was a valid measure, a Pearson correlation was computed comparing it to the Rosen drawing test. The relationship between tests is -. 704, $p<.05$. (Figure 1).

Figure 1 – Rosen total scores by average number of object placements.



Subjects were then given the Rosen Drawing Test (Rosen, 1981) as a quantitative measure of visual-motor integration/impairment. This is a 15-item figure copy test, with items ranging in difficulty from simple geometric designs to overlapping 3-dimensional Euclidean figures. Thereafter the mMMSE (Stern, 1987) was administered to subjects as an indicator of the subject's current mental status.

Once subjects completed the testing, (and for all analyses) they were categorized into groups based on their mental status score. The mMMSE score range is from 0 to 55 and individuals receive points for each correct response. Scores of 44 and less were considered in the cognitively impaired range and scores above 44 were considered cognitively normal. This cutoff score was derived based upon scoring criteria from the MMSE (Folstein, 1975; Stern, 1997). On the original Folstein examination a score of 23 or below is indicative of impairment. The equivalent score on the mMMSE is 44 (.55 times an individual mMMSE score less .74). The correlation between the mMMSE and mMMSE is .9998. T-tests were done to compare cognitively normal and cognitively impaired participants' number of object placements and Rosen Drawing test scores. Chi-square analyses were done for mMMSE groups based on three outcome measures - completion of the object assembly task, execution strategy errors and completion of the Rosen Drawing test.

Sample distributions of cognitive status stratified by demographic variables of age and education are presented in Table 3 and Table 4. For the relationship of age and level of education to visual-motor tests/tasks, median

cutoff scores were used to compare groups of subjects. Chi-square analyses were done for completion of the object assembly task, execution strategy errors and completion of the Rosen Drawing test. Analyses were performed on SPSS for Windows (v.9, SPSS, Inc., Chicago, IL)

Table 3

Groups formed by mMMSE based on Age

		Age		Total
		<77	77 or Above	
Groups:	Impaired	4	18	22
	Normal	21	7	28
Totals		25	25	50

Table 4

Groups formed by mMMSE based on Education

		Education groups		
		7-12	13 and up	Total
Groups by	Impaired	15	7	22
	Normal	10	18	28
Totals		25	25	50

Secondary Study

Study Participants

The subject pool was 883 non-demented women from a community-based sample in northern Manhattan with a clinical dementia rating of 0 (Rubin, et al.,

1989). Women were recruited randomly from a listing of Medicare recipients or were volunteers from senior citizen centers and senior housing locations. Out of 883 non-demented women, 156 were excluded, leaving 727 women remaining in the sample. Women were excluded due to significant neurological impairment or incomplete information. The ethnicity of this sample is mixed and consisted of the following: 200 African American women (27.5%), 200 Caucasian women (27.5%), 318 Hispanic women (43.7%) and 9 other (1.2%). No significant differences in race were found between either source of participants.

Cognitive Testing

Data from a brief but comprehensive neuropsychological battery were available on all participating. The battery included tests of verbal memory (the Selective Reminding Test), orientation, abstract reasoning, attention and construction. For the Selective Reminding Test, individuals are required to learn a list of 12 unrelated words over 6 trials. After each trial, subjects are reminded of the words they did not recall. Then individuals are again asked to recite the entire list of words. After a delay of 15 minutes, individuals are again tested on the 12 words by being asked to recall as many words as possible. Orientation was assessed by administering ten items from the Mini Mental Status Examination (Folstein, 1975). Abstract reasoning and concept formation was assessed by administering the Similarities subtest of the Wechsler Adult Intelligence Scale – Revised (WAIS-R) (Wechsler, 1981). Word finding ability was assessed using the Boston Naming Test (Kaplan, et al., 1983).

Visual-motor Integration Testing

From this neuropsychological battery, data were available on three visual-spatial tasks: recognition and matching of figures from the Benton Visual Retention Test (BVRT – Appendix 7) and the Rosen Drawing Test five-item modification (Appendix 8). A multiple-choice version of the Benton Visual Retention Test (BVRT; Benton, 1955) was used to assess nonverbal memory. Subjects viewed a geometric design for 10 s. It was then removed from view, and the subject was asked to recognize the design in a four-choice multiple-choice array. Stimuli corresponded to Form D of the original Benton Visual Retention Test. For the matching task, the individual was required to identify a target geometric design from a four-choice multiple choice array, which is presented simultaneously (APPENDIX 7). The Rosen Drawing Test (long form) has been used in the primary study of this dissertation as a test of constructional ability. The modification on which data was available for this cohort consisted of five items instead of the usual 15 drawings. Individuals are asked to reproduce drawing and are scored based on their accuracy (APPENDIX 8). Individuals receive a point for each correct drawing, up to a maximum score of five. Similar to prior published analyses for this data set, age, education level and ethnicity are treated as covariates for all analyses. Analyses were performed on SPSS for Windows (v.9, SPSS, Inc., Chicago, IL)

Design and Procedure

Data were obtained from a community based epidemiological aging and dementia study of women in northern Manhattan. Physicians at Columbia

Presbyterian Medical Center administered physical and neurological examinations to each subject. A battery of neuropsychological tests assessing memory, abstract reasoning, visual-spatial abilities, and language were also administered. Medical histories were obtained for subjects, including information about current and past estrogen use.

Multiple analysis of covariance (MANCOVA) analyses were performed for the three outcome measures – Rosen Drawing Test, Benton Visual Retention Test (recognition condition), and Benton Visual Retention Test (matching condition) based on hormone use history. Thereafter, post hoc univariate analyses were performed for the three outcome measures. Analysis of the data was performed in two ways. One analysis examined two groups of women – women who have taken estrogen at least once as compared to women who have never taken estrogen. A second analysis examined three groups of women – women who have never taken estrogen; women who have less than a year of estrogen use and women who have taken estrogen one year or more. An alpha level of .016 was used for the three post-hoc univariate analyses in order to avoid a false positive result, which might have occurred performing multiple univariate analyses. Repeated measures ANCOVAs were performed to assess change over time on the outcome measures (i.e. Rosen Drawing Test and Benton Visual Retention Test).

One question addressed is whether women who have taken estrogen score significantly different from women who have never taken estrogen on visual-spatial tests. The second question addressed is whether women who

have taken estrogen score significantly different from women who have never taken estrogen on visual-spatial tests over time.

Summary

This chapter has presented the methodology used in conducting the primary and additional secondary study. The primary study examined the relationship of mental status on visual-motor performance. Once women were recruited and found eligible to participate, tests were administered, including a test of mental status. Scores on this test determined whether women were categorized as cognitively normal or cognitively impaired. Subjects were seated in front of a graph pad, and a test of visual-motor integration performed. Subjects were observed and assessed based on their ability to complete this test as well as a test of drawing. The average number of object placements was determined and scored for each individual. Scores were obtained for a drawing test of visual-motor integration. Subjects were assessed based on their ability to complete the object assembly task and the Rosen Drawing test. Subjects hand grasp was also observed to detect execution strategy errors.

The secondary study of this dissertation examined scores on the 5-item Rosen Drawing Test and Benton Visual Retention Test from a different data set. Subjects were categorized according to estrogen use history – having taken estrogen, never having taken estrogen; estrogen use < 1 year and estrogen use > 1 year. Analyses were done to determine significant differences among the groups. Analyses attempted to examine whether women displayed visual-spatial deficits based on hormone use group. Also addressed were whether

women (in each hormone group) had less decline over time on visual spatial tasks.

Chapter III

Analyses and Results

Overview

The primary study of the dissertation attempted to determine whether there was a relationship between mental status score and visual-motor performance. The relationship between tests of constructional ability (Rosen Drawing Test) and object assembly (execution strategies, average number of errors on object placement, completion of object task) to mental status (mMMSE) was examined. If hypotheses are supported, constructional ability and the object assembly task should both be related to mental status. Both tasks require visual-motor and visual-spatial abilities to properly execute the movement.

The secondary study of this dissertation was to determine the relationship between estrogen use and visual-motor functioning. In a prior study, women who never used estrogen replacement scored lower on test of verbal memory. From an anatomical perspective, verbal memory and visual-spatial abilities have been linked to parietal lobe functioning. Analyses were conducted to determine if in this sample of women visual-motor performance was also affected.

Results – Primary Study

Ability to perform tests of constructional ability (Rosen Drawing Test) and object assembly (execution strategies, average number of errors on object placement, completion of object task) and scores of mental status (mMMSE) was investigated. A major brain area for visual-motor integration is the parietal lobe. Activation of the parietal lobe is associated with visual-motor performance.

Tasks in this dissertation required normal visual-motor abilities to properly execute the movement. Demographic information for age and education are also presented and controlled for. Dependent measures are average number of object placements, Rosen drawing score, completion of the object assembly task, completion of the Rosen Drawing test and execution strategy errors. Neuropsychological characteristics of subjects for the Rosen Drawing Total Score and average number of object placements are presented in Table 6.

Table 6– Neuropsychological Characteristics of Subjects for Primary Study

Neuropsychological characteristics of subjects for primary study

Groups formed by mMMSE		Rosen total score	# of object placements
impaired	N	18	14
	Mean	5.6111	2.7293
	Std. Deviation	4.5522	1.6199
normal	N	28	28
	Mean	12.5714	1.3143
	Std. Deviation	2.4560	.3288
Total	N	46	42
	Mean	9.8478	1.7860
	Std. Deviation	4.8211	1.1658

Forty-two subjects (84%) were able to complete the object assembly task as compared to 8 subjects (16%) who were unable to complete the task ($t=3.67$, $p<.01$). Subjects categorized as impaired displayed a greater number of object placements (2.729) as compared to women categorized as normal (1.314). When examining the Rosen Drawing test, 46 subjects (92%) were able to complete the test as compared to 4 (8%) who were unable to complete the test. Subjects categorized as impaired had an average drawing score of 5.61 as compared to 12.57 for women categorized as normal ($t=-5.95$, $p<.01$).

Pearson correlation coefficients were calculated to examine the association between mental status score, and average number of object placements. Chi square analyses and independent sample t-tests were performed to assess the relationship between mental status score, age and education on visual-motor tests. Scores for mental status ranged from 0 to 55. Individuals who were unable to complete the mMMSE test were given an overall score of 0. Age for subjects ranged from 64 to 98, with a mean age of 78.2. Education ranged from 8 years to 19 years, with a mean age of 13.4.

Separate Pearson chi-square analyses for age and education were conducted for execution strategy errors and completion of the bead task. Age and education were divided into two categories by taking a median split for each. A 2 x 2 Pearson chi square analyzing age and execution strategy errors yielded a significant difference between groups, X^2 (1, N = 48) = 8.042, p<. 01. This suggests that execution strategy errors are not independent of age. Twenty-three individuals under age 77 were able to grasp beads appropriately as compared to thirteen 77 or older. No significant results were found comparing age to completion of the bead task. No significant results were found comparing level of education to execution strategy errors or completion of the bead task.

Mental Status Effects

Hypothesis 1. Individuals who scored in the impaired range of a test of mental status display greater difficulty completing a three-dimensional object assembly task than individuals who score in the normal range, when age and level of education are controlled.

Analysis and Results: A 2 x 2 Pearson Chi Square analysis was done to examine whether mental status (impaired vs. normal) was related to completion of the object assembly task. Analysis yielded a significant difference between groups, X^2 (1, N = 50) = 8.98, p<. 01. One cell has an expected count of less than five. A Fisher's exact test was done and yielded a significant result, p<. 01. Results suggest a relationship between cognitive status and whether individuals could complete the object assembly task (Table 6). Two individuals refused to complete this task, and were placed in the no category.

Groups formed by mMMSE * Completed bead task Crosstabulation

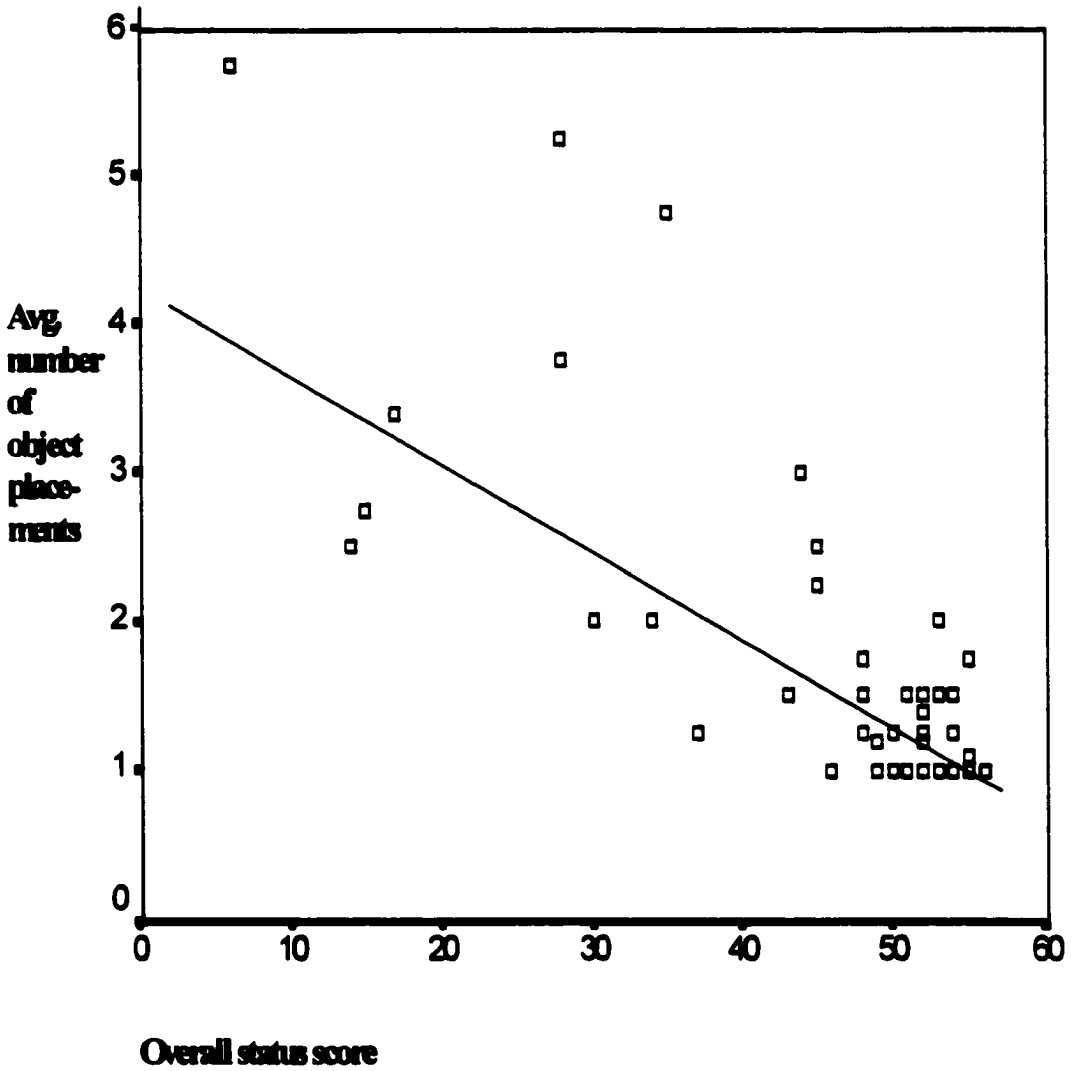
			Completed bead task		
			no	yes	Total
Groups formed by mMMSE	impaired	Count	8	14	22
		Expected Count	3.5	18.5	22.0
		Residual	4.5	-4.5	
	normal	Count	0	28	28
		Expected Count	4.5	23.5	28.0
		Residual	-4.5	4.5	
Total		Count	8	42	50
		Expected Count	8.0	42.0	50.0

Hypothesis 2. Individuals who score in the impaired range on a test of mental status produce a larger average number of object placements than individuals who score in the normal range, when age and level of education are controlled.

Analysis and Results: A Pearson correlation coefficient was calculated to determine whether a relationship existed between the mMMSE and average number of object placements. A strong negative correlation resulted indicating

that the greater the number of object placements subjects performed, the lower the mMMSE score (r=-. 748, p<. 001). (Figure 2).

Figure 2 – mMMSE scores by average number of object placements



A high number of object placements is indicative of difficulty executing the task, and a low score on the mMMSE is indicative of cognitive impairment.

An independent samples t-test was done to examine the relationship between mental status and average number of object placements. Eight individuals are not included in this analysis because they did not complete the object placement test. Of those eight individuals, two were refusals. All eight individuals were from the cognitively impaired group. Thirty-three percent of subjects were categorized as cognitively impaired (n=14) and demonstrated an average of 2.73 object placement attempts compared to sixty-six percent of subjects who were categorized as cognitively normal (n=28). Normal individuals demonstrated an average of 1.31 object placement attempts. The difference was found to be significant: $t(40) = 4.49$, $p < .01$ (Table 7).

Table 7

Group Statistics

	Groups formed by mMMSE	N	Mean	Std. Deviation	Std. Error Mean
AVG#ERR	impaired	14	2.7293	1.6199	.4329
	normal	28	1.3143	.3288	6.214E-02

To provide a validation measure for object placement, an independent sample t-test was done to examine the Rosen Drawing Test overall score and two groups of subjects: subjects who were categorized as cognitively impaired (based on mMMSE score) versus subjects categorized as cognitively normal. Results were consistent with object placement analyses. Fifty-one (51%) percent of subjects were categorized as cognitively normal (n=28) and demonstrated an

average score of 13 on the Rosen Drawing test as compared to thirty-nine percent of subject categorized as cognitively impaired (n=18) who demonstrated an average score of 5.6 on the Rosen Drawing test. Four individuals refused to perform this test. The results for this comparison were significant: t (44) = -6.7, p<. 01. (Table 8)

Table 8

Group Statistics

	Groups formed by mMMSE	N	Mean	Std. Deviation	Std. Error Mean
ROSTOTAL	impaired	18	5.6111	4.5522	1.0730
	normal	28	12.5714	2.4560	.4641

Hypothesis 3. Individuals who score in the impaired range on a test of mental status display more execution strategy errors when attempting an object placement task as compared to individuals who score in the normal range, when age and level of education are controlled.

Analysis and Results: A 2 x 2 Pearson Chi Square analysis was done and yielded a significant difference between groups, X^2 (1, N = 48) = 22.4, p<. 001. This suggests that execution strategy errors are not independent of mental status score. There is a relationship between mental status and whether individuals properly grasp objects (Table 9). One hundred percent (100%) of normal individuals grasped appropriately. Sixty percent (60%) of impaired individuals had execution strategy deficits. Two individuals refused to perform the object assembly task.

Table 9

Groups formed by mMMSE * planning errors? Crosstabulation

			planning errors?		
			yes	no	Total
Groups formed by mMMSE	impaired	Count	12	8	20
		Expected Count	5.0	15.0	20.0
		Residual	7.0	-7.0	
	normal	Count	0	28	28
		Expected Count	7.0	21.0	28.0
		Residual	-7.0	7.0	
Total		Count	12	36	48
		Expected Count	12.0	36.0	48.0

Secondary Study

This section presents the results for the secondary study of this dissertation. The effects of estrogen use in postmenopausal women on visual motor abilities have been analyzed. The literature has been mixed as to whether estrogen enhances or dampens visual-spatial abilities in women. Two hypotheses with accompanying results are presented. For statistical analyses, age, ethnicity and education were used as covariates. Subject characteristics are presented in Table 10. Women in this study were all considered cognitively normal.

Table 10

Characteristics for Elderly Women in Secondary Study

	Never used estrogen	Ever used estrogen	Used estrogen ≤ 1 yr.	Used estrogen > 1 yr.
# of women	646 (89%)	81 (11%)	44 (6%)	37 (5%)
Age at initial Evaluation* (y)	74.3 ± 6.8	73.8 ± 7.4	75.2 ± 7.2	72.2 ± 7.4
Education	9.1 ± 4.5	11.0 ± 4.5 **	10.0 ± 4.5	12.2 ± 4.2**

* Values are means ± SD
** Significantly different from never users ($P < .05$)

Overall women with no history of estrogen use completed 9.1 years of education as compared to 11.0 for women who had ever used estrogen. Overall, years of formal education were higher for women reporting estrogen use greater than one year. There were no differences between women with and without estrogen use histories in terms of age.

727 women were included in this analysis of which 81 had used estrogen. Information about dosage was not obtained from women. Out of 727 women, 81 reported ever using estrogen. The average duration for women who reported taking estrogen was 4.55 ± 8.64 years and the median was 1 year. Out of 81 women, 37 (5% of the total sample) had reported using estrogen greater than one year (mean = 9.83 years). Forty-four women (6% of the total sample) reported using estrogen one year or less. At the time of evaluation 12 women (2% of the total sample) reported current estrogen use. The majority of women received estrogen replacement at menopause. The time period since last estrogen use and cognitive evaluation for women who reported a history of

estrogen use was 24.5 ± 11 years. The distribution of women by neuropsychological test is provided in Table 11.

Table 11

Means and SD's on Neuropsychological Measures of Construction

	Never used Estrogen		Ever Used Estrogen		Estrogen use ≤ 1 yr.		Estrogen use > 1 yr.	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Rosen Drawing Test	2.74	1.08	3.16	1.12	2.84	. 96	3.54	1.19
Benton Recognition	6.61	2.15	7.32	1.97	6.93	1.74	7.78	2.14
Benton Matching	8.01	1.9	8.85	1.57	8.5	1.59	9.27	1.45

There was no significant relationship between constructional abilities (Rosen Drawing test and Benton Visual Retention Test) and when women last used estrogen covarying for age at time of evaluation (r = -. 0.6 to .02, p= .63 to .87).

Estrogen Effects

Hypothesis 4. Women with a history of estrogen use will display significantly higher scores on tests of visual–spatial abilities as compared to normal elderly women with no history of estrogen use.

Analysis and Results: 3 groups: There was a suggestion of a dose effect such that women with no history of estrogen use scored lower on all neuropsychological measures as compared to women who had used estrogen for less than one year who scored lower than those who had used estrogen for more than one year (Table 11). Nevertheless, results of the MANCOVA

comparing these three groups on the Rosen Drawing Test and BVRT (recognition and matching) were not significant ($F = 1.196$, $p > .05$).

Post-hoc ANCOVA analyses comparing three groups of women on the Rosen Drawing test yielded no significant main effect comparing women who have never taken estrogen, women who have taken estrogen one year or less and women who have taken estrogen greater than one year for the Rosen Drawing Test, $F (2, 722) = 3.16$, $p = .043$ (effect size = .009, observed power = .606). Although not significant, women with no history of estrogen use had a mean Rosen Drawing test score of 2.74 as compared to 2.8 for women with a year or less of estrogen use and 3.2 for women with greater than one year of estrogen use (Table 11).

ANCOVA data comparing three estrogen use groups on the Benton Visual Retention Test (recognition condition) yielded no significant differences comparing women who had never taken estrogen, women who had taken estrogen one year or less and women who had taken estrogen greater than one year, $F (2, 718) = .243$, $p > .05$ (effect size = .005, observed power = .446).

ANCOVA data comparing three estrogen use groups on the Benton Visual Retention Test (matching condition) did not yield a significant difference comparing women who have never taken estrogen, women who had taken estrogen one year or less and women who had taken estrogen greater than one year, $F (2, 724) = .678$, $p > .05$ (effect size = .002, observed power = .165). Significant differences were found in the error variance between the groups;

therefore, prior to analysis data for this variable were transformed adding a constant of five to subjects' scores and using a log function.

Analysis and results: 2 groups: Results of the MANCOVA comparing two groups of women, estrogen users to women who never took estrogen, while statistically controlling for the effects of age, education and ethnicity, did not yield a significant result, ($F = 1.089$, $p > .05$).

Post-hoc ANCOVA analyses comparing estrogen never users and ever users yielded no significant results for the Rosen Drawing Test, $F (1, 722) = 3.33$, $p = .068$ (effect size = .006, observed power = .535. Women with no prior history of estrogen use had a mean Rosen Drawing score of 2.74 as compared to 3.16 for women with a history of estrogen use (Table 11).

Results of the ANCOVA for the Benton Visual Retention Test (recognition condition) yielded no significant effects comparing women who have taken estrogen to women who have never taken estrogen $F (1, 718) = .465$, $p> .05$. (effect size = .001, observed power = .101).

Results of the ANCOVA for the Benton Visual Retention Test (matching condition) yielded no significant effect comparing women who have taken estrogen to women who have never taken estrogen $F (1, 725) = .970$, $p> .05$. (effect size = .001, observed power = .166). Means and standard deviations are listed in Table 11. Because there were significant differences in the error variance between groups, the data were transformed, adding a constant of 5 to each subjects' score and using a log function.

Hypothesis 5. Cognitively normal elderly women with a history of estrogen use will show less decline on tests of visual-spatial abilities longitudinally as compared to cognitively normal women with no prior estrogen use.

Overall, results for the two and three group repeated measures ANCOVAS on the Rosen Drawing test, BVRT Matching Test and BVRT Recognition Test yielded no significant results. Results for each comparison are listed below.

Analysis and Results: Rosen Drawing Test

Follow-up data was available for 519 cases and is presented in Table 12. Repeated measures ANCOVA examining test scores over time for women who had taken estrogen compared to women who had never taken estrogen did not yield a significant result, $F(1, 517) = .37$, $p > .05$ (Figure 3).

Figure 3 – Repeated measures ANCOVA for Rosen Drawing Test comparing Estrogen Users and Estrogen Never Users over Time

F (1, 517)=. 37, p>. 05

Repeated measures ANCOVA examining estrogen use over time for women who have never taken estrogen, taken estrogen one year or less, or taken estrogen one year or more did not yield a significant result, F (2, 516)=. 70, p>. 05 (Figure 4).

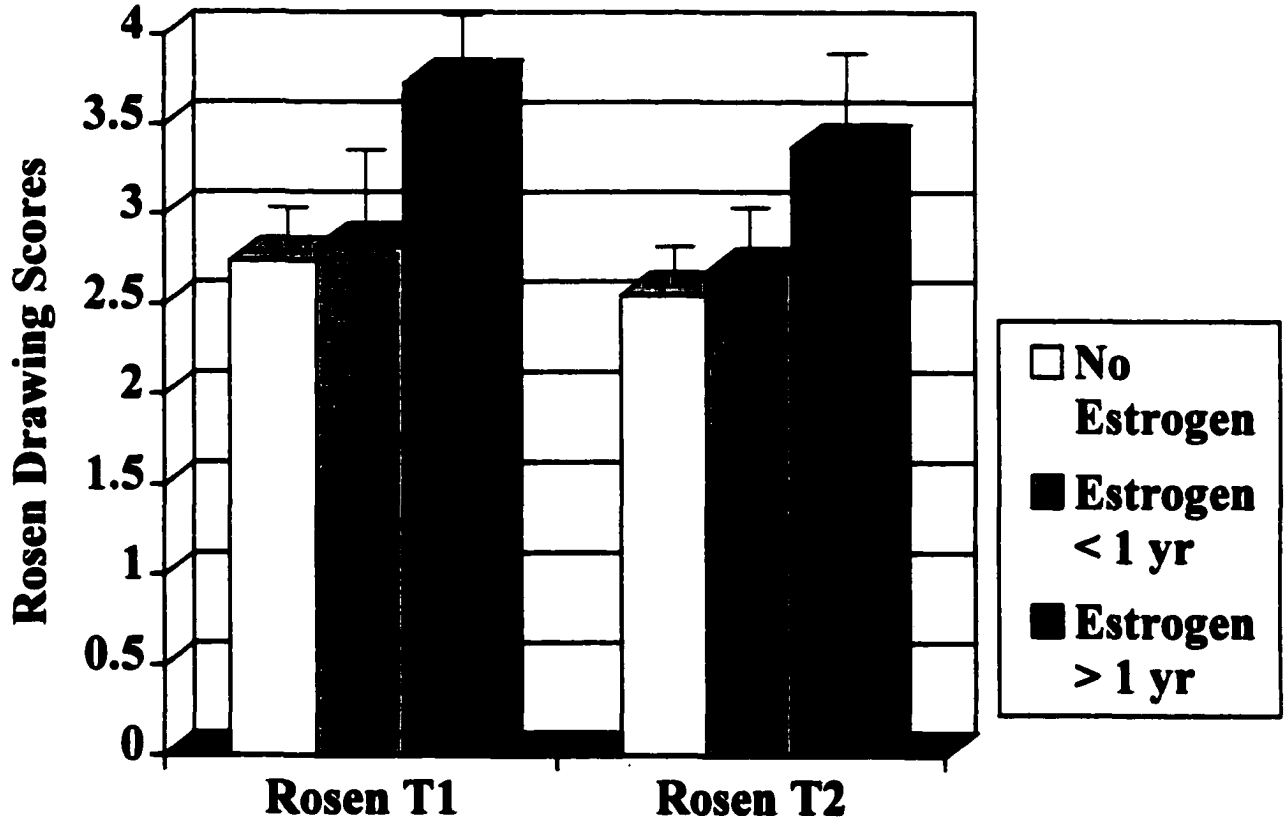
Table 12

Means and SD's on Neuropsychological Measures of Construction Over Time

		Never used Estrogen		Ever Used Estrogen		Estrogen use ≤ 1 yr.		Estrogen use > 1 yr.	
		T1	T2	T1	T2	T1	T2	T1	T2
Rosen Drawing Test	Mean	2.74	2.55	3.24	3.00	2.82	2.68	3.54	1.19
	SD	1.12	1.07	1.11	.99	1.00	.88	1.05	1.00
Benton Recognition	Mean	6.59	6.53	7.56	7.66	6.97	7.03	8.23	8.37
	SD	2.16	2.24	1.80	1.88	1.80	1.82	1.57	1.71
Benton Matching	Mean	7.92	8.28	9.00	9.17	8.44	8.94	9.63	9.43
	SD	1.94	1.89	1.46	1.12	1.74	1.23	.61	.94

T1 = baseline visit
T2 = follow up visit (at 2 years)

Figure 4 - Repeated measures ANCOVA for Rosen Drawing Test comparing Estrogen Users < 1 yr., Estrogen Users > 1 yr. and Estrogen Never Users over Time

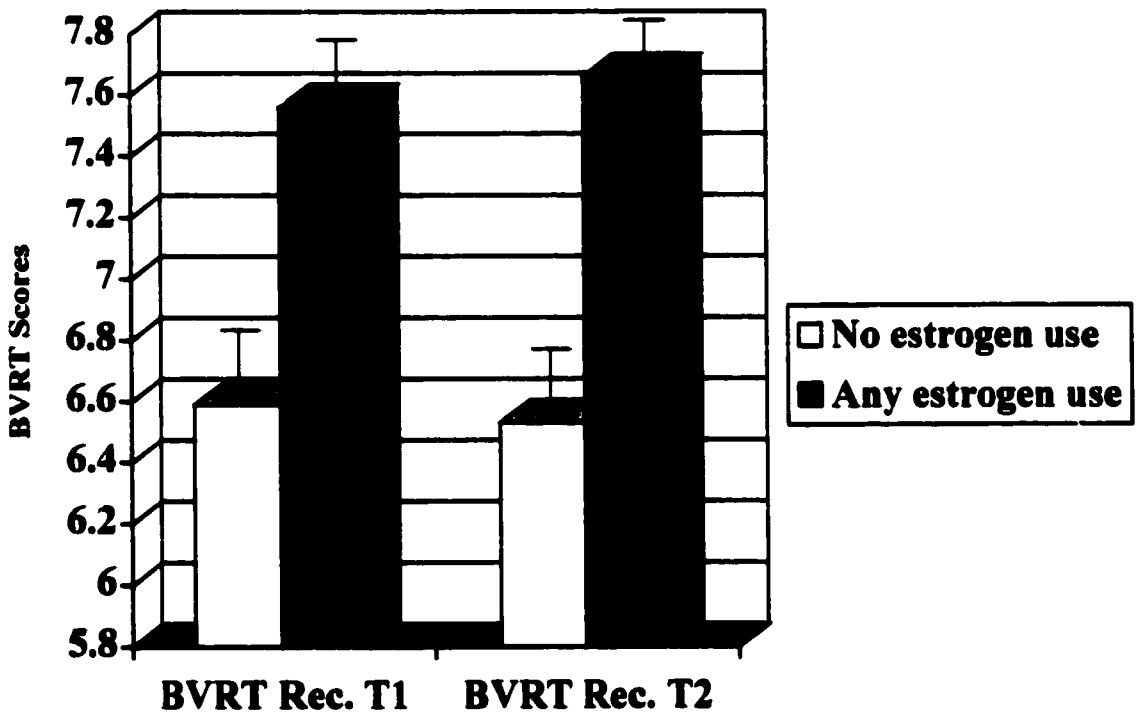


F (2, 516)=. 70, p>. 05.

Analysis and Results: Benton Visual Retention Test

Follow-up data was available for 515 subjects for the BVRT recognition condition. Repeated measures ANCOVA examining BVRT Recognition Scores over time for women who had taken estrogen compared to women who have never taken estrogen did not yield a significant result, F (1, 513)=. 31, p>. 05 (Figure 5).

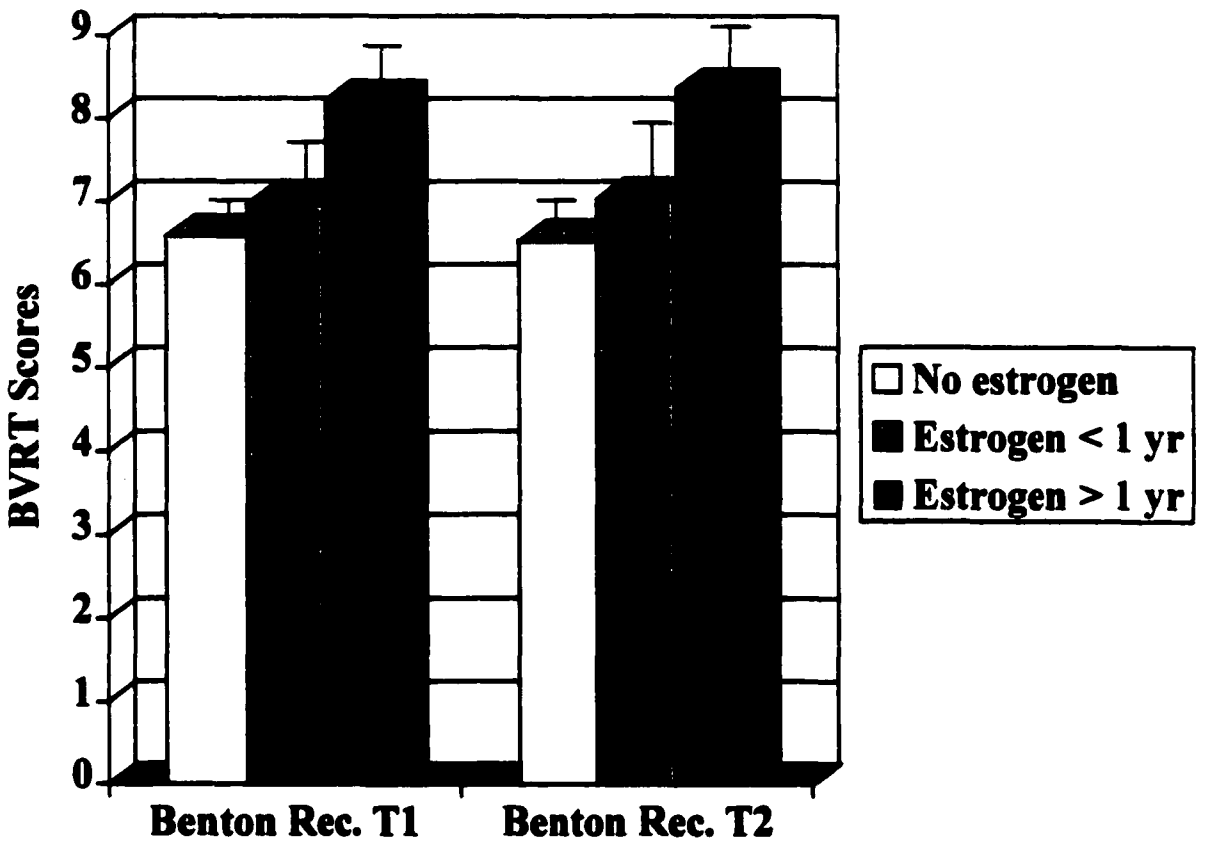
Figure 5 - Repeated measures ANCOVA for BVRT (recognition) comparing Estrogen Users and Estrogen Never Users over Time



F (1, 513)=. 31, p>. 05.

Repeated measures ANCOVA examining BVRT Recognition over time for women who had never taken estrogen, taken estrogen one year or less, or taken estrogen one year or more did not yield a significant result, $F(2, 509) = .16$, $p > .05$ (Figure 6).

Figure 6 - Repeated measures ANCOVA for BVRT (recognition) comparing Estrogen Users < 1 yr., Estrogen Users > 1 yr. and Estrogen Never Users over Time

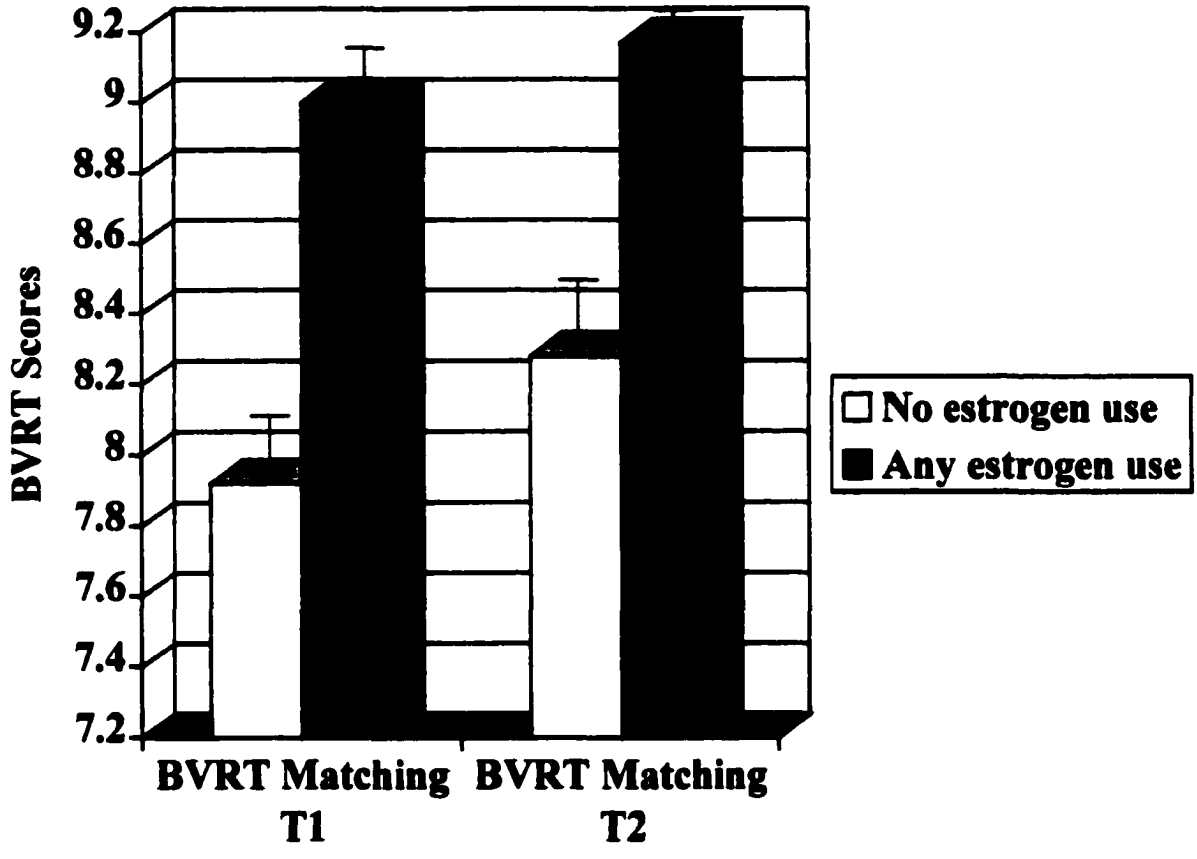


F (2, 509)= .16, p>. 05.

Analysis and results: BVRT Matching

Follow-up data was available for 516 subjects for the BVRT matching condition. Repeated measures ANCOVA examining estrogen use over time for women who had taken estrogen compared to women who had never taken estrogen did not yield a significant result, $F(1, 514) = .63$, $p > .05$ (Figure 7).

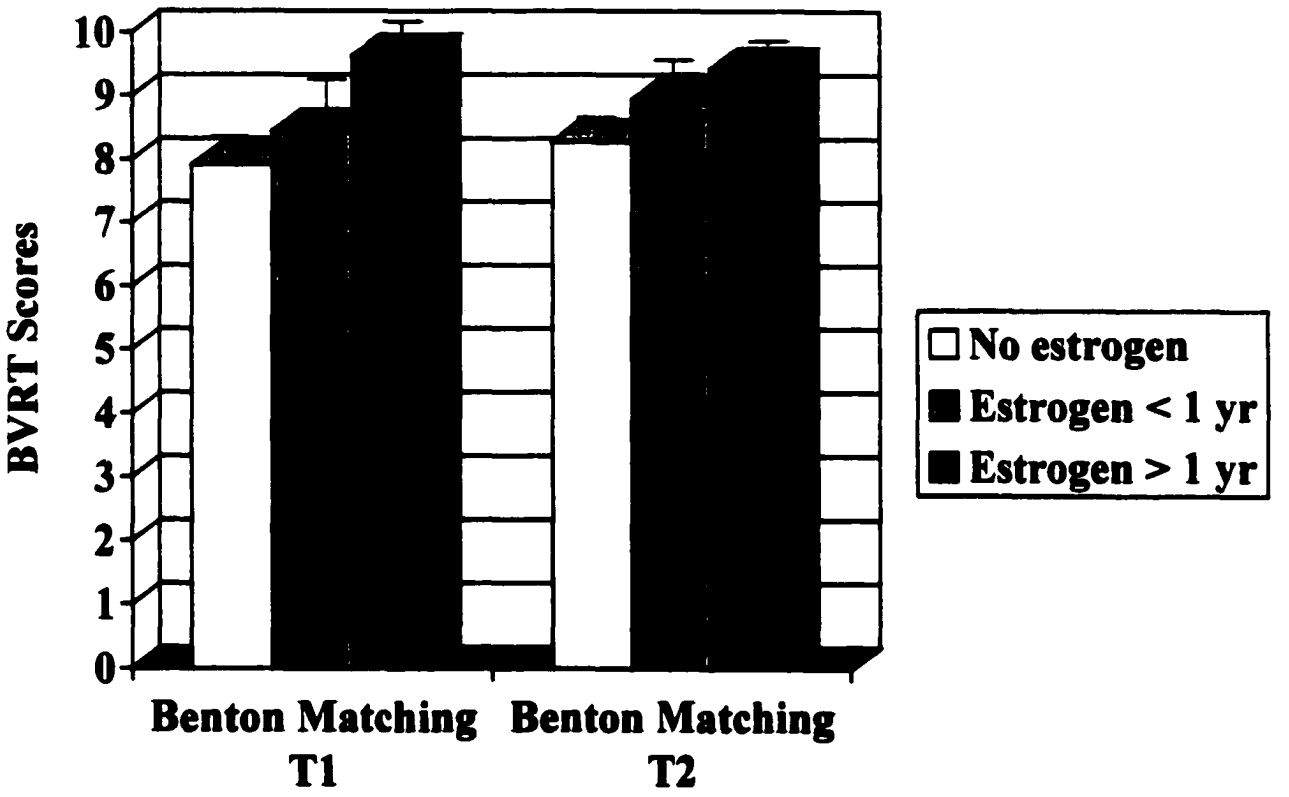
Figure 7 - Repeated measures ANCOVA for BVRT (matching) comparing Estrogen Users and Estrogen Never Users over Time



F (1, 514)=. 63, p>. 05

Repeated measures ANCOVA examining estrogen use over time for women who have never taken estrogen, taken estrogen one year or less, or taken estrogen one year or more did not yield a significant result, $F(2, 513)=1.53$, $p>.05$ (Figure 8).

Figure 8 - Repeated measures ANCOVA for BVRT (matching) comparing Estrogen Users < 1 yr., Estrogen Users > 1 yr. and Estrogen Never Users over Time



F (2, 513)=1.53, p>. 05

Chapter IV

Discussion, Study Limitations and Future Directions for Research

Overview

The goals of this dissertation were to investigate the relationship between mental status and performance on visual-motor/visual-spatial tests. In addition, a secondary goal was to determine whether estrogen use enhanced visual-spatial abilities in women with a history of estrogen replacement use. In elderly women, the primary study found significant effects for mental status on visual-motor performance. The data indicated that when individuals were cognitively impaired, object assembly, hand placement and execution strategy were disturbed. The method of detecting visual-spatial deficits incorporated a constructional ability task with hand/arm movements in an attempt to create a novel measure of visual-motor abilities. When demographic variables such as age were examined, women in the older age categories were found to perform significantly poorer than women in the younger group. Although this age effect was found, impairment of this type is not considered a part of normal aging and severe deficits have been shown to relate to mental status (Muramoto, 1984). For the secondary study of estrogen use, no significant effects were found for women who had taken estrogen as compared to women who have never taken estrogen although trends were seen. Discussions of the results are organized according to each study and hypothesis.

Primary Study

We hypothesized that women who scored in the impaired range of a mental status test as compared to women who score in the normal range would: have greater difficulty completing a three - dimensional object assembly task; produce a larger number of object placements; and display execution strategy errors when age and education are controlled.

A significant difference in performance was found for women categorized as cognitively impaired versus cognitively normal. This suggests a relationship between mental status score and performance. Women found to be cognitively impaired had difficulty in completing visually guided movements. Out of twenty-eight individuals in the normal mental status range only one could not complete the task. This individual reported not being able to complete the task because of time constraints.

In chapter one literature was presented that supports a relationship between parietal lobe functioning and visual-motor performance. In order to execute movement properly, the parietal lobe must be able to integrate visual and motor abilities (Milner and Goodale, 1993). In this way, movements can be performed with accuracy. Research by Faugier-Grimaud, et al., (1978) demonstrated that monkeys with inferior parietal lobe lesions produced awkward grasps and were not able to shape the contralateral hand properly. They also found that monkeys were impaired in visual pattern discrimination. The three-dimensional object assembly task in the current study may be tapping into a similar domain of brain functioning. Mishkin, Lewis and Ungerleider (1982)

postulated a dorsal stream system that allows individuals to locate where an object is in space. If disrupted, reaching and grasping objects would be impaired. It would appear that individuals in the current had difficulty with the grasping of the objects and the placing of objects on the stand, consistent with a dorsal stream system deficit. The task required an appropriate reach, hand grasp movement (execution), and movement of the object to the appropriate location in space (object placement). This study also demonstrated a relationship between overall cognitive status and 3-dimensional arm-hand movement. Women with impaired scores on the mMMSE had greater difficulty placing objects on a stand, as compared to women with normal scores. The mMMSE does not specifically look at arm and hand placement, although does provide two items of constructional ability (drawing items).

Visual spatial abilities are vast, and there are many kinds of tasks that researchers use to test for deficits. Clock drawing (Esteban-Santillan, 1998), block design (Benton, 1983), figural measures (Rosen, 1981) are all believed to be visual-spatial in nature (Lezak, 1983). Asking an individual to move in 3-dimensional space may provide a novel way of detecting subtle changes associated with abnormal mental decline. Moreover, if an individual in daily living is having difficulties with hand-arm movements, this may be an indicator of a more global problem. Although significant differences were found for women based on age, this result is not considered an age effect as age has been found to exert only a weak effect on this type of deficit (Maruff, 1995). Individuals may

perform at a slower place (longer reacting time), but even very elderly women with normal mental status scores could complete the task.

Literature has indicated that many individuals who have Alzheimer's Disease also have performance deficits associated with early parietal lobe involvement (Grossi, et al., 1993; Esteban-Santillan, et al, 1998). Therefore, visual motor movement deficits may be an early sign of a resulting parietal lobe deficit.

Women who were categorized as impaired based on mMMSE scores made a greater number of object placement errors as compared to women categorized as normal based on mMMSE scores. The average number of attempts for individuals with an impaired mental status score was significantly different than women in the normal range: 2.7 as compared to 1.3. There was a tendency for women to pick up the object, and miss the stand. We do not attribute these errors to vision or motor problems, as women were screened for pure visual or motor impairments. When we look at the literature with non-human primates, similar kinds of deficits can also be seen. Monkeys were at times able to find a food object, but not able to carry out the movement to satisfactory conclusion (Mishkin, Lewis and Ungerleider 1982). Thus, their movements were therefore distorted. Our results are similar to the findings of Dijkerman, et al., (1998) in which subjects were asked to reach and grasp for objects by inserting their fingers into holes presented in disks. Subjects were unable to adjust the hand appropriately and complete the movement. These deficits again are associated with an integration deficit.

Additionally, it may appear that the range of average number of object placements between the groups is close, however, it must be considered that the analysis does not include women who were unable to complete the task. Since the most impaired women did not finish the object placement test, it was not possible to include their data in the analyses. As a result, a separate hypotheses examining completion of the task was performed.

While it was not possible to measure precise hand movements in this study, it was possible to detect deficits in reaching and grasping for objects. Women were videotaped while performing this task and were coded for statistical analyses either as utilizing correct execution strategies or incorrect execution strategies. The operational definition of execution strategy errors was placing the hand around the object improperly so that readjustment was necessary, over or under reaching for the objects. Women who were categorized as having execution errors could not appropriately grip the objects and/or reach for the objects. Women that displayed strategy errors were in the impaired mental status category. For these women, scores on the mMMSE were mild compared to the more severely impaired women. Again, it must be kept in mind that those women with perceptual errors; pure visual deficits and pure motor deficits were excluded from this study. The object placement test was designed to detect only an integration problem, which contributed to the movement problem.

The 3-dimensional object assembly task utilized in this study was designed by modifying the Stanford Binet Bead Memory Test, which was originally created to detect short-term memory deficits (Stanford-Binet, 1986).

For this dissertation it was used as a dual-purpose test – examining constructional ability and hand/arm movement.

Examining hand and arm movements may be a novel way of examining visual-spatial deficits. While traditional means of testing individuals provides information (Lezak, 1983; Esteban-Santillan, et al., 1998), important aspects of deficits may be overlooked, when for example an individual is asked to draw an object. The placement of the hand or the individuals reach may provide additional cues as to the kinds of deficit individuals' manifests. However, the movement is not the focus of the test. The test used in this study has individuals place objects on a stand and might be considered an object assembly task similar to block design tests. Additionally, an important component of this test is videotaping arm and hand movements to detect errors in reaching and grasping.

Study Limitations

While significant differences between groups were found for this study, there are several limitations. Many of the participants in this study were tested in their homes due to mobility limitations (i.e. amputees, leg paralysis). Deficits of reaching and grasping were detected by observing videotapes of subjects performing an object assembly task. Precise measurements of thumb/forefinger opposition could not be done. Instruments that are used in a laboratory to measure reach; grasp and finger opposition could not be utilized. Studies done in the laboratory offer a controlled environment, where computerized equipment can be used to further define the impairment, or subtype of impairment.

Another limitation of the study is the small sample size, especially with respect to individuals with impaired mental status. The majority of the individuals in the impaired mental status range were from a home care population and access to this sample of women was limited. It was often difficult to obtain informed consent, as in many cases family members were reluctant to give consent so that their family member could be evaluated.

Additionally, difficulties arose because of unequal variance between cognitively normal and impaired individuals. Due to the unequal variance among groups, non-parametric tests had to be performed.

Primary Study Summary

This primary study of this dissertation has presented data and methods in support of a relationship between impaired mental status and visual-motor integration. Briefly, our study demonstrated that patients who scored high on the mMMSE did not display execution strategy errors when completing the object assembly task, and produced fewer object placements. Furthermore, patients who demonstrated high scores the mMMSE also scored higher on the Rosen Drawing Test. High scores on both examinations are indicative of normal functioning.

Current literature supports a relationship between cognitive status and visual-motor integration (Milner & Goodale, 1993; Ghillardi, 1998). Milner, et al. (1993) and Jeannerod (1994) hypothesize that when individuals are cognitively impaired, difficulties arise reaching and grasping for objects. They suggested this is a visual-motor integration deficit associated with parietal lobe functioning.

This study was novel because it examined the arm, shaping of the hand and the grasp. The task in this experiment demonstrated that elderly women with impaired mental status performed significantly worse than women with normal mental status scores. Hand and arm movements could be observed, as well as ability to complete the task and number of object placements. Placing objects in three-dimensional space may be a novel indicator of a visual-spatial impairment and activities of daily living. Individuals must on a daily basis do many kinds of visual motor tasks, such as tying ones shoelaces, or reaching for a glass.

For future directions of this research, brain-scanning methods to examine activation of specific brain regions may prove to be useful in mapping brain areas active in normal elderly individuals versus impaired elderly individuals. This method might also be useful in detecting specific areas within the parietal region, particularly those areas associated with dorsal stream processing.

Secondary Study

We hypothesized that women with a prior history of estrogen use would display significantly higher scores on tests of visual–spatial abilities as compared to normal elderly women with no history of estrogen use. However, no significant effects were found comparing estrogen users to women who have never taken estrogen for the Rosen Drawing test. However, a trend was found comparing women who have never taken estrogen, women who have taken estrogen one year or less and women who have taken estrogen greater than one year for the Rosen Drawing Test, where scores for women who had taken any estrogen replacement were higher than women who had never taken estrogen. Whether this result is clinically significance remains to be seen. However, it is important to consider the small number of women in the sample who reported having ever taken estrogen. When examining the two-group analysis, significance was not found, although again, a trend was seen in the data. Estrogen users did have better scores on the Rosen drawing Test compared to women who did not use estrogen, demonstrating a potentially enhancing effect of estrogen use on visual-spatial abilities.

In prior published data of this sample set, a significant effect of estrogen use of estrogen use was observed on tests of verbal memory, language and verbal abstract reasoning (Jacobs, 1998). Studies have demonstrated that parietal regions of the brain are associated with verbal working memory and visual-spatial skills (Harmony, et al., 1999; Milner & Goodale, 1993). The trends of this dissertation are consistent with previous research, which show a

relationship between verbal memory, visual-spatial ability and estrogen use enhancing cognition. Estrogen has been found to have beneficial effects on cerebral blood flow during figural memory tasks (Resnick, et al., 1998). For example, the inferior parietal region of the brain was found to have higher blood flow for estrogen users during the figural memory task as compared to nonusers (Resnick, et al., 1998). There are questions as to estrogen's effects on the parietal lobe. However, Berman, et al., (1997) suggests that estrogen affects parietal lobe functioning by acting as a neuromodulator. It has also been suggested estrogens plays an important role in increasing the growth of neurons in the frontal, temporal, occipital and parietal region of the brain (Brinton, et al., 1997).

The length of time for estrogen use may be an important factor in determining its effects on cognition. The average length of time for estrogen users in this study was nine years for women categorized as > 1 year of estrogen use as compared to three months for women categorized as $\leq$ 1 year.

Some researchers have questioned the effects of estrogen on visual-spatial abilities. Particularly, whether estrogen enhances or dampens visual-spatial abilities (Sherwin, 1998). In this study, although not significant, estrogen appears to have a potentially enhancing effect. When we compare the three groups of women, women with a history of estrogen use do have higher Rosen Drawing test scores than women who have never used estrogen, however these results were statistically significant.

No significant differences were found when comparing estrogen users to never users in the two and three group conditions for the BVRT recognition test. Maki (submitted) and Resnick (1999) have extensively used the Benton Visual Retention Test in their studies. Their own studies have produced varying results when examining the data. Maki (submitted) found no effect of estrogen replacement therapy on the BVRT, although in previous studies significant findings were reported for estrogen users compared to nonusers. Dr. Maki attributes this possibly to effect size, which was lower in her most recent study. Similarly, it may be that there was not enough statistical power to detect a difference for the BVRT in this dissertation. The statistical power in this dissertation for the two-group and three-group analysis was low. This is one reason why univariate ANCOVAs were considered important follow-up post-hoc analyses as compared to MANCOVAs – they served to increase the power of the analyses. Research using the BVRT by Resnick, et al., (1997) detected differences based on estrogen use for visual-spatial memory when power was sufficient. Having a sample size with equal numbers of estrogen users and non users may help to address the issue of observed power.

Overall a protective effect of estrogen use on visual memory was found by Resnick (1997). However, these results are contrary to results by Sherwin (1994) who did not detect significant differences in visual memory but found that estrogen influenced verbal memory. In the prior published article of this data set Jacobs (1998) did find an enhancing effect of estrogen on verbal memory

consistent with Sherwin (1994). Further testing may be necessary to address the effects of estrogen on visual-spatial abilities.

No significant differences were found for women who have taken estrogen compared to women who have never taken estrogen (2 group model) for the Benton Visual Retention Matching test, p=. 325. Although not statistically significant, we again did see higher BVRT test scores for women who had taken estrogen. Post-hoc ANCOVA results comparing three groups of women did not yield a significant result, p=. 508. However, Levene's test of equality of error variances in the two and three-group analyses were statistically significantly. Therefore, the data was transformed. By transforming the data, the observed power decreased significantly. Before transformation of the data, a trend was seen in the data for the 2-group BVRT analysis. The extremely low power may be why a significant result was not achieved.

The BVRT versions used in this study required the subject to simply point to an array of figures, or recognize an array of figures after a ten second presentation of the items. The scores of these test versions are not sensitive to variations in hand movements. Resnick, et al., (1997; 1998) and Maki, et al., (in press; 2000) use a version of the BVRT that is similar to the Rosen Drawing Test. These investigators report significant findings for the BVRT when comparing estrogen users to women who did not take estrogen. The version of the BVRT used in their research required women to copy ten figures of increasing complexity after a ten-second exposure. These researchers found that hormone replacement users maintained a stable performance over time as

compared to women who did not receive hormone replacement for the BVRT. The greatest differences were seen in distortion errors, which they believe are most sensitive to age effects. In the secondary study of this dissertation only trends were seen. However, significant findings may not have been found for several reasons. As previously stated, power was a problem in this sample, and it may have been too low to see any effect. It might be beneficial in future studies to analyze the Rosen Drawing data in a different way. The Rosen Drawing test begins with easy figures and progressively becomes more difficult. If the early easier items are not included in the analysis, and only the more difficult items are qualitatively analyzed, differences may emerge based on estrogen use. The early easier items may have distorted the findings because they were relatively simple to perform.

Important to consider in this data set is that the majority of individuals reported never taking estrogen (635) and only a small sample had ever taken estrogen. When we examine the effect size between groups, more observed power was found in the two-group comparison than in the three groups. When power is sufficient, we may see an effect of estrogen use on visual-spatial abilities.

We hypothesized that women with a prior history of estrogen use will have significantly higher scores on tests of verbal ability and visual-spatial abilities as compared to women with no prior estrogen use over time. However, no significant effects were found for estrogen use over time (2 years) for the Rosen Drawing Test and Benton Visual Retention Test. it is possible that a longer

length of time of estrogen administration is required to see an effect. While researchers have found changes in cognition over time for estrogen users (Resnick, et al., 1997), the lack of effect in this sample of women may be due to other factors, including problems with the sample population and restricted range of scores on measures, since having such a restricted range leaves little room for detecting change.

Study Limitations

There were limitations to this study, which must be considered when examining the data. First, the analyses do not account for all variables that might be interacting. These findings are also from an observational study and there may be other factors involved that contributed to the differences among groups, including lifestyle and socioeconomic differences. This is sometimes called "the healthy user bias" (Matthews, et al., 1996). Estrogen users tend to be better-educated and younger than non-estrogen users (Rodstrom, et al., 1999). It is possible that women who are more educated and younger may take better care of themselves, practice healthier eating habits, and have healthier lifestyles. To attempt to control for this bias, age, education and ethnicity were statistically controlled. However, there may be differences in the type of women who elect to take estrogen replacement. In all likelihood estrogen was prescribed because of hormone deficiency, perhaps due to hysterectomy. It may be that some women in this sample had better access to health care than other women.

A large sample of women participated in this retrospective study and investigators were relying on women's' recall of the length of time estrogen was

taken. Unfortunately the majority of women never took estrogen (89%). Out of eighty-one individuals who had taken estrogen, only 37 (5%) had taken it over one year. Estrogen dosage information was not obtained from participants and may be important in predicting changes in cognition and memory. As investigators were relying on women's' recall of past estrogen use, many were unaware of the dosage taken or the type of estrogen (for example Premarin) dispensed. In years past, estrogen was prescribed at a much higher dosage than today, which may have affected the results.

Currently Sano, et al., (in progress) is attempting to determine whether administering estrogen or placebo has any effects on memory and cognition in postmenopausal elderly women. This is a placebo-controlled, double blind study, a much more controlled way of determining the effects of estrogen on cognition. This may help to determine true effects of estrogen on cognitive functioning, including verbal and visual-spatial abilities. In a controlled trial the dose of estrogen is known, as well as the length of time of use.

Secondary Study Summary

In a multi-ethnic, community sample of elderly non-demented women, estrogen use was found to be related to visual-spatial ability. Women who had used estrogen demonstrated higher scores on visual spatial tests as compared to non-users, although these differences were not significant. Many researchers are exploring the effects of estrogen use during the postmenopausal period, and the potential benefits of estrogen use. While information on the effects of estrogen is ongoing, it has shown improvements in women's health

physiologically as well as cognitively. Woolley (1990) has found effects of estrogen on the brain and differences were found in the number of dendritic spines for high versus low levels of estrogen where a positive correlation between dendritic spines and estrogen level.

In a prior study, with this data set, women who had taken estrogen were found to demonstrate improvements in verbal memory as compared to non-estrogen users. This dissertation study suggests that estrogen use may enhance cognitive functioning and visual-spatial ability among post-menopausal women.

Overall conclusions

In examining visual spatial abilities among the two studies, interesting findings emerge. In the primary study, significant results were found for the number of object placements and the Rosen Drawing Test by mental status. For the secondary study, although we did not see significant results, we did see a trend for estrogen users to perform better on the Rosen Drawing Test. No trends were seen for the BVRT (matching and recognition). However, these results raise some important questions. It may be that object assembly and the Rosen drawing test are tapping into some domain of visual-spatial abilities that is not being captured by the BVRT. Both the object assembly task and Rosen Drawing test require precise hand movements to properly perform the task.

Visual-spatial performance has been linked to parietal lobe functioning and dorsal stream processing (Milner & Goodale, 1993; Jeannerod, 1994; Faugier-Grimaud, et al., 1978). In both studies tests of visual-spatial abilities

were used and may be tapping into some common domain of functioning. For example, when we look at the data for the Rosen Drawing Test, significant results were found for the primary study, and trends were seen for the secondary study. This Rosen Drawing test assesses visual-spatial and visual-motor performance. In the primary study cognitively impaired women scored significantly lower than cognitively normal women, and in the secondary study, all the women were cognitively normal; however, estrogen users showed enhanced performance, or perhaps, less decline in performance as compared to non-users. Both visual-spatial performance results are considered to be related to dorsal stream functioning (Milner & Goodale, 1992).

Another important difference when considering the estrogen sample is the difference between the Rosen Drawing Test and the BVRT. Resnick, et al., (1998) use a version of the BVRT that requires the subject to draw figures, similar to the Rosen Drawing Test. With the drawing version of the BVRT, Resnick et al., (1998) found significant results for women based on estrogen use history. The versions of the BVRT used in this dissertation (matching and recognition) required that the subject only locate figures in a four-choice array. Milner & Goodale (1992) addressed the question of locating the object in space versus identifying the object, and related this to dorsal stream and ventral stream processing, respectively. The BVRT matching and recognition versions would seem to tap into dorsal stream processing by asking the subject to select where a figure is. However, there is no active motor component, such as holding a pen and drawing a figure. The parietal region is thought to be the integration area for

visual-motor performance (Jeannerod, 1994;Faugier-Grimaud, et al., 1978; Biguer, et al., 1982). Drawing requires precise movements of the hand and arm on a sheet of paper to properly execute the task. Hand and eye movement coordination is also required. Accuracy of this type was not necessary for estrogen users with the 4-choice array BVRT. Women simply had to place their finger on one of four quarters of a letter size page of paper, perhaps requiring more concentration than motor output. Had the BVRT in this dissertation been the version used by Resnick, et al., (1998), it may have been more visual-motor in nature. It may be that tasks that require drawing are more sensitive to cognitive change.

APPENDIX 1
Summary

Subject # _____ Age_____ Education_____

Sex_____

I. History

1. Visual defects? _____
2. Motor defects? _____
3. Other deficits? _____ (explain)
4. Estrogen Repl. _____ (if yes, age of 1st repl. therapy)
5. Handedness _____ (Left/right)
6. AD Family Hx _____ (Yes/No)

II. Motor

Alternating movements _____ (normal/
Finger/Thumb opposition _____ impaired)

III. Visual

Visual acuity _____ (according to chart)

IV. Perception

Normal _____ (yes/no)

V. Mental Status

mMMSE score _____

VI.ADL Measure

# of deficits as reported in ADL's _____

VII. Stanford-Binet Bead Memory Task

Of attempts on stand? _____
Failures to plan? _____

FOR # OF ATTEMPTS

BALL = CONE = SAUCER = TUBE =

Study ID: C J M ___-___-____ Date: __/__/____

Name: _____ Examiner: _____

Time: 0 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10

FORM SP. MODIFIED MINI-MENTAL STATUS EXAM (mMMS)
and
MINI-MENTAL STATUS EXAM (Folstein MMS)

ITEMS	mMMS		MMS	
	Points	Score	Points	Score
ORIENTATION				
1. What is the year? _____	1	___	1	___
2. What is the day of the week? _____	1	___	1	___
3. What is the month? _____	1	___	1	___
4. What is the date? _____	1	___	1	___
5. What is the season? _____	1	___	1	___
6. What is the name of this place? _____	1	___	1	___
7. What is the adress of this place? _____	1	___	1	___
8. What floor of the building are we on? _____	1	___	1	___
9. What city are we in? _____	1	___	1	___
10. What borough are we in? _____	1	___	1	___
REGISTRATION Name 3 Objects (Tell patient to try to remember them.): 11. APPLE ___ TABLE ___ PENNY ___ Record number of trials: ___	3	___	3	___

ITEM		mMMS		MMS	
		Points	Score	Points	Score
Digit Span:					
12. Total	___ a maximum of 6 forw/4 back is permitted for total mMMS score.	10	___	N/A	N/A
				N/A	N/A
13. Forward	___ number of highest span correctly repeated	9	• ___	N/A	N/A
14. Backwards	___ number of highest span correctly repeated	8	• ___		

Digits Forward	Circle	Digits Backwards	Circle
5-8-2	3	2-4	2
6-9-4	3	5-8	2
6-4-3-9	4	6-2-9	3
7-2-8-6	4	4-1-5	3
4-2-7-3-1	5	3-2-9-7	4
7-5-8-3-6	5	4-9-6-8	4
6-1-9-4-7-3	6	1-5-2-8-6	5
3-9-2-4-8-7	6	6-1-8-4-3	5
5-9-1-7-4-2-8	7	5-3-9-4-1-8	6
4-1-7-9-3-8-6	7	7-2-4-8-5-6	6
5-8-1-9-2-6-4-7	8	8-1-2-9-3-6-5	7
3-8-2-9-5-1-7-4	8	4-7-3-9-1-2-8	7
2-7-5-8-6-2-5-8-4	9	9-4-3-7-6-2-5-8	8
7-1-3-9-4-2-5-6-8	9	7-2-8-1-9-6-5-3	8

ATTENTION AND CALCULATION				
15. Serial 7's: 93 ___ 86 ___ 79 ___ 72 ___ 65 ___	5	___	N/A	N/A
16. Spell "WORLD" Backwards: D ___ L ___ R ___ O ___ W___	1	___	5	___
17. Add Change: Sum of 3 pennies, 1 nickel, 1 dime and 1 quarter ___ (.43)	1	___	N/A	N/A
RECALL				
Ask for 3 objects repeated above: (Delay at least 3 minutes) 18. APPLE ___ TABLE ___ PENNY ___	3	___	3	___

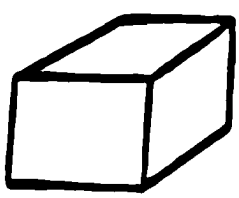
ITEM	Points	mMMS	Points	MMS
GENERAL KNOWLEDGE				
Name current and past 4 presidents in reverse order:	5	___	N/A	N/A
19. Clinton ___				
Bush ___				
Reagan ___				
Carter ___				
Ford ___				
LANGUAGE				
Name the following objects:				
19. Wristwatch _____	N/A	N/A	1	___
20. Pen _____	N/A	N/A	1	___
Name 10 pictured objects:				
21. House _____	1	___	N/A	N/A
22. Scissors _____	1	___	N/A	N/A
23. Camel _____	1	___	N/A	N/A
24. Tennis Racquet _____	1	___	N/A	N/A
25. Wreath _____	1	___	N/A	N/A
26. Pretzel _____	1	___	N/A	N/A
27. Igloo _____	1	___	N/A	N/A
28. Dominoes _____	1	___	N/A	N/A
29. Escalator _____	1	___	N/A	N/A
30. Pyramid _____	1	___	N/A	N/A
Repeat the following:				
31. "No ifs, ands or buts" ___	1	___	1	___
32. "The train came into the station over an hour late." ___	1	___	N/A	N/A
Command:				
33. "Take this piece of paper in your right hand, ___	1	___	1	___
34. fold it in half ___	1	___	1	___
35. and put it on the floor." ___	1	___	1	___
Read and follow the directions:				
36. "Close your eyes." ___	N/A	N/A	1	___
37. "Close your eyes and open your mouth." ___	1	___	N/A	N/A
38. Write a sentence. ___	1	___	1	___

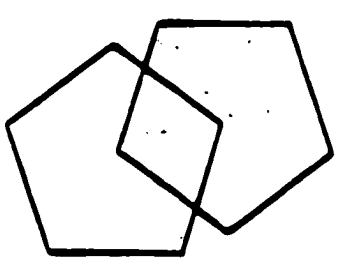
ITEM		Points	mMMS	Points	MMS
CONSTRUCTION					
Copy designs:					
39. Circle/diamond	___	1	___	N/A	N/A
40. Cube	___	1	___	N/A	N/A
41 Intersecting pentagons	___	N/A	N/A	1	___

TOTAL mMMS SCORE: _____/57 * **Do not include items 13. and 14. in score.**

TOTAL MMS SCORE _____/30

COPY



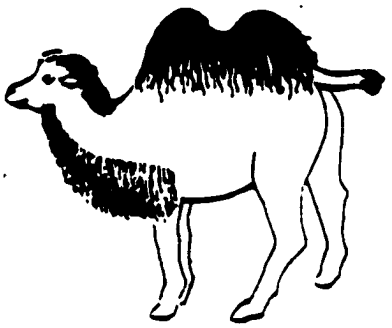


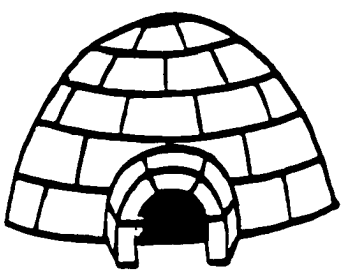
CLOSE YOUR EYES

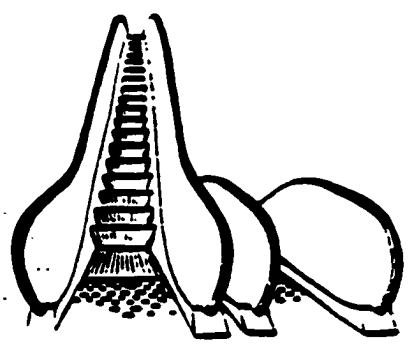
CLOSE YOUR EYES AND OPEN YOUR MOUTH.

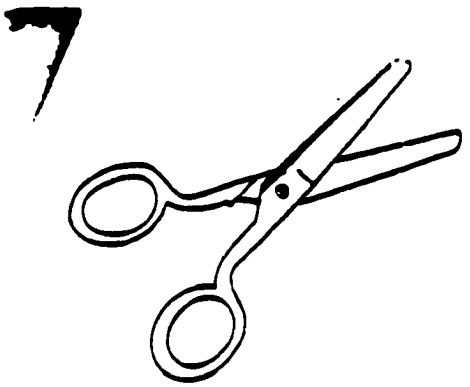
Patient behavior during interview and testing:

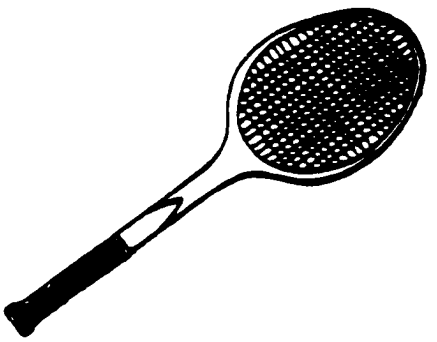
Agreeable	0
Uncooperative	1
Mute	2

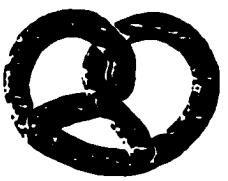


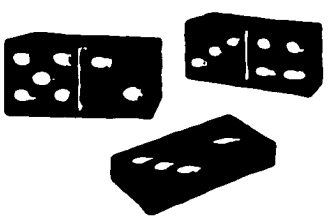


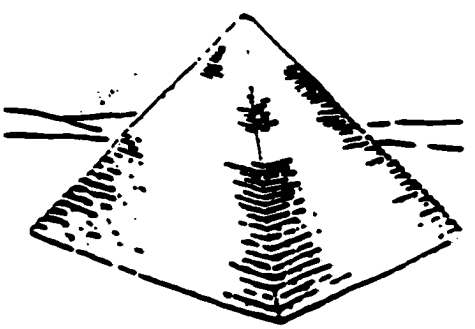












APPENDIX 3

MODIFIED MINI-MENTAL STATE EXAM (mMMS)

MANUAL FOR ADMINISTRATION

Introduction

This mental state examination is a modification of the test described by Folstein et al. Additions include a digit span test, more extensive assessment of language and additional construction items. In addition to an overall score, eight subtest scores can be derived.

These instructions are intended to ensure standard administration of the mMMS in order to maintain inter-rater reliability. Therefore, it is important to use only the instructions and cues described here when administering this instrument. Clinically useful information might be obtained by giving the patient additional "hints" or cues after standard administration has been completed, but this information should not be used to modify a patient's score.

Several general rules should be kept in mind when administering the test:

1. All responses should be recorded exactly as given.

2. When a patient gives more than one answer he should be encouraged to choose one of them, although no cueing for a specific choice should be provided. "Which one is it?" or "Choose one" can be useful prompts to get a patient to choose a single response.

3. Since it is better to score an incorrect response than no response, patients should be encouraged to give an answer even if they are unsure. "What's your best answer?" or "Try" can be helpful prompts. An incorrect response can give some evidence that the patient understood the question.

4. Scoring should follow the rules described in each section. No partial credit can be given.

5. Assessment of function is most useful when optimum performance can be elicited. Patients should be able to understand the task demands and have enough opportunity to respond in order to elicit a valid measure.

When the testing is completed, total score should be filled out on the form along with the patient's name, examiner's name and the date.

Administration

ORIENTATION

Instructions:

(a) Begin by asking, **"What is today's date?"** Each scorable item that was not supplied should then be queried. When a year or season is near transition, an incorrect answer can be prompted with **"Are you sure?"** If a patient gives the date when prompted for day, he should be given credit if the response is correct. The year can be prompted with "Nineteen..." Day or season can be prompted with a list of relevant names.

(b) **"Where are we now?"** Each scorable item should be queried.

Scoring:

Each item is worth one point. No partial credit is given. Each site will develop its own list of acceptable responses for address but these must include the street name with or without a building number. For example, at Columbia Presbyterian Medical Center if a patient provides an avenue for the address, he must be asked for a cross (numbered) street. Acceptable responses include 168th Street, 168th and Broadway, 168th and Fort Washington. For hospital any correct name, except generic names such as medical center or hospital, is acceptable.

REGISTRATION

Name 3 Objects

Instructions:

"I am going to name three objects. I want you to listen and repeat them when I'm done. Later I'll ask you to recall them: apple, table, penny." Ask the patient to repeat them. If necessary repeat until patient can say all 3 words at one time. **"Remember these objects because later I'll ask you to recall them."**

Scoring:

Score one point for each correct response in the first trial. Note in the appropriate place the number of trials needed for the patient to repeat all 3 words.

Digit Span - Forward

Instructions: Use standard WAIS or Wechsler Memory Scale Administration: "I am going to say some numbers. Listen carefully, and when I am through, say them right after me." Use the numbers on the score sheet. Start with a span of three numbers, reading them at the rate of one per second. Do not group the numbers. Let the pitch of voice drop with the last digit of each series. If the span is repeated correctly increase the span by one. If there is an error, go to the second trial of the same span. If both are failed discontinue. Note: only one reading of a series of digits is permitted.

Scoring: The score is the number of digits in the highest span correctly repeated. A maximum of 6 can be applied towards the total mMMS score but the subtest score can have a maximum of 9 points.

Digit Span - Backward

Instructions: "Now I am going to say more numbers, but this time when I stop, I want you to say them backwards. For example, if I say 9-1-7, what would you say?" If the patient responds correctly say, "Here are some others," and continue with the actual test items. If incorrect say, "No, 9-1-7 backwards is 7-1-9. Here are some more numbers. Remember to say them backwards: 3-4-8." If there is difficulty grasping the concept of backwards, the examiner can say, "I'm asking you to say the numbers in reverse order. For example, if I say 1-2-3, backwards that would be ...3-2-1."

Start actual testing with a span of 2 numbers. If the span is repeated correctly increase the span by one. If there is an error go to the second trial of the same span. If both are failed discontinue. Other rules for administration are the same as for Digit Span - Forward.

Scoring: The score is the number of the highest span correctly repeated. A maximum of 4 is permitted for the total mMMS score and a maximum of 7 is permitted for subtest score.

ATTENTION AND CALCULATION

Serial Sevens

Instructions: "Subtract 7 from 100, then keep on subtracting 7's until I tell you to stop." If necessary the wording can be changed to get across the instruction. For example, "Take 7 from 100," or "Count backwards from 100 by 7's" are an

acceptable alternatives. If the patient can't remember an answer he gave (i.e. what number to take 7 away from) or the instructions (i.e. that he is to subtract 7's), reminding is permitted. The first subtraction error is corrected but subsequent errors are not corrected. Continue for a total of 5 subtractions.

For more impaired patients give each part of the instruction separately. Say **"Subtract (take away) 7 from 100."** If the answer is correct say, **"Now take 7 from that."** Repeat this after each subtraction and continue as described above. If the patient clearly cannot do subtraction, discontinue after the second incorrect answer

Scoring: One point is given for each correct subtraction yielding a maximum score of 5. Answers subsequent to errors are scored as correct if they are 7 less than the error.

"WORLD" Backwards

Instructions: **"The word WORLD is spelled W-O-R-L-D. Spell WORLD backwards."** Repeat spelling if necessary. As explanantion you may also say, **"Start from the end and go to the beginning."** Allow additional trials if the patient requests them.

Scoring: Score one point for correct reverse spelling.

Addition

Instructions: **"Now I am going to give you some change to add together. What is the sum of 3 pennies, 1 nickel, 1 dime and a quarter?"** These instructions can be repeated and the patient may even add while they read, but the coins should always be read in order (i.e. from pennies to quarter) using the coin names not their value.

Scoring: Score one point if correctly added.

GENERAL KNOWLEDGE

Naming Presidents

Instructions: **"Who is the president of the United States?"** If the correct answer is given ask, **"Who was the president before him?"** If correct answer is again given, continue the above question until 3 more presidents are named (total of 5). If an incorrect answer is given for the first response, supply the correct response. If incorrect answer is given at any subsequent point use one of these: **"No there was**

someone between him and [last correct response]" or "No, try to think who was before [last correct response]," or "No it was [correct response]." Then say, "Who was the president before him?" and continue as above. Discontinue after 2 incorrect responses.

Scoring: Score one point for each correct response up to 5 presidents.

RECALL

Instructions: "Now what were those 3 objects I asked you to remember?" If needed, explain the source of these 3 objects with, "I asked you to repeat 3 words earlier and to remember them. Can you recall them now?" If the patient gives an incorrect response say, "No, try again." If no items are recalled say, "One of the words was APPLE. Can you recall the others?"

Scoring: One point for each response froa total of 3 points.

LANGUAGE

Naming

Instructions: This test uses 10 pictures to be named. Point to the picture and say, "What is this?" If the patient gives the function or description of a picture say, "Yes, but what is this called?" or "What's its name?" If the response indicated that he misidentified the picture say, "No, that's not what it is. Try again." No other cues should be provided.

Scoring: Score one point for each correct reponse for a total of 10 points.

Repetition

Instructions: "Repeat after me; no ifs ands or buts. Repeat after me again; the train came into the station over an hour late." One repetition of each is permitted at the patient's request.

Scoring: One point for precise repetition of each sentence.

Follow Command

Instruction: **Present a piece of paper at the patient's midline. Say, "Take this paper in your right hand, fold it in half, and put it on the floor."** One repetition is permitted at the patient's request, but the entire command must be repeated. The patient is allowed to fold the paper using both hands.

Scoring: One point for each of the 3 segments (1) take in right hand; (2) fold in half; and (3) place on floor. A total of 3 points.

Reading

Instruction: Present card with command. Say, **"Read this and do what it says."** The patient can be reminded not just to read the sentence but to obey it.

Scoring: Instructions must be followed completely to give 1 point.

Writing

Instruction: **"Write a sentence [about today's weather]."** The last part is optional, but it helps the patient organize himself.

Scoring: One point for any complete sentence even if not about weather. Spelling and punctuation are not scored but the patient must write a complete sentence.

CONSTRUCTION

Instructions: **"Copy this design."** Present the card with first design. Repeat the instruction for the second design.

Scoring: One point for each correct design for a total of 2 points. The first design must have a circle and diamond of approximately the same size and in the proper orientation. The left vertex of the diamond must touch the circle. The second design requires a 3-dimensional opaque cube that accurately reproduces the sample.

APPENDIX J

ROSEN DRAWING TEST

NAME:_____

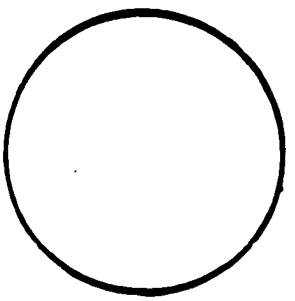
DATE OF TESTING:_____

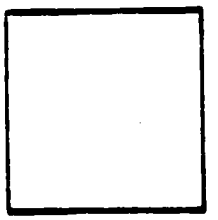
SEX:_____

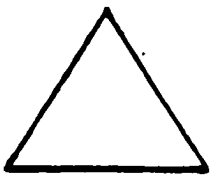
DATE OF BIRTH:_____

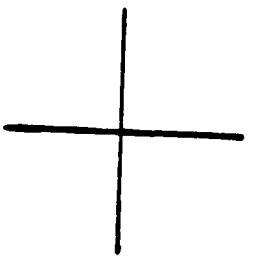
HANDEDNESS:_____ **AGE:**_____

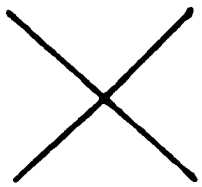
EDUCATION:_____

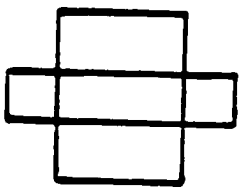


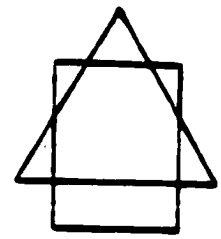


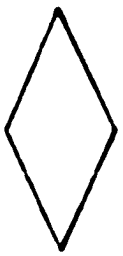


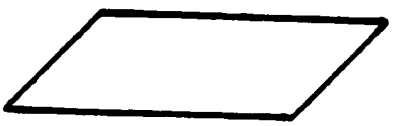


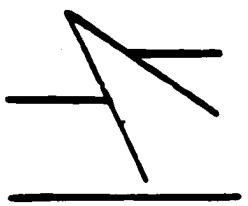


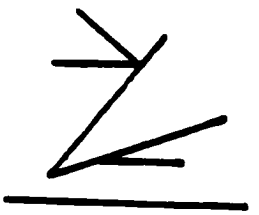


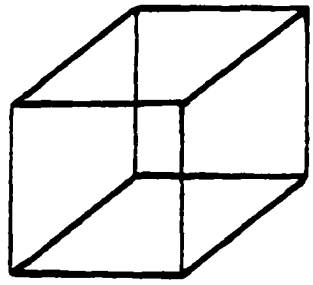


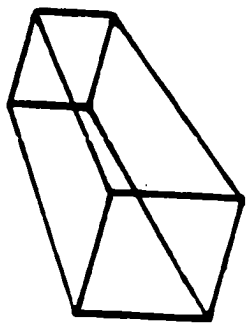


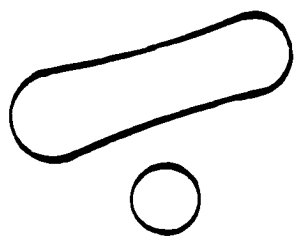


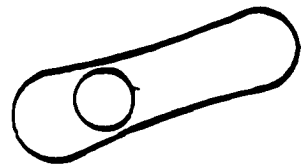












APPENDIX 5

The Rosen Drawing Test
Instructions for Administration and Scoring

Introduction

The Rosen Drawing Test is designed to assess constructional abilities. Fifteen designs are included, which range from simple shapes and those tapping topological concepts to overlapping, Euclidian and three-dimensional designs.

Administration

Provide the patient with a pencil. Place the drawing in front of the patient, point to the first figure and say: "Draw one just like this." Continue for each figure, having the patient draw below or at the side of the sample figure.

Multiple Attempts. If a drawing does not appear to be the best attempt or if the subject is dissatisfied with the work, additional attempts may be made. Ask the patient to try again. In general, the intent is to assess an individual's "best performance", so multiple attempts may be permitted to achieve a maximal drawing.

Extraneous Features. Provide information as needed about any errors or extraneous features which appear in the original. For example, on xeroxed copies, intersecting lines may appear to have spaces in them. You should inform the patient that these are not features that need to be copied.

General Procedural Rules

1. Avoid naming the drawing.
2. Expose only one design at a time.
3. Permit only minor erasures.

Closing In Very impaired individuals may attempt to draw on top of the original. This is known as "closing in". If the patient begins to draw on top of the design say: "Draw it here," and instruct him by pointing anywhere else on the page. This verbal instruction can be given for each design. If he continues to draw on top of the original, move his hand elsewhere. Actually moving the hand should be done only once throughout the entire 15 items.

When the patient continues to draw on top of the design after these instructions "closing in" is scored as present.

Scoring

Two alternate scoring systems may be used. In the 15 point system, each figure receives 1 point. In the 19 point system, figures 9-13 can receive up to 2 points.

General Considerations

1. Score only the best attempt
2. Tremor or other motor difficulties should not affect scoring. Scoring is based on the qualitative features of the construction
3. Small gaps at places where lines join are permitted (~~gaps~~). ≤ 1/8 inch
4. Constructions do not have to be the same size as the original.
5. Unless otherwise specified, the constuction should be scored as an integral unit, without regard to its orientation to the base of the page.

Specific scoring rules

Salient aspects of each figure are outlined on the next page. These delimit the minimal level that is scorable. Some scoring rules refer to the actual figures when description of specific angular relations becomes cumbersome.

1. Circle — any closed figure approximating a circle or ellipse.

2. Triangle — 3-sided, closed figure with straight lines

3. Square — 4-sided, closed figure with straight lines
at least 2 right angles
one side no more than twice the other

4. "X" — 2 lines crossed at approximately right angle
rotated approximately 45 degrees from base of page
lines do not have to bisect each other

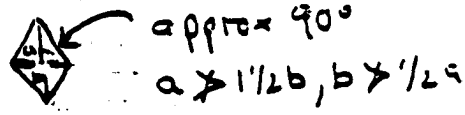
5. Cross — 2 lines crossed at approximately right angle
one line approximately parallel to base of page
lines do not have to bisect each other

6. Overlap 1 — 2 rectangular figures, overlapping as in sample
symetry or size of pieces extending from the overlap is not important

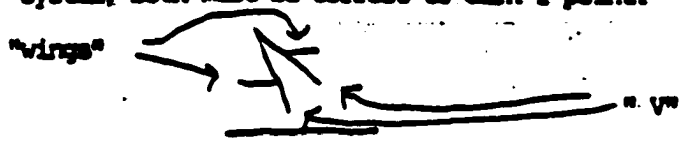
7. Overlap 2 — triangle and square, overlapping as in sample
symetry or size of pieces extending from the overlap is not important

8. Parallelogram
opposite sides approximately parallel
horizontal lines longer than vertical lines
angles approximately as in figure

9. Diamond — 4-sided figure with approximately equal sides
resting on one vertex
lines connecting opposite sets of vertices cross at approximately right angle (see figure)
lines connecting opposite sets of vertices nearly bisect each other (eg. in figure, segments a and b are no more than 1 1/2 time length of one another)
diamond is higher than it is wide



10. "V" 1 — For scoring purposes, figure is divided into central "V" and extending "wings". In the 19 point scoring system, each receives 1 point if correct. In the 15 point scoring system, both must be correct to earn 1 point.



V (in reference to horizontal line at base of figure)
bottom line of V at least 10 degrees off perpendicular
top line of V at least 10 degrees off parallel

Wings
both parallel to horizontal line at base of figure
left wing lower than right wing

11. "V" 2 For scoring purposes, figure is divided into central "V" and extending "wings". In the 19 point scoring system, each receives 1 point if correct. In the 15 point scoring system, both must be correct to earn 1 point.

V (in reference to horizontal line at base of figure)
bottom line of V at least 10 degrees off parallel
top line of V at least 10 degrees off perpendicular

Wings
top left wing perpendicular to V
lower left wing parallel to horizontal line at base of figure
two left wings meet at V
right wing parallel to horizontal line at base of figure
left wings higher than right wing

12. 3-D Figure In the 19 point scoring system, each of the following sets of criteria receives 1 point if correct. In the 15 point scoring syst both must be correct to earn 1 point.

Set 1
2 squares or equilateral parallelograms, the top one displaced to the left
at least 2 correctly connected sides
no extra lines other than minimal extensions of existing lines

Set 2
All of set one plus
equilateral parallelograms with angles as in figure
top parallelogram smaller than bottom one
all vertices connected

13. Cube In the 19 point scoring system, each of the following sets of criteria receives 1 point if correct. In the 15 point scoring system, both must be correct to earn 1 point.

Set 1
2 squares, overlapping as in figure to create a third small square (see figure)

at least 2 correctly connected sides
no extra lines other than minimal extensions of existing lines

Set 2
All of set one plus
all vertices connected
all lines approximately of equal length

14. "Peanut" 1 2 separate, closed figures

15. "Peanut" 2 2 closed figures, one within the other

APPENDIX
HUNTER COLLEGE CONSENT FORM

A. I, _____, understand that investigators at Hunter College are conducting a study examining human visual motor and visual spatial abilities in adults. I have been informed that this study involves research and that the purpose is to study visual motor and visual spatial abilities in order to advance our understanding of coordinated hand-eye movements and to aid in the diagnosis and treatment of neurodegenerative disorders. This research is being conducted as a doctoral dissertation project.

B. The expected duration of my participation is no more that 45 minutes for one session only.

The procedures are as follows:

1. A brief medical history will be obtained to determine chronic illnesses.
2. Visual acuity will be measured using a Snellen-like chart.
3. Hand movement performance will be measured by opening and closing the hand and alternating movements of the fingers.
4. The modified Mini Mental Status test will be administered.
5. A test of object assembly will be administered consisting of placing beads on a stand, and drawing a cube. During this task, the subjects hand movements will be videotaped in order to assist investigators in quantifying the data.

D. There are no real risks in this procedure. Tests of object assembly are performance and pencil and paper tests which require no extreme physical exertion.

E. The benefits that may be gained from this procedure are: none. Benefits may be gained if consistent information is found in neurophysiological abilities, which would assist clinicians in planning patient treatment. Findings from the study will be made available to the participant.

F. I understand that I will receive a copy of this consent, and that the information obtained from me in this study is strictly confidential.

G. I have the opportunity to ask questions about the procedures used and can at any time withdraw from participating if I so choose without penalty or loss of benefits. I may review the completed videotape and if I so choose, may ask that it not be used (either in whole or in part). If I have questions about this study, I may contact Christine M. Weber, (Ph.D. Candidate and Principle Investigator) at 718-699-7613 or 212-305-2503 or Dr. Victoria Luine, Advisor at 212-772-4223.

H. I understand that the information obtained in this study will be kept confidential and my participation is anonymous. Videotapes will be viewed by investigators conducting this study. They will be stored in a locked cabinet at Hunter College.

I I agree voluntarily to participate in this study

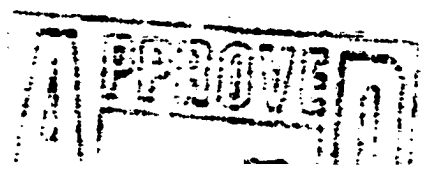
Signature of Subject_____ Date_____

INVESTIGATOR'S STATEMENT

I have offered an opportunity for further explanation of this procedure to the individual whose signature appears above

_____
Graduate Student - Biopsychology

_____Ph.D.
Faculty Advisor



STUDY ID _____ DATE _____

Matching and Recognition

APPENDIX 7

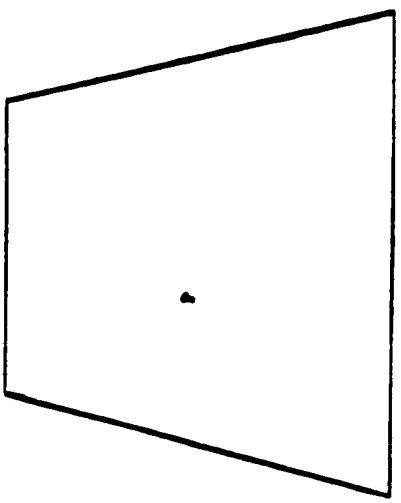
BENTON VISUAL RETENTION TEST

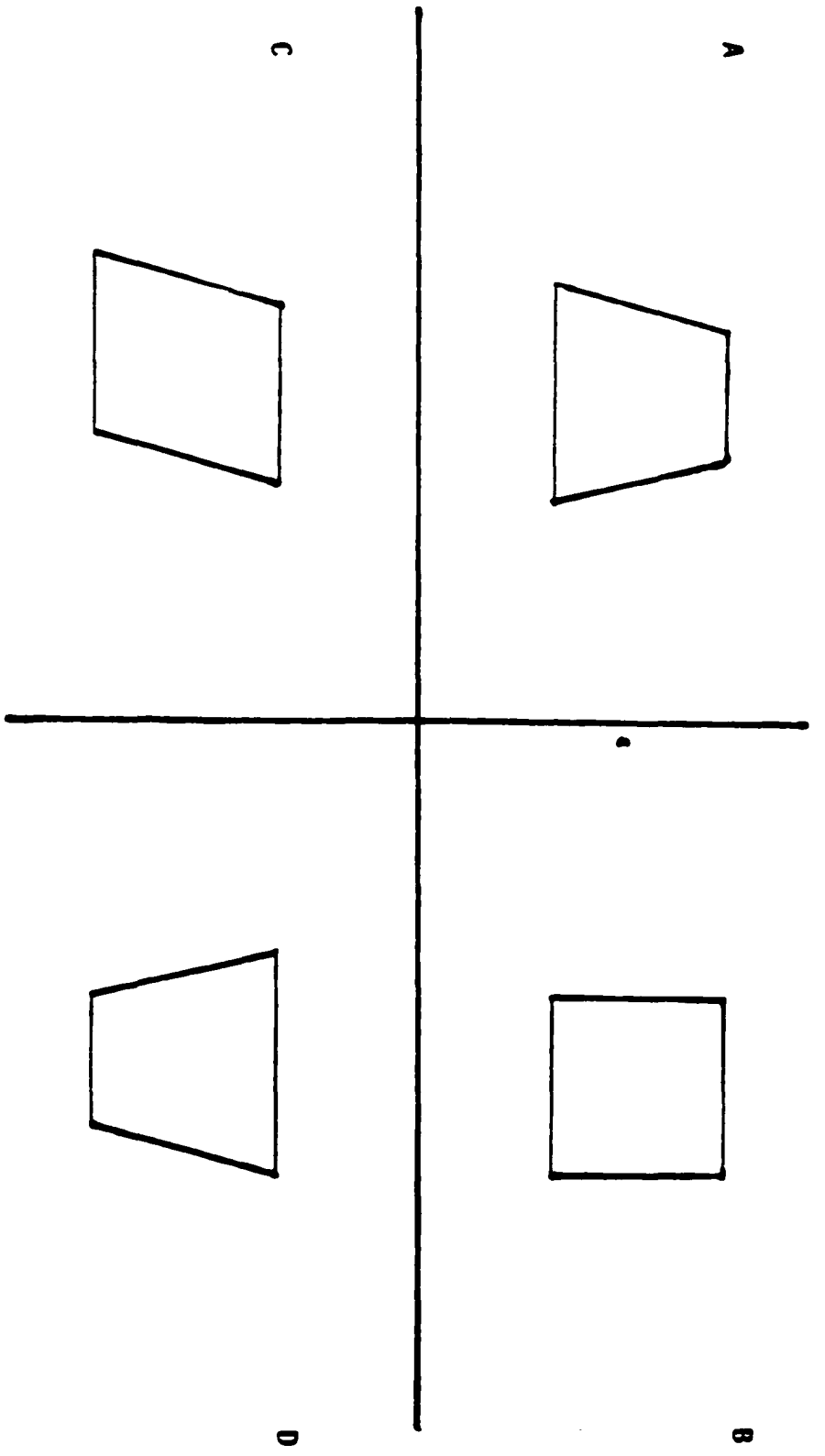
Practice items (given at time 2): 1.____ D 2.____ A 3.____ D

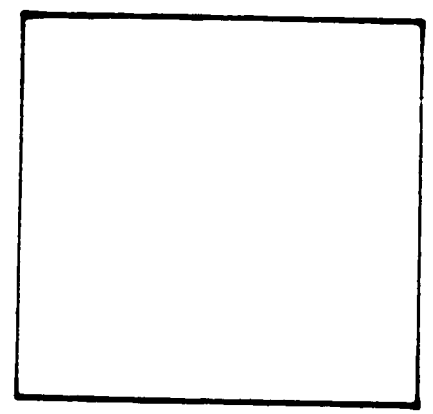
MATCH			DELAY		
Number	Choice	Answer	Number	Choice	Answer
C1	_____	D	D1	_____	B
C2	_____	B	D2	_____	C
C3	_____	C	D3	_____	C
C4	_____	C	D4	_____	D
C5	_____	B	D5	_____	C
C6	_____	D	D6	_____	D
C7	_____	B	D7	_____	B
C8	_____	A	D8	_____	D
C9	_____	A	D9	_____	C
C10	_____	C	D10	_____	B

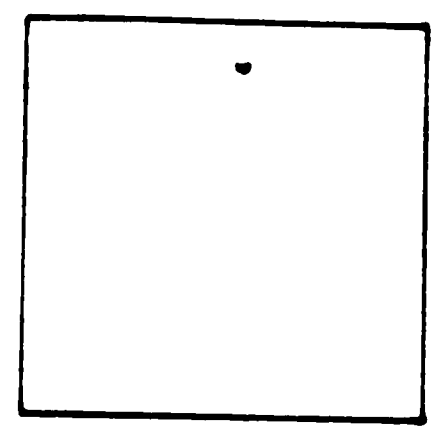
CORRECT _____/10

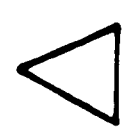
CORRECT _____/10











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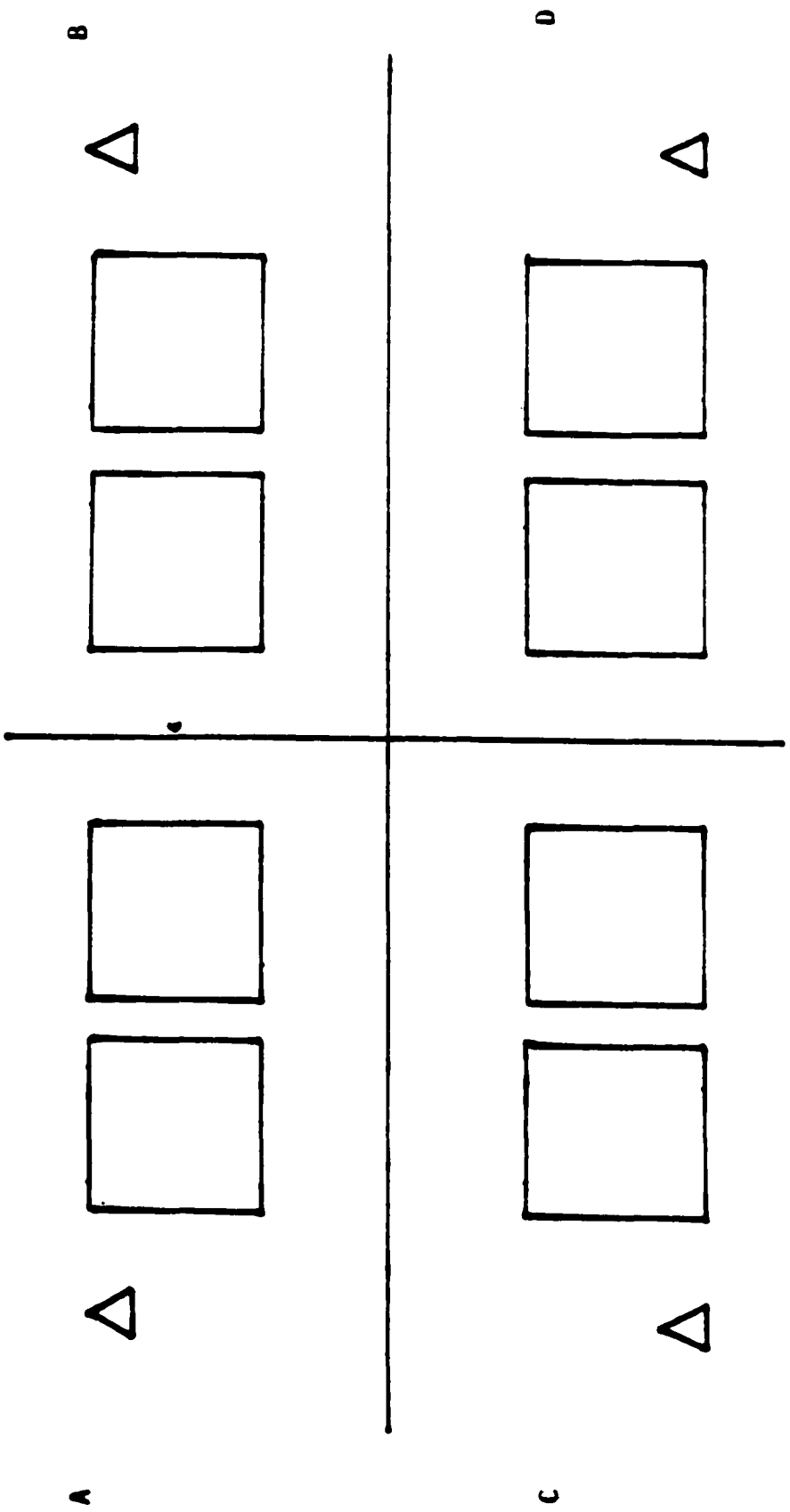

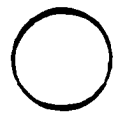

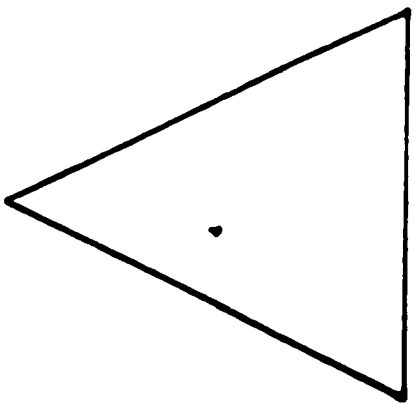

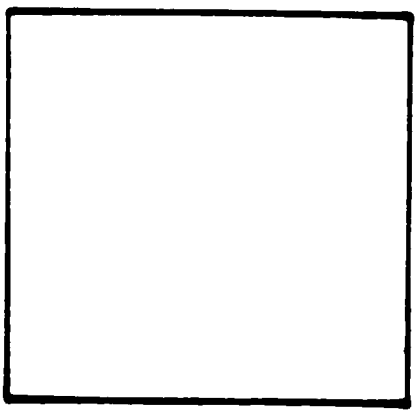

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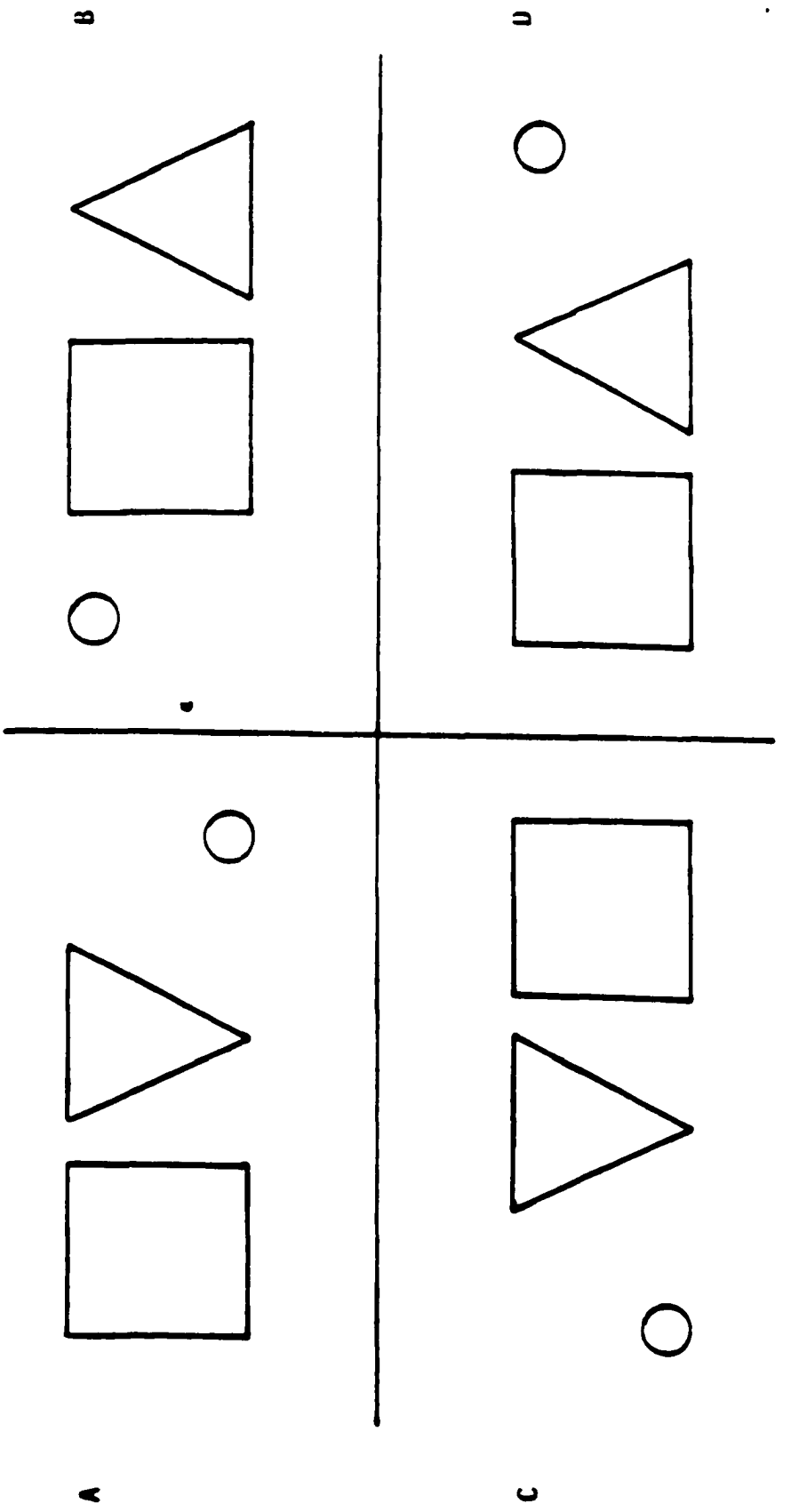

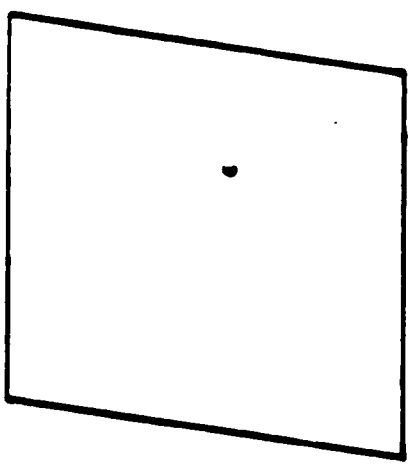

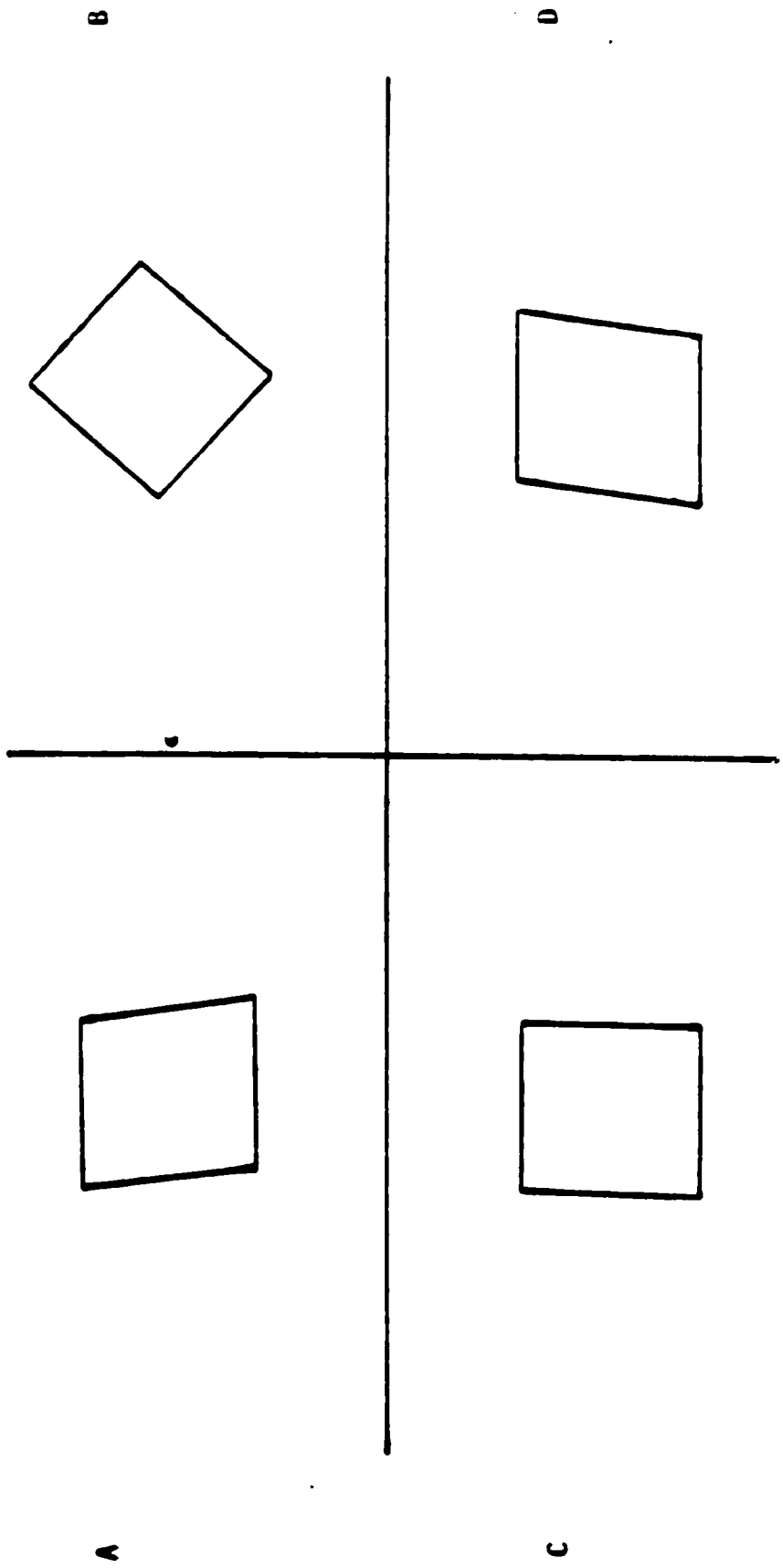

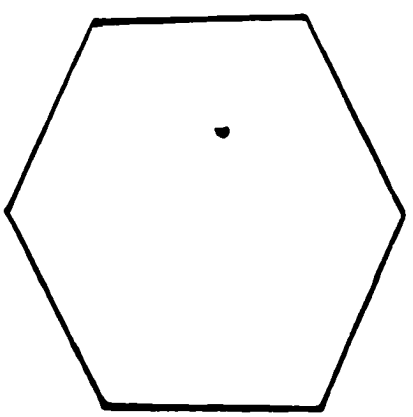

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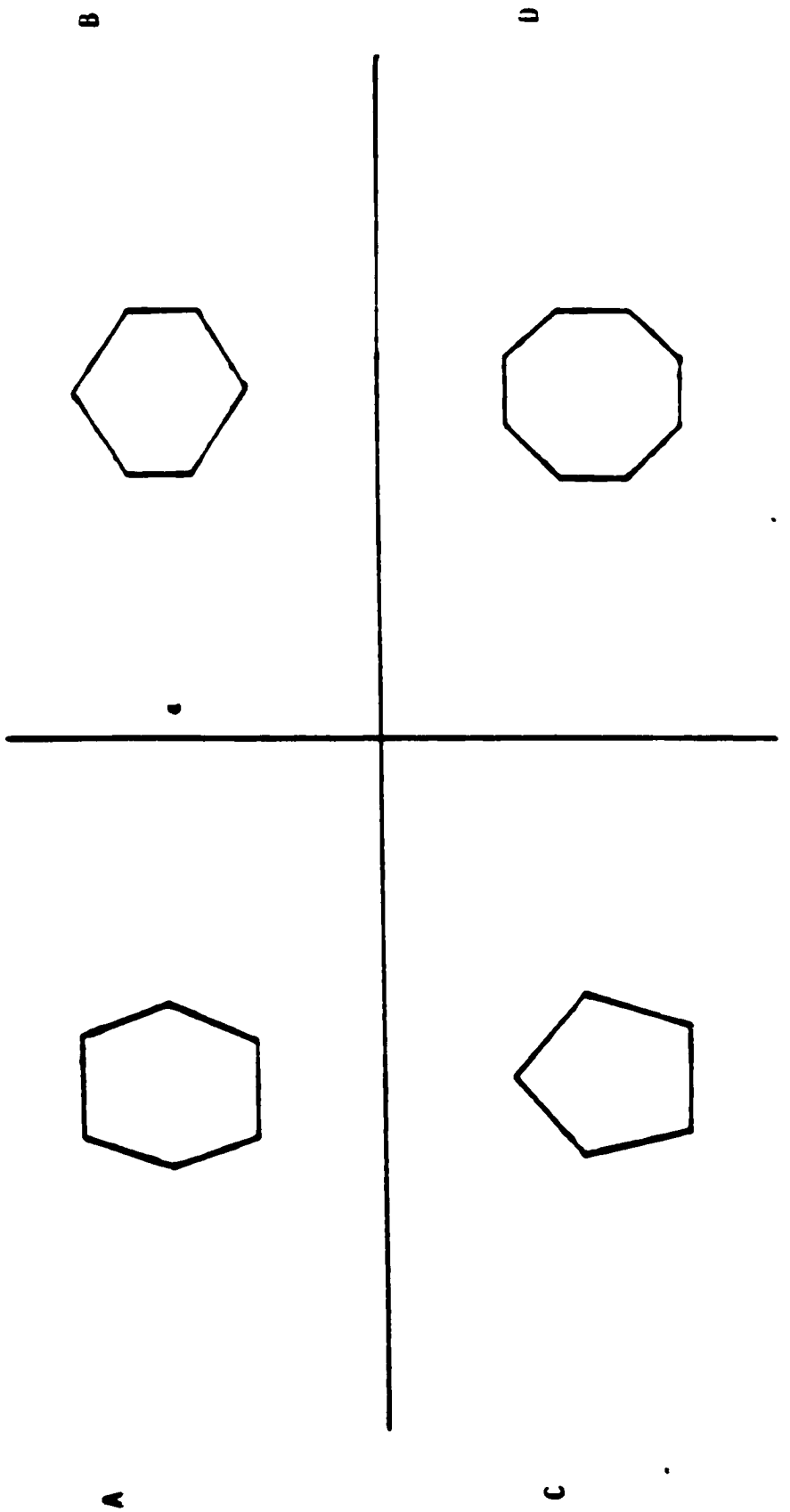

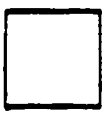

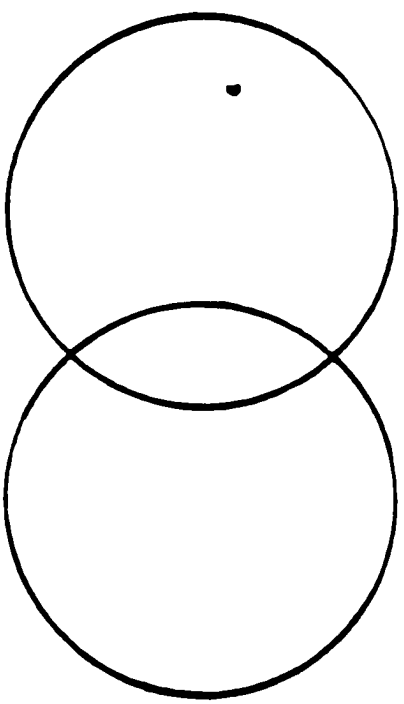

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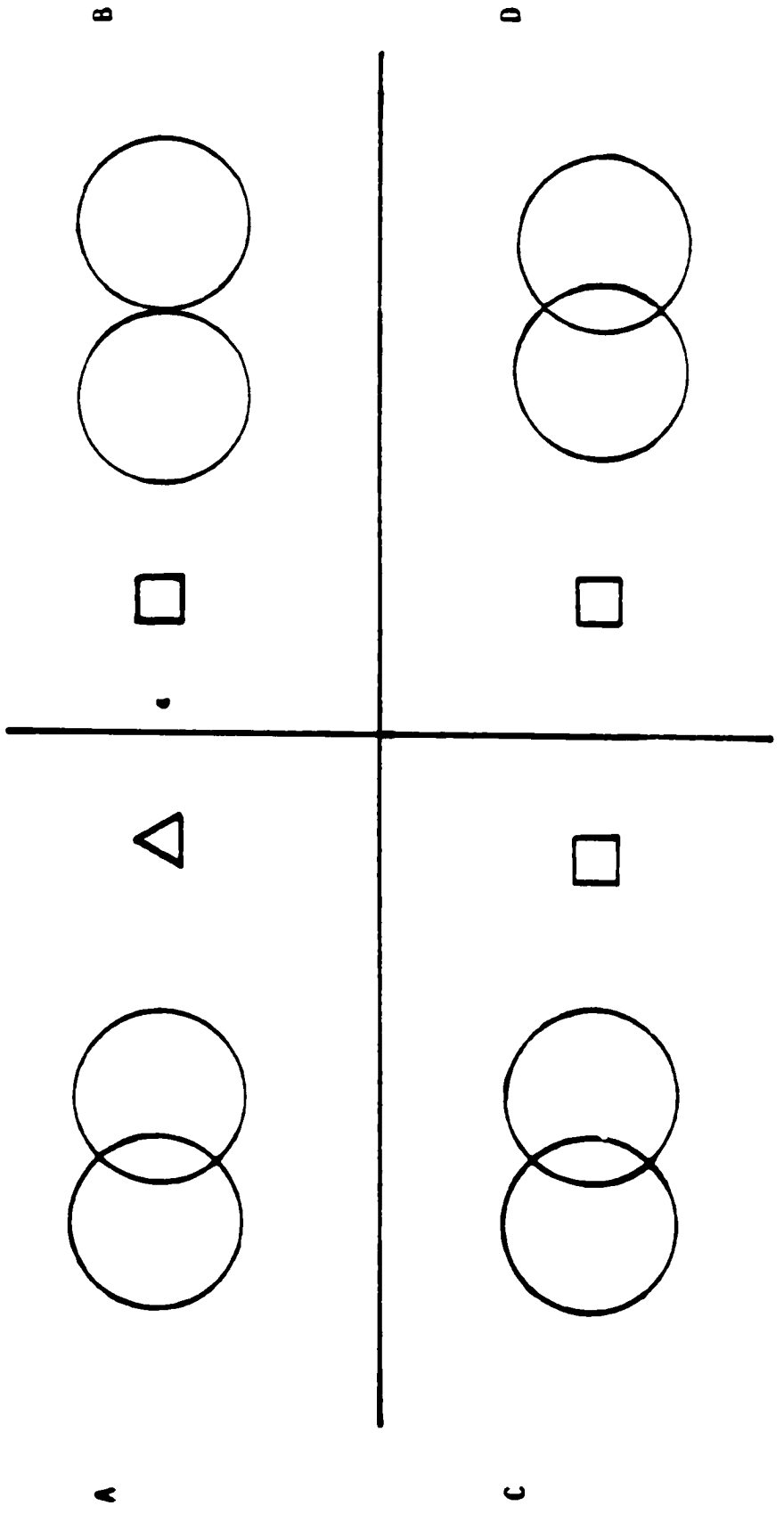

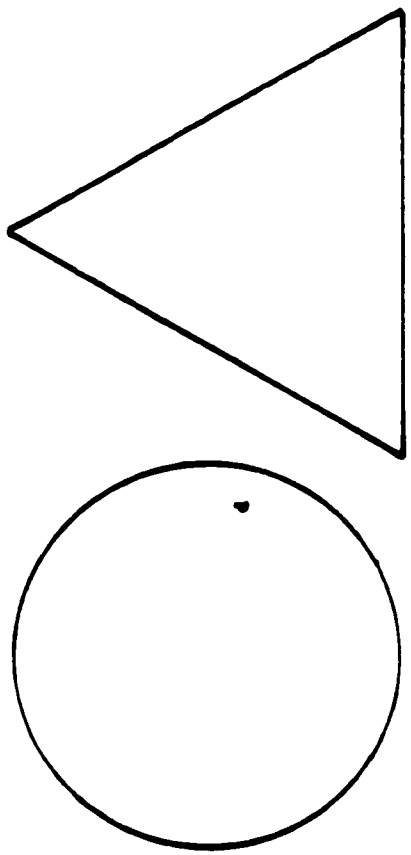

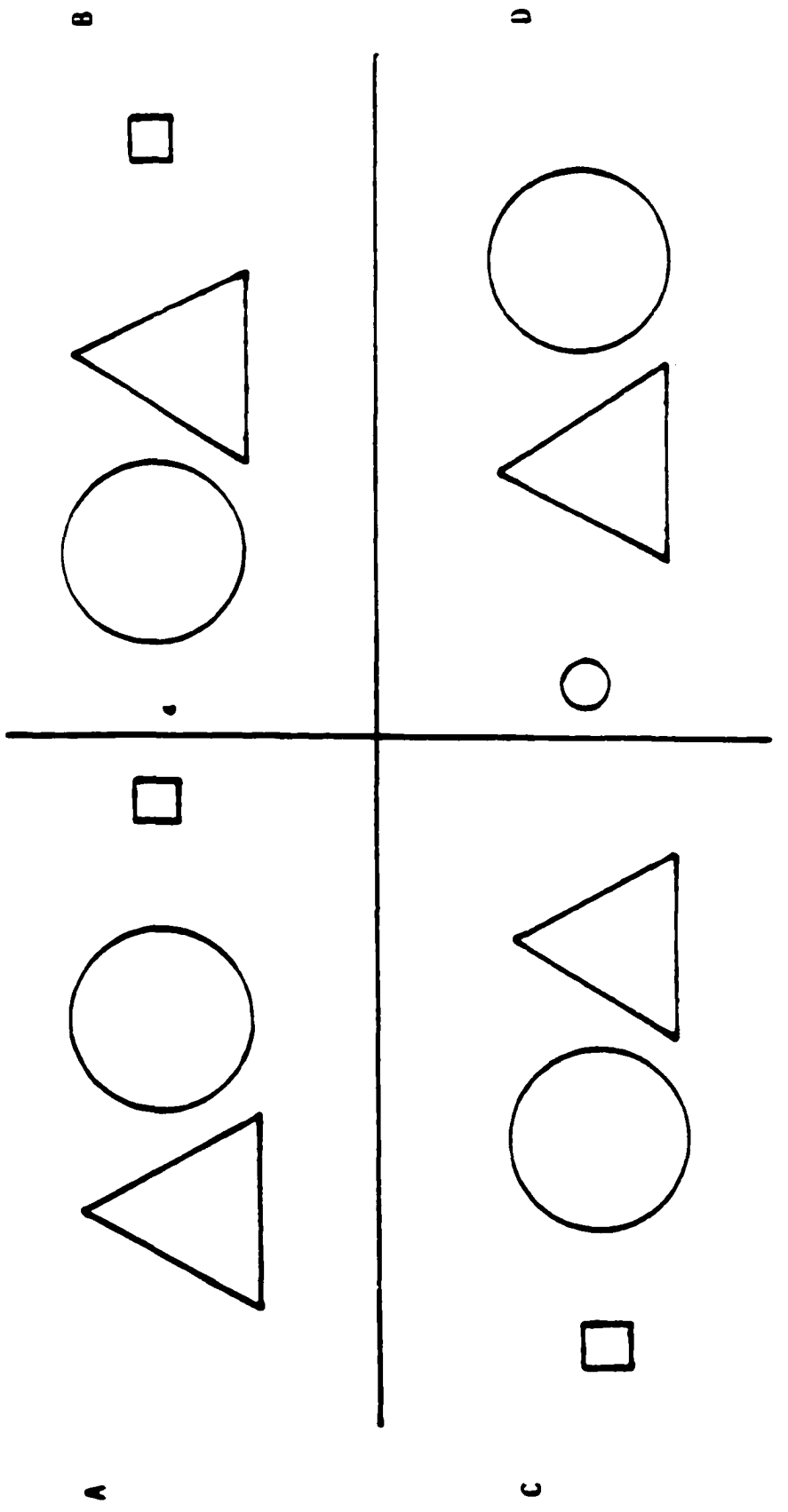

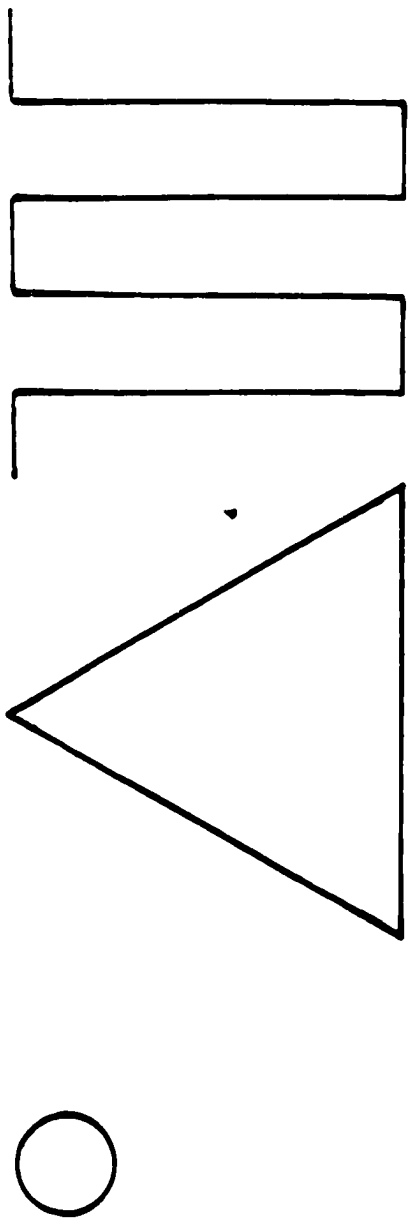

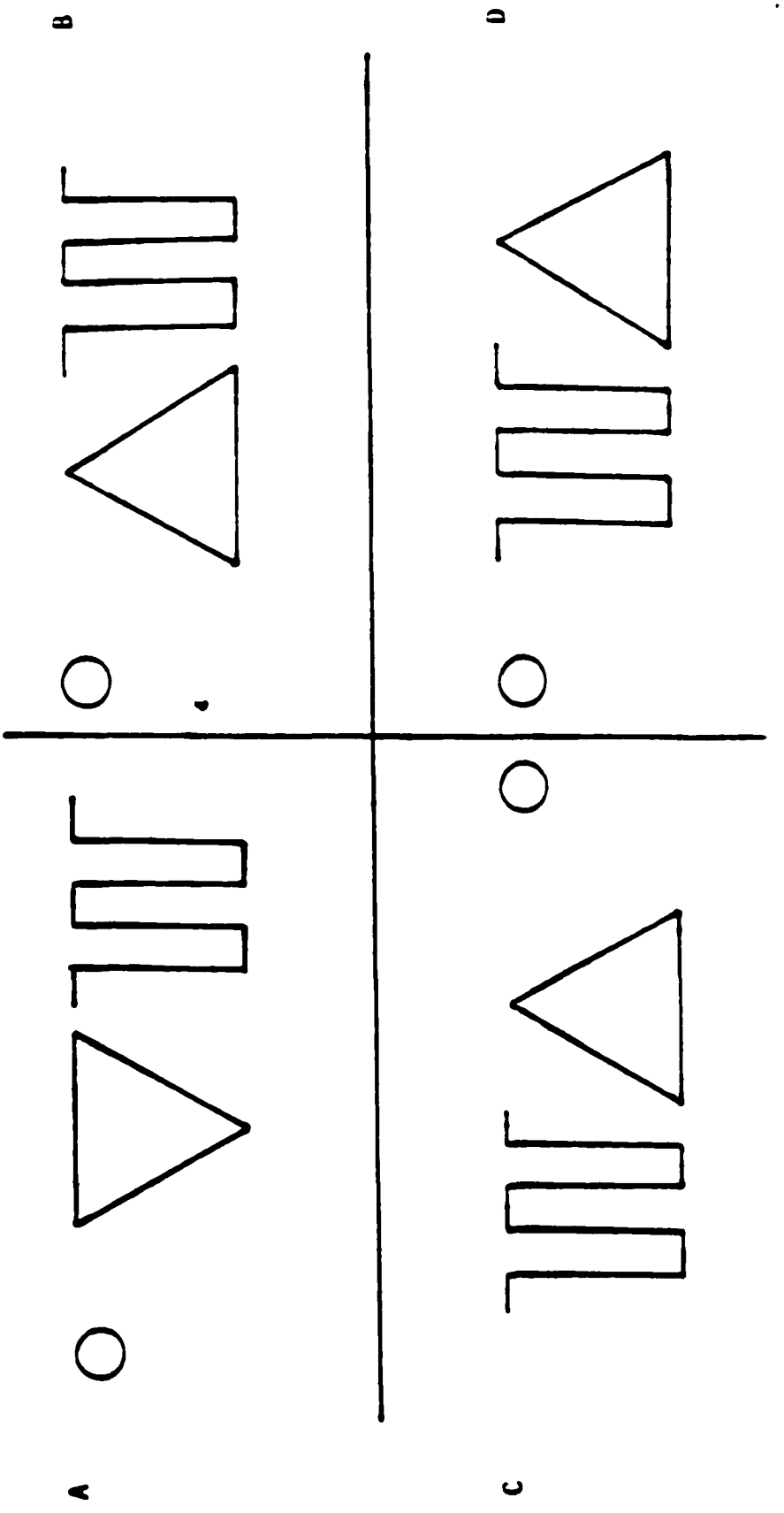

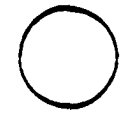

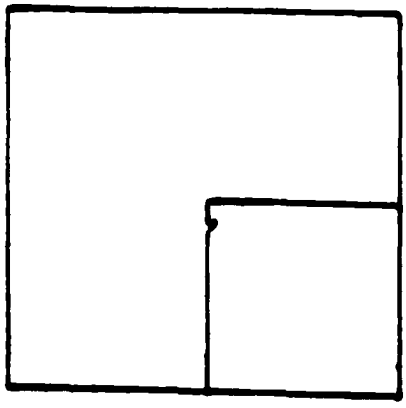

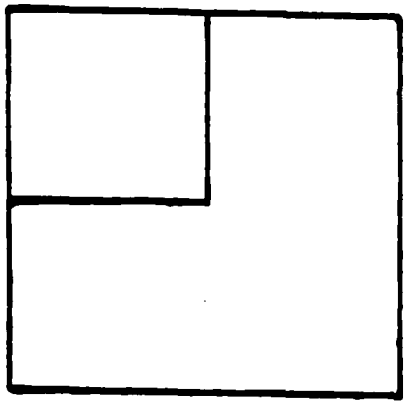

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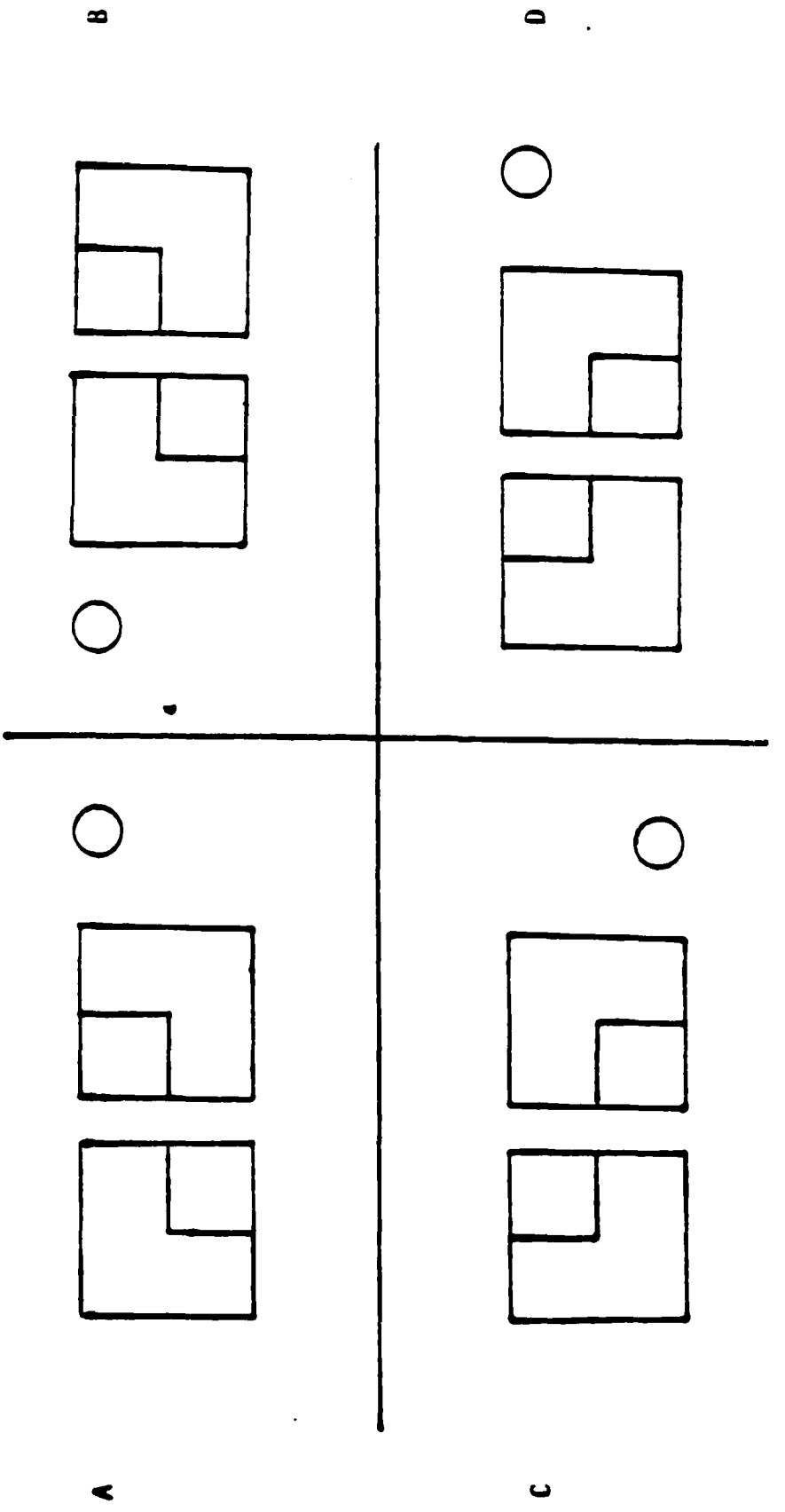

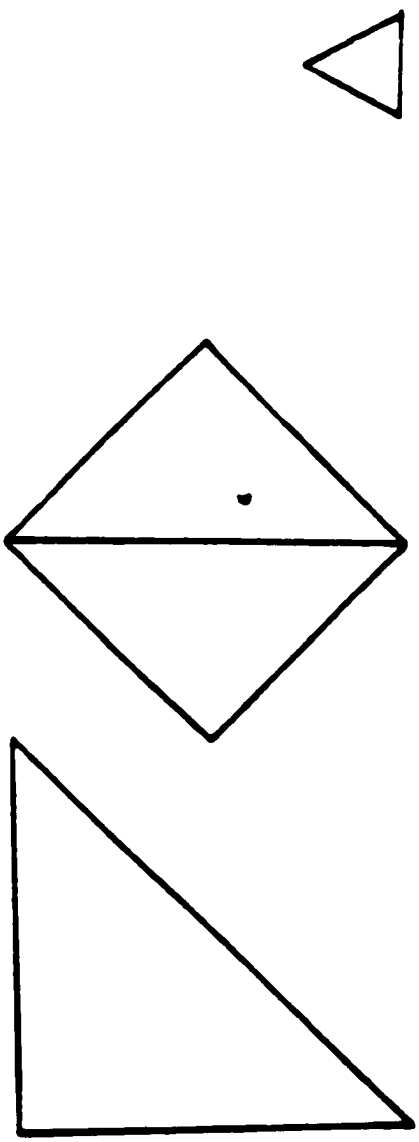

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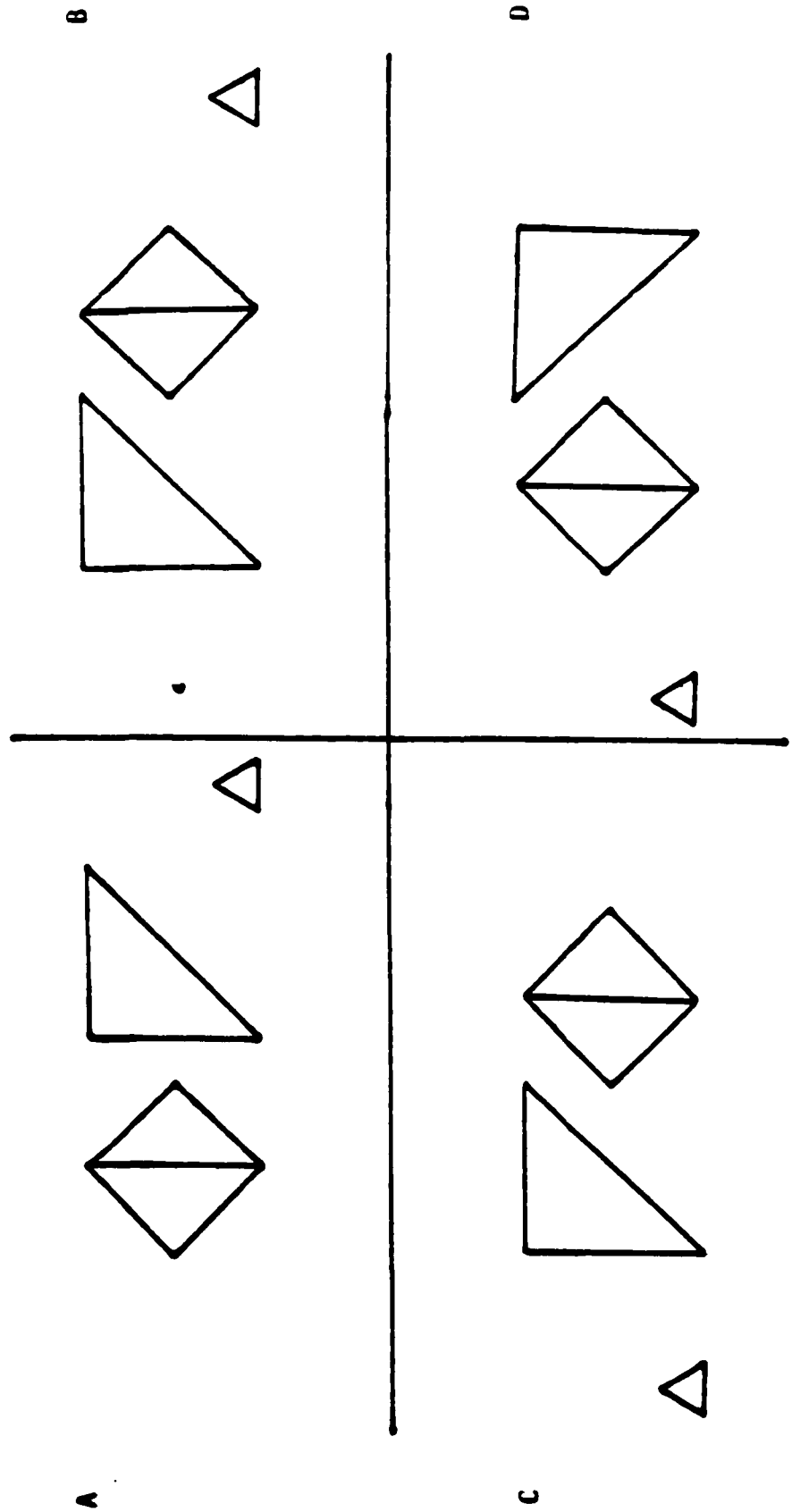

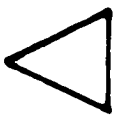

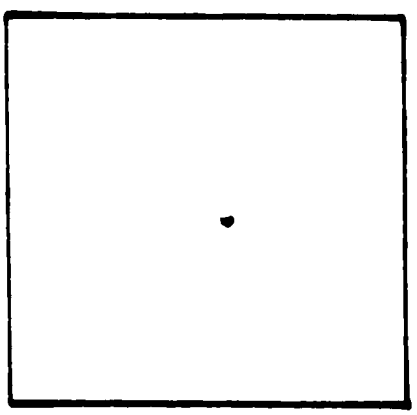

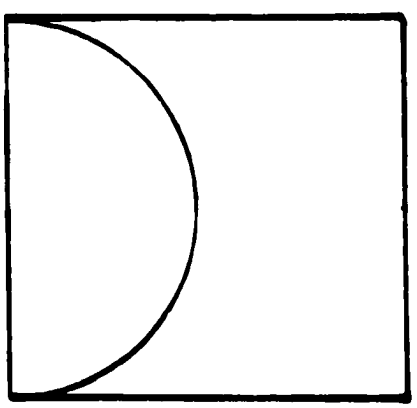

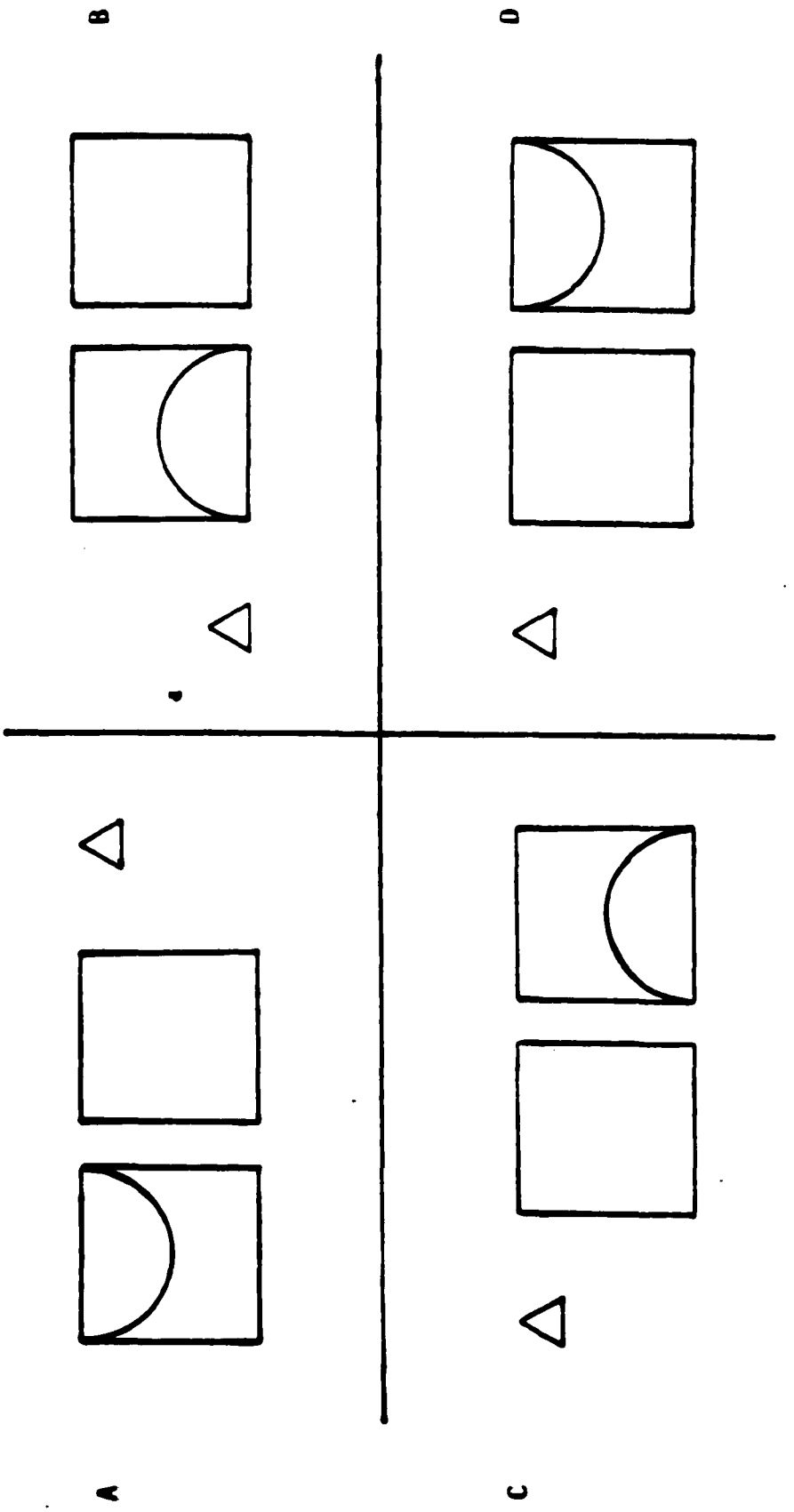

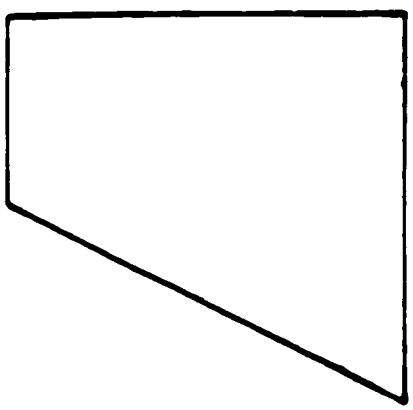

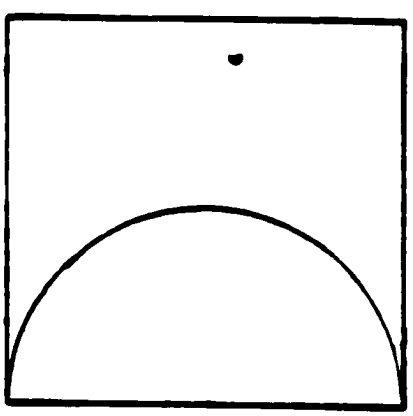

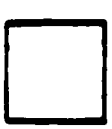

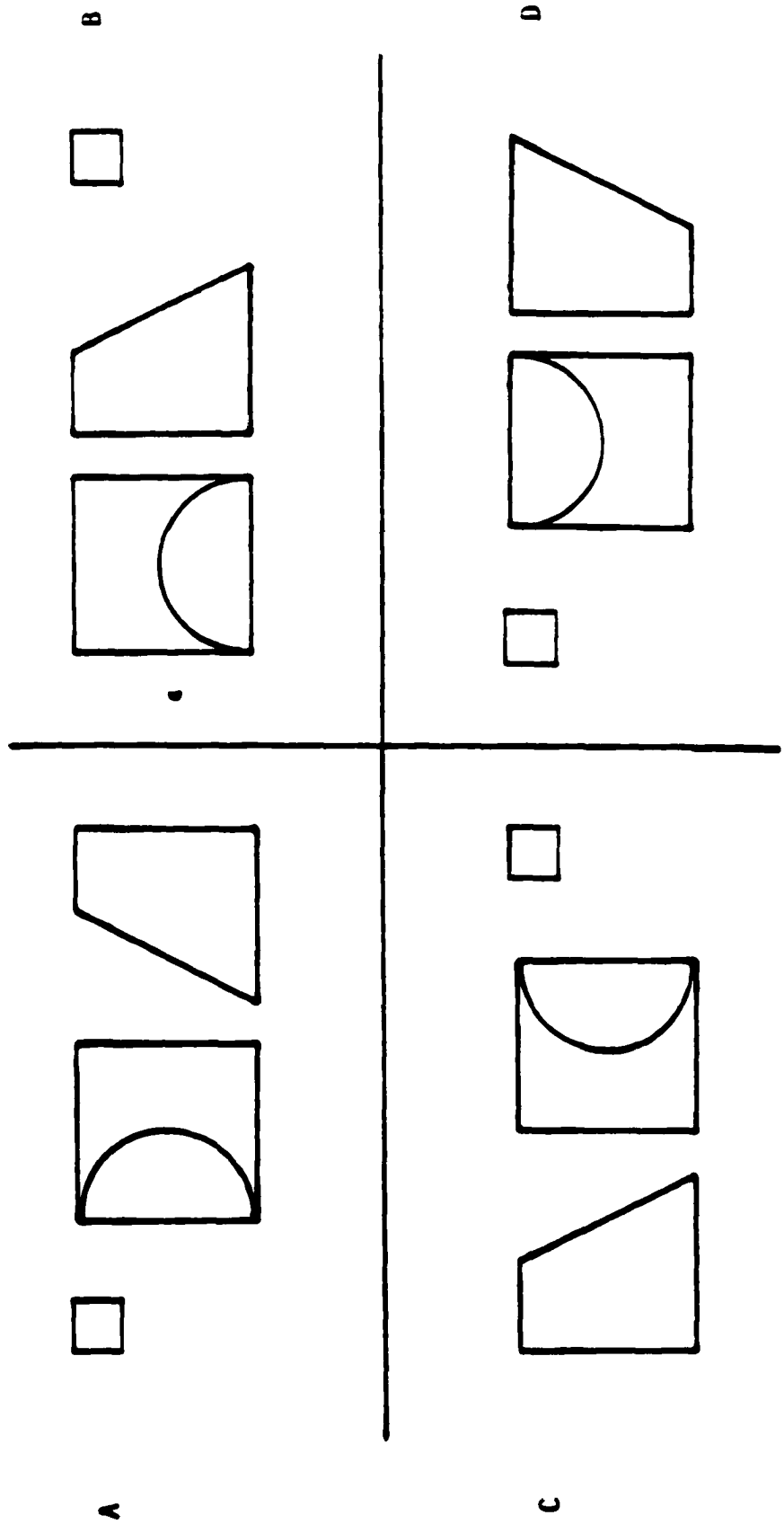

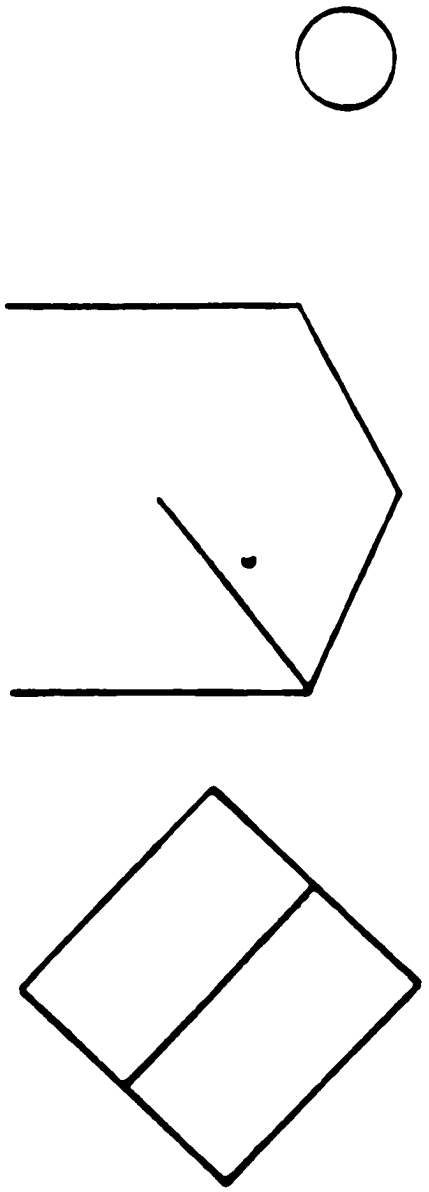

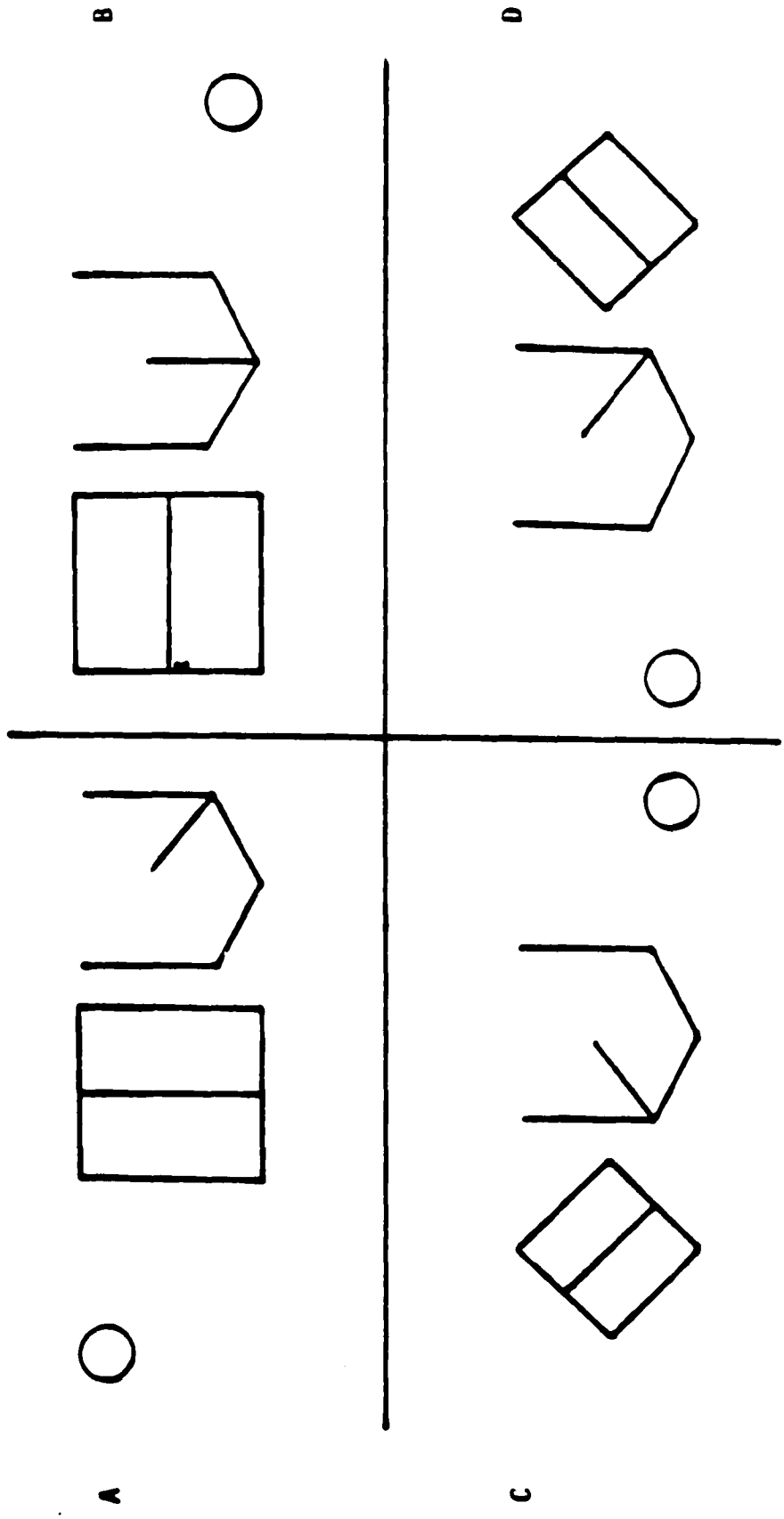

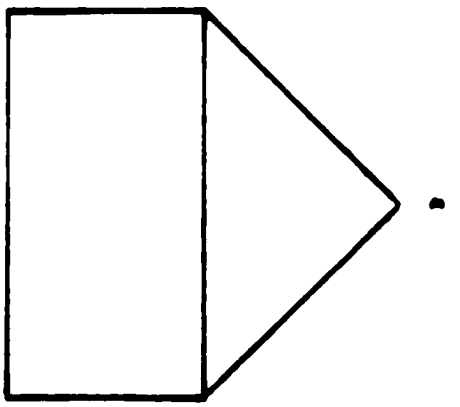

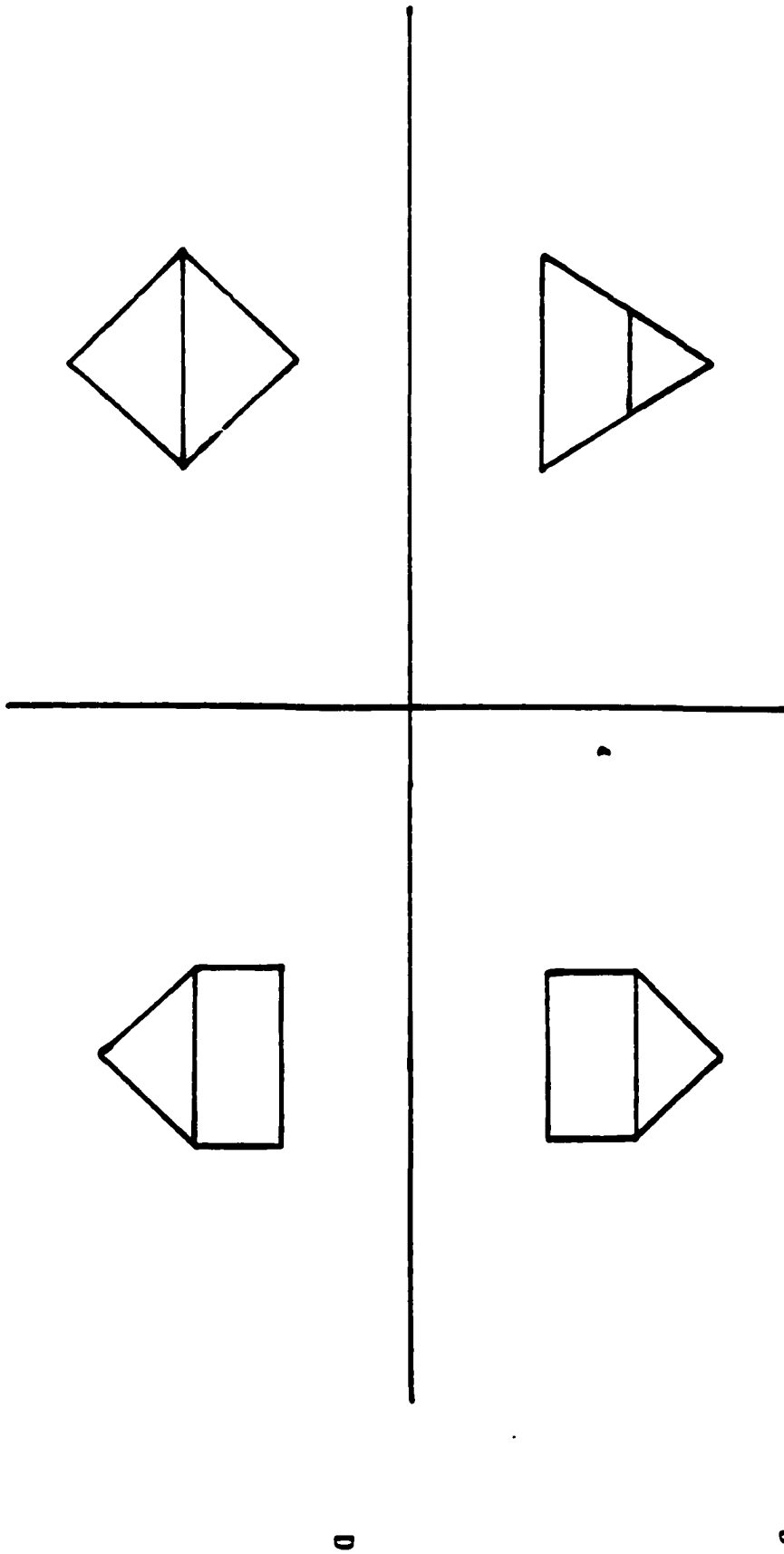

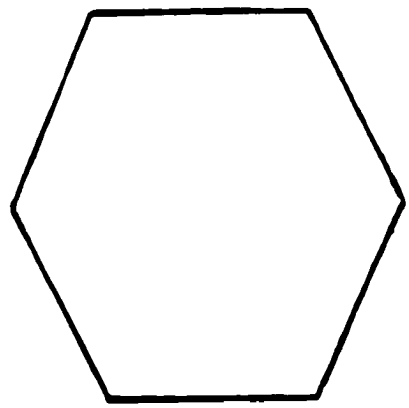

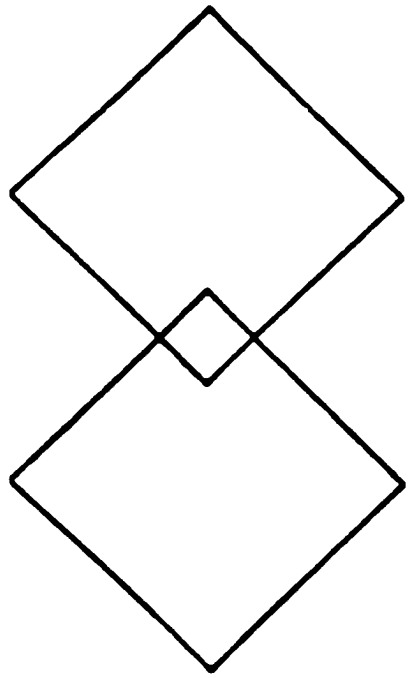

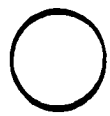

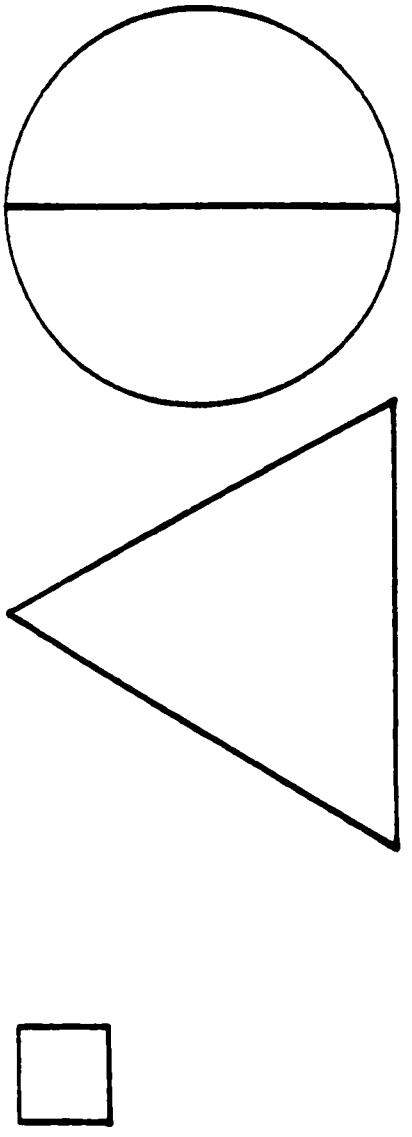

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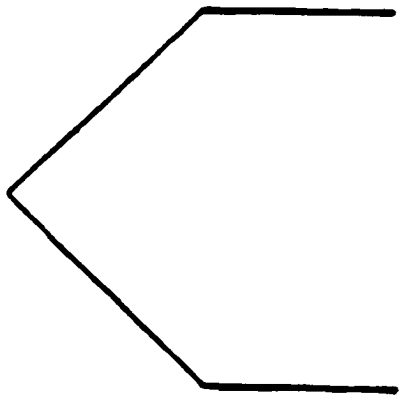

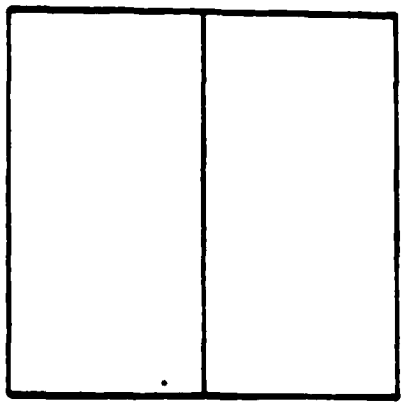

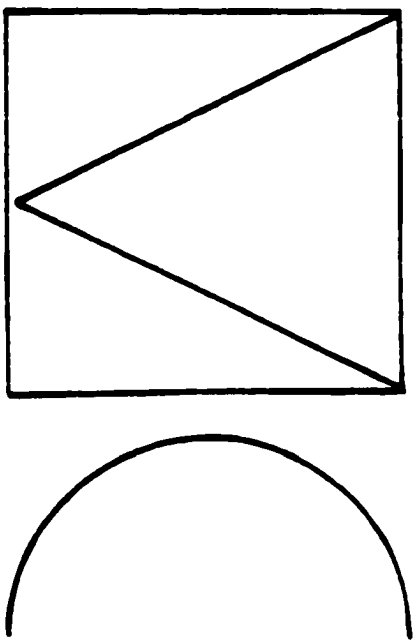

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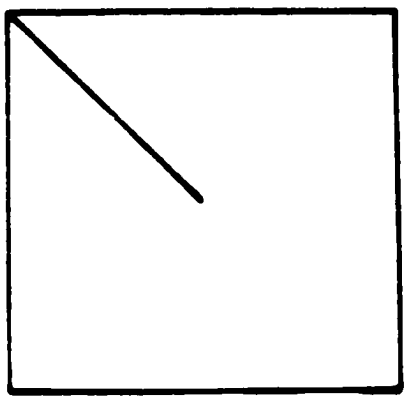
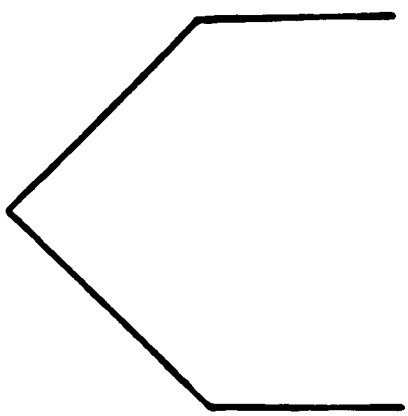
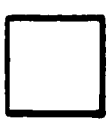
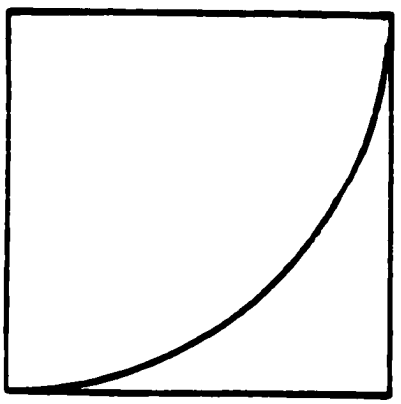
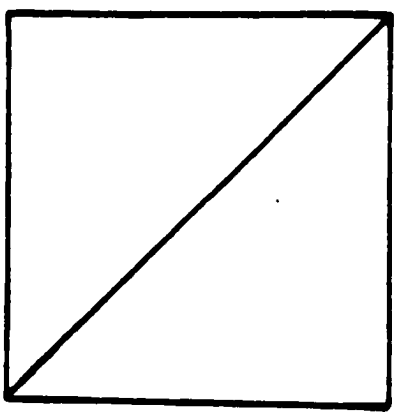
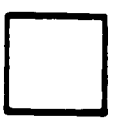












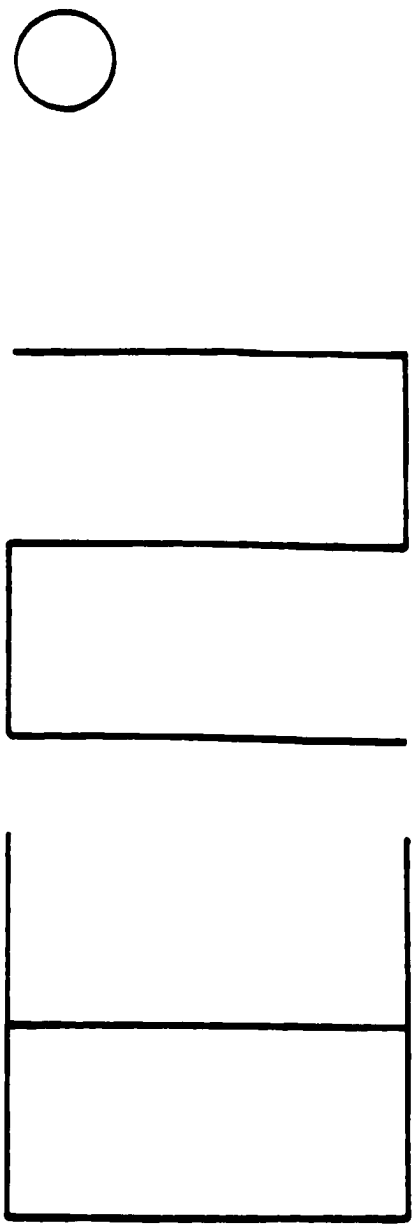
The relationship

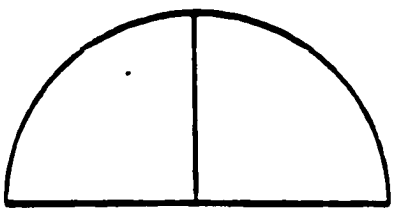
C

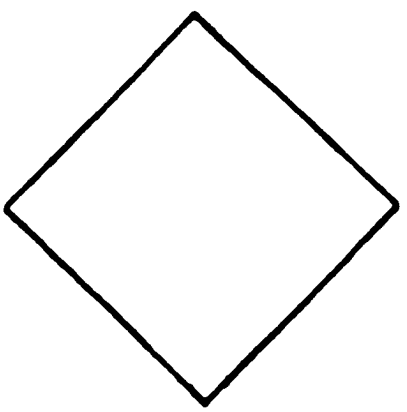
A

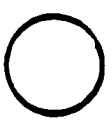
D

B









The relationship

APPENDIX 8

ROSEN DRAWING TEST

5-ITEM

NAME:_____

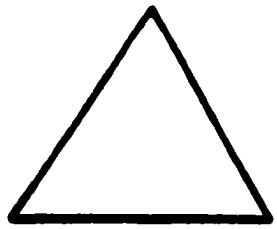
DATE OF TESTING:_____

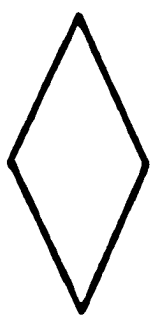
SEX:_____

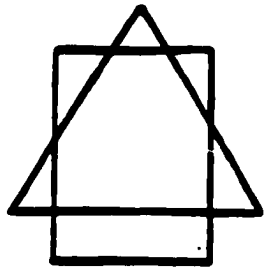
DATE OF BIRTH:_____

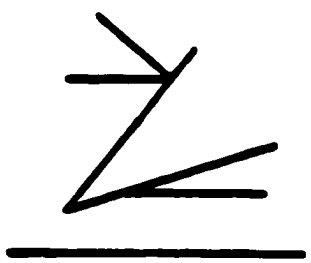
HANDEDNESS:_____ **AGE:**_____

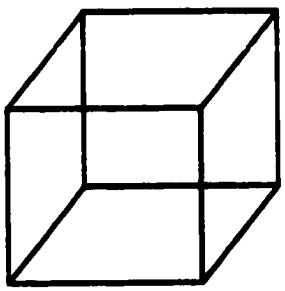
EDUCATION:_____











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