TRANSITIVE INFERENCE IN TEMPORAL LOBE EPILEPSY

By

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To my family

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Recent findings in cognitive neuroscience reveal that transitive inference (TI) tasks, which require the formation and recognition of stimulus associations across experiences, have good specificity in the measurement of hippocampal functioning. Extant research has focused on animals and healthy adults. This study is the first to apply the TI paradigm in temporal lobe epilepsy (TLE), which is a syndrome that provides a model to study hippocampal contributions to memory. Primary aims were 1) to examine TI performance and relationship to side of surgery in TLE and 2) to compare the clinical utility of the TI task to standard neuropsychological tests.

Participants included 24 patients with TLE, who had undergone anterior temporal lobectomy (ATL; left n=8, right n=16), and 24 healthy controls. They completed a computer-based TI task, which was adapted from a paradigm that has demonstrated selective right hippocampal activation in functional imaging studies (Heckers et al., 2004). During training, participants view pairs of patterned shapes and learn the "winner" in each pair (e.g., A>B, B>C). They are tested on their ability to recollect the correct response for previously seen pairs and to make inferences about novel pairings (e.g., A>C). The critical condition involves making inferences across a series of overlapping pairs that form a hierarchy (A>B>C>D>E).

On the test, patients who had undergone right ATL performed significantly worse than healthy controls on TI for visual information. Left ATL patients performed in the intermediate range; however, the task did not discriminate between patients based on side of surgery. Results provide some evidence of a laterality effect and suggest that TI may be sensitive to hippocampally-mediated memory function. There is a clear need for better neuropsychological measures to assess language non-dominant (usually right) temporal lobe function, given the poor sensitivity and specificity of current tests. In this study, the conventional nonverbal memory measure, the Rey Complex Figure Test, did not discriminate between groups. The TI task and the conventional nonverbal measure yielded similar operating characteristics with good positive predictive power but poor sensitivity. The TI task showed modest clinical promise, and modifications that may improve its clinical utility are suggested.

CHAPTER 1
BACKGROUND AND SIGNIFICANCE

Relational Memory

Relational memory refers to the capacity to create a flexible and integrated representation of an experience that mediates associations among elements of the experience (Cohen, Poldrack, & Eichenbaum, 1997). Both the individual elements as well as their larger structure are encoded in relational memory. Anatomic data suggest that the hippocampus is essential for relational binding, linking multiple inputs together to represent their relationships and to code overlapping features across different experiences (Cohen et al., 1999).

The concept of relational memory fits into the current framework of multiple memory systems. This framework arose out of research on amnesia, which first implicated the hippocampus in memory (Scoville & Milner, 1957). The current framework focuses on a distinction between declarative and nondeclarative memory processing (Squire, 2004). Declarative memory is characterized by the conscious recollection of facts and events, while nondeclarative memory does not involve conscious recollection and is demonstrated through facilitation of performance rather than recollection.

Given that relational memory involves the mediation of associations between information, it can be integral for both declarative and nondeclarative memory. For example, relational memory is essential for a form of declarative memory that involves representing episodes. In episodic memory, an individual encodes how different elements relate to form a representation of a complex event (e.g., a party, a final examination), what is unique about the event, and how it links to other episodic memories through common elements (Eichenbaum, 2000; O'Reilly & Rudy, 2001).

The Hippocampus: The Physiological Basis for Relational Memory

According to relational memory theory, the hippocampus subserves relational mechanisms important for binding together the cognitive, affective, and contextual features of a learning event into an integrated memory (Eichenbaum, 2004). The hippocampus is uniquely positioned to serve as a relational binding mechanism (Eichenbaum, 2000). Information from association cortices converges on the parahippocampal and perirhinal cortices, which in turn project to the entorhinal cortex (Preston & Gabrieli, 2002). The entorhinal cortex serves as the primary input mechanism to the hippocampus and provides segregated input from a wide range of cortical areas.

The placement of the hippocampus as the source of converging cortical input and its capacity to form associations make it well equipped to serve as the site of relational memory. Although input to the hippocampus is segregated with regard to sensory modality or point of origin, the structure of the hippocampus itself is thought to lend itself to associational processing. Within the hippocampus, information proceeds in an orderly, unidirectional manner. O’Reilly and Rudy (2001) developed a biologically-based computational model of hippocampal function and proposed that relational binding occurs in a rapid, automatic manner. Integral to this model are the auto-associative binding features of CA3, an area in the hippocampus (Eichenbaum, 2004; O’Reilly & Rudy, 2001). Hippocampal properties that are prominent in the CA3 region and contribute to the capacity to form associations include broad recurrent connections and the prevalence of rapid synaptic plasticity, known as long-term potentiation (Eichenbaum, 2004). The physiological basis of the proposed architecture to support relational memory processing is one of the strengths of the relational memory concept.

While the hippocampal formation is necessary for processing relations among multiple stimuli, an emerging idea is that surrounding cortices mediate performance on simpler tasks that rely on stimulus novelty or familiarity (Preston & Gabrieli, 2002). Medial temporal structures implicated in more recognition-based “item” memory include the perirhinal cortex (Aggleton & Brown, 1999; Brown & Aggleton, 2001; Koehler, Danckert, Gati, & Menon, 2005) and entorhinal and parahippocampal cortices (Davachi & Wagner, 2002). The distinction between item and relational memory is subtle but important, and focuses on whether the stimulus has been encoded as an item, which is a unitized whole, or as a relational representation, which preserves the constituent elements as well as the larger structure. It is important to recognize that most clinical memory tests are not designed to be sensitive to this distinction.

Paradigms to Assess Relational Memory

Several paradigms have been developed to specifically assess relational memory. Two of the most widely used paradigms, paired associate learning and transitive inference (TI), both incorporate rapid, incidental learning.

Paired associate learning

One paradigm to assess relational memory involves learning paired associates (e.g., Giovanello, Schnyer, & Verfaellie, 2004; Meltzer & Constable, 2005). The subject is trained on a series of pairs, A-B, C-D, E-F, where A-F can be words or pictures. During a test phase, the subject is presented with intact pairs (e.g., A-B), novel pairs (e.g., Y-Z), and recombined pairs (e.g., A-F; items presented previously, but not together). Due to their similar exposure histories, items in intact and recombined pairs are equally familiar to subjects and so differ only in whether they were previously associated. Performance differences on intact versus recombined pairs provides an index of relational memory, while performance differences on recombined versus novel pairs provides a measure of item memory. Thus, the paired associate paradigm allows unique assessment of relational and item memory and eliminates the confound of familiarity on performance. This paradigm has demonstrated sensitivity to hippocampal function in amnesic patients with medial temporal lobe damage (Kroll, Knight, Metcalfe, Wolf, & Tulving, 1996) and in functional imaging studies (Giovanello et al., 2004; Meltzer & Constable, 2005).

Transitive inference

Another approach to test relational memory involves training subjects with distinct stimuli that share common elements and then testing whether these experiences have been linked in memory to solve new problems (Eichenbaum, 2000). In the TI paradigm, subjects are exposed to a series of overlapping stimulus pairs (e.g., A>B, B>C, where ">" means "is preferred to" in regards to the likelihood of obtaining reinforcement when that item is selected over the other). A measure of relational memory is provided by the subject's ability to make an inference about stimuli that were not previously presented together, but are related through the overlapping pairs. For example, TI would be demonstrated by the knowledge that A>C. The overlapping pairs are likely stored as a flexible representation that can be manipulated mentally to solve the transitive problem (Heckers, Zalesak, Weiss, Ditman, & Titone, 2004). Although this effect is "episodic" in the sense that it arises out of exposure to the stimuli, it is "inferential" in that it involves reference to a memory representation that is not based on direct experience, since during learning, A and C were never presented together.

The TI paradigm is based on a well-validated animal model, and the capacity for TI has been demonstrated in rodents (Dusek & Eichenbaum, 1997), pigeons (von Fersen, Wynne, Delius, & Staddon, 1991), and nonhuman primates (McGonigle & Chalmers, 1977) that were trained in instrumental learning formats. This paradigm has also been applied to humans in a comparative approach. In healthy adults, TI has primarily been tested using visual materials, such as geometric designs (Heckers et al., 2004, Heckers & Zalesak, 2009), faces (Nagode & Pardo, 2002), and face-house pairings (Preston, Shrager, Dudukovic, & Gabrieli, 2004).

TI was selected as the primary measure for the current study because it appears to uniquely capture the role of the hippocampus in encoding relationships among multiple stimuli, rather than simply encoding relationships between two simultaneously presented items as in paired associates. It extends the concept of paired associates to evaluate relationships across pairs. In addition, TI may be better representative of daily demands on memory processing, as this paradigm highlights the application of memory in a novel situation. The ability to utilize information learned across situations, to make inferences, and to apply that knowledge in a novel situation is critical for higher cognitive function.

Converging Evidence for the Role of the Hippocampus in Relational Memory

The concept of relational memory adds significantly to our understanding of how the hippocampus is involved in memory. Studies utilizing the paradigms described in the preceding section have provided strong support for the relational memory account in the animal, neuroimaging, and neuropsychological literatures.

Animal models

In a review of animal studies, Eichenbaum (2000) reported that deficits in well-validated tasks used in the animal memory literature, such as a water maze and TI, reflect problems in relational memory. Several studies have demonstrated relational memory deficits in rodents with hippocampal lesions. For instance, Fortin, Agster, and Eichenbaum (2002) showed that hippocampally-lesioned rats were impaired on learning the sequential order of a series of odors, but not on recognition of previously learned odors. Similarly, Dusek and Eichenbaum (1997) found that hippocampal disconnections from cortical and subcortical pathways selectively impaired TI in odor learning. Later studies have attempted to pinpoint the role of the hippocampus. The hippocampus may help to acquire the underlying representations necessary for TI in rodents (Van der Jeugd et al., 2009). On a different note, Devito, Kanter, and

Eichenbaum (in press) showed that hippocampal damage produced after mice learned an overlapping sequence did not substantially affect original learning but resulted in severe impairment in subsequent TI. This finding implies that the hippocampus is important for accessing the representation in a way necessary to perform TI.

Neuroimaging of healthy adults

Neuroimaging studies of healthy adults also provide evidence of the role of the hippocampus in relational memory. In a review of the functional imaging literature, Cohen and colleagues (1999) concluded that the relational memory concept provided a better explanation of the data than other accounts of hippocampal functioning, which focus on novelty, the explicit-implicit memory distinction, or spatial mapping. The functional imaging studies typically rely on a difference analysis, such that the pattern of activation observed during an item memory task or other "control task" is compared to activation observed during a relational memory task. Areas that are selectively activated during the relational memory task, in comparison to the "control task," are considered to reflect a unique contribution to relational memory.

Functional imaging studies indicate that the framework for relational memory is laid down during the encoding process. For instance, greater hippocampal activation was observed during training for overlapping premise pairs that permitted TI compared to those that did not (Nagode & Pardo, 2002). Similarly, other studies have demonstrated hippocampal involvement during encoding of novel associations involving visual information (Rombouts et al., 1997; Sperling et al., 2001). Later studies have expanded on this work to show that the extent of hippocampal activation during relational encoding correlates with performance on subsequent memory tasks. Hippocampal activity is greater during encoding of relational information that is successfully remembered on subsequent recall and recognition tasks (Davachi & Wagner, 2002; Jackson & Schacter, 2004; Staresina & Davachi, 2006).

While the majority of studies have focused on encoding processes, several have examined retrieval processes. Encoding and recall of associative memories are functions of an integrated hippocampal system (Meltzer & Constable, 2005). Research has revealed hippocampal activation during recognition of relational information, but not item information (Preston et al., 2004; Yonelinas, Hopfinger, Buonocore, Kroll, & Baynes, 2001). Furthermore, some studies support the idea that relational encoding is associated with anterior hippocampal activity, while retrieval is associated with posterior hippocampal activity (Meltzer & Constable, 2005; Prince, Daselaar, and Cabeza; 2005). In both studies, the overlap of encoding and retrieval effects was maximal in the middle of the longitudinal extent of the hippocampus, near the CA3 area.

Neuroimaging studies also provide evidence of selective hippocampal activation, relative to other temporal regions, during TI tasks (Nagode & Pardo, 2002; Preston et al., 2004) and other relational memory tasks (Koehler et al., 2005). For instance, Heckers and colleagues (2004) identified a distributed network of brain regions, including the pre-supplementary motor area, bilateral frontal cortex, bilateral parietal cortex, bilateral posterior temporal cortex, and pulvinar, involved in TI for overlapping visual (nonverbal) stimulus pairs. Importantly, difference analysis demonstrated selective right anterior hippocampal activation during TI and bilateral activation in the anterior parahippocampal gyrus during other task conditions. Moreover, in a similar study (Zalesak & Heckers, 2009), greater hippocampal activation was associated with more cognitively demanding aspects of TI. Specifically, greater right hippocampal activation was observed for inferences about pairs derived from more adjacent items in the hierarchy, while greater left hippocampal activation was associated with inference pairs that did not contain end items versus those that did.

Studies of amnesia

Neuropsychological evidence also supports the relational memory account. Patients with amnesia due to hippocampal damage have shown selective difficulty with memory for associations (Kroll et al., 1996) and for configural learning, similar to the childhood “rock, paper, scissors” game (Rickard & Grafman, 1998). While a few studies have failed to replicate these results (Stark, Bayley, & Squire, 2002; Stark & Squire, 2003), potentially due to characteristics of the medial temporal lobe damage in their participants, these findings have been confirmed in a number of studies.

For instance, impaired between-item associations (e.g., face-face, face-word) with preserved single item recognition has been observed in six patients with hippocampal lesions (Turriziani, Fadda, Caltagirone, & Carlesimo, 2004). Likewise, Mayes and colleagues (2004) reported that a patient with bilateral hippocampal lesions was impaired on memory for cross-modal associations (e.g., object-location, face-name), but not memory for individual items or intra-item associations. Hippocampal amnesics experience problems remembering relations among items, even with very short delays (Hannula, Tranel, & Cohen, 2006; Olson, Page, Moore, Chatterjee, & Verfaellie, 2006).

The impairment in relational memory is not confined to declarative memory tasks and extends into the nondeclarative domain as well. Priming, a measure of nondeclarative memory, is demonstrated when previous exposure to a stimulus leads to a faster reaction time or improved accuracy when the stimulus is shown again. Investigators have observed impaired priming for new associations in patients with amnesia. For instance, amnesics with focal medial temporal lobe lesions demonstrated impaired priming both for associations between two words and for associations between two features of a single stimulus, but showed preserved item priming (Yang et al., 2003). In a meta-analysis on implicit memory in organic amnesia, amnesics were found to perform equivalently to controls on indirect tests of familiar information, but worse on indirect tests for novel item and associative information (Gooding, Mayes, & van Eijk, 2000).

Relational Memory: Application to Temporal Lobe Epilepsy

The previous section showed how relational memory is characterized by the formation of a flexible, integrated representation that relies on hippocampal functioning. Strengths of the relational memory concept include a well-grounded physiological basis and converging empirical support from studies of animals, healthy adults, and clinical populations. To date, there have been no studies of relational memory in temporal lobe epilepsy (TLE) using the experimental paradigms described in the preceding sections.

Several studies are suggestive of relational memory deficits in TLE, although none have directly contrasted relational memory with memory for items. For instance, patients with left TLE did not profit in learning a word list when words belonged to schemas about events, while those with right TLE benefited from these loose associations (Helmstaedter, Gleissner, Di Perna, & Elger, 1997). In a post-surgical sample, patients with left TLE performed worse than those with right TLE on memory for word pairs in declarative and nondeclarative formats (Savage, Saling, Davis, & Berkovic, 2002). Similarly, the extent of surgical resection has been associated with a decreased ability to learn associations between objects and faces (Weniger, Boucsein, & Irle, 2004).

Evaluating relational memory in TLE has the potential to provide significant information about the role of the hippocampus. Through EEG monitoring and neuroimaging techniques, the complex partial seizures of TLE have been demonstrated to be predominantly of hippocampal origin (Engel, 1996). The most common structural abnormality is unilateral mesial temporal sclerosis (Engel, 1996), which is the only neuropathologic finding in the majority of patients (Trennery, Westerveld, & Meador, 1995). Thus TLE provides a naturally occurring model of hippocampal pathology that can be used to examine hippocampal contributions to memory. Examining relational memory in TLE has the potential not only to provide support for relational memory theory in a new population, but also to improve clinical care. The following sections describe the role of neuropsychology in the clinical care of epilepsy and detail problems with current clinical memory tests used to assess TLE patients. The key idea is that many of these problems can be rectified through the development of more sensitive and specific tests of hippocampal function.

The Role of Neuropsychological Testing in the Surgical Treatment of Epilepsy

Despite medical treatment, approximately 30 percent of the total epilepsy population continues to experience seizures that are considered intractable (Helmstaedter, 2004). The seizures associated with mesial TLE are among the most resistant to antiepileptic drugs (Engel, 2001). For treatment refractory TLE cases, surgery to remove a portion of the anterior temporal lobes is an option, giving patients a 70 to 90 percent chance of becoming seizure free (Engel, 2001). The best surgical candidates show unilateral hippocampal sclerosis, ictal and interictal abnormalities limited to relatively discrete neural zones, and focal/lateralized neuropsychological deficits (Helmstaedter, 2004; Loring, 1997). The current standard of care for pre-surgical candidates includes neuropsychological testing designed to yield information about localization and lateralization of seizure focus and to help predict whether iatrogenic postoperative cognitive disability will result from the planned resection (Helmstaedter, 2004). The degree of deviation from expected pattern of performance on neuropsychological testing may serve as a prognostic indicator of post-operative cognitive decline.

While recovery of cognitive function is often noted after surgery, there is also a risk for cognitive decline. Estimates are that approximately 40 percent (range 10-60 percent) of patients experience verbal memory loss after anterior temporal lobectomy (ATL; Chelune, 1995; Loring, Barr, Hamberger, & Helmstaedter, 2007; Stroup et al., 2003). The risk for cognitive decline is inversely related to the functional adequacy of the tissue to be resected in the surgical temporal lobe (Chelune, 1995). For example, post-surgical patients tend to show a greater loss in verbal memory if they had better baseline verbal memory functioning, which is indicative of more functionally adequate underlying tissue (Helmstaedter, 2004; Stroup et al., 2003). Therefore, neuropsychological testing provides valuable information that can help physicians and patients inform their decisions about likely outcomes of treatment.

Assessment of Memory Functioning in TLE

Impaired declarative memory is a hallmark symptom of TLE. The material-specific framework guides our understanding of memory in TLE. Material-specific predictions link memory for verbal material with the language dominant temporal lobe (usually left) and memory for nonverbal material with the language non-dominant temporal lobe (usually right; Milner, 1975). Factor analytic results suggest that the constructs of verbal and nonverbal memory are robust within the TLE population (Davis, Andresen, Witgert, & Breier, 2006).

The literature consistently shows a strong link between impaired verbal memory and left TLE (Helmstaedter, 2004; Hermann, Seidenberg, Schoenfeld, & Davies, 1997; Strauss et al., 1995) and left hippocampal atrophy (Griffith et al., 2003; Martin et al., 1999; Trennery, 1996). In contrast, findings are mixed regarding the association between nonverbal memory and right TLE. Research generally has not demonstrated a reliable relationship between performance on nonverbal/visual memory measures and right TLE or right hippocampal volume (Griffith et al., 2003; Helmstaedter, 2004; Martin et al., 1999; O'Brien, Bowden, Bardenhagen, & Cook, 2003; Trennery, 1996).

While verbal memory is typically assessed by story-recall or list-learning paradigms, there is little agreement on which tests best identify nonverbal memory impairments. Currently most clinical assessments incorporate measures of figural reproduction, such as the Visual Reproductions subtest of the Wechsler Memory Scale-Third Edition (Wechsler, 1997b) or the Rey Complex Figure Test (Meyers & Meyers, 1995), which ask the examinee to draw the figure from memory after a single presentation. A few studies have demonstrated some lateralizing value of figural reproduction tests in TLE (Glosser, Cole, Khatri, DellaPietra, & Kaplan, 2002; Jones-Gotman, 1991).

However, the sensitivity of these tests to detect memory dysfunction specific to right TLE is questionable. For instance, a meta-analysis was conducted on 33 studies of TLE that used the Wechsler Memory Scale subtests of Logical Memory and Visual Reproductions to assess verbal and nonverbal memory respectively (Lee, Yip, and Jones-Gotman, 2002). While the verbal task was sensitive to left hemisphere dysfunction both pre- and post-operatively, the efficacy of the nonverbal task to assess right hemisphere dysfunction was not confirmed.

Further compelling evidence of the poor lateralizing capability of figural reproduction tests comes from a study by Barr and colleagues (1997). In a sample of approximately 750 patients, they detected no significant differences between patients with right and left TLE on either Wechsler Memory Scale Visual Reproductions or the Rey Complex Figure Test. Their analyses were well powered and controlled for potential confounds, limiting any concerns about inadequacies in design. Similar negative findings have been noted in other studies of TLE using the Brief Visuospatial Memory Test-Revised (Benedict, 1997), a figural reproduction test with multiple learning trials, and the Continuous Visual Memory Test (Trahan & Larrabee, 1988), a figural learning and recognition test (Barr, Morrison, Zaroff, & Devinsky, 2004; Snitz, Roman, & Beniak, 1996).

One reason for the poor performance of conventional nonverbal memory tests in this context is that they focus primarily on object/item memory, a function that may not specifically reflect the hippocampal contribution to memory. Other possible reasons exist (see below). Nonverbal tests that tap aspects of spatial memory may be more promising. For instance, several researchers have proposed alternative scoring methods for the Rey Complex Figure. Loring, Lee, and Meador (1988) showed that qualitative scoring criteria assessing distortion and misplacement errors discriminated between right and left TLE, differences that were not evident when traditional scoring criteria were used. These results were replicated by Frank and Landeira-Fernandez (2008). Likewise, Breier and colleagues (1996) found that a spatial scoring system for the Rey Complex Figure was more sensitive to right hippocampal dysfunction than a figural scoring system; however, subsequent studies have not detected differential sensitivity to right TLE using this scoring (Kneebone, Lee, Wade, & Loring, 2007; McConley et al., 2008). Experimental spatial memory tests are also promising. Patients with right TLE have shown worse performance than those with left TLE on a task requiring them to remember spatial details in complex scenes (Baxendale, Thompson, & Paesschen, 1998) and on a task requiring them to change position while remembering the location of hidden objects in a spatial array (Abrahams et al., 1999).

Improving Detection of Memory Dysfunction in Right TLE

As indicated above, there are several possible explanations for the failure to demonstrate a consistent link between nonverbal memory performance and right TLE. Some researchers suggest that nonverbal memory may not be as strictly lateralized or localized as verbal abilities, which could help to account for the findings (Helmstaedter & Kurthen, 2001; Loring et al., 2007). Other explanations focus on test characteristics that may contribute to their insensitivity to nonverbal memory dysfunction.

The nature of the test stimuli, in particular their level of abstractness, should be considered. Many authors have raised concerns about the verbalizability of stimuli, such that nonverbal tests may be contaminated by verbal encoding (Barr et al., 1997). Griffith and colleagues (2003) found that the left hippocampus explained a significant portion of the variance in nonverbal memory performance, which may be considered to support this contention. Similarly, McConley and colleagues (2008) noted modest correlations between left hippocampal volume and figural reproduction performance. Moreover, Helmstaedter, Pohl, and Elger (1995) found that patients with right TLE showed memory impairment for designs only when their complexity exceeded verbal learning capacity. An additional concern is that many measures involve reproduction of designs, which is confounded by motor and constructional abilities. A recognition format would bypass this concern.

Another explanation for the mixed findings relates to the type of nonverbal memory assessed. Results described previously indicate that spatial memory tests may be more closely tied to language non-dominant hippocampal function than tests of figural or object memory. These findings could be interpreted in the context of relational memory theory. As spatial memory involves integrating relationships to represent the environment, it could be considered a subset of relational memory (Cohen et al., 1999). The success of some spatial measures in the identification of neuropsychological morbidity in TLE suggests that other relational memory paradigms may also have clinical assessment value.

Most studies on TLE are conducted in clinical settings and use commercially available assessments rather than experimental paradigms. However, commercial tests may not provide the most sensitive measure of hippocampally-mediated memory function. Measures, such as TI, that are specifically designed to assess relational memory may show better sensitivity to hippocampally-mediated memory function in TLE.

Purpose of Current Study

The primary aim of the present study was to examine TI in patients with intractable TLE who underwent ATL. There are no published studies of TI in TLE, and results have the potential to provide support for relational memory theory in a new population. TI performance and its relationship to side of surgery were examined. It was hypothesized that material-specific deficits in performance would be observed; such that TI for patterned visual stimuli would be impaired in patients with right ATL relative to patients with left ATL and healthy controls. Deficits were expected to be most evident on the TI condition, although it was expected that right ATL patients may demonstrate deficits on other conditions involving premise pairs from the overlapping hierarchy. In addition, the current study sought to replicate behavioral findings from Heckers and colleagues' (2004) study, such as the TI effect for response latencies, which predicts that reaction times will be slowest for pairs involving TI.

The secondary aim was to compare the clinical utility of the TI task to established clinical memory tests. The experimental TI task addresses some of the concerns about conventional nonverbal memory tests by utilizing a recognition format and stimuli that are difficult to verbalize. The Rey Complex Figure Test was selected as the standard measure of nonverbal memory because it is widely used in epilepsy surgery centers to assess memory dysfunction associated with right TLE (Barr et al., 1997; Frank & Landeira-Fernandez, 2008). It was hypothesized that the TI task would provide more accurate detection of right-sided resection than the standard test of nonverbal memory.

CHAPTER 2
METHODS

Participants

Participants included patients with intractable temporal lobe epilepsy (TLE; n=27), who had undergone a standard anterior temporal lobectomy (ATL), and healthy controls (n=24). Participants were 18 years of age or older. Exclusion criteria were: 1) history of developmental disability or mental retardation resulting in Wechsler Abbreviated Scale of Intelligence (WASI; Psychological Corporation, 1999) Full-Scale IQ < 70; 2) history of Axis I psychiatric disturbance resulting in hospitalization; 3) cranial radiation or chemotherapy treatment (within 1 year); or 4) other neurological illness (e.g., cerebrovascular disease, brain tumor, severe traumatic brain injury). Controls were required to be free of any neurological disease. After completion of testing, three epilepsy patients were excluded from further analyses. Two were eliminated due to concerns about comprehension since English was a second language, and another was excluded due to current psychiatric symptoms that resulted in failure to complete the testing session.

Procedures

Recruitment Strategy

The study was approved by the University of Florida Institutional Review Board (#240-2007). Epilepsy patients were recruited from the Comprehensive Epilepsy Program at the University of Florida. Patients who had undergone ATL from January 2000 to January 2008 were pre-screened in medical records to determine if they met inclusion/ exclusion criteria for the study. Seventy-seven patients (38 left ATL, 39 right ATL) met eligibility criteria and were contacted by mail. A letter was sent that informed them of the opportunity to participate in a research study and briefly described the study. Enclosed was an addressed, stamped postcard that could be returned, should they desire additional information or want to volunteer.

Potential participants were mailed up to three times in order to optimize participation. The overall response rate to the mailing was 56%. Seven patients were unable to be contacted due to change in address. Participation in the study was completed by 39% of patients. Twelve patients responded to the mailing but did not participate for various reasons [distance to travel (n=3), failed to meet inclusion criteria after additional screening (n=4), declined (n=3), unable to schedule (n=2)]. Healthy controls were recruited by asking epilepsy patients whether their family members or friends might be interested in participating and also by community flyer. All potential participants underwent a 10-minute screening by phone regarding demographic and medical information relevant to study eligibility.

Assessment Procedures

Eligible candidates were scheduled for testing and assigned a subject number for identification. Participants were tested at University of Florida, in their home, or at the local Epilepsy Foundation in their town of residence. The assessment was administered by a graduate student in psychology or a trained undergraduate research assistant. The duration of the testing session was three to four hours. Informed consent procedures were completed. Then, a neuropsychological battery consisting of experimental and traditional measures was administered. Participants were compensated $10 per hour for their time, and those tested at the University of Florida were also offered a $3 parking voucher.

Demographic information, including age, gender, ethnicity, handedness, and years of education, was collected. The epilepsy patients were also asked to provide medical information and to consent to release information from their treatment in the Comprehensive Epilepsy Program. Relevant medical information was then collected from the patient’s medical record. Medical variables included age at onset of epilepsy, family history of epilepsy, current medications, neuroimaging results, seizure laterality and localization, current and previous seizure frequency, Wada memory support, cerebral speech dominance, date of surgery, type of surgery, and post-surgical outcome.

Measures

Transitive Inference Task

The transitive inference (TI) task was presented on a laptop computer using stimulus-presentation software (E-prime). It was closely modeled after the paradigm developed by Heckers and colleagues (2004). They demonstrated selective right hippocampal activation during functional imaging of the TI condition, while other task conditions implicated medial temporal areas, such as the anterior parahippocampal gyrus. Their stimuli (Heckers et al., 2004) were adapted for use in the current study. They consist of thirteen visually distinct pattern fills created from Corel Draw, which were selected to be of similar levels of visual interest (Figure 2-1). The patterns were randomly assigned to pairs of ellipses or pentagons.

The stimuli composed a series of four non-overlapping visual stimulus pairs (which will be represented in text by lower case letters a>b, c>d, e>f, g>h) and a series of four overlapping visual stimulus pairs (which will be represented in text by uppercase letters A>B, B>C, C>D, D>E). During training, participants learned the “winner” in each pair. They were then tested on their ability to recollect the correct response for previously seen pairs and to infer the correct response for novel pairings. More detailed information on training and testing procedures follows and is also summarized in Table 2-1.

Training

The training was designed to ensure that participants would learn the correct response for each pairing and would also be likely to hierarchically encode the overlapping stimulus set (Heckers et al., 2004). Training was conducted first on the non-overlapping pairs and then on the overlapping pairs. A correct choice was reinforced by a "smiley face." Sample instructions are provided. For the non-overlapping pairs, participants were instructed:

> You are going to see pairs of objects on the screen. Press the red key to choose the left object and the yellow key 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.

Prior to training for the overlapping pairs, participants were instructed:

> 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.

Participants were also provided examples before beginning training for each stimulus set. Training for each stimulus set consisted of 144 trials, whereby each pair was presented 36 times. The training procedure was separated into three blocks (Table 2-1). The first and second blocks consisted of 60 trials. The first training block was "frontloaded" to contain twice as many representations of two of the pairs, while the second training block was "backloaded" to contain more representations of the other two pairs. For example, participants viewed 20 instances of AB and BC, and 10 instances of CD and DE in the first training block for the overlapping set. During the second block, participants viewed 20 instances of CD and DE, and 10 instances of AB and BC. According to Heckers and colleagues (2004), the initial front-loading of pairs is necessary for healthy adults to correctly make inferences during the test. The third training block consisted of 24 trials containing equal numbers of the four stimulus pairs. Throughout the training trials, the presentation of the pairs and the position of the two stimuli within each pair were randomized.

Test

During testing, memory for previously viewed pairs and the ability to infer the correct response for novel pairings were assessed. No reinforcement was provided. 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.

Two blocks of testing were administered, and each block consisted of 80 trials divided into 10 trials of a particular type (Trained Non-overlapping, Inference Non-overlapping, Trained Overlapping, Inference Overlapping). Participants were asked to make inferences about five novel pairings from the non-overlapping stimulus set and five novel pairings from the overlapping stimulus set (Table 2-1). An inference from the non-overlapping set always paired an object that had been a "winner" with an object that had never been reinforced. Therefore, the problem could be solved by simply remembering the reinforcement history of each object. In contrast, inferences from the overlapping set could pair objects that had not been consistently reinforced during training (i.e., object had been "winner" and "loser" depending on its partner). For instance, B>D is a critical pair, in which both objects were reinforced on 50% of training trials. In order to solve this transitive problem, it would be essential to encode the overlapping set as a hierarchy and to remember how a stimulus relates to other stimuli in the hierarchy.

Scoring and interpretation

Indices derived from performance included accuracy and latency scores. A key score was accuracy (percentage correct) for the Overlapping Inference condition, which reflects the process of TI. In the context of the current study, it was expected that patients who had undergone right

ATL would demonstrate significant difficulty making inferences about visual stimulus pairs from the overlapping set. Latency scores also provided information on relational memory processing. Based on the findings of Heckers and colleagues (2004), significantly longer latencies were expected on responses for overlapping vs. non-overlapping pairs and for responses requiring an inference, with latencies most pronounced on inferences about overlapping pairs.

Post-test assessment

Following the computer-based task, it was assessed whether participants were explicitly aware of the hierarchical nature of the stimuli (similar to Titone, Ditman, Holzman, Eichenbaum, & Levy, 2004). Participants were presented with two hand-held stimulus cards representing B and D and asked which would be the winner if they were paired. They were then given five cards representing all the stimuli from the overlapping set and asked to rank order them according to "dominance" (i.e., which stimulus was most likely to be a winner). The experimenter provided no further information, allowing participants to decide what attribute to use to order the cards.

Each stimulus in the arrangement was then assigned a difference score, which was derived by subtracting its correct position (1, 2, 3, 4, 5) from the position the participant selected (1, 2, 3, 4, 5) and taking the absolute value of the result. For example, a stimulus in the correct position would be assigned a difference score of zero, whereas a stimulus in the third position that should be in the first position would be assigned a difference score of two. Difference scores were summed to yield a total hierarchical awareness score (range 0–12). Lastly, participants were asked whether they were aware that the stimuli were hierarchically organized and to describe their strategies for solving the task.

Standard Neuropsychological Tests

Conventional neuropsychological measures were used to assess general intellectual functioning, verbal and nonverbal memory, language, attention, and executive function. The following tests are peer-reviewed, well-validated measures to assess these domains. All tests were administered and scored according to standardized procedures outlined in the test manuals. Resulting performances were demographically corrected to remove inherent differences due to age. In addition, the normative data provided corrections for different educational levels for the measures indicated by an asterix.

1) Wechsler Abbreviated Scale of Intelligence (WASI; Psychological Corporation, 1990). The Vocabulary subtest and the Matrix Reasoning subtest were administered. In Vocabulary, the examinee is asked to orally define words. In Matrix Reasoning, the examinee is asked to select a pattern to complete an abstract design. Performance on these two subtests can be combined to yield an estimate of general intellectual functioning.

2) Hopkins Verbal Learning Test-Revised (HVLT-R; Brandt & Benedict, 2001). The HVLT-R is a measure of the processes involved in learning and remembering verbal information. The examinee's ability to learn a 12-word list over three trials is examined. Free recall of the list is assessed after a 20- to 25-minute delay, followed by a recognition trial.

3) Wechsler Memory Scale-Third Edition selected verbal subtests (WMS-III; Wechsler, 1997b). In Logical Memory, participants are read two brief stories and asked to retell them immediately and after a 30-minute delay. In Verbal Paired Associates, participants are asked to learn a list of eight abstract word pairs over four learning trials. During the immediate and 30-minute delayed recall, the examiner reads the first word in each pair, and the examinee is asked to recall the second word. Both subtests also include a recognition trial.

4) Rey Complex Figure Test and Recognition Trial (RCFT; Meyers & Meyers, 1995). The RCFT assesses visuospatial constructional ability and nonverbal memory. The test involves copying a complex geometric design, which the participant then draws from memory after a 3-minute delay and after a 30-minute delay. A recognition trial follows the delayed free recall. The drawings are scored based on the accuracy and placement of the elements of the design.

5) Boston Naming Test-II (BNT-II; Goodglass & Kaplan, 2000).* This measure of confrontation naming includes 60 black-and-white ink drawings. Participants are asked to name each picture, and semantic and phonemic cues can be provided.

6) Digit Span subtest from the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III; Wechsler, 1997a). On the Digit Span subtest, examinees are read a string of digits and asked to recall them in order. The string increases by one after two trials are completed correctly. Then, using the same procedure, the ability to recall digit strings in reverse order is tested.

7) Trail Making Test (Army Individual Test Battery, 1944; Reitan, 1958).* This test measures visuomotor speed, attention, tracking, and set-shifting. In Part A, participants are required to connect numbers from 1 to 25 and instructed to do so as quickly as possible. In Part B, participants are asked to connect letters and numbers in order, shifting between sets.

8) Wisconsin Card Sorting Test (WCST; Heaton, 1981).* This measure of mental flexibility and problem solving requires examinees to sort two decks of 64 cards with colored shapes printed on them. The cards should be sorted based on unstated principles, such as color, form, or number.

9) Edinburgh Handedness Inventory (Oldfield, 1971). This ten-item questionnaire assesses hand preference for a range of activities. A laterality quotient ranging from –1 (left-hand dominance) to +1 (right-hand dominance) can be calculated.

Table 2-1. Protocol for the transitive inference task

Part 1: Training for non-overlapping pairs	
Stimuli pairs	Eight ovals with geometric, patterned fills Combined in pairs, with one stimulus in pair arbitrarily designated as winner (a>b, c>d, e>f, g>h)
Parameters	left/right position counterbalanced random presentation within each block feedback on every trial such that selecting winner results in smiley face
Blocks	Block 1: "front-loaded," 60 trials ab and cd appear 20 times each; ef and gh appear 10 times each Block 2: "back-loaded," 60 trials ef and gh appear 20 times each; ab and cd appear 10 times each Block 3: "balanced," 24 trials ab, cd, ef, gh appear 6 times each
Part 2: Training for overlapping pairs	
Stimuli pairs	Five pentagons with geometric, patterned fills Combined to form a series of overlapping pairs in a hierarchy (A>B, B>C, C>D, D>E)
Parameters	left/right position counterbalanced random presentation within each block feedback on every trial such that selecting winner results in smiley face
Blocks	Block 1: "front-loaded," 60 trials AB and BC appear 20 times each; CD and DE appear 10 times each Block 2: "back-loaded," 60 trials CD and DE appear 20 times each; AB and BC appear 10 times each Block 3: "balanced," 24 trials AB, BC, CD, DE appear 6 times each
Part 3: Test	
Stimuli pairs	previously viewed non-overlapping and overlapping pairs 5 novel pairings from non-overlapping set: a>d, a>f, c>f, c>h, e>h 5 novel pairings from overlapping set: A>C, A>D, B>D, B>E, C>E
Parameters	left/right position counterbalanced no reinforcement
Blocks	Block 1 and Block 2: Each block is 80 trials divided into sets of 10 trials of a particular type (Non-Overlapping Trained, Non-Overlapping Inference, Overlapping Trained, Overlapping Inference)

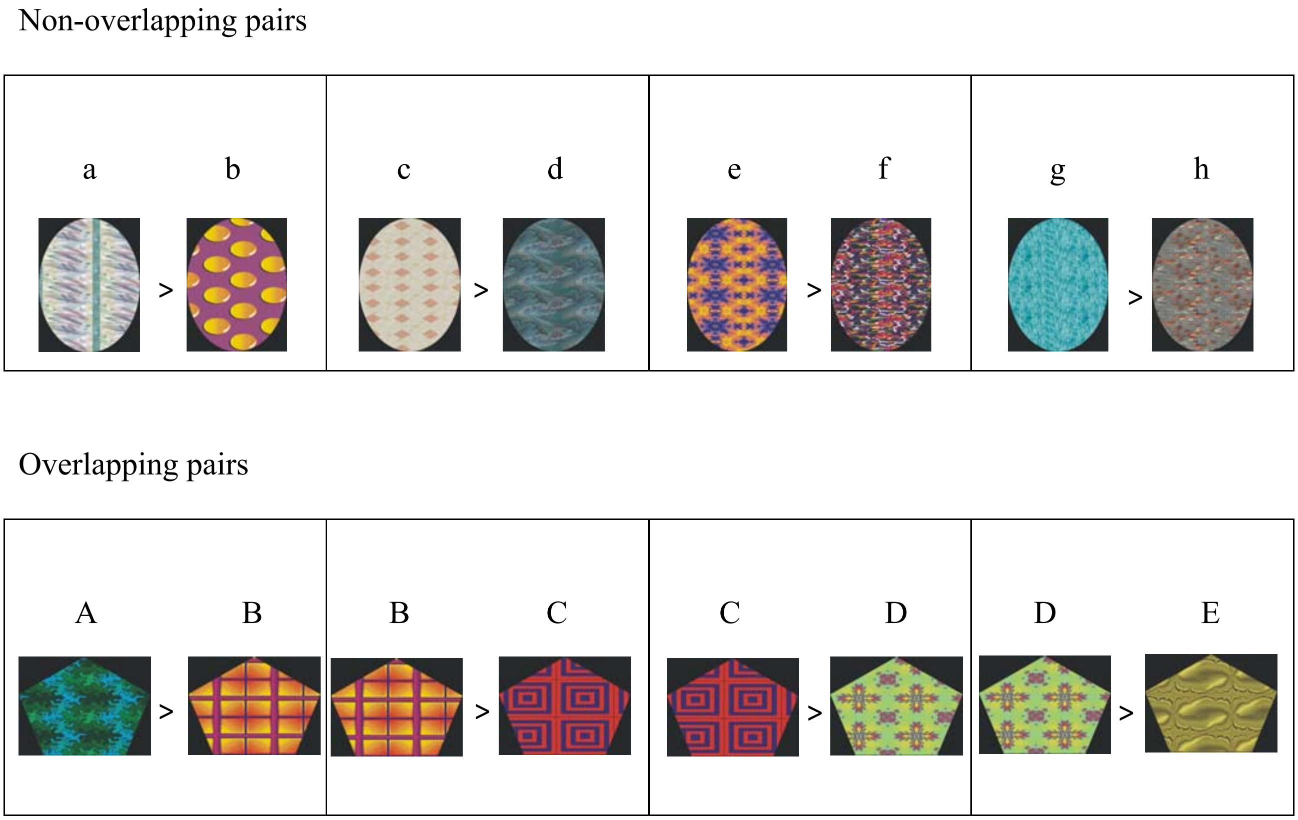

Figure 2-1. Transitive inference stimuli.

CHAPTER 3
RESULTS

Data were analyzed using the SPSS 16 statistical software package. An alpha level of .05 was used throughout the analyses.

Demographic and Clinical Characteristics of Participants

Descriptive statistics were generated for the total sample and the groups (right ATL, left ATL, control) (Table 3-1). The groups were contrasted on demographic and clinical variables using one-way analyses of variance (ANOVAs), independent samples t-tests, and Pearson chi-square tests. Participants ranged in age from 20 to 66 years (M = 41.8, SD = 14.0). Educational level ranged from nine to 20 years (M = 14.9, SD = 2.8). Gender composition of the sample was evenly balanced, with 50% female. The sample was predominantly Caucasian (83%), with a smaller proportion of African-Americans (13%) and persons of Hispanic origin (4%). With the exception of one patient, all participants reported primarily right-hand dominance as assessed by the Edinburgh Handedness Inventory. No group differences were detected on demographic characteristics including age [$F(2, 18.7) = .54$, $p = .59$], education [$F(2, 44) = 2.80$, $p = .07$], gender [$\chi^2(2) = .42$, $p = .81$], or race/ethnicity [$\chi^2(4) = 3.83$, $p = .43$].

The epilepsy groups were well matched on disease characteristics (Table 3-1). Mean age at onset of epilepsy was 20.5 years (SD = 14.1), and the mean duration of epilepsy was 19.6 years (SD = 14.0). 41.7% of patients had experienced a mild to moderate traumatic brain injury, which may have been a risk factor in the development of their epilepsy. The time from surgery to study evaluation ranged from eight to 95 months, with a mean of 55 months (SD = 26.8). Regarding surgery outcome, 66.7% of patients were classified as seizure and aura free after surgery. No group differences were detected on clinical variables, including age at onset of epilepsy [$t(22) = -.77$, $p = .45$], duration of epilepsy [$t(22) = 1.10$, $p = .28$], family history of epilepsy [$\chi^2(1) = .89$, $p = .37$], history of febrile seizures [$\chi^2(1) = .50$, $p = .48$], pre-surgical seizure frequency [$t(22) = .33$, $p = .75$], seizure classification [$\chi^2(1) = .27$, $p = .60$], pre-surgical MRI results [$\chi^2(2) = 2.68$, $p = .26$], time since surgery [$t(22) = -1.34$, $p = .19$], or post-surgical seizure outcome [$\chi^2(2) = .66$, $p = .72$]. Also, no patient had a history of vagal nerve stimulator implantation.

Data Preparation

Score Derivation

Scores for accuracy and response latency were derived for performance on the transitive inference (TI) task. Accuracy scores were generated by taking the mean percentage correct. Latency scores were derived by first eliminating all response times greater than 15 seconds, which likely reflected the influence of extraneous factors. Then, for each individual participant, the median response time for correct responses was derived for each part of the task. This resulted in the elimination of 3,765 data points out of 21,504. Accuracy and latency scores were derived for training on each stimulus set (Block 1: Trials 1-48, Block 2: Trials 49-96, and Block 3: Trials 97-144) and for the test conditions: 1) Non-overlapping Trained, 2) Non-overlapping Inference, 3) Overlapping Trained, and 4) Overlapping Inference.

Data Screening

The assumptions of univariate normality were checked for each of the dependent variables. This preliminary examination showed that distributions for TI accuracy scores were mildly to moderately negatively skewed. Therefore, square-root transformation was performed to improve normality. In subsequent analyses, results using the square-root transformed accuracy data are reported. The analyses were also conducted using the raw TI accuracy data, which yielded the same pattern of results as the square-root transformed data. The TI reaction times scores showed some evidence of positive skewness and elevated kurtosis for several variables. An outlier replacement strategy was applied to improve normality of the reaction time distributions. For each variable, scores greater than 2.5 standard deviations above the mean were replaced with the reaction time value at 2.5 standard deviations above the mean. In subsequent analyses, assumptions of the general linear model were tested when indicated, and appropriate corrections were applied if the assumptions were not met.

Aim 1: Transitive Inference Task Performance

Performance on the TI task was evaluated using accuracy and latency scores for the training and test conditions. It was hypothesized that inferences about the overlapping pairs would be impaired in patients who underwent right ATL relative to patients with left ATL and healthy controls. It was expected that right ATL patients may show deficits on other conditions of the task, but deficits would be most evident on the Overlapping Inference condition.

Accuracy: Training

Descriptive statistics for accuracy (percentage correct) are presented in Table 3-2. Training performance for each stimulus set was evaluated using a 3 (Group: right ATL, left ATL, control) x 3 (Training: Block 1, Block 2, Block 3) mixed between-within ANOVA.

First, training for the non-overlapping pairs was examined (Figure 3-1). For the within-subjects factor, Mauchly's test was significant ($p < .05$), suggesting a violation of the sphericity assumption and indicating that the variances in the differences between blocks were not equivalent. Thus, Greenhouse-Geisser df corrections are reported. Levene's test also reached significance for Block 3 of Training, indicating that the assumption of equality of error variances across groups was not met for this block. The effect of training was significant, $F(1.61, 72.62) = 83.56$, $p < .001$, $\eta^2 = .65$. Bonferroni adjusted post-hoc tests showed significant improvement across training from Block 1 to Block 2 ($p < .001$) and from Block 2 to Block 3 ($p < .001$). Neither the main effect of group [$F(2, 45) = 2.35$, $p = .11$, $\eta^2 = .09$], nor the interaction between group and training block [$F(3.23, 72.62) = .56$, $p = .66$, $\eta^2 = .02$] was significant. Given that the power to detect group differences was only .45, exploratory one-way ANOVAs were conducted to further examine performance on each block. Group differences were detected only on Block 1 of the task, $F(2, 45) = 4.34$, $p = .02$, $\eta^2 = .16$. Patients with right ATL were found to perform more poorly than controls on Block 1, $t(45) = 2.73$, $p = .03$.

Training performance on overlapping pairs was also evaluated (Figure 3-2). The main effect of training was significant, $F(2, 90) = 19.97$, $p < .001$, $\eta^2 = .31$. Bonferroni adjusted post-hoc tests showed that participants improved across training from Block 1 to Block 2 ($p = .001$) and from Block 1 to Block 3 ($p < .001$). A trend for improvement from Block 2 to Block 3 ($p = .08$) was observed. Neither the main effect of group [$F(2, 45) = 2.17$, $p = .12$, $\eta^2 = .09$], nor the interaction between group and training block [$F(4, 90) = 1.97$, $p = .10$, $\eta^2 = .08$] was significant. Given that the power to detect differences between groups was only .42, exploratory one-way ANOVAs were conducted to further examine performance on each block. Group differences were detected only on Block 2 of the task, $F(2, 45) = 3.90$, $p = .03$, $\eta^2 = .15$. Patients with left ATL performed more poorly than controls on Block 2, $t(45) = 2.53$, $p = .04$.

Taken together, these findings demonstrate that participants improved across training for both the non-overlapping and overlapping sets. Each group achieved mean accuracy of at least 85% on the third training block for non-overlapping pairs and at least 78% on the third training block for overlapping pairs. Groups achieved fairly comparable levels of learning for the non-overlapping and the overlapping stimulus sets by the third training block.

Accuracy: Test

Test performance was evaluated using a 3 (Group: right ATL, left ATL, control) x 4 (Condition: Non-overlapping Trained, Non-overlapping Inference, Overlapping Trained, Overlapping Inference) mixed between-within ANOVA. For the within-subjects factor, Mauchly's test was significant ($p < .05$), suggesting a violation of the sphericity assumption. Thus, Greenhouse-Geisser df corrections are reported. A significant effect of condition was observed, $F(1.76, 79.06) = 6.83$, $p = .003$, $\eta^2 = .13$. Bonferroni adjusted post-hoc tests revealed greater accuracy on the Non-overlapping Trained condition than on either Overlapping Trained ($p = .01$) or Overlapping Novel ($p = .02$) conditions (Table 3-2). The main effect of group was also significant, $F(2, 45) = 3.94$, $p = .03$, $\eta^2 = .15$. Bonferroni adjusted post-hoc analyses showed that patients with right ATL performed more poorly than controls ($p = .03$) on the task (Figure 3-3). The interaction between group and condition was not significant, $F(3.51, 79.06) = .73$, $p = .56$, $\eta^2 = .03$.

The primary hypothesis was that patients with right ATL would show selective difficulty with the TI condition (i.e., inferences about overlapping pairs). Therefore, given the limited power (.21) of the preceding analysis to detect an interaction, exploratory one-way ANOVAs were conducted to further evaluate performance on the test conditions. Group (right ATL, left ATL, control) was the between-subjects factor and accuracy score for the test condition was the dependent variable. Group differences were not observed on Non-overlapping Trained [$F(2, 45) = 1.71$, $p = .19$, $\eta^2 = .07$] or Non-overlapping Novel [$F(2, 45) = 1.93$, $p = .16$, $\eta^2 = .08$] conditions. A trend toward group differences was detected on the Overlapping Trained condition [$F(2, 45) = 2.68$, $p = .08$, $\eta^2 = .11$], with right ATL performing more poorly than controls. The only test condition in which significant group differences were detected was the Overlapping Inference condition [$F(2, 45) = 4.96$, $p = .01$, $\eta^2 = .18$] (Figure 3-3). Bonferroni adjusted post-hoc tests showed that patients with right ATL performed worse than controls, $t(45) = 3.15$, $p = .009$. This finding supports the hypothesis that patients would have selective difficulty with nonverbal TI after right ATL.

Level of initial learning was considered as a source of variability in test performance. Although groups achieved fairly comparable levels of learning during training, differences were observed on several individual training blocks. Therefore, analyses of covariance (ANCOVAs) to control for initial learning were conducted. The covariate was accuracy on the third training block for the appropriate stimulus set. Again, group was the between-subjects factor and accuracy score for the test condition was the dependent variable. These analyses revealed the same pattern as reported in the previous analysis. For Non-Overlapping Inference, initial learning was significantly related to performance, $F(1, 44) = 84.16$, $p < .001$, $\eta^2 = .66$. There was no main effect of group, $F(2, 44) = 1.10$, $p = .34$, $\eta^2 = .05$. For Overlapping Inference, initial learning was also significantly related to performance, $F(1, 44) = 45.43$, $p < .001$, $\eta^2 = .51$. A main effect of group was observed, $F(2, 44) = 4.93$, $p = .01$, $\eta^2 = .18$. Bonferroni adjusted post-hoc tests revealed that patients with right ATL performed worse than controls, $t(44) = 2.99$, $p = .01$, on this TI condition.

Intra-group variability in test performance was observed, as evidenced by large standard deviations (Table 3-2). Demographic and clinical variables were examined to determine whether any were related to test performance (Table 3-3). Age was significantly related to performance in three of the four test conditions, such that older age was associated with lower accuracy scores. The relationship between age and test performance did not appear to be an artifact of an underlying relationship between duration of epilepsy and test performance as these two variables were not significantly correlated. Moreover, within the epilepsy sample, a series of partial correlations controlling for duration of epilepsy revealed moderate relationships between age and these test conditions ($r = .39$ to $.50$).

Therefore, ANCOVAs were run for these three test conditions, with group as the between-subjects factor, accuracy score as the dependent variable, and age as the covariate. Age was a significant covariate in all the analyses ($p < .05$). Only on the Overlapping Inference condition was a main effect of patient group observed, $F(2, 44) = 4.54$, $p = .02$, $\eta^2 = .20$. Again, Bonferroni adjusted post-hoc tests showed that patients with right ATL performed worse than controls, $t(44) = 3.00$, $p = .01$, on this TI condition.

In addition, seizure freedom was considered as a potential influence on test performance (Table 3-3). Two left ATL patients and two right ATL patients continued to have seizures after surgery, which is a less successful outcome and indicates that epileptogenic tissue remains in their brains and is potentially disturbing cognitive functions. Test performance was re-examined when these four patients were excluded from the sample. ANCOVAs with group as the between-subjects factor, accuracy score for the test as the dependent variable, and age as the covariate revealed the same pattern of results observed in the larger sample. These analyses, coupled with the non-significant correlations between seizure freedom and test performance, suggest that including these patients in the sample should not have a major impact on the results.

In light of the poor performance of right ATL patients on the Overlapping Inference condition, an examination of individual inference pairs was made (Figure 3-4). The critical inference pair, BD, contained stimuli that had both been reinforced 50% of the time during training. The remaining four inference pairs contained end items and would be expected to have a lesser degree of difficulty. Thus, the largest disparity between groups would be expected on the BD pair. In view of the small sample and skewed distributions of some scores, performance on individual pairs was examined with the Kruskal-Wallis *H* test, which is the nonparametric analogue to the between-subjects ANOVA. Group was the independent variable, and accuracy for the pair was the dependent variable. Accuracy for the pairs, AC, AD, and BE, did not differ significantly between groups ($p > .35$). Group differences were observed on the BD pair [$\chi^2(2) = 6.31$, $p = .04$, $\eta^2 = .13$] and the CE pair [$\chi^2(2) = 6.24$, $p = .04$, $\eta^2 = .13$]. Post-hoc analyses, using either the Mann Whitney *U* test or rank sums test, showed that patients who underwent right ATL performed more poorly than controls on BD ($p < .05$). Post-hoc tests revealed no significant group differences on the CE pair.

Hierarchical Awareness

Following the computer-based task, it was assessed whether participants were aware of the hierarchy in the overlapping stimulus set. First, they were presented with hand-held cards representing B and D stimuli from the overlapping set and asked to select the winner. The proportion of participants who correctly selected B was 56.2% of patients with right ATL, 75.0% of patients with left ATL, and 87.5% of controls. A chi-square analysis revealed that these differences were not statistically significant, $\chi^2(2) = 5.00$, $p = .08$, but showed a trend in the predicted direction.

Participants were then presented with five hand-held cards representing the stimuli from the overlapping set and asked to arrange them in order of dominance. A hierarchical awareness score (range 0–12) was derived, with lower scores indicative of greater hierarchical awareness. The hierarchical awareness score was related to performance on the Overlapping Inference condition ($r = .56$, $p < .001$), after controlling for the influence of age and initial learning. Awareness of the hierarchy accounted for 32% of the variance in scores on the Overlapping Inference condition. Hierarchical awareness scores were calculated for each group, control ($M = 3.1$, $SD = 2.9$), left ATL ($M = 3.7$, $SD = 4.6$), and right ATL ($M = 4.4$, $SD = 2.9$). A one-way ANOVA with group as the between-subjects factor and hierarchical awareness as the dependent variable was performed. No group differences were detected, $F(2, 45) = .76$, $p = .47$, $\eta^2 = .03$.

After the ordering task, participants were asked whether they were aware that the stimuli in the overlapping set formed a hierarchy. The proportion of participants who endorsed hierarchical awareness was 31.2% of patients with right ATL, 42.9% of patients with left ATL, and 62.5% of controls. A chi-square test indicated that these did not represent significant group differences, $\chi^2(2) = 3.87$, $p = .14$.

Reaction Time: Training

Descriptive statistics for median reaction time are presented in Table 3-4. Training performance for each stimulus set was evaluated using a 3 (Group: right ATL, left ATL, control) x 3 (Training: Block 1, Block 2, Block 3) mixed between-within ANOVA.

First, training on the non-overlapping stimulus set was evaluated (Figure 3-5). For the within-subjects factor, Mauchly's test was significant ($p < .05$), suggesting a violation of the sphericity assumption. Thus, Greenhouse-Geisser df corrections are reported. The effect of training was significant [$F(1.31, 59.11) = 45.50$, $p < .001$, $\eta^2 = .50$]. Bonferroni adjusted post-hoc tests showed improved reaction times from Block 1 to Block 2 ($p < .001$) and from Block 2 to Block 3 ($p = .02$). There was also a main effect of group [$F(2, 45) = 3.63$, $p = .03$, $\eta^2 = .14$]; however, Bonferroni-corrected post-hoc analyses did not show significant group differences. Post-hoc tests that were not adjusted for multiple comparisons revealed that controls had faster reaction times than patients with left ATL ($p = .02$) or right ATL ($p = .05$). The interaction between group and training block was not significant [$F(2.63, 59.11) = .23$, $p = .85$, $\eta^2 = .01$]. Given that the power to detect differences between groups was only .64, exploratory one-way ANOVAs were conducted to further examine performance on each block. Group differences were detected on Block 3 [$F(2, 45) = 6.08$, $p = .005$, $\eta^2 = .21$]. Control subjects demonstrated faster reaction times on Block 3 than patients with left ATL, $t(45) = 3.01$, $p = .01$, and patients with right ATL, $t(45) = 2.62$, $p = .04$.

Training performance on overlapping pairs was also evaluated (Figure 3-6). The main effect of training was significant [$F(2, 90) = 25.74$, $p < .001$, $\eta^2 = .36$]. Bonferroni adjusted post-hoc tests showed that reaction times improved across training from Block 1 to Block 2 ($p < .001$) and from Block 1 to Block 3 ($p < .001$). Neither the main effect of group [$F(2, 45) = 3.03$, $p = .06$, $\eta^2 = .12$], nor the interaction between group and training block [$F(4, 90) = 1.14$, $p = .34$, $\eta^2 = .05$] was significant. Given the trend toward group differences showing right ATL performing worse than controls and the limited power (.56) to detect group differences, exploratory one-way ANOVAs were conducted to examine reaction times for each block. A trend toward group differences was observed on Block 1 [$F(2, 45) = 2.92$, $p = .06$, $\eta^2 = .11$] and Block 3 [$F(2, 45) = 2.91$, $p = .06$, $\eta^2 = .11$].

In summary, participants demonstrated quicker reaction times as training progressed for both the non-overlapping and the overlapping sets. On the final training block for non-overlapping pairs, controls showed faster reaction times than either of the two epilepsy groups. No significant group differences were observed on reaction times during training for the overlapping pairs.

Reaction Time: Test

Test performance was evaluated using a 3 (Group: right ATL, left ATL, control) x 4 (Condition: Non-overlapping Trained, Non-overlapping Inference, Overlapping Trained, Overlapping Inference) mixed between-within ANOVA. The main effect of group was not significant, $F(2, 43) = 2.01$, $p = .15$, $\eta^2 = .08$, (Figure 3-7). There was a main effect of condition, $F(3, 129) = 6.90$, $p < .001$, $\eta^2 = .14$. Bonferroni adjusted post-hoc tests showed that participants exhibited significantly slower reaction times on the Overlapping Trained condition compared to the Non-overlapping Trained ($p = .001$) and Non-overlapping Inference ($p = .006$) conditions. The main effect was moderated by a significant interaction between group and condition, F(6,

129) = 2.86, $p = .01$, $\eta^2 = .12$. Decomposing this interaction revealed that control participants had faster reaction times on the Non-overlapping Trained condition compared to either patients with right ATL ($p = .04$) or left ATL ($p = .04$). Participants exhibited comparable reaction times on conditions involving the overlapping stimulus set.

In addition, reaction times on the test were analyzed to ascertain if the TI effect reported by Heckers and colleagues (2004) could be replicated. The TI effect would be demonstrated by an interaction between sequence and inference, such that reaction times would be slowest on responses requiring inference across the overlapping pairs. Reaction times on the test were analyzed using 2 (Sequence Type: overlapping, non-overlapping) x 2 (Inference Type: present, absent) repeated measures ANOVAs. In the control group, a main effect of sequence was observed, $F(1, 22) = 28.61$, $p < .001$, $\eta^2 = .56$, such that controls showed significantly faster reaction times on the non-overlapping compared to the overlapping pairs. Neither the main effect of inference [$F(1, 22) = 1.01$, $p = .33$, $\eta^2 = .04$] nor the interaction between sequence and inference was significant [$F(1, 22) = .59$, $p = .45$, $\eta^2 = .03$]. This analysis was also conducted in the epilepsy sample. In the epilepsy patients, a main effect of sequence was observed, $F(1, 22) = 6.13$, $p < .02$, $\eta^2 = .22$, such that patients also showed significantly faster reaction times on the non-overlapping compared to the overlapping pairs. Again neither the main effect of inference [$F(1, 22) = .16$, $p = .69$, $\eta^2 = .01$] nor the interaction between sequence and inference was significant [$F(1, 22) = .13$, $p = .72$, $\eta^2 = .01$].

Aim 2: Comparison of Transitive Inference and Standard Neuropsychological Tests

The secondary aim of the study was to compare the clinical utility of the TI task to established clinical memory tests. It was hypothesized that the TI task would provide more sensitive detection of language non-dominant side of surgery than standardized neuropsychological tests of memory. Results from the previous section showed that accuracy on the Overlapping Inference test condition appeared most sensitive to right ATL. Therefore, this 'TI score' was selected to represent performance in the subsequent analyses for this aim.

Standard Neuropsychological Test Performance

Performance on standard neuropsychological tests was examined using a series of one-way ANOVAs with group as the independent variable (right ATL, left ATL, control) and test score as the dependent variable (Table 3-5). Groups were comparable on intellectual functioning, which was in the average range.

As expected, significant group differences were observed on verbal memory tests, including scores for HVLT-R Total [$F(2, 44) = 7.63$, $p = .001$, $\eta^2 = .26$], HVLT-R Delayed Recall [$F(2, 44) = 6.51$, $p = .003$, $\eta^2 = .23$], WMS-III Logical Memory Total [$F(2, 43) = 4.39$, $p = .02$, $\eta^2 = .17$], WMS-III Verbal Paired Associates Total [$F(2, 44) = 9.53$, $p < .001$, $\eta^2 = .30$], and Verbal Paired Associates Delayed Recall [$F(2, 42) = 5.49$, $p = .008$, $\eta^2 = .21$]. Group differences were also observed on the Boston Naming Test-II [$F(2, 41) = 7.51$, $p = .002$, $\eta^2 = .27$]. Bonferroni-corrected post-hoc tests showed that patients with left ATL performed worse than controls on these verbal memory scores and on the Boston Naming Test-II ($p < .05$). Furthermore, the HVLT-R (Total and Delayed Recall) and the WMS-III Verbal Paired Associates (Total) discriminated between side of surgery, such that patients with left ATL performed significantly worse than those with right ATL ($p < .05$).

In contrast, group differences were not observed on a measure of nonverbal memory, the Rey Complex Figure Test. Mean scores for immediate and delayed recall on this measure ranged from the 5th to the 20th percentile across groups. Also, group differences were not detected on measures of attention or executive function.

Relationship between Transitive Inference and Standard Neuropsychological Tests

A series of partial correlations controlling for age examined relationships between the experimental task and neuropsychological test performance (Table 3-6). Both non-TI (i.e., inferences about non-overlapping pairs) and TI (i.e., inferences about overlapping pairs) were examined. All significant correlations were positive and ranged from small to moderate (r = .3 to .4). *Non-TI* was significantly correlated with two verbal memory measures (WMS-III Logical Memory and Verbal Paired Associates) and several measures of attention/ executive functioning (WAIS-III Digit Span, Trail Making Test Part B, and Wisconsin Card Sorting Test Errors). In addition, non-TI and TI were correlated with the copy condition of the Rey Complex Figure Test, a visuospatial, constructional measure. *TI* was significantly correlated with WAIS-III Full-Scale IQ score, WMS-III Logical Memory (Total and Delayed), the Rey Complex Figure Test (Immediate and Delayed), and Trail Making Test Part B.

Prediction of Right vs. Left Side of Resection

Binary logistic regression was conducted to evaluate neuropsychological predictors of side of surgery. Two neuropsychological scores were entered as predictors, the Rey Complex Figure Test Delayed Recall raw score and the TI score. Age was also specified as an a priori predictor. The model achieved an overall classification accuracy of 73.9%, which is not a significant improvement [$\chi^2(3, 23) = 3.03$, p = .39] over the base rate classification of 65%. While the model correctly classified 93.3% of those who underwent right ATL, it correctly classified only 37.5% of those who underwent left ATL. Odds ratios (i.e., post-test probability of having undergone right ATL) were calculated as .97 for the Rey Complex Figure score and 1.43 for the TI score.

Receiver operating characteristic (ROC) curve analyses were performed to determine cut scores that minimize diagnostic errors. The ROC curve analyses plot the rate of false positives (i.e., false prediction of right ATL in someone with left ATL) against the rate of true positives (i.e., correct classification of right ATL). The area under the curve represents how well each measure predicts right-sided resection, with larger areas indicative of stronger predictors.

ROC curve analysis for the Overlapping Inference score revealed area under the curve of .68 (SE = .12, 95% CI = .44–.91) (Figure 3-8). A cut score of 75% yielded the following operating characteristics: sensitivity = 50%, specificity = 87.5%, positive predictive power = 89%, and negative predictive power = 47%. Thus, while a score below the cut-off indicated a high probability that a patient had undergone right ATL, only half the patients who underwent right ATL were detected with this cut score. Using a higher cut score identified more patients who underwent right temporal lobe surgery, but yielded an unacceptably high rate of false positives. For example, a cut-score of 85% yielded sensitivity = 62.5%, specificity = 62.5%, positive predictive power = 76.9%, and negative predictive power = 45.5%.

To further examine TI performance, independent samples t-tests and Pearson chi-square tests contrasted right ATL patients who performed above (n=8) and below (n=8) the 75% cut score. No significant group differences ($p > .10$) were detected on demographic or clinical variables, including age, years of education, age at onset of epilepsy, duration of epilepsy, months since surgery, language or memory dominance, or presence of pre-surgical hippocampal sclerosis. Group differences were detected on self-reported hierarchical awareness [$\chi^2(1) = 7.27$, $p = .007$], such that 100% of patients who performed below the cut score denied hierarchical awareness, while only 37.5% of patients who performed above the cut score did not endorse it.

ROC curve analysis was also conducted to evaluate the predictive utility of the Rey Complex Figure Test (Figure 3-8). This analysis used the age-corrected score for Delayed Recall. Area under the curve was .66 (SE = .11, 95% CI = .43–.88). Operating characteristics were calculated for cut scores at T = 30 (sensitivity = 40%, specificity = 100%, positive predictive power = 100%, negative predictive power = 47%) and at T = 35 (sensitivity = 60%, specificity = 50%, positive predictive power = 69%, negative predictive power = 40%).

Table 3-1. Demographic and clinical characteristics by group

	Right ATL (n=16)	Left ATL (n=8)	Control (n=24)
Age	43.9 (11.1)	43.9 (15.5)	39.7 (15.4)
Years of education[a]	14.3 (2.7)	13.4 (2.1)	15.7 (2.9)
Gender (% female)	44%	50%	54%
Race (% Caucasian)	87.5%	100%	75%
History of mild-moderate TBI	50.0%	25.0%	0%
History of psychiatric diagnosis	25.0%	25.0%	0%
Handedness (laterality quotient)	0.84 (.18)	0.52 (.67)	0.86 (.16)
Age at onset of epilepsy (yrs.)	22.1 (14.4)	17.4 (13.8)	—
Duration of epilepsy (yrs.)	17.4 (12.3)	24.0 (16.9)	—
Family history of epilepsy	31.2%	50.0%	—
History of febrile seizures	25.0%	12.5%	—
Pre-surg. seizure frequency (per month)	8.4 (11.5)	10.1 (11.4)	—
Seizure classification			
Complex partial	93.7%	87.5%	—
Generalized	6.2%	12.5%	—
Pre-surgical MRI results			
No abnormalities	37.5%	12.5%	—
Hippocampal sclerosis	56.2%	62.5%	—
Other lesion/ abnormality	6.2%	25.0%	—
Language dominance (Wada)[b]			
Left	100%	71%	—
Mixed	0%	29%	—
Months since surgery	60.1 (27.7)	44.9 (23.2)	—
Post-surgical seizure freedom			
Seizure free	68.7%	62.5%	—
Aura only	18.7%	12.5%	—
Continued seizures	12.5%	25.0%	—

Note. Data presented as mean (standard deviation), except for those variables listed as percent of sample. [a]In control group, one subject was missing years of education. [b]One left ATL and two right ATL patients missing Wada language dominance data.

Table 3-2. Transitive inference accuracy scores as percent correct by group

	Right ATL (n=16)	Left ATL (n=8)	Control (n=24)
Training: Non-overlapping pairs	77.9 (20.2)	81.4 (10.5)	88.1 (15.6)
Block 1	66.0 (16.6)	68.7 (12.7)	78.9 (16.3)
Block 2	82.2 (23.5)	83.9 (14.3)	91.2 (18.4)
Block 3	85.4 (24.4)	91.7 (8.6)	94.1 (15.0)
Training: Overlapping pairs	74.6 (15.6)	73.0 (10.5)	81.7 (12.9)
Block 1	69.5 (13.1)	69.8 (8.0)	73.0 (14.9)
Block 2	76.3 (18.4)	71.1 (12.3)	85.8 (15.2)
Block 3	77.9 (18.2)	78.1 (17.2)	86.4 (13.3)
Test			
Non-overlapping learned	85.0 (22.5)	90.6 (12.6)	94.1 (15.7)
Non-overlapping inference	82.0 (28.4)	82.8 (23.6)	92.8 (20.6)
Overlapping learned	76.2 (16.9)	82.2 (17.5)	87.2 (15.3)
Overlapping inference	71.2 (22.1)	82.2 (23.7)	89.1 (15.5)

Note. Data presented as mean (standard deviation) of percentage correct, with 50% representing chance performance and 100% representing error-less performance.

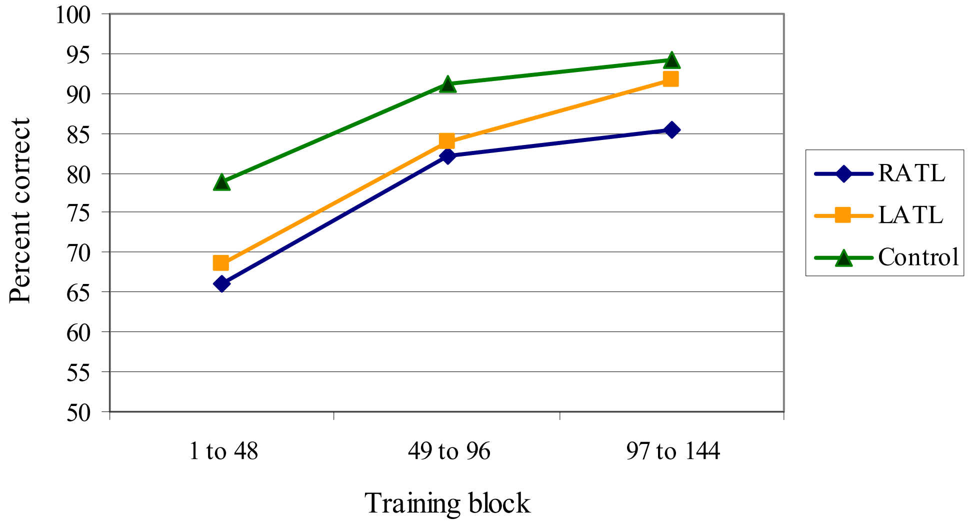

Figure 3-1. Accuracy for non-overlapping pairs by training block.

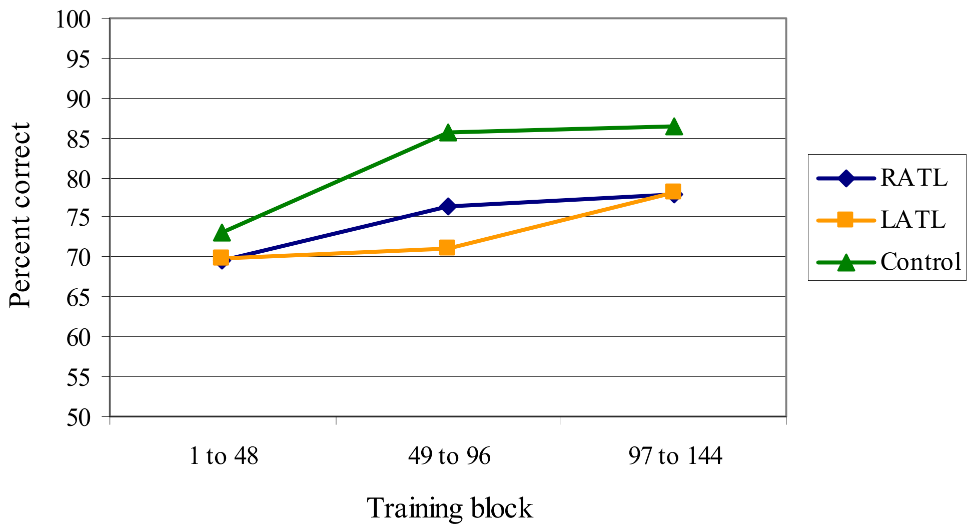

Figure 3-2. Accuracy for overlapping pairs by training block.

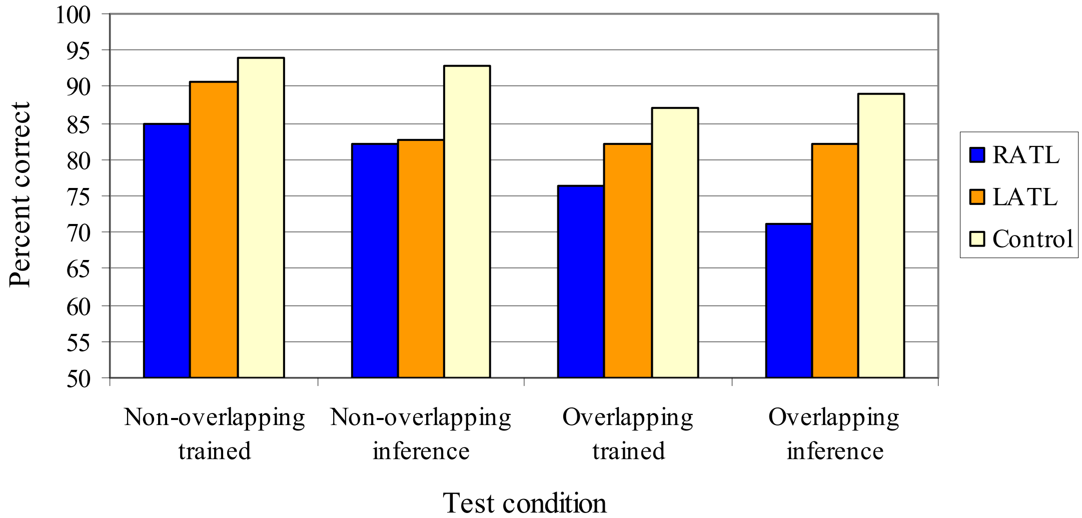

Figure 3-3. Accuracy by test condition.

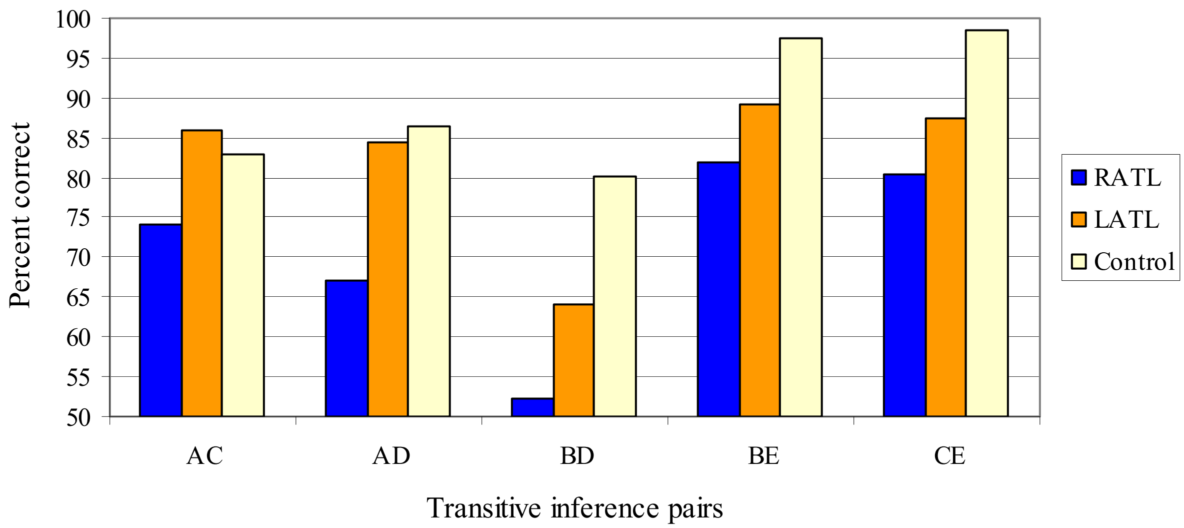

Figure 3-4. Accuracy for overlapping pairs requiring transitive inference.

Table 3-3. Correlations between TI test, demographic characteristics, and clinical variables

	Non-overlapping trained	Non-overlapping inference	Overlapping trained	Overlapping inference
Age	-.25	-.33*	-.47**	-.46**
Years of education	.18	.25	.17	.20
Age at onset (yrs.)	-.30	-.38	-.10	-.13
Duration of epilepsy (yrs.)	-.06	-.13	-.26	-.18
Seizure freedom	.26	.34	.02	.22

Note. Square-root transformed accuracy scores were used in the Pearson bivariate correlations.
*p < .05. **p < .01.

Table 3-4. Transitive inference reaction times by group

	Right ATL (n=16)	Left ATL (n=8)	Control (n=24)
Training: Non-overlapping pairs	1177.8 (473.9)	1339.9 (294.9)	908.7 (295.7)
Block 1	1470.5 (587.7)	1592.4 (321.2)	1260.1 (506.6)
Block 2	1143.2 (474.2)	1272.9 (257.9)	905.4 (360.9)
Block 3	1075.1 (445.4)	1205.7 (363.7)	788.5 (235.5)
Training: Overlapping pairs	1436.8 (476.5)	1377.6 (286.5)	1147.2 (364.7)
Block 1	1644.8 (646.0)	1706.7 (349.6)	1304.9 (469.0)
Block 2	1411.4 (512.6)	1310.6 (302.3)	1133.0 (369.7)
Block 3	1366.7 (488.9)	1223.7 (343.4)	1058.7 (344.6)
Test			
Non-overlapping learned	1163.5 (336.6)	1243.4 (355.7)	865.4 (323.6)
Non-overlapping inference	1217.0 (463.7)	1262.4 (575.6)	871.1 (544.6)
Overlapping learned	1343.4 (510.7)	1261.4 (363.7)	1210.7 (524.0)
Overlapping inference	1404.3 (577.8)	1148.9 (341.2)	1156.0 (524.3)

Note. Data presented as mean (standard deviation) of median response time in milliseconds for correct responses.

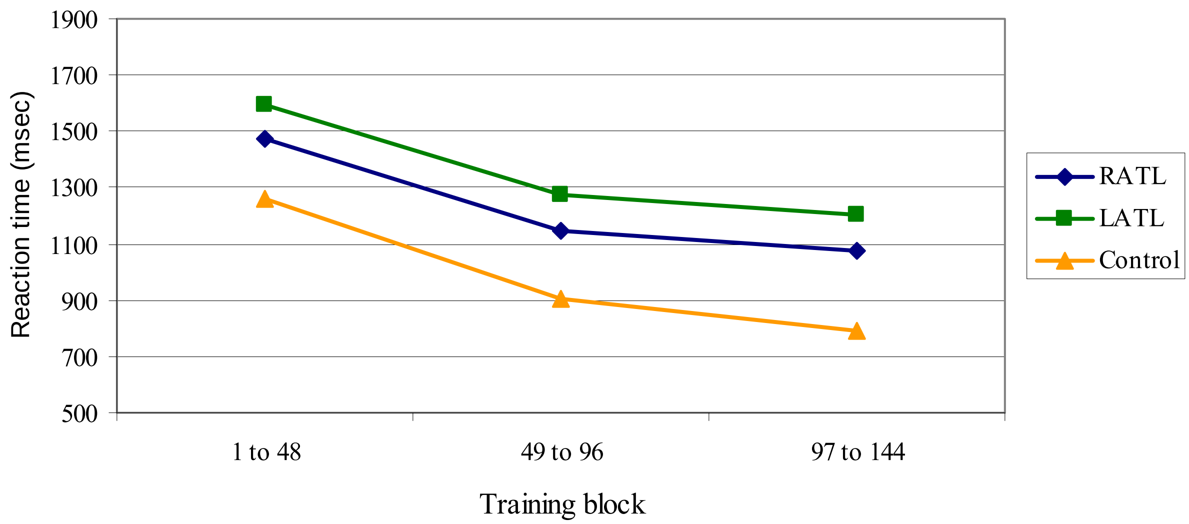

Figure 3-5. Reaction time for non-overlapping pairs by training block.

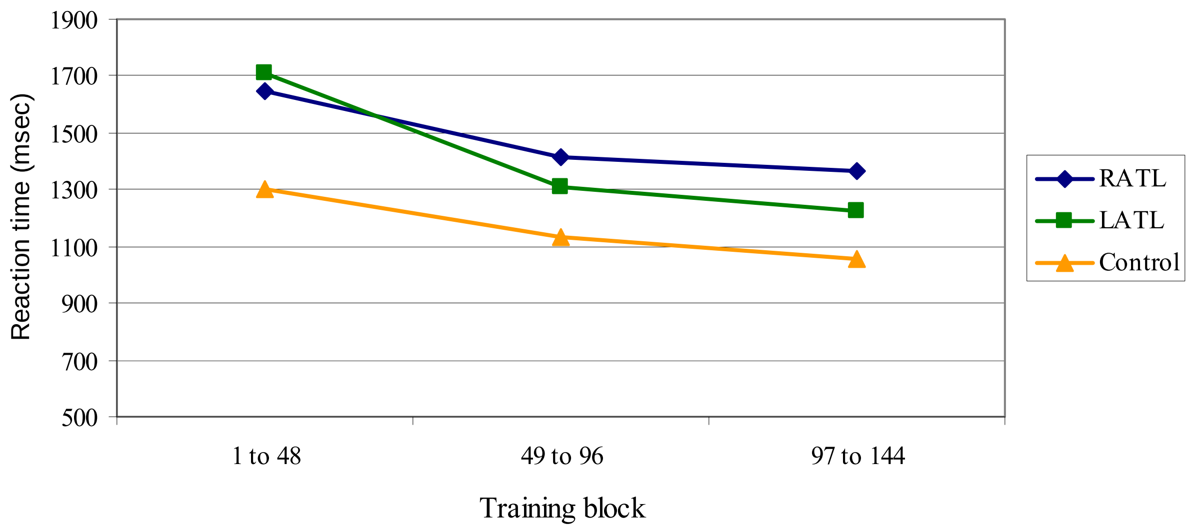

Figure 3-6. Reaction time for overlapping pairs by training block.

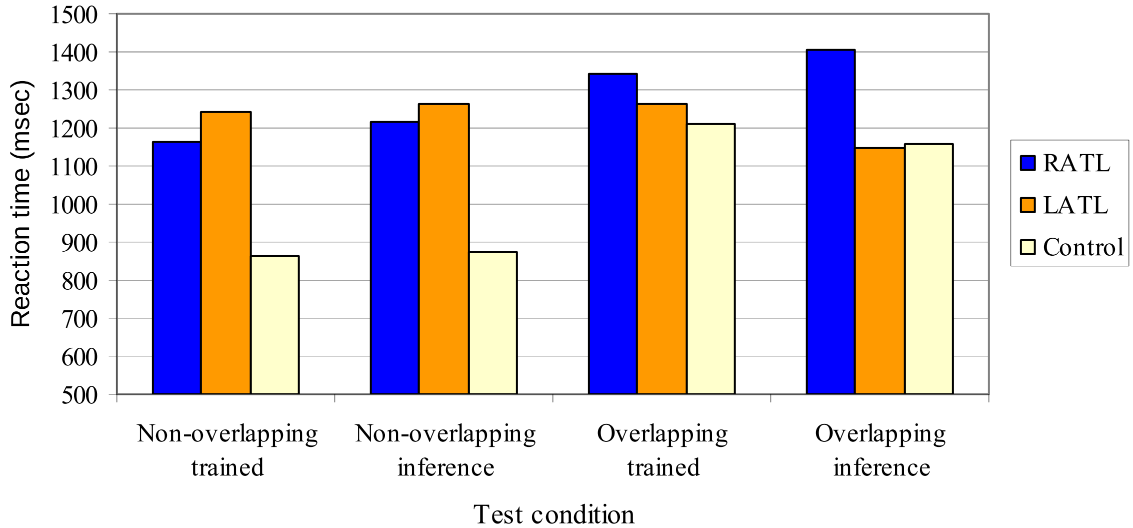

Figure 3-7. Reaction time by test condition.

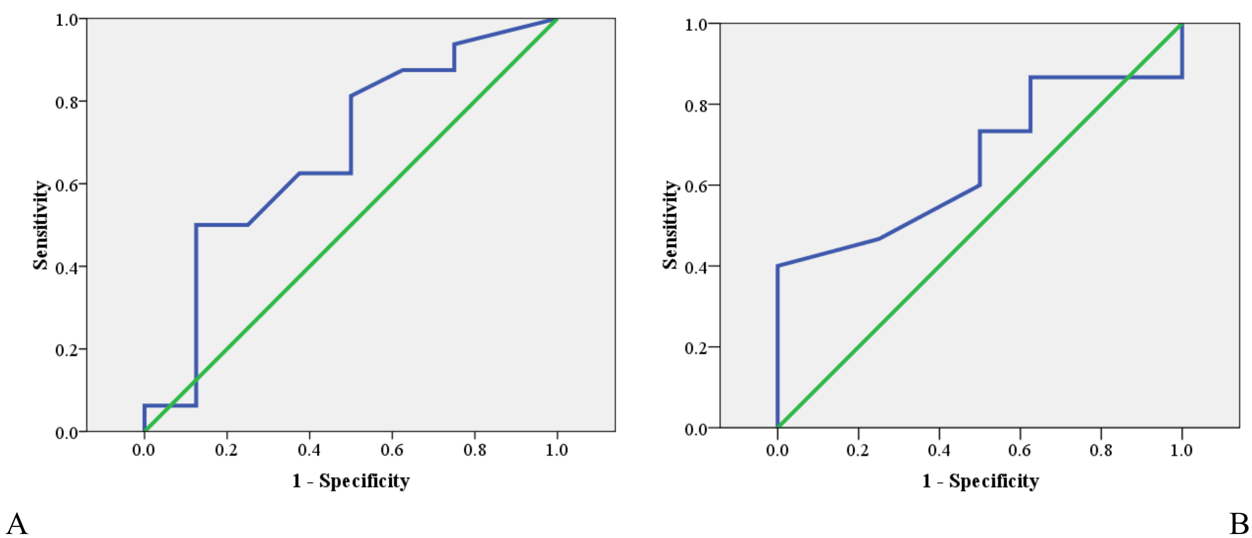

Figure 3-8. Receiver operating characteristic (ROC) curves for the prediction of right anterior temporal lobectomy. A) Transitive inference (accuracy for overlapping pairs). B) Rey Complex Figure Test delayed recall.

Table 3-5. Neuropsychological test performance by group

	Right ATL (n=16)[a]	Left ATL (n=8)[b]	Control (n=24)[c]	*F*	*p*
WASI Full-Scale IQ (SS)	101.5 (13.0)	102.1 (9.9)	104.4 (10.8)	.30	.74
HVLT-R					
Immediate total (T)	41.7 (10.2)	30.0 (9.4)	44.3 (7.8)	7.63	.001
Delayed recall (T)	42.4 (13.6)	26.1 (8.0)	43.2 (11.8)	6.51	.003
WMS-III Logical Memory					
Immediate total (ss)	9.4 (2.1)	8.4 (3.4)	11.3 (2.8)	4.39	.02
Delayed recall (ss)	10.1 (2.6)	9.7 (2.6)	11.6 (2.4)	2.50	.09
WMS-III Verbal Paired As.					
Immediate total (ss)	10.5 (2.1)	6.9 (3.1)	11.1 (2.3)	9.53	<.001
Delayed recall (ss)	10.9 (2.6)	8.3 (3.8)	11.8 (1.9)	5.49	.008
Rey Complex Figure Test					
Copy (raw)	29.7 (4.8)	31.8 (2.2)	31.0 (4.2)	.81	.45
Immediate recall (T)	34.9 (13.6)	41.7 (9.2)	38.3 (15.0)	.67	.51
Delayed recall (T)	34.1 (12.7)	39.9 (9.3)	37.6 (12.0)	.70	.50
Recognition (T)	41.7 (10.1)	43.7 (5.3)	48.4 (11.5)	2.03	.14
Boston Naming Test-II (T)	43.2 (9.8)	34.1 (4.1)	51.3 (13.3)	7.51	.002
WAIS-III Digit Span (ss)	10.9 (3.3)	9.9 (4.0)	11.6 (3.2)	.75	.48
Trail Making Test					
Part A (T)	39.9 (12.3)	46.4 (11.2)	43.9 (10.4)	1.03	.36
Part B (T)	47.1 (8.5)	50.0 (9.3)	47.9 (12.3)	.19	.83
Wisconsin Card Sorting Test					
Errors (T)	45.2 (10.9)	50.4 (10.6)	50.6 (7.6)	1.38	.26
Perseverations (T)	45.1 (10.3)	53.3 (12.7)	51.4 (8.7)	2.04	.14

Note. SS=Standard Score, T=T score, ss=scaled score. [a]Missing data for right ATL included two Full-Scale IQ, one Digit Span, four WCST, one Trail Making Test, three Boston Naming Test, one Verbal Paired Associates Delayed, one Logical Memory, and one Rey Complex Figure Test. [b]Missing data for left ATL included one Full-Scale IQ, one WCST, and one Verbal Paired Associates Delayed. [c]One control was only administered experimental measures. Two controls were missing the Full-Scale IQ, and two controls were not administered the WCST.

Table 3-6. Partial correlations between transitive and non-transitive inference and performance on standard neuropsychological tests after controlling for age

	Non-transitive inference	Transitive inference
	r	*r*
WASI Full-Scale IQ	.26	.41**
HVLT-R		
Immediate total	-.10	.21
Delayed recall	.11	.21
WMS-III Logical Memory		
Immediate total	.31*	.32*
Delayed recall	.35*	.39**
WMS-III Verbal Paired Associates		
Immediate total	.30*	.24
Delayed recall	.07	.14
Rey Complex Figure Test		
Copy (raw)	.37*	.33*
Immediate recall	.14	.33*
Delayed recall	.14	.32*
Delayed recognition	.26	.27
Boston Naming Test-II	.26	.28
WAIS-III Digit Span	.40**	.16
Trail Making Test		
Part A	-.04	.24
Part B	.39**	.38*
Wisconsin Card Sorting Test		
Errors	.34*	.24
Perseverations	.26	.22

Note. Square-root transformed accuracy scores represent performance on the TI task. Standard, scaled, or T scores represent performance on standard neuropsychological measures unless otherwise noted. N=47. Missing data included five Full-Scale IQ, one Digit Span, seven WCST, one Trail Making Test, three Boston Naming Test, two Verbal Paired Associates Delayed, one Logical Memory, and one Rey Complex Figure Test. $*p < .05$. $**p < .01$.

CHAPTER 4
DISCUSSION

Transitive Inference Performance in Temporal Lobe Epilepsy

This study examined performance on a transitive inference (TI) paradigm in patients who had a history of intractable TLE and who had undergone standard ATL for seizure relief. During training on the task, participants demonstrated learning of the visual stimulus pairs through improved accuracy and faster reaction times as training progressed. Epilepsy patients achieved similar levels of accuracy as controls. On the test, patients who had undergone right ATL performed significantly worse than control participants, and patients who had undergone left ATL performed in the intermediate range. Significant performance differences were not observed between patients based on side of surgery.

Importantly, the right ATL group performed more poorly on the TI condition, which involved making inferences across a series of overlapping pairs that formed a hierarchy. On the TI condition, patients with right ATL achieved a mean score of only 71% correct, while patients with left ATL and control participants achieved mean scores of 82% and 89% respectively. The effect size for this group difference was in the medium range, and this difference remained evident after controlling for the effects of age and initial learning. This finding supports the primary hypothesis that patients with right ATL would have selective difficulty with TI for patterned shapes. As expected, the true TI pair (BD), in which both stimuli had been equally reinforced during training, was the most difficult individual pair for right ATL patients.

An examination of demographic and clinical variables showed that age was significantly related to accuracy scores. Older individuals tended to perform more poorly, which is consistent with prior research indicating that older adults experience difficulty with the relational organization of propositions within memory, although previous studies had employed samples with considerably older ages than were represented in the current study (Ryan, Moses, & Villate, 2009). Other demographic and clinical variables, including level of education, age at onset of epilepsy, duration of epilepsy, and post-surgical seizure freedom, did not show a significant relationship with accuracy scores.

On reaction times for the test, the only group difference noted was faster performance by controls than either epilepsy patient group on the Non-overlapping Trained condition. This finding likely reflects reductions in cognitive and psychomotor speed associated with chronic temporal lobe epilepsy (Hermann et al., 2006) and with the use of antiepileptic drugs (Motamedi & Meador, 2004). Moreover, results showed that the non-overlapping conditions may have been easier for participants, as evidenced by higher accuracy scores (Non-overlapping Trained > Overlapping Trained, Overlapping Inference) and faster reaction times (Non-overlapping Trained, Non-overlapping Inference > Overlapping Trained). Since memory demands were less for these conditions, they may have had a greater likelihood of detecting differences in basic, speeded processing capacities.

After the computerized task, hierarchical awareness was measured by asking participants to order the stimuli in the overlapping set. Their ability to demonstrate knowledge of the hierarchy accounted for 32% of the variance in performance on the TI condition, after controlling for the effects of age and initial learning. Significant group differences in self-reported hierarchical awareness were not observed, although twice as many controls (62%) as right ATL patients (31%) endorsed hierarchical awareness. Libben and Titone (2008) reported that participants who are aware of the hierarchy may be more likely to use a logic-based strategy to solve the transitive problem, while participants who are unaware may be more likely to use a stimulus-driven strategy.

The current study utilized a TI paradigm closely modeled after the task developed by Heckers and colleagues (2004). The results partially replicated their behavioral data. In their healthy, young adult sample, participants achieved a mean of greater than 90% on all test conditions. Healthy controls in the current study achieved similar mean scores, ranging from 87 to 94% on the various test conditions, while the scores of epilepsy patient tended to be lower. Regarding reaction time data, Heckers and colleagues (2004) noted a main effect of sequence (i.e., reaction times faster for non-overlapping than for overlapping pairs), a main effect of inference (i.e., reaction times quicker for responses that did not require an inference), and an interaction between sequence and inference (i.e., the TI effect: reaction times slowest on responses requiring an inference across overlapping pairs). In the current study, the effect of sequence was replicated, but no main effect of inference nor interaction effect was observed in either control participants or epilepsy patients.

Transitive Inference and Cognitive Neuroscience Research

The post-surgical ATL population provides a model to study hippocampal contributions to memory, and the current results suggest a link between hippocampal function and TI. Functional imaging studies have identified a distributed neural network involved in TI judgments, including areas of the cortex, hippocampus, and thalamus (Heckers et al., 2004; Zalesak & Heckers, 2009). This research has consistently highlighted the integral role of the hippocampus in TI and has demonstrated selective hippocampal activation during TI of geometric designs (Heckers et al., 2004; Zalesak & Heckers, 2009), faces (Nagode & Pardo, 2002), and face-house pairings (Preston et al., 2004). The translational paradigm of TI is also supported in studies of animals, which showed that hippocampally-lesioned rodents exhibit impaired TI (Devito et al., in press; Dusek & Eichenbaum, 1997).

Functional imaging studies have indicated that encoding and recall of associative memories are functions of an integrated hippocampal system (Davachi & Wagner, 2002; Jackson & Schacter, 2004; Meltzer & Constable, 2005). The behavioral data from the current study also provide information about the processes involved in relational memory. Groups achieved fairly comparable levels of learning during training for the overlapping pairs, suggesting that the pairs were encoded to a similar degree across groups. On the test, patients with right ATL showed a trend towards poorer performance on the condition that tested memory for overlapping pairs and showed significantly poorer performance than controls on the condition requiring TI across the overlapping pairs. This pattern of performance suggests that consolidation and retrieval of relational information was difficult for patients with right ATL. In particular, the ability to flexibly use retrieved information and apply it to solve a novel problem was impaired.

It was hypothesized that laterality effects would be observed in the current study, such that TI for nonverbal information would be more difficult for patients with right ATL than patients with left ATL. While the task did not clearly discriminate side of surgery, patients with right ATL did perform more poorly than controls. Past research on TI has not been designed to address questions of laterality, and hemispheric lateralization observed during functional imaging is not easily interpreted. Heckers and colleagues (2004) demonstrated right anterior hippocampal activation during TI with the paradigm adapted for use in the current study. However, in a later study using a similar paradigm (Zalesak & Heckers, 2009), lateralization effects were less clear and varied based on the aspect of TI that was studied. Activation was greater in the right hippocampus for pairs that were more adjacent in the hierarchy, but greater in the left hippocampus for comparisons of pairs that did not contain end items versus those that did. The lateralization of TI is deserving of further study using functional imaging and behavioral paradigms.

More broadly, TI reflects relational memory processing because it examines whether representations that share common elements have been linked in memory to solve new problems (Eichenbaum, 2000). These results provide support for the relational memory account of hippocampal function in a new population, patients with complex partial epilepsy of temporal lobe origin. The findings also suggest a laterality effect for TI, such that relational memory processing for visual/nonverbal information is difficult for TLE patients with right hippocampal pathology and side of surgery.

Clinical Applications of Transitive Inference

A secondary aim of the study was to compare the clinical utility of the TI task to conventional neuropsychological measures. The TI score (i.e., accuracy on inferences for overlapping pairs) was chosen to represent performance because it appeared most sensitive to differential performance in TLE. Material specific-predictions link memory for verbal material to the language dominant temporal lobe (usually left) and memory for nonverbal material to the language non-dominant temporal lobe (usually right; Milner, 1975). Accordingly, the TI task was compared to the standard measure of nonverbal memory, the Rey Complex Figure Test.

In the current study, results support the strong link between impaired verbal memory and left TLE, which has been consistently demonstrated in the literature (Helmstaedter, 2004; Hermann et al., 1997, Strauss et al., 1995). Scores from the HVLT-R and the WMS-III Verbal Paired Associates discriminated patients with left ATL from those with right ATL. Both measures assess verbal list learning capacity and showed large effect sizes in discriminating between groups. The largest effect size ($\eta^2 = .30$) was observed for the WMS-III Verbal Paired Associates Total score, which suggests that memory for word pairs as opposed to single words may be more sensitive to left TLE. This pattern would be predicted by relational memory theory. The WMS-III Logical Memory subtest did not demonstrate the capability to discriminate between patients based on side of surgery, although patients with left ATL did perform worse than controls on this task.

Conversely, the conventional nonverbal memory measure did not discriminate between groups (right ATL, left ATL, control). This finding is consistent with previous research, which has not found a reliable link between right TLE and nonverbal memory (Barr et al., 1997; Helmstaedter, 2004; Lee et al., 2002; Martin et al., 1999). Of note, the epilepsy patient groups and the control group performed in the impaired to low average range on the Rey Complex Figure Test. The low scores may be indicative of the false lateralizing figural memory performance sometimes observed in left TLE (Loring et al., 2007).

The TI task may have more promise as a behavioral indicator of right hippocampal dysfunction than the Rey Complex Figure Test. The motor and constructional abilities involved in figural reproduction may confound the assessment of memory, while the TI task uses a recognition format to bypass this concern. Furthermore, analysis revealed significant group differences on TI (right ATL < control) with a medium effect size ($\eta^2 = .18$ to $.20$). In contrast, the Rey Complex Figure Test did not detect significant group differences, and a small effect size ($\eta^2 = .03$) was noted for both the immediate and delayed recall conditions of this measure.

The clinical utility of these measures was further explored using logistic regression and receiver operating characteristic (ROC) curve analysis. Neither measure was a significant predictor of side of surgery, and operating characteristics were similar for both measures. Low cut scores are suggested: 75% for the TI score and 30 for the Rey Complex Figure Test Delayed Recall T score. The cut scores were set to optimize positive predictive power and specificity, which resulted in low sensitivity. For instance, at the 75% cut score on TI, positive predictive power was 89%, but only half of patients with right ATL were detected. Higher cut-offs yielded unacceptably high rates of false positives.

Taken together, these findings provide limited support for our secondary hypothesis that the TI task would be more sensitive to right ATL than the conventional nonverbal memory measure. The TI task detected differences between right ATL patients and controls, while the Rey Complex Figure Test did not. However, neither measure discriminated between epilepsy groups with sufficient accuracy to be used with confidence at the single-patient level.

Previous research has not compared TI to results of standard neuropsychological testing. Partial correlations controlling for age provided some evidence of convergent and discriminant validity for the experimental task. All significant correlations were in the small to moderate range (r = .3 to .4). TI showed a moderate correlation with an estimate of intellectual functioning, suggesting that it taps some general cognitive abilities. TI also showed modest correlations with the Rey Complex Figure Test recall measures, which provides some degree of convergent validity. Both transitive and non-transitive inference scores were associated with a measure of contextual, verbal recall and Trail Making Test Part B. The relationships between TI and other measures of verbal memory, language, attention, and executive function were not significant, which provides evidence of discriminant validity. Non-transitive inference, however, showed low correlations with several measures of attention and executive function. This relationship was unexpected and may suggest a frontal lobe contribution.

Limitations and Future Directions

A limitation of the current study is the relatively small sample size that may have resulted in some of the analyses being underpowered. In light of the limited power, several exploratory analyses were conducted that were, strictly speaking, not statistically justified using the models that were generated. The initial power analysis was based on the one published study of TI in a clinical population. This study compared individuals with schizophrenia to nonpsychiatric controls using nearly identical stimuli and a comparable paradigm (Titone et al., 2004). The TI effect ($d = .80$) was large (Cohen, 1988). A power analysis (power = .80) revealed that 63 participants would be needed to detect a large effect in an omnibus three-group test using an alpha level of .05. Therefore, an optimal sample size would have included at least 20 participants per group. While the control and right ATL groups were close to this target, greater difficulty was encountered in recruiting patients who had undergone left ATL.

One methodological concern is the verbalizability of stimuli in the task. Nonverbal tests may be contaminated by verbal encoding (Barr et al., 1997). Studies that support this idea have shown an association between nonverbal memory and left hippocampal volume in TLE (Griffith et al., 2003; McConley et al., 2008). In another study, patients with right TLE showed memory impairment for designs only when their complexity exceeded verbal learning capacity (Helmstaedter et al., 1995). In the current study, all participants were questioned about the strategies they used to complete the TI task. Some participants reported applying verbal labels to the stimulus patterns (e.g., "plaid"), while others reported focusing on the visual patterns and denied using any verbal strategies. In future studies, it will be essential to generate stimuli that are difficult to verbally label in order to develop a more pure measure of nonverbal relational memory.

In addition to considering new stimuli, the TI task could potentially benefit from other revisions as well. First, it could be beneficial to program the task to ensure that a specific learning criterion is met during training (e.g., 80%). The advantage to this procedure would be ensuring that all participants achieve a minimal level of learning, which is important when evaluating neurologically impaired populations. Secondly, on the test, 52% of participants achieved greater than 90% correct on the TI condition. This ceiling effect suggests that a more difficult task could yield greater information about the range of performance. Designing a more difficult TI task could be easily accomplished by creating a larger hierarchy of overlapping pairs that consists of more than five items. This would include more true TI pairs, like B>D, which do not contain end items.

Also, condensing the task to focus only on the overlapping pairs may optimize clinical utility and brevity. Results showed that conditions with overlapping pairs tended to be more difficult, as evidenced by lower accuracy scores and slower reaction times. The paradigm in the current study included conditions to demonstrate dissociations between transitive vs. non-transitive inferential problems and between overlapping vs. non-overlapping pairs. This type of paradigm may be more useful in neuroimaging studies, in which it is critical to design tasks that highlight functional dissociations between neuroanatomical regions. In contrast, in a clinical study, the information provided by the additional conditions with non-overlapping pairs is less useful.

This study focused on a nonverbal task, given the dearth of behavioral measures sensitive to language non-dominant hippocampal function. However, the study design did not permit a full evaluation of material specificity. A verbal TI analogue would be needed to fully evaluate the material-specific model of memory. The author developed a verbal TI task using non-words as stimuli and piloted this task with healthy adults and with several epilepsy patients. Individuals tended to perform more poorly on the verbal task and described it as more difficult. While the nonverbal task may have permitted dual encoding resulting in better performance, the verbal task may have facilitated strictly verbal encoding. Because of difficulties obtaining adequate pilot data on the verbal measure, it was eliminated from the study. In the future, it will be important to refine this methodology to develop a verbal TI analogue of a similar level of difficulty, in order to facilitate comparison and to evaluate laterality effects.

Lastly, the current study evaluated TI in patients who had undergone ATL. Examining the paradigm in post-surgical epilepsy patients is an initial step. The next step would be to evaluate TI in pre-surgical epilepsy patients to determine whether the paradigm shows sensitivity to right temporal dysfunction in this patient group. The clinical implications in this patient group are more relevant, as the eventual applied goal of this research is to develop more effective pre-surgical tools to assist in the diagnosis of localized/lateralized seizure onset and to predict the likelihood of post-surgical decline in cognitive function (Helmstaedter, 2004).

Conclusion

The current study is the first to examine TI in TLE. The study showed that TI for visual information is difficult for patients who underwent right ATL. Results provide some limited support for the material-specificity of TI. More broadly, the findings suggest a link between hippocampal function and TI, which is consistent with the relational memory concept. In light of the lack of behavioral measures sensitive to language non-dominant hippocampal function, the TI paradigm may have clinical promise. In future research, it would be beneficial to continue studying TI capacities in the TLE population, using some of the modifications suggested in preceding sections and expanding the work to include pre-surgical epilepsy patients.

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BIOGRAPHICAL SKETCH

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