DIFFERENTIATING DEMENTIA SUB-TYPES USING NOVEL NEUROCOGNITIVE PROBES

By

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A THESIS PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
MASTER OF SCIENCE

UNIVERSITY OF FLORIDA

2011

To my family and friends

ACKNOWLEDGEMENTS

I thank my research chair, Dr. Russell Bauer for his guidance and support. He has been an invaluable leader and resource throughout this project, from conceptualization to analysis. I would also like to thank the other members of my committee, William Perlstein, Patricia Durning, and Steven Boggs. Finally, I am grateful for the loving support from my family throughout my gradual studies.

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August 2011

Chair: Russell M. Bauer
Major: Psychology

Differentiating subtypes of dementia is important from a treatment and counseling perspective. Regarding treatment, certain medications have particular effectiveness in slowing the progression of particular types of dementia. Regarding counseling, correct diagnosis can lead to more accurate prediction of disease progression, which is useful information for families. This project seeks to differentiate dementias associated with medial temporal dysfunction (Alzheimer's disease, AD) from those primarily involving lateral temporal and frontal lobe damage (Frontotemporal dementia, Semantic dementia, FTD) using reasoning tasks (transitive inference (TI), syllogistic reasoning(SR)) previously shown to be sensitive to damage in these regions. Six participants diagnosed with AD, four with FTD, five with mild cognitive impairment (MCI) and 17 healthy controls were enrolled in this study. All participants completed both reasoning tasks. The control group performed close to ceiling on both tasks. The SR task was shown to successfully differentiate all participants with cognitive impairment from the healthy controls. The TI task successfully differentiated the dementia (AD/FTD) groups from the MCI and healthy control group. Education was found to be a

significant factor related to task performance such that participants with higher education scored higher. Although there was a trend toward the hypothesized double dissociation, the sample size was not large enough to yield a statistically significant distinction between AD and FTD group performance on the reasoning tasks. Future studies could further elucidate the nature of impairment in these reasoning tasks associated with medial temporal lobe insult and the factors (medical, health, psychosocial) which contribute to successful performance. It is hoped that the addition of these sensitive neurocognitive probes will contribute positively to disease diagnosis in the context of an interdisciplinary dementia workup.

CHAPTER 1
BACKGROUND

Declarative memory is representational and provides a method for modeling the external world. While non-declarative memory relies on a network distributed across cortical, subcortical and cerebellar regions, declarative memory is mediated primarily by a distributed memory system that prominently includes the medial temporal lobe (MTL) memory system. MTL is involved in the assimilation of sensory inputs into a unified, autobiographical experience to be stored for later retrieval, a process referred to as episodic memory. In contrast, the lateral temporal lobe (temporal cortex) codes multimodal representations necessary to support semantic memory and general knowledge not tied to specific episodes. MTL structures are implicated in rapid, conjunctive learning while more lateral structures are suggested to mediate recognition and slower associative learning over repeated trials.

The MTL is responsible for the transformation of experience into durable memory that can be consciously remembered following a filled delay (Lepage, 1998; Paller and Wagner, 2002; Wagner, 1999; Squire and Wixted, 2010; Ranganath, 2010). More specifically, the hippocampal formation (hippocampus, subiculum, parahippocampal and dentate gyri) is necessary for declarative memory tasks that require the processing of relationships between multiple stimuli *(*Preston and Gabrielli*,* 2002; Langston et al, 2010*).* Within the literature there is much debate about the specialized function of the individual structures within the hippocampal formation. Theory supports the hippocampus and parahippocampal gyrus as critical for declarative memory. In the last decade, researchers have worked to parse the unique contribution of each MTL structure to declarative memory (Ranganath, 2010). In 2002, Davachi and Wagner

showed hippocampal activation during a relational processing task using an fMRI paradigm. Relative to the relational task, item-based processing was associated with greater entorhinal cortex and parahippocampal gyrus activation, pointing to a functional dissociation between these structures and the hippocampus. This dissociation is supported by several current theories including relational memory theory and complementary learning systems theory (Ranganath, 2010). Although arriving at this conclusion somewhat differently, these theories suggest that there is a distinction between recollection and item-recognition and that these cognitive processes are mediated by different neural regions. The perirhinal cortex is capable of supporting item-recognition in the absence of relational information (as is the case with hippocampal lesion). Item-based recognition can be achieved simply by making familiarity judgments. It does not require making associations between items or the contexts in which those items were previously encountered. However, recollection of the autobiographic context in which those items were learned requires multi-modal sensory input to be bound into a unified representation of the experience during which the item was encountered. The hippocampus is required for the development of these conjunctive representations of information and for their later recall.

However, these findings remain in controversy. Stark, Bayley and Squire (2002) showed that the hippocampus is equally involved in associative tasks and recognition memory, as well as in single-item declarative memory tasks. However, it is unclear whether this experiment was capable of clearly dissociating these two processes. Indeed, Heckers et al. (2004) contest this argument suggesting a dissociation between hippocampus and parahippocampal function. In their study, participants performed a

transitive inference task while hippocampal and parahippocampal activation was recorded using BOLD fMRI. Their results showed activation in the hippocampus when participants recalled relations among test items, while the parahippocampal gyrus activated during familiarity and recency judgments about test items. These authors concluded that the parahippocampal gyrus supports immediate access to previously learned information while the hippocampus creates a flexible representation of stored information. Preston and Gabrieli (2002) state that tasks relying on relational processing (e.g., paired-associative learning) would be greatly affected by hippocampal damage. By showing that amnesia patients with focal hippocampal lesions performed poorly on associative learning tasks, these authors hypothesized that the hippocampus is essential for encoding multiple relations between experience, rather than multiple elements of a single experience. Thus, the hippocampus may contribute uniquely to the ability to infer relationships among sequences of items.

Paired-associative learning tasks are considered among the most sensitive clinical measures of impaired memory (Erickson and Scott, 1977). Transitive inference (TI), a form of associative reasoning, has been shown to be sensitive to medial temporal/hippocampal damage in animals and humans (Wynne, Delius, and Staddon, 1991; Devito, Kanter, and Eichenbaum, 2010). Human neuroimaging studies have verified the key contribution made by the hippocampus to this task (Heckers, et al., 2004). In a typical TI task, participants are shown a series of paired stimuli (A-B, C-D) in a response-reward paradigm, and selection of one member of the pair (underlined in this example) is consistently reinforced. After being exposed to a number of trial pairings, healthy participants are able to construct a hierarchy from overlapping pairs of

reinforced stimuli such that A>B, B>C, C>D, D>E occurs, where > denotes a reinforced response. When items A and B are presented together, the selection of A is reinforced. However, when B and C are paired, B is reinforced and C is not, and so forth. Once all pairs have been shown, previously unpaired (e.g., A-C, B-D) stimuli are presented together, and the subject is directed to choose the correct response. TI ability is shown in the participant's ability to derive the implied hierarchical relationship among untrained stimuli. For example, when A and E are paired together, A is the correct response because it has always been reinforced while E has never been reinforced. When B and D are paired, both of which have been reinforced on 50 percent of trials, B is the correct response because B>C and C>D. TI shows promise as a sensitive neurocognitive probe of medial temporal function, and has been shown to be sensitive to medial temporal/hippocampal damage (Barker), but it has not yet been evaluated in dementia.

Syllogistic reasoning (SR) tasks are similar to transitive inference tasks except that they capitalize on previously-learned associative relations, while TI involves the episodic formation of new associations. Additionally, TI involves the ability to form a hierarchical representation of the whole stimulus set. In contrast, SR tasks provide a preexisting relation such as direction (e.g., A is east of B; B is east of C; what is the relationship between A and C?) and evaluate the ability to reach an appropriate conclusion. Since this type of reasoning depends upon existing knowledge structures (semantic memory), rather than the formation of new episodic memories, it is more sensitive to cortical damage. In particular, patients with lateral temporal damage attendant to Frontotemporal dementia (FTD) have shown impairment on such tasks.

Tierney et al. (2009) demonstrated that patients with a subtype of FTD (semantic dementia) were impaired on SR tasks with familiar stimuli.

In contrast to the anterolateral temporal and frontal polar cortical damage that exists in FTD, Alzheimer's disease (AD) involves from its outset pathological changes that primarily affect the transentorhinal cortex, hippocampus, and other MTL structures. The primary defect is a defect of episodic memory. Therefore, theory-driven evaluation of dissociable performance patterns in these dementia sub-types may offer unique insights into the memory functions of these neuroanatomical regions. In early stages of dementia, AD and FTD are difficult to distinguish on the basis of clinical examination or neuroimaging. The current study evaluates the utility of TI (which focuses on a particular form of episodic memory) and SR (which focuses on the ability to draw conclusions from semantic relations) in differentiating these two forms of dementia.

Based on this background, the primary aim in this project is to evaluate the ability of two novel learning tasks (transitive inference, syllogistic reasoning) to differentiate between medial-temporal and lateral-temporal insult. Early clinical detection of dementia is critical to providing effective symptom management and family support. There are no published studies examining the potential for these two learning tasks to provide valuable information that can aid healthcare professions during the diagnostic process, so investigating the ability of these tasks to differentiate between participants diagnosed with either AD or FTD may lead to a useful new diagnostic tool. Additionally, results have the potential to further the understanding of relational memory and its neuroanatomical underpinnings. The hypothesis is that TI is differentially sensitive to episodic memory impairments resulting from hippocampal system damage, while SR is

differentially sensitive to cortical semantic impairment. The key experimental predication is that AD patients should perform worse on TI than on SR, while patients with FTD should show the opposite pattern. Healthy controls should show no, or less significant, impairments on either task.

The second aim of the study was to evaluate the sensitivity of these measures to preclinical levels of impairment broadly known as Mild Cognitive Impairment. The development of neurobehavioral probes sensitive to preclinical impairment is a critical step in identifying individuals at risk for developing dementia in the future. Preclinical detection of dementia can have a dramatic impact on clinical care (Boustani, et al., 2003). As the two dementia populations are most difficult to discern early in the disease progression, the second aim in this project is to evaluate the effectiveness of the two learning tasks in assessing the presence of preclinical dementia symptoms by effectively distinguishing participants diagnosed with MCI from healthy controls and those diagnosed with either dementia sub-type. The TI and SR tasks were, therefore, evaluated to determine whether they are sensitive enough to detect mild cognitive impairment. Moreover, the hypothesis stated that participants with MCI would perform worse on both tasks than healthy controls but better than participants diagnosed with either AD or FTD.

CHAPTER 2
METHODS

Participants

Participants were recruited from the University of Florida Memory and Cognitive Disorders Clinic and included patients with Alzheimer's disease (AD; N=6), Frontotemporal Dementia (FTD; N=4), Mild Cognitive Impairment (MCI; N=5) and healthy controls (N=17). Exclusion criteria were: 1) history of learning disability; 2) severe head injury; 3) substance abuse sufficient to have warranted medical or behavioral treatment; 4) psychiatric disorder with hospitalization. Patients with >40% leukoaraisosis, as judged by the neuroradiologist during interdisciplinary consensus conference, were also excluded. Controls were required to be without any neurologic diseases. After testing was complete, one control was excluded from further analyses due to a history of severe head injury that was reported only after testing was completed.

Procedures

Recruitment Strategy

Participants were recruited from the Memory and Cognitive Disorders Clinic at the University of Florida, all of whom had signed consents to participate in clinical research. During the course of routine clinical care, participants underwent (a) clinical neurological evaluation by a board certified behavioral neurologist, (b) laboratory workup for treatable causes of dementia, (c) structural neuroimaging (MRI or CT) of the brain, and (d) comprehensive neuropsychological evaluation. After data collection, patients were discussed individually in an interdisciplinary consensus conference attended by a behavioral neurologist, nurse practitioner, neuroradiologist, and clinical

neuropsychologist. Considering all data, the healthcare team renders a consensus diagnosis of the patient's condition.

Participants in this study were recruited from those receiving a diagnosis of AD, FTD or MCI. The study also involved recruiting the spouses of study participants to serve as healthy age- and education-matched controls to establish normative standards for the experimental tasks. Additional controls were recruited via an Institutional Review Board-approved (IRB) National Public Radio advertisement.

After the consensus conference, patients returned to the Memory and Cognitive Disorders clinic for feedback regarding the results of their testing. During that visit, the clinician informed the patients of this study and asked them if they were interested in participating. Those patients that expressed interest were subsequently contacted, and an individual appointment for testing was arranged. If spouses were available and agreed to participate as controls, they were tested at the same time. Additional controls were recruited using an IRB-approved National Public Radio advertisement. People who heard the advertisement and were interested in participating called the lab. After a brief phone screener, people who met inclusionary criteria were scheduled for testing. In the description that follows, "participant" is used to describe both patient participants and healthy individuals serving as controls.

Experimental Test Session

Participants were tested on a laptop in a small quiet examination room. Informed consent was obtained before the test session began. Each experimental test session lasted approximately two hours and consisted of two computer-assisted cognitive tasks: Transitive Inference (TI) and Syllogistic Reasoning (SR).

Measures

Transitive Inference (TI) Task

The Transitive Inference (TI) task and stimuli were adapted from Heckers, et al. (2004), who found right hippocampal activation using blood oxygen level dependent (BOLD) fMRI during performance of the TI task. The task was presented on a laptop using stimulus-presentation software E-Prime (Psychology Software Tools, Inc., 2007). The stimuli set was comprised of a series of four non-overlapping visual stimulus pairs (such that a>b, c>d, e>f, g>h) and a series of four overlapping visual stimulus pairs (e.g. A>B, B>C, C>D, D>E) (Figure 2-1). During training, participants learned the "winner" of each of the non-overlapping stimulus pairs. There was one button corresponding to each visual stimulus presented during each stimulus trial and participants responded to each stimulus pair by pressing one of these buttons on the laptop keyboard. Each response button was assigned to the visual stimuli on the ipsilateral side of the laptop (e.g., left button corresponded to the leftmost stimulus, right to right). Correct choices were reinforced with a "smiley face" presented on-screen between individual trials. Incorrect choices did not receive the "smiley face" reinforcement. Participants were presented with written instructions between each trial block and were provided with examples prior to beginning training for each stimulus set. Participants were given these instructions prior to beginning training for the non-overlapping pairs:

> You are going to see pairs of objects on the screen. Press the red key (Note: red key was on the left) to choose the left object and the yellow key (Note: yellow key was on the right) to choose the right object. Your job is to learn which object is the winner in each pair. When you pick the winner, a smiley face will appear. You won't see the smiley face if you pick the incorrect object. Initially you will have to guess which object is the winner in each pair. Once you find out which object is the winner in a pair, remember the answer for the next time you see that particular pair.

Participants were given these instructions prior to beginning training for the overlapping pairs:

> In this next part, you will see new objects. Again your job is to pick the correct object, the one that produces the smiley face. In this part, a particular object will not be paired with the same partner each time. Whether an object is correct depends on its partner. As before, each time a specific pair of objects is presented, the same one will always be correct. However, if an object is paired with a new partner, it may or may not be correct.

Training for each stimulus set consisted of 144 trials, each pair being presented 36 times over the course of three training blocks. Across all three training blocks, the presentation of pairs and the location of individual stimuli within a pair on the screen was randomized. The first two training blocks consisted of 60 trials. The first training block was "frontloaded" such that it contained twice as many presentations of two stimulus pairs. The second block was "backloaded" so that it contained twice as many presentations of the other two pairs. Heckers et al. (2004) described this frontloading as necessary for healthy adults to form the hierarchy required to make accurate inferential judgments during the test conditions. The third block contained 24 trials where each stimulus pair was presented an equal number of times.

After training was complete, participants were then tested on their ability to recall the correct response from previously seen pairs (A>B) and to infer the correct response for novel stimulus pairings (A>E, B>D). During the testing phase, no reinforcement was provided. Written instructions were presented on the laptop, and then two testing blocks were administered. Prior to beginning the test phase, participants were instructed:

> In this section, you will see pairs from Part 1 and Part 2. Your job is to pick the correct object. You will no longer see the smiley face, even if you pick the correct object. Pick the object that you think would be correct based on

what you learned in practice. In this part, you will also see objects paired in new ways. When this happens, please make your best guess about which object should be correct. Think about what you learned in practice and about the objects in relation to their partners. The objects will be on the screen for a limited time, so try to respond as quickly and as accurately as you can.

Each testing block consisted of 80 trials divided into 10 trials of a particular type (Trained Non-overlapping pairs, Novel Non-overlapping pairs, Trained Overlapping pairs, Novel Overlapping pairs). Accuracy for each trial was recorded by E-prime (Psychology Software Tools, Inc., 2007) software for data analysis.

Syllogistic Reasoning (SR) Task

The Syllogistic Reasoning (SR) task and stimuli were adapted from Oshin and colleagues (2009), who showed impairments in SR in patients with the FTD semantic dementia subtype. The task was presented on a laptop using Superlab software (E-prime). The stimulus set was composed of 10 arguments involving explicit spatial relations (Figure 2-2). The content of these arguments involved sentences that describe spatial relationships between familiar geographic locations (e.g., countries). These locations were chosen such that participants should be familiar with and have stored semantic knowledge of them. While the geographic locations were designed to be familiar to the participants, their locations as presented in the syllogisms were not always accurate. By describing the geographical places in non-actual locations, this task forced participants to use an associative learning strategy rather than simply recall their location on a map. Each argument consisted of three sentences: two premise sentences and one conclusion sentence. Before experimental trials began, written and verbal instructions directed the participants to read the arguments and decide whether

or not they believed the conclusions of the arguments to be valid. The written instructions provided were

> For this task you will be told about the location of countries and states in relation to each other. Then you will be asked to decide whether or not the conclusion presented is valid based on the information provided. This may require ignoring what you know about the actual location of those places.
>
> The first two sentences will describe the location of three countries or states. Based on that information, decide if the last sentence follows from that information. If it does, then this is valid. If the last sentence does not follow the information provided, then it is invalid. You can disagree either because the conclusion does not agree with the first two sentences, or because there is not enough information to make a decision.

A tutorial consisting of six practice arguments was then given to explain the concept of validity to the participants. A valid argument does not require the information presented in the premises or defined in the conclusion to be factual. Rather, to be valid the conclusion of an argument must follow logically from the information given in the premises. If the conclusion does not follow from the information provided in the premise, it is an invalid argument. During this tutorial, the experimenter gave feedback regarding the correctness of the participant's choice. The test condition consisted of 10 trials, each comprised of one syllogistic argument. The 10 arguments were presented in a random order to each participant. Participants read each argument and decided whether they believed the argument to be “Valid” or “Not Valid.” They then responded using two keys on the laptop keyboard. No time restraints were placed on either trial. E-prime (Psychology Software Tools, Inc., 2007) software recorded participants’ responses for data analysis.

CHAPTER 3
RESULTS

Data were analyzed using the SPSS 17 statistical software package. An alpha level of .05 was used throughout the analysis.

Demographic Characteristics of Participants

Demographic data for all participants are presented in Table 1. The groups were compared on demographic variables using a one-way analysis of variance (ANOVAs). Participants ranged in age from 51 to 89 years old (M= 68.1, SD= 8.5). Education level ranged between 12 and 20 years (M= 16.7, SD= 2.7). Gender composition of the sample was balanced, with 53% males. The sample was predominantly Caucasian (88%), with a smaller proportion of African Americans (6%), and people of Asian (3%) or Hispanic (3%) descent. No significant differences were found for gender [$F(3, 31) = .22$, $p = .88$] or ethnicity [$F(3, 31) = 2.19$, $p = .11$]. Group differences were detected on age [$F(3, 31) = 4.00$, $p = .017$] and education [$F(3, 31) = 7.85$, $p = .001$]. Bonferroni adjusted post-hoc tests revealed that the FTD group was significantly younger than the AD group ($p = .03$). A trend suggesting that the FTD group was younger than the MCI group was also observed ($p = .06$). Additional Bonferroni-corrected post-hoc analyses showed that the healthy controls had more years of education than the AD group ($p = .001$) and the FTD group ($p = .04$). The MCI group was also more educated than the AD group ($p = .03$) but not the FTD group ($p = .22$). There was no significant difference in education level between the AD and FTD group ($p = 1.00$).

Data Preparation

Accuracy scores were derived from performance on both the TI and SR tasks. Accuracy scores were generated by computing the mean percent correct. For the TI

task, accuracy scores were computed for each test condition: 1) Non-overlapping Training; 2) Overlapping Training; 3) Non-overlapping Novel; 4) Overlapping Novel. For the SR task, an overall accuracy score was computed from the one, 10-trial test condition.

The assumption of univariate normality was tested for each of the dependent variables. This analysis showed that the accuracy data for both the SR and TI tasks was normally distributed. In further analyses, additional assumptions of the general linear model were tested and adjusted statistics were reported where necessary.

Aim 1: Dementia Detection using Transitive Inference and Syllogistic Reasoning Tasks

Performance on the TI and SR tasks used percent accuracy for the test conditions. Training conditions were not included in the proceeding analyses. The hypothesis suggested that a double dissociation between group and task performance would emerge (i.e., that the AD group would perform more poorly than the FTD group and healthy controls on the TI task, while the FTD group would perform worse than the AD group and healthy controls on the SR task).

Testing for a Double Dissociation

In order to test the hypothesis that a double dissociation between group and task performance exists, a 4 (Group: MCI, AD, FTD, Control) x 2 (Task: SR, TI) mixed between-within ANOVA was conducted. The overlapping novel condition of the TI task was used during this analysis as it is this condition that specifically involves transitive inference. For the within-subject effect, Mauchley's test was not significant. The main effect of task was not significant, $F(1,28) = .95$, $p = .34$, $\eta^2 = .03$. The task x group interaction effect was also not significant, $F(3,28) = .48$, $p = .70$, $\eta^2 = .05$. Thus, a

double dissociation between group and task performance was not observed. For the between-subject effect, Levene's test was not significant. Tests of between-subjects effects revealed that there was a significant group effect, $F(3, 28) = 10.42$, $p = .000$, $\eta^2 = .53$. Further analyses were conducted to investigate this main effect of group.

TI Accuracy

Accuracy on the TI task was evaluated using a 4 (Group: AD, FTD, MCI, Healthy Control) X 4 (Condition: Non-overlapping Training, Overlapping Training, Non-overlapping Novel, Overlapping Novel) mixed between-within ANOVA. For the within-subject effect, Mauchly's test was significant ($p<.001$), indicating a violation of the sphericity assumption. Therefore, Greenhouse-Geisser df adjustments are reported. The main effect of the condition was not significant, $F(2.13, 59.50) = 1.02$, $p = .37$, $\eta^2 = .035$. Thus, one result is that all four TI conditions were equally difficult as there was no difference in accuracy across conditions. The main effect of group was significant, $F(3, 28) = 4.57$, $p = .01$, $\eta^2 = .33$ (Figure 3-1). Bonferroni- adjusted post-hoc comparisons revealed that participants with AD performed significantly worse than participants with MCI, FTD, or the healthy control group during the overlapping training condition. Also on the overlapping training condition, participants with MCI were observed to tend towards ($p = .06$) performing worse than those with FTD or healthy controls. During the non-overlapping test condition, participants with AD ($p = .002$) and those with FTD ($p = .03$) performed worse than those participants with MCI or healthy controls. Finally, participants with AD and FTD ($p = .003$) performed equivalently, and worse than those in the MCI or healthy control groups. There was no group difference for the non-overlapping training condition. The interaction between condition and group was not significant, $F(6.38, 59.50) = 1.78$, $p = .11$, $\eta^2 = .16$.

Since age and education (in years) were different across dementia groupings, analyses of covariance (ANCOVA) to control for these variables were conducted. Group remained the between-subject factor, and test accuracy was the dependent variable. Again, Mauchly's test was significant (p<.001), indicating that the assumption of sphericity was violated. To correct for this violation, Greenhouse-Geisser df adjustments are reported. The main effect of test condition remained non-significant. None of the within-subjects interactions were significant. Age was not observed to affect performance across test conditions [$F(1,26) = .13$, $p = .72$, $\eta^2 = .005$]; neither was group [$F(3,26) = 1.10$, $p = .37$, $\eta^2 = .11$]. However, the effect of education level was significant [$F(1,26) = 6.14$, $p = .02$, $\eta^2 = .19$] such that higher education predicted better performance on the overlapping training condition (p = .003), the non-overlapping Novel condition (p = .03), and the overlapping Novel condition (p = .02). Education did not have a significant effect on performance during the non-overlapping training condition.

SR Accuracy

Accuracy on the SR task was evaluated using a 4 (Group: AD, FTD, MCI, Healthy Control) X 1 (Condition: Test) univariate ANOVA. Levene's test of equality of error variance was not significant. Therefore, the assumption of equal variances was not violated, and unadjusted statistics are reported. There was a significant group effect in SR performance [$F(3,31) = 9.91$, $p = .000$, $\eta^2 = .52$] (Figure 3-2). Bonferroni-adjusted post-hoc tests showed that the MCI group (p = .03), AD group (p = .003) and FTD group (p = .001) all performed significantly worse than the healthy control group. There was no significant difference between any of the dementia groups on SR task performance (Table 2).

Because groups differed on age and education, a separate ANCOVA was conducted to evaluate the effect of these demographic variables on group SR performance. The results when controlling for age and education mirrored the results of the original analysis. The main effect of education was significant, $F(1, 31) = 16.33$, $p = .000$, $\eta^2 = .39$. Higher education predicted better performance. The AD group was less educated than the MCI group ($p = .03$) and the control group ($p = .001$). The FTD group was less educated than the control group ($p = .04$). The main effect of group was also significant, $F(3, 31) = 6.15$, $p = .003$, $\eta^2 = .42$. Helmert contrasts showed that the control group performed significantly better than all three dementia groups ($p = .03$). Participants with FTD did not perform better than those with AD and MCI ($p = .41$). It is possible that the poor performance previously observed in the FTD group was due to the FTD participants being less educated rather than to a true dementia-related impairment. Once the effect of education was controlled for the performance of the FTD group was no different than the AD or MCI group.

Aim 2: Preclinical Dementia Detection Using Transitive Inference and Syllogistic Reasoning Tasks

TI Accuracy

A discriminant function analysis was conducted in order to investigate the ability of the TI task to differentiate the MCI group from the healthy control group. The grouping variable was Group (MCI, Control) and the independent predictor variables were TI condition (Non-overlapping Trained, Overlapping Trained, Non-overlapping Novel, Overlapping Novel). Tests of equality of group means revealed that there were differences in group performance on the overlapping trained condition alone ($p = .03$).

Group differences in performance approached significance for the non-overlapping novel (p = .07) and the overlapping novel condition (p = .08).

Since the power of the discriminant function analysis was limited by the small sample size, scores on the overlapping novel condition for the MCI and control groups were plotted (Figure 3-3). The overlapping novel condition was tested because it is the test condition which requires transitive inference. The N of the two groups was unequal. So, the weighted mean of the group centroids was calculated and used as the cutoff score. The weighted mean of the group centroids was 0.3325. Participants whose performance was less than 33.25% on the overlapping novel condition were classified as MCI and those with greater accuracy were classified as healthy controls. Using this cutoff score, the discriminant function successfully classified all healthy controls but was unable to correctly classify any participants with MCI. Therefore, the overlapping novel condition of the TI task has a sensitivity = 0% and specificity = 77.3%.

SR Accuracy

In order to assess the ability of the SR task to discriminate between participants with MCI and healthy controls, a discriminant function analysis was conducted. Again, Group (MCI, Control) was the grouping variable and SR task accuracy was the independent predictor. There was a significant difference between group performance on the SR task (p = .003) such that healthy controls performed better than participants diagnosed with MCI, $\chi 2$ = .64, p = .003. The canonical correlation showed that 60% of the variance in SR performance could be accounted for by group membership. The discriminant function successfully classified 86.4% of participants into the correct group. It was 100% accurate at determining the healthy controls and 40% accurate at classifying MCI participants based on SR task performance. Further, the discriminant

function analysis revealed that the SR task has a specificity = 100% and sensitivity = 85%.

CHAPTER 4
DISCUSSION

Associative Reasoning Performance across Dementia Sub-Types

This study examined performance on a transitive inference task and a syllogistic reasoning task in patients diagnosed with AD, FTD, and MCI. Successful TI performance required the establishment of a unitized episodic memory of the reinforcement relationships among individual stimuli based on pairwise learning of stimulus-response associations. The key condition was the evaluation of performance accuracy in the overlapping novel (not trained) stimulus pairs. Healthy controls demonstrated the best learning and performance as they were able to learn the hierarchy and make accurate inferences during the test conditions (Table 3). Participants in the dementia and MCI groups displayed varying levels of impairment on this task. The SR task required participants to make judgments about the validity of syllogisms involving semantically familiar geographic locations. Participants diagnosed with any cognitive impairment (MCI, AD, FTD) performed worse than healthy controls but not differently from each other. This is most likely a power effect due the limited sample size of this study.

The first training condition of the TI task did not yield significant group differences. All participant groups performed similarly and adequately during the non-overlapping training phase. Participants with AD performed worse on the second training condition than FTD participants or controls. Both AD and FTD groups performed worse than healthy controls on both test conditions (Non-overlapping Novel, Overlapping Novel). These results were no longer significant when the effects of age and education were

removed via analysis of covariance. However, this pattern of performance remained, as is evident from visual inspection.

Participants with AD and FTD performed below healthy adults on the SR task. The effect sizes for all of the above results were moderate. While these results do not reveal a statistically significant dissociation as predicted, the obtained results do show trends in the predicted direction. For this reason, we believe that the experimental hypotheses have not been disconfirmed because of relatively low power incurred by small sample sizes

Detecting Preclinical Cognitive Impairment using Associate Learning Tasks

This study also sought to evaluate the ability of the TI and SR tasks to detect preclinical signs of the cognitive deficits inherent in the neurodegenerative diseases AD and FTD. During training for the TI task, there was no group difference on the non-overlapping training condition. There was, however, a trend which suggested that participants with MCI performed worse than the FTD group and healthy controls, and similarly to the AD group on the overlapping novel condition. Further, the MCI group performed, along with healthy adults, better than both dementia groups on the two test conditions of the TI task. Thus, the TI task was able to distinguish between participants with severe cognitive impairment and those with mild to no cognitive impairment.

A different pattern of performance was seen on the SR task. Participants with MCI were distinguished from healthy adults but not from either dementia group. Additionally, this effect was not diminished when controlling for age and education. Therefore, the SR task successfully differentiated healthy adults from adults with any degree of cognitive impairment. The SR task in this study did not work as effectively here as it did

in the Oshin et al study using FTD/SD patients. This is most likely because participants with SD were underrepresented in the current FTD sample.

Associative Learning Tasks and Functional Neuroanatomy Research

The hippocampus encodes flexible memories which are available to multiple response systems and that can be applied inferentially to novel situations (O'Reilly, 2001). The hippocampus supports rapid conjunctive learning while the temporal cortex mediates slow conjunctive learning. The hippocampus is specialized to rapidly learn the details that define a particular experience. The cortex is specialized for gradually extracting semantic generalities and relationships, and as such can effectively produce established knowledge but cannot update it based on episodic experience if the hippocampal system is damaged. By functioning to extract, over time, the generalities from experience, the cortex creates semantic representations of information from memories that are initially encoded episodically.

The distinction between hippocampal (episodic) and cortical (semantic) contributions to memory is will documented over several decades of research and is a central theme in a contemporary neuroanatomic theory of memory called “Multiple Trace Theory” (Nadel, Samsonovich, and Moscovitch, 2000; Moscovitch and Rosenbaum, 2005; Wang and Morris, 2010). MTT states that the hippocampus is critical for encoding and retrieval of all episodic memories, regardless of age. However, the hippocampus is not the site of memory storage; its role is to establish re-entrant networks with cortex wherein information is stored in the cortical regions that originally processed it. Through the kind of retrieval and re-encoding that takes place through multiple recollection, hippocampal-cortical interactions become less dependent on the original context in which they were learned, and eventually become dissociated from

their original episodic or autobiographical origins, and becomes more knowledge-based. MTT explicitly describes the episodic-semantic dimension as a hippocampal-cortical continuum, and this continuum is reflected in the conceptual framework for this study.

Effective performance in transitive inference requires the ability to learn and create an ordered episodic representation of stimulus relationships based on a sequence of stimulus-response pairings. Because the resulting representation is dependent on memory for the specific episode, it should be dependent on the hippocampus, which is consistent with previous functional imaging (Heckers) and human performance (Barker) data. The ability to make validity judgments about syllogisms when the information within those syllogisms is familiar means that semantic information should be dependent not on the hippocampus, but on the neocortex of the temporal lobe. In this study, AD was used as a model for hippocampal insult and FTD as a model for lateral temporal lobe insult. It was shown that AD and FTD participants were impaired both on TI and SR tasks. However, the trends within the data suggest that there was a functional dissociation between AD and FTD performance on these tasks. If this is so, then this study offers further support for the distinction between neocortical and hippocampal involvement in learning and memory, but may require larger sample sizes to demonstrate this dissociation reliably.

Clinical Applications of Associative Learning Tasks

The results of this study offer promise for the potential future use of TI and SR tasks in the differential diagnosis of dementia. Although the study lacked sufficient power to fully refute or verify these claims, the dementia groups' pattern of performance suggests that people with different dementia sub-types may indeed perform differently on these tasks. If that is the case, these tasks could add valuable information to the

diagnostic process. These tasks are relatively easy to administer, take less than two hours to complete, and include computer-assisted scoring. The noninvasive nature of these tasks compared to neuroimaging or biochemical assays suggests a positive risk-benefit ratio.

Modifications could adjust these tasks to make them even more clinically useful. Due to its brevity, the SR task already has an administration time of approximately 25 minutes. However, due to the large number of trials, the TI task takes at least an hour for participants to complete. Previous work with the TI task has shown that the overlapping novel condition is the most theoretically important condition because it alone evaluates the development of a flexible episodic memory of stimulus relationships. Therefore, this condition might be the most sensitive to dysfunction in the hippocampal system. Once participants finish the training trials, trials within the other conditions could be reduced or omitted. By testing only the overlapping novel pairs, administration time would lessen. Additionally, more efficient training could be implemented for both tasks. In order to increase standardization and reliability of test results, an accuracy floor could be set in place such that patients must achieve a designated level of task proficiency before reaching the test condition. This could be particularly useful with the SR task. It is unclear how effectively the six-trial tutorial used in the current study explained the concepts of validity to the participants. A better training phase could be devised such that participants would be required to demonstrate understanding of and ability to make validity judgments on syllogisms with content other than familiar geographic locations before the SR test phase begins. For the TI task, an accuracy base rate of 80% could be used to guarantee that participants all be tested

after achieving the same level of learning during the training conditions. These modifications could increase task sensitivity and specificity while decreasing administration time.

Limitations and Future Directions

This study did not replicate the main effect of TI condition reported in previous studies (Heckers et al., 2004; Barker et al., 2010). This is potentially due to the relatively small sample size which limited the analytical power to find significant results. These previous studies have shown that the test conditions (Non-overlapping Novel, Overlapping Novel) are more sensitive to disease than the training conditions (Non-overlapping Trained, Overlapping Trained), and that the Overlapping Novel condition is more difficult than the Non-overlapping Novel condition. Health controls perform equally across all four conditions (Table 3). Conversely, participants with dementia perform worse on the later test conditions, particularly the overlapping novel condition. This can be easily seen in the pattern of performance exhibited by the FTD group. Although statistical significance was not reached in this study, the pattern of performance across groups suggests that the increasing sensitivity of the TI conditions to disease was evident in this paradigm. For example, the performance of participants in both the MCI and FTD groups was worse during the test conditions than during the training conditions. Even though the FTD group performed better than the MCI or AD groups on the first three conditions, FTD group performance fell to the level of impairment seen in these other two dementia groups on the Overlapping Novel condition. This result suggests that participants diagnosed with FTD were capable of better performance on the TI task than those with AD or MCI. Further, the overlapping novel condition was sensitive enough to detect impairment in the FTD group.

Although including age and education as covariates diminished the significant effect of dementia group on performance across TI condition, visual inspection of group performance across task conditions offers hope that the hypothesized effect may actually exist. Figure 3-1 illustrates group performance across TI task condition. As is evident from visual inspection of the figure, healthy participants perform best across all conditions. In accordance with the hypotheses, participants with FTD perform better than those with AD on the TI task across the first three conditions. The final, overlapping novel condition is sensitive enough to detect impairment in both AD and FTD populations. This was noted as a decline in FTD group performance to the level of impairment observed in the AD group. This pattern of group performance was also seen when age and education were included in the analyses as covariates. Therefore, one conclusion attests that the loss of significant results when including covariates is a manifestation of the relatively low power of this study and not a reflection of low sensitivity within the task.

Again, although this study did not have the sufficient powers to find detailed and significant results, visual inspection of the SR data suggests that performance on this task supports the central hypothesis. The healthy control group performed best on the SR task. In line with the level of neurological insult, participants diagnosed with MCI performed better than those with AD or FTD. Moreover, their performance was not dramatically better than that of participants with AD, and participants with FTD performed worse than those with AD on the SR task. Based on this pattern within the data, it is reasonable to suspect that given a larger sample group and the associated increased statistical power, the hypotheses in this study may in fact be validated.

No group performed worse than 50% correct on either the TI or the SR task. Thus, these tasks might not be difficult enough to elicit the predicted group distinctions. Analyses of individual participant accuracy on both associative learning measures showed that accuracy on the TI task ranged from 25 to100% across conditions. Accuracy on the SR task ranged from 40 to 100% during the test condition. These tasks, then, appear to be difficult enough to elicit a wide range of accuracy among participants. Nevertheless, making the tasks, particularly the SR task, more difficult could increase group differences. Investigating this potential source of increased task sensitivity and specificity is a definite future direction for this research.

There were several factors which were not taken into account in this study which may need to be addressed in future investigations. First, Dementia severity was not considered as a variable. It is possible that the results of this study are actually due to inherent differences in the severity of dementia between groups. For instance, rather than exhibiting greater impairment on overlapping training condition of the TI task because it relies on hippocampal functioning which is impaired in this population, participants with AD may simply be more severely impaired from a cognitive perspective, and, therefore, more impaired on the measures used in this study. Thus, their poor performance could be due to greater global impairment, not focal impairment in transitive inference. An objective, widely used measure of global cognitive function, such as the Dementia Rating Scale-2 or the Mini-Mental State Examination, is available on these patients and could be used as an index of dementia severity in future studies. Additionally, correlational analyses relating performance on these associative learning tasks to traditional neuropsychological measures of learning and memory could further

elucidate the relationship between dementia sub-type, dementia severity, and performance on neurocognitive tasks.

A further limitation to this study is that patients were assigned to groups on the basis of interdisciplinary consensus conference rather than by a “gold standard” of postmortem pathological verification. Are individual patients performing differently than hypothesized because they are actually incorrectly diagnosed? This difficulty associated with generating a differential diagnosis between dementia sub-types was the impetus for this study. Thus, it is possible that the consensus diagnosis for one or more of the patients included in this study is incorrect. Longitudinal follow-up assessment of the participants in this study could be conducted in order to confirm their initial diagnosis. Although early after onset they are difficult to distinguish, they become more distinct over time. FTD typically progresses more quickly (Roberson, Hesse, Rose, 2005). The neural atrophy associated with these pathologies becomes more distinct as the diseases progress, and the cognitive impairments become more pronounced. The hippocampal atrophy initially indicative of AD spreads as the disease progresses to include lateral-temporal and frontal lobe structures. As atrophy spreads, cognitive and functional impairments become more widespread. In AD, these include impairments in language, in semantic and executive functions. As FTD worsens, resulting cognitive impairments may include disinhibition, loss of social tact, emotional lability or flattened affect, and poor problem-solving skills. Thus, one- to two-year follow-up assessments should successfully confirm or deny the diagnoses used in this study.

The current approach would benefit from the addition of structural neuroimaging data that objectively documents visible changes in hippocampal or cortical systems.

Functional MRI could also be used to examine and differentiate brain regions which are active during transitive inference from those involved in syllogistic reasoning tasks. By studying metabolic brain activity while participants perform these tasks, it could be verified not only that the regions of interest underlie associative learning, but also that the same structures are active across the different task conditions. Understanding which regions of the brain are involved in learning the TI hierarchy compared to those needed to manipulate that information during the inference trials could further our understanding of the neural structures which aid conjunctive learning and memory.

Genetic predictors of dementia could also be evaluated (APOE epsilon-4; presenilin) as an adjunct to these studies, as could neurochemical markers of disease (amyloid beta, tau) detectible in cerebrospinal fluid. Ideally, longitudinal investigation of a large population of individuals beginning prior to the development of disease and continuing through dementia diagnosis and progression, would be needed to fully address some of the issues addressed in this study

Conclusion

This current study evaluated the ability of transitive inference and syllogistic reasoning tasks to differentiate between AD, FTD and MCI. The study showed that transitive inference is impaired in participants diagnosed AD and FTD, and that syllogistic reasoning involving familiar, geographic locations is impaired in participants with AD, FTD and MCI. Results provide modest support for the utility of these associative learning tasks in the clinical diagnosis of dementia. These findings further support the functional distinction between the hippocampus and parahippocampal cortices. Future research could further the understanding of the relationship between

associative learning and dementia sub-types by controlling for additional clinical factors and conducting a larger study in hopes of finding more detailed results.

Table 3-1. Demographic Characteristics by Group

	AD (n=5)	FTD (n=4)	MCI (n=6)	Control (n=17)
Age	73.8 (4.7)	58.8 (10.2)	72.6 (13.6)	67.0 (5.0)
Years of Education	13.7 (2.7)	14.5 (2.5)	17.6 (2.2)	18.0 (1.8)
Gender (% male)[a]	66.70%	50%	80%	41.20%
Race (% Caucasian)[a]	83.3%	100%	80%	88.2%

Data presented as mean (standard deviation) except where noted (a) and presented as percent.

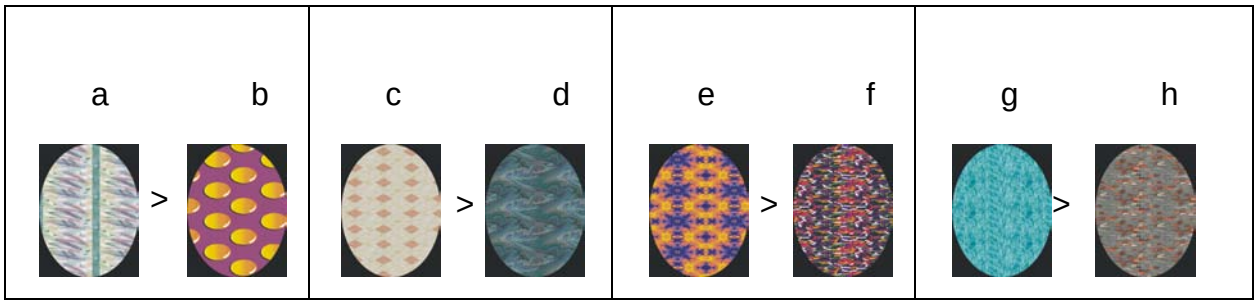
Table 3-2. Syllogistic Reasoning Accuracy by Group

Group	Mean	Std. Deviation	N
MCI	.70	.26	5
AD	.65	.20	6
FTD	.58	.17	4
Control	.94	.09	17

Table 4-1. Transitive Inference Accuracy across Condition by Group

	Group	Mean	Std. Deviation
Non-Overlapping Trained	MCI	0.76	0.19
	AD	0.62	0.21
	FTD	0.71	0.25
	Control	0.80	0.20
Overlapping Trained	MCI	0.70	0.11
	AD	0.56	0.10
	FTD	0.73	0.23
	Control	0.81	0.09
Non-Overlapping Novel	MCI	0.73	0.21
	AD	0.63	0.13
	FTD	0.68	0.22
	Control	0.87	0.12
Overlapping Novel	MCI	0.71	0.24
	AD	0.61	0.16
	FTD	0.56	0.17
	Control	0.86	0.14

A)



B)

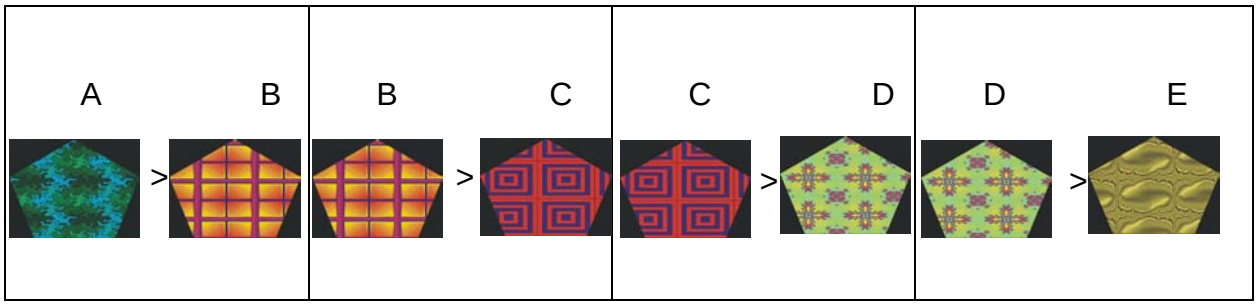


Figure 2-1. Transitive Inference Stimuli. A) Non-overlapping pairs. B) Overlapping pairs.

Oregon is east of California.

California is east of Ohio.

Therefore, Oregon is east of Ohio.

Figure 2-2. Example Syllogism

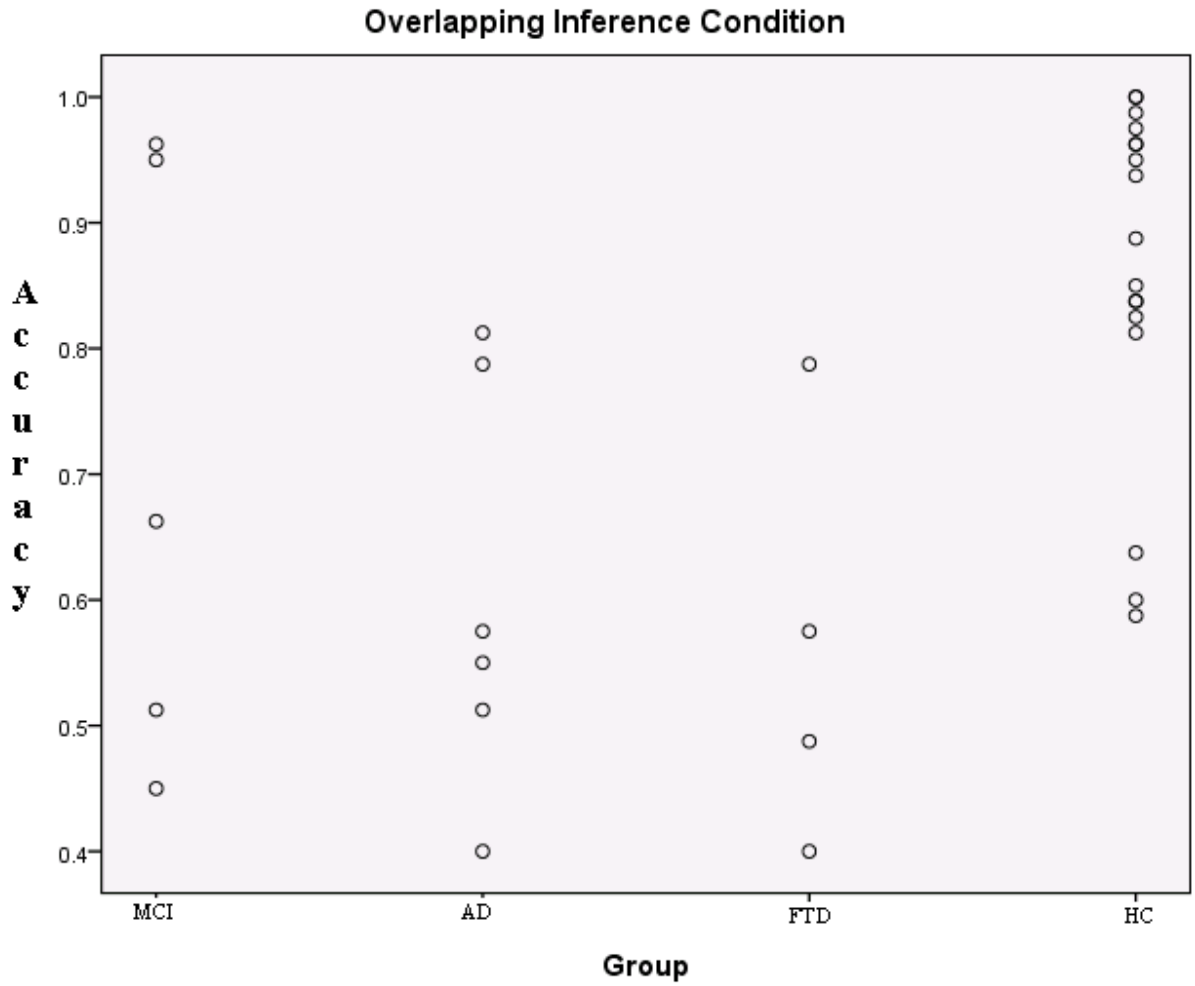


Figure 3-1. Overlapping Novel TI Condition: All Groups.

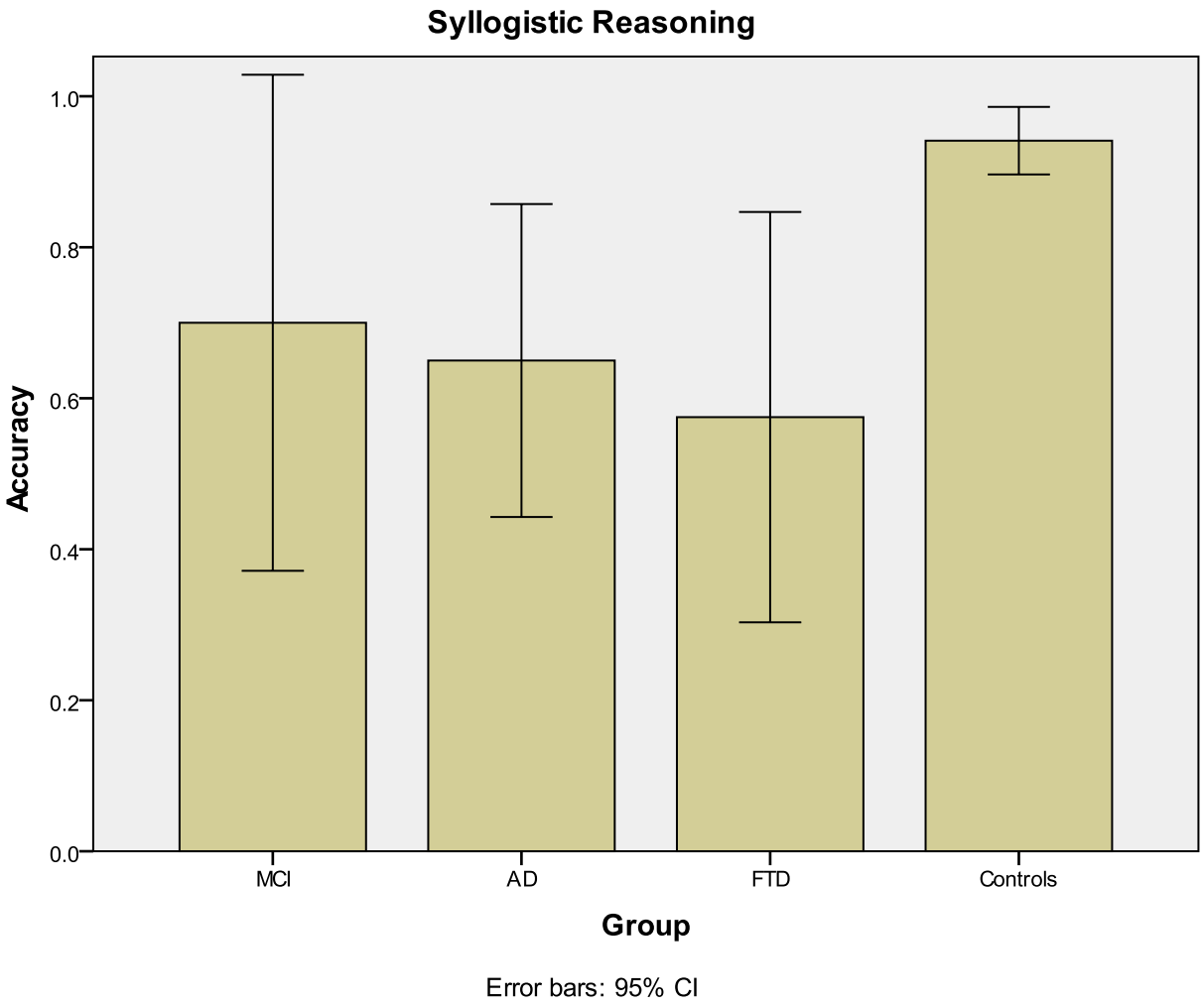


Figure 3-2. Group SR Task Accuracy

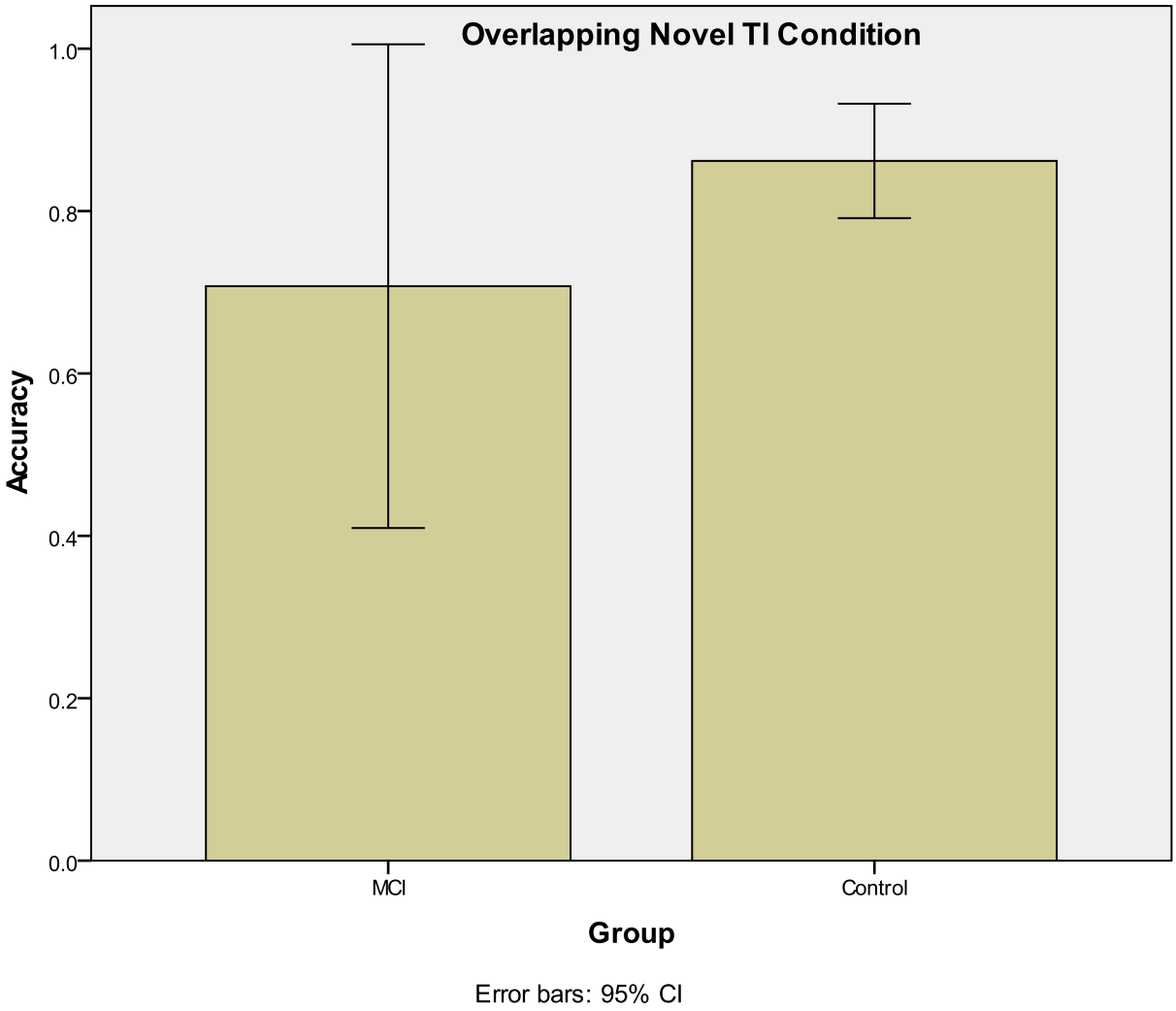


Figure 3-3. Overlapping Novel TI Condition: MCI vs. Healthy Controls

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BIOGRAPHICAL SKETCH

Taylor Kuhn was born in Athens, Georgia and grew up in Melbourne, Florida. He received his bachelor's degree in psychology in 2008 from the University of Florida. After a short travel break, he began graduate training in clinical neuropsychology. His graduate work has focused on memory disorders, functional information processing and dementia. He is currently pursuing a doctorate in clinical neuropsychology at the University of Florida.