EXECUTIVE DYSFUNCTION IN POST-AMYGDALO-HIPPOCAMPECTOMIZED EPILEPSY PATIENTS

by

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Abstract

EXECUTIVE DYSFUNCTION IN POST-AMYGDALO-HIPPOCAMPECTOMIZED EPILEPSY PATIENTS

by

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There are two hypotheses regarding executive dysfunction in temporal lobe epilepsy (TLE). The nociferous hypothesis posits that epileptogenic cortex adversely affects the fronto-striatal regions that mediate executive functions, thereby resulting in performance deficits. The hippocampal hypothesis suggests that such impairments are due to direct hippocampal involvement in the mediation of executive functions and that performance deficits are directly attributable to hippocampal pathology.

The current study aimed to clarify the role of temporal lobe (TL) pathology in executive functions and to examine the impact of such variables as lesion side, gender, and modality on executive functions. Patients scheduled to undergo amygdalo-hippocampectomies to control their TLE were administered the following tests of executive functions before and one year after surgery: Wisconsin Card Sorting Test (WCST), Controlled Oral Word Association Test (COWAT), Ruff Figural Fluency Test (RFFT), and Trail Making Test (TMT). There were 42 right-handed pre- and post-amygdalo-hippocampectomized TLE patients

(20 men and 22 women). Eleven women and 9 men underwent right TL (RTL) resection, and 11 women and 11 men underwent left TL (LTL) resection.

A mean z-score for each of the dependent measures in pre- and post-surgical conditions was compared to the normative sample's expected mean score of 0 via a one-sample t-test. Further, a repeated-measures ANOVA was conducted with gender (male vs. female) and side of involvement/resection (left vs. right) as between-subjects factors and testing time (pre- vs. post-surgery) as the within-subjects factor for each of the dependent variables.

Executive deficit was noted both pre- and post-surgically, and no significant improvement or decline was noted post-surgery, despite significant post-surgical seizure reduction. Therefore, the current study, while supporting reports of executive impairment in TLE patients, cannot provide support for either the nociferous or the hippocampal hypothesis. On the WCST, women performed more poorly than men, possibly reflecting more distributed functional brain organization. RTL patients performed more poorly on the RFFT than did LTL patients, further demonstrating that the RFFT is more dependent on right- than left-hemispheric mediation. The absence of significant deterioration in executive functions further validates TL resection as a safe treatment alternative for intractable seizures.

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Introduction

The temporal lobe serves a well-documented role in memory functions. However, there is no consensus in the current literature regarding the role of the temporal lobe in executive system function. Some studies suggest that there is no executive impairment in temporal lobe pathology (Martin, Sawrie, Gilliam et al., 2000). Others show that impairment is selective -- side or modality specific (Giovagnoli, 2001). There are two hypotheses (Hermann & Seidenberg, 1995) regarding executive system dysfunction in temporal lobe epilepsy. The nociferous cortex hypothesis posits that epileptogenic cortex adversely affects the extratemporal regions that mediate executive system abilities, thereby resulting in performance deficits. The hippocampal hypothesis suggests that such impairments are due to the fact that the human hippocampi are directly involved in the mediation of some executive system functions and performance deficits are therefore directly attributable to hippocampal pathology.

The purpose of the current study was to clarify the role of the temporal lobe in the executive system function and to examine such variables as lesion side, gender, and modality (verbal vs. non-verbal) of the measure. In order to do this, patients who were scheduled to undergo amygdalo-hippocampectomies to control their temporal lobe epilepsy were administered neuropsychological tests that are known to be sensitive to executive deficits. Testing was done before and after surgery. It was expected that, after surgery, patients would do better on the executive function tests.

Seizures and Epilepsy

Epilepsy is a brain disorder, which occurs when the electrical signals in the brain are disrupted. This change in neuronal activity (neurons may fire up to 6 times as fast as the normal rate of about 80 times a second.) causes seizures, which can cause brief changes in one's sensations, emotions, and behavior. They may also induce convulsions, muscle spasms and loss of consciousness (Brodie & Schachter, 2000).

There are many possible causes of epilepsy. The etiology of this syndrome is complex, arising from the contribution of multiple genetic and non-genetic factors. It is commonly accepted that epilepsy results from an abnormality in brain wiring and neurotransmitter imbalance. This atypical wiring can result from known brain pathology, such as scarring after a traumatic injury, metabolic and developmental disorders, toxins and recreational drugs (secondary seizures), or may have no apparent underlying cause (idiopathic seizures). In idiopathic cases, an estimated 500 genes may play a role in disease development, either by directly altering protein production or by increasing one's resistance to pharmacological treatments.

Either an abnormally high level of excitatory neurotransmitters that increase neuronal activity, or an abnormally low level of inhibitory neurotransmitters that decrease neuronal activity in the brain cause epilepsy. In both cases, the resulting excesses of neuronal activity can cause epilepsy. In this regard, inhibitory neurotransmitter GABA, or gamma-aminobutyric acid (Meldrum, 1991), an excitatory neurotransmitters glutamate (McNamara, 1994), have been

identified as playing a key role in epilepsy etiology.

When this abnormal neuronal activity is localized to one part of the brain, the resulting condition is a partial seizure. Typically, in partial seizure, there is no loss of consciousness, seizures usually last just a few seconds and may be accompanied by auras - unusual sensations that often signal that seizure is about to begin. In contrast, generalized seizures are a result of abnormal neuronal activity in many, often disparate, parts of the brain. Generalized seizures are often accompanied by loss of consciousness and/or massive muscle spasms. There are many seizures that are not associated with epilepsy. These seizures usually result from an extreme physiological state, such as a high fever or during eclampsia, or from a psychological condition.

Upon diagnosis (EEG monitoring, video monitoring and Magnetoencephalogram (MEG) testing is a typical battery of examinations for diagnosis), epilepsy is often controlled pharmacologically. The most commonly prescribed medications are Carbanazapine, Valproate or Phenytoin. Surgery is considered when seizures cannot be controlled pharmacologically. Three broad categories of epilepsy that can be treated successfully with surgery are: partial seizures, seizures that begin as partial seizures before spreading to the rest of the brain, and unilateral multifocal epilepsy with infantile hemiplegia (such as Rasmussen's encephalitis) (Bleck, 1987). The most common type of surgery for epilepsy is removal of a seizure focus (often called topectomy or lesionectomy). Usually, the more well defined the seizure focus is the better the post-surgical prognosis (Bleck, 1987). Other types of surgery include lobectomy (i.e. temporal

lobe resection, reportedly having up to 70 - 90 percent success rate) (Brodie & Schachter, 2000), subpial transection (Morrell, Whisler, & Bleck, 1989), callosotomy, or severing the bundle of neural connections between the right and left cerebral hemispheres, and similar procedures involving the anterior and posterior commissures (Brodie & Schachter, 2000). One of the more radical surgical procedures to treat epilepsy is hemispherectomy (Bleck, 1987).

Other treatment strategies of epilepsy include vagus nerve stimulation, transcranial magnetic stimulation, and biofeedback. Vagus nerve stimulator delivers short bursts of electrical energy to the brain via the vagus nerve. Transcranial magnetic stimulation is a procedure, which uses a strong magnet held outside the head to influence brain activity. An additional line of research is currently investigating development of implantable devices that can deliver drugs to specific parts of the brain. Furthermore, researchers are looking into altering certain environmental and life-style factors, such as diet, which might alleviate seizure disorders (Brodie & Schachter, 2000).

Unfortunately, many patients (about 20 percent) continue to experience seizures even with treatment, a condition known as intractable epilepsy (Jallon, 2002). Although the mechanism of complete recovery is unknown, patients who begin to treat their condition immediately after diagnosis have a better success rate (Brodie & Schachter, 2000).

While research concerned with the prevention and treatment of epilepsy must continue to be the most important line of investigation, surgical treatment of epilepsy opens the door to study more basic functions of the brain and how they

might be affected in pathology. This more fundamental line of investigation does not necessarily bring immediate solutions for the treatment of underlying pathology, but it furthers our understanding of the brain, in general, which in turn helps guide future research into the prevention and treatment of many neurological disorders, including epilepsy. One particularly interesting avenue of investigation is concerned with the role of the temporal lobes in general and of the amygdalo-hippocampal complex specifically in the executive functions.

Executive Functions and the Temporal Lobe

Executive Functions

Currently, the concept of executive functions is inextricably linked to the function of the frontal lobes. To that effect, the groundwork for defining the executive functions system was laid by Alexander Luria as early as 1966 (Luria, 1966). At the time, he proposed the existence of a system in charge of intentionality, the formulation of goals, the plans of action subordinate to the goals, the identification of goal-appropriate cognitive routines, the sequential access to these routines, the temporally ordered transition from one routine to another, and the editorial evaluation of the outcome of our actions.

Subsequently, two broad types of cognitive operations linked to the executive system figured most prominently in the literature. The first one is the organism's ability to guide its behavior by internal representations (Goldman-Rakic, 1987) - the formulation of plans and then guiding behavior according to these plans. The second one, formulated by Milner (1982), is that an organism

must be capable not only of guiding its behavior by internal representations, but also capable of "switching gears" when something unanticipated happens. To deal effectively with such transitions, a particular ability is needed -- mental flexibility that is the capacity to respond rapidly to unanticipated environmental contingencies. Sometimes this is referred to as an ability to shift cognitive set.

More recently, Fuster (1997) enlarged on the premise originally developed by Luria by suggesting that the so called "executive systems" can be considered functionally "homogeneous" in the sense that they are in charge of actions, both external and internal (such as, for example, logical reasoning). In general, the executive functions are not unique to humans. However, the uniqueness of the human executive functions is in the *extent* to which they are capable of integrating such factors as time, informational novelty, and complexity, and possibly ambiguity.

Currently, an ever-increasing body of research is being dedicated to the study of executive functions. Unfortunately, the main thrust of many such investigations has been reductionistic in character, and insight into the nature of executive functions has been limited. Numerous attempts have been made to show that the key to the nature of executive functions lies along the lines of such distinctions as sensory modalities, linguistic vs. non-linguistic, object vs. spatial ("what" vs. "where"), etc.

This approach has gained particular prominence in the investigation of one aspect of executive functions, so-called working memory. In the study of working memory, two main lines of scientific inquiry can be clearly discerned: one guided

by a premise of *domain specificity* and the other guided by the premise of *process specificity*. According to the domain specificity theory, different regions of the brain process different types of information, for example, spatial information versus object information (Goldman-Rakic, 1987, 1998). This theory is an extension of the object vs. spatial ("what" vs. "where") visual processing streams found in posterior cortices (Mishkin, Ungerleider, & Macko, 1983). According to the process specificity theory, which draws on earlier human lesion studies (Petrides & Milner, 1982), different regions of the brain are responsible for maintenance and manipulation of information (Petrides, 1994, 1995). In the study of the long-term memory processes, Tulving's *hemispheric encoding-retrieval asymmetry* (Tulving, Kapur, Craik, Moscovitch, & Houle, 1994; Tulving, Markowitsch, Kapur, Habib, & Houle, 1994) stands out. According to this theory, episodic encoding results in greater left than right hemispheric activation, and episodic retrieval results in greater right than left hemispheric activation. More specifically, left prefrontal cortical regions are differentially more involved in retrieval of information from semantic memory and in simultaneously encoding novel aspects of the retrieved information into episodic memory. Right prefrontal cortical regions, on the other hand, are differentially more involved in episodic memory retrieval (Fletcher & Henson, 2001).

Fuster (1997) refers to this conceptual approach as neural "balkanization." This line of investigation may be useful for heuristic purposes and probably represents a sensible way to conduct well-controlled experiments. However, in the attempt to reduce the executive functions to modality and process specific sub-

parts, one might come to a point when a necessity arises to invent a new sub-system for each new finding. Unless research is guided by a comprehensive unified theory of executive functions that transcends all the more specialized lines of inquiry, the actual picture of executive functions may prove to be difficult if not impossible to construct.

The Temporal Lobe

On the gross anatomical level, the temporal lobe extends superiorly to the lateral sulcus and the line forming the inferior boundary of the parietal lobe. Posteriorly, it extends to the line connecting the top of the parieto-occipital sulcus and the preoccipital notch. On the medial surface, its posterior boundary is an imaginary line from the preoccipital notch to the splenium of the corpus callosum. The rest of the inferior surface is made up of the broad and often discontinuous occipitotemporal (fusiform) gyrus and the parahippocampal gyrus. These are separated from one another by the collateral sulcus. The occipitotemporal gyrus is partly in the occipital lobe and partly in the temporal lobe. The parahippocampal gyrus is continuous with the cingulate gyrus around the splenium of the corpus callosum. They are connected through the isthmus of the cingulate gyrus. The anterior end of the parahippocampal gyrus turns backward and forms a medially directed structure called the uncus. The superior border of the parahippocampal gyrus is the hippocampal sulcus. Folded into the temporal lobe at the hippocampal sulcus is the hippocampus. Hippocampus and amygdala are parts of the system that historically has been known as the limbic system (Carpenter &

Parent, 1995).

The lateral neocortical portion of the temporal lobes is cytoarchitectonically defined as Brodmann areas (BA) (Brodmann, 1912): 20, 21, 22, 37, 38, 41, and 42. These areas are also described by gyri that form them: Heschl's gyrus (BA 41 & 42), the superior temporal gyrus (BA 22), the middle temporal gyrus (BA 21, 37 & 38), and the inferior temporal gyrus (BA 20 & 37). In addition, the sulci of the temporal lobes contain a considerable amount of cortical tissue. The most prominent ones are the Sylvian (lateral) fissure, containing cortex forming the insula, which includes gustatory and association cortex; and the superior temporal sulcus. The superior temporal gyrus continues into the lateral sulcus. Part of the superior temporal gyrus forms the temporal operculum. The inferior temporal gyrus continues onto the inferior surface of the lobe.

On the medial surface, the temporal lobes are comprised of phylogenetically older cortex known as archicortex and paleocortex. Among the structures formed by the older cortex of the temporal lobes are the fusiform gyrus, parahippocampal gyrus, uncus, and the hippocampus and amygdala, which are not parts of the neocortex (Kolb & Whishaw, 1995).

The Function of the Temporal Lobe

More than a century after Karl Wernicke (Wernicke, 1874) described a language deficit following damage to the temporal lobe, the investigation in the function of the temporal lobes continues. A small area of the portion of the superior temporal gyrus that lies in the lateral sulcus is known as the primary

auditory cortex. It is situated within the Sylvian fissure. There, auditory signals from the cochlea (relayed via several subcortical nuclei) first reach the cerebral cortex. This part of the cortex (primary auditory cortex) is involved in hearing. Adjacent areas in the superior, posterior and lateral parts of the temporal lobe are involved in high-level auditory processing. In humans this includes speech and language, for which the left temporal lobe in particular seems to be specialized. Wernicke's area which spans the region between temporal, occipital and parietal lobes seem to play a key role (in conjunction with Broca's area), which is located within the frontal lobe) (Kolb & Whishaw, 1995). The functions of the left temporal lobe are not limited to low-level perception but extend to comprehension, naming, and other language functions, and even to verbal memory. Today it is commonly accepted that the temporal lobe is involved in numerous complex aspects of learning and memory (Kolb & Whishaw, 1995). The underside (ventral) part of the temporal cortex appears to be involved in high-level visual processing of complex stimuli such as faces (fusiform gyrus) and scenes (parahippocampal cortex). Anterior parts of this ventral stream for visual processing are involved in object perception and recognition (Tanaka, 1993; Ungerleider & Haxby, 1994).

The medial temporal lobe (near the saggital plane that divides left and right cerebral hemispheres) is thought to be involved in declarative memory processing, particularly in episodic memory (Strange, Fletcher, Henson, Friston, & Dolan, 1999). Deep inside the medial temporal lobe, the hippocampus plays an integral memory function, and it is also considered by some researchers to play a part in controlling spatial behavior, at least in some mammalian species. In

addition, the parahippocampal gyrus, hippocampus and amygdale, traditionally, were considered to be integral parts of the limbic system. This system was thought to be associated with the processing of emotions (Maclean, 1955), even though today the existence of the limbic system as a well-integrated functional entity is being increasingly challenged.

Kolb & Wilshaw (1995) have identified eight principal symptoms of temporal lobe damage: 1) disturbance of auditory sensation and perception, 2) disturbance of selective attention of auditory and visual input, 3) disorders of visual perception, 4) impaired organization and categorization of verbal material, 5) disturbance of language comprehension, 6) impaired long-term memory, 7) altered personality and affective behavior, and 8) altered sexual behavior.

Selective impairment of attention to visual or auditory input is common with damage to the temporal lobes (Milner, 1968). Lesions of the left temporal lobe result in decreased recall of verbal and visual content, including speech, written language, perception, and meaningful object recognition (Frisk & Milner, 1990). Lesions of the right temporal lobe result in decreased recognition of tonal sequences and many musical abilities, as well as recall of non-verbal material, such as music and drawings (Zatorre, 2001). Right-sided lesions can also affect recognition of visual content (e.g., recall of faces; Milner, 2003).

Seizures of the temporal lobe can have dramatic effects on an individual's personality. Temporal lobe epilepsy can cause perseverative speech and thoughts, paranoia, and aggressive rages (Blumer & Benson, 1975). As a reflection of the well accepted importance of the temporal lobe in memory

functioning, most commonly used tests to assess temporal lobe functioning are the word-list learning tests, such as the California Verbal Learning Test, Rey-Complex Figure test, and the Wechsler Memory Scale test (Lezak, 1995; Taylor, 1969).

The Role of the Hippocampus in Learning and Memory

In their recent review of the role of the hippocampus in learning and memory, Barr and Goldberg (2003) pointed to the fact that the common view of this brain structure as mostly involved in the processes of learning and memory is based on so-called double-dissociation studies. Referring to the now well-known case study study of HM (Scoville & Milner, 1957), one of the more commonly cited references in relationship to the origins of the hippocampal model of memory, Barr and Goldberg (2003) emphasize that surgery on this patient included resection of not only the hippocampus but also several other medial temporal lobe structures. It was later assumed (Penfield & Milner, 1958) that removal of the hippocampus was critical for producing the memory disturbance, and reports of more specific memory disturbances following temporal surgery were yet to follow (Milner, 1958, 1967)

Subsequently, a study of the effects of frontal and temporal lobe resection on performance on the Wisconsin Card Sorting Test (Grant & Berg, 1948) reported a double dissociation between card sorting and memory performance in frontal lobe subjects and hippocampectomized controls (Milner, 1964). Thus, the independence of neural systems subserving memory functions and executive

functions was presumably established. According to Barr and Goldberg (2003), although many scientists continued to argue against the sole role of the hippocampus in memory function (Douglas, 1967; Gray, 1982; Horel, 1978; Isaacson, 1972; Mishkin, 1978; Pribram & McGuinness, 1975) this particular theory became increasingly popular.

More recently, according to Barr and Goldberg (2003), a number of studies showed the critical role that the frontal lobes can play in working memory tasks (Fuster, 1997; Goldman-Rakic, 1987) and in tests of episodic memory (Wheeler, Stuss, & Tulving, 1995). Conversely, executive function deficits have been reported in epilepsy patients with hippocampal dysfunction (Hermann, Wyler, & Richey, 1988; Horner, Flashman, Freides, Epstein, & Bakay, 1996; Martin, Sawrie, Gilliam et al., 2000; Trenerry & Jack, 1994). Some researchers have suggested that these findings are due to the effects of hippocampal damage on the functions of the frontal lobes (Corkin, 2001; Hermann & Seidenberg, 1995). The mechanism of these effects is thought to be an abnormal interictal (between seizures) discharge originating in the epiliptogenics regions (i.e., hippocampus) exhorting a disrupting influence on the frontal lobes through abundant fronto-hippocampal connections. Yet, others have suggested that such findings are a direct reflection of hippocampal involvement in executive functioning (Upton & Corcoran, 1995).

Despite the attempts by many theorists to account for hippocampal function in terms of an integrated functional system, which includes connections to fronto-striatal structures (Nauta, 1972; Pribram, 1986), according to Barr and Goldberg

(2003), the hippocampus and the frontal lobes were continued to be viewed as separate, functionally unrelated structures.

Barr and Goldberg (2003) also point out that the more recent failures to activate mesial temporal structures with memory tasks in neuroimaging studies (Tulving & Markowitsch, 1997) and the failure to replicate lesion-based studies reporting dissociations between memory and executive functions (Tulving, Kapur, et al., 1994) in functional neuroimaging experiments further necessitates revision of current thinking about the role of the hippocampus in cognition. Barr and Goldberg (2003) conclude that, at this point in time, there is no convincing evidence to demonstrate that the hippocampus is solely involved in memory, as opposed to being a part of much larger a cognitive system related also to attentional and executive functions. They further propose that in any new theory about the hippocampus, the density of its connections with other cortical regions, particularly the frontal lobes, cannot be ignored.

Several reports investigating the role of the temporal lobe in general and the amygdalo-hippocampal complex specifically in executive functions are particularly interesting (Giovagnoli, 2001; Hermann & Seidenberg, 1995; Martin, Sawrie, Edwards, et al., 2000; Martin, Sawrie, Gilliam, et al., 2000). These studies used neuropsychological tests shown to be sensitive to executive function deficits. Tests such as the Wisconsin Card Sorting Test (WCST), the Controlled Oral Word Association Test (COWAT), the Ruff Figural Fluency Test (RFFT), and theTrail Making Test (TMT) are among those most commonly used.

There are two hypotheses regarding the role of the hippocampus in

executive functions: nociferous cortex hypothesis and hippocampal hypothesis. Nociferous cortex hypotheis posits that epileptogenic cortex adversely affects the extratemporal regions that mediate executive system abilities (i.e., the frontal lobes). By contrast, the hippocampal hypothesis suggests that the hippocampi are directly involved in the mediation of executive functions (Hermann and Seidenberg, 1995).

To test the two hypotheses regarding the executive system dysfunction in temporal lobe epilepsy Hermann and Seidenberg (1995) administered the WCST to anterior temporal lobectomy (ATL) patients pre- and post-surgically. The researchers found that there was an improvement in the performance on the WCST after surgery. They suggest that their findings supported the nociferous cortex hypothesis (Hermann & Seidenberg, 1995).

Another group of scientists (Martin, Sawrie, Edwards et al., 2000), investigated performance of patients with temporal lobe epilepsy (TLE) on a test of executive function. The study investigated the contribution of such variables as, bilateral hippocampal sclerosis, mesial temporal lobe abnormalities beyond the hippocampus, and temporal neocortical abnormalities, and severity of seizures to performance on the WCST in patients with TLE who underwent ATL. The scientists reported that patients with more severe seizures performed more poorly on the WCST. They also reported that presence of temporal lobe abnormalities did not affect the WCST performance (as measured by number of categories achieved and number of perseverative errors). Their findings indicate that the presence of temporal lobe structural abnormalities do not significantly affect

executive function as measured by the WCST. The researchers suggest that poor performance on the WCST in patients with TLE is not related to the function of the temporal lobe per se and is likely to be related to metabolic disruption of the frontostriatal complex.

The same group of investigators (Martin et al., 2000) examined the effects of seizure laterality and seizure control on executive functioning using the WCST, Trails B and the COWAT in TLE patients who underwent ATL. They report that only verbal fluency improved after seizures were controlled. The researchers attribute this improvement to extrahippocampal metabolic normalization following surgery, which is consistent with the nociferous cortex hypothesis.

Giovangoli (2001) investigated the contribution of TLE and hippocampal lesions to memory deficits and sorting impairment. In her study, TLE patients were compared to patients with frontal lobe epilepsy (FLE). Modified Wisconsin Card Sorting Test (MWCST) was used to measure sorting ability. The two-syllable word span and the selective reminding procedure were used to evaluate memory. The researcher reports that in the patients with left hippocampal sclerosis sorting performance positively correlated with performance on memory tests. According to Giovangoli, these results suggest that TLE patients with left hippocampal damage are impaired on card sorting tasks due to impairment in learning and memory.

To summarize, two hypotheses have been formulated regarding executive system dysfunction in temporal lobe epilepsy:

- The nociferous cortex hypothesis posits that epileptogenic cortex

adversely affects the fronto-striatal regions that mediate executive system abilities, thereby resulting in performance deficits The mechanism of these effects is thought to be due an abnormal interictal (between seizures) discharge, originating in the epiliptogenic regions (i.e., hippocampus), exhorting a disrupting influence on the frontal lobes through fronto-hippocampal connections.

-The hippocampal hypothesis suggests that executive impairments are due to the fact that the human hippocampi are directly involved in the mediation of executive system functions, such as working memory, and that performance deficits are therefore directly attributable to hippocampal pathology (Hermann & Seidenberg, 1995).

Furthermore, regardless of which of these two hypotheses might better represent the relationship between the temporal lobes and the executive functions system, what appears to be obvious is that damage to mesial temporal lobe structures can cause executive deficits. It is worth noting that although most of the studies discussed above report executive deficits associated with hippocampal pathology, not all of them report a homogeneous picture of executive deficits. For example, Giovangoli's report (2001) suggests that sorting impairment is more prevalent in patients with left hippocampal damage than in patients with right hippocampal damage. Martin and his colleagues (Martin, Sawrie, Edwards, et al., 2000) report only selective executive function normalization after becoming seizure-free. They state that seizure-free patients do better on verbal generation tasks as opposed to sorting tasks.

The following study was intended to clarify the role of the temporal lobe in

executive functions and thus the mechanisms by which temporal lobe damage may produce executive deficit by using some of the previously reported measures in determining the effects of laterality (i.e., left- or right-sided focus), processing modality (verbal vs. nonverbal), and also by investigating an additional variable - gender. There is converging evidence in the scientific literature pointing to gender-related hippocampal differences. This evidence is drawn from such diverse fields of neuroscience as animal models (Andrade, Madeira, & Paula-Barbosa, 2000), studies of sexual dimorphism (different pathological changes in brain structures in men versus women) in human depression (Frodl et al., 2002), studies of temporal lobe ictal behavior in humans (Tezer, Kurne, Soylu, & Saygi, 2004), and human cognition in epilepsy (Trenerry, Jack, Cascino, Sharbrough, & Ivnik, 1995). These studies report gender differences in: neuronal volume and connectivity of rat subiculum (i.e., more neurons in male rats but greater connectivity in female rats); gray and white matter hippocampal reduction in major depression in humans (i.e., greater volume reduction in male patients); patterns of ictal behavior in epilepsy patients; and greater memory recovery in female than male patients after temporal lobectomy.

Of particular interest is a study done by Trenerry and colleagues (Trenery et al., 1995). The authors studied right-handed patients post temporal lobectomy to determine whether there are sex differences in verbal memory performance after surgery. The researchers used Logical Memory percent retention from the Wechsler Memory Scale-Revised to assess verbal memory. Their results showed that women improved while men declined in postoperative verbal memory

performance. In addition, they report that the difference between right and left hippocampal volumes predicted verbal memory performance in both groups. Pre-surgically, they found a positive correlation in verbal memory performance and, both, the left and right hippocampal volumes, in left temporal lobectomy women only. Their data supports the presence of sex differences in hippocampal function. The authors concluded that verbal memory abilities mediated by hippocampus are less lateralized in women with left temporal lobe epilepsy and mesial temporal sclerosis. By extension, if executive functions are conceptualized to be interdependent with memory functions, particularly working memory functions, these findings point to the importance of accounting for gender differences when investigating executive deficits in hippocamapal pathology.

Methods

Hypotheses

The purpose of this study was to clarify the role of the temporal lobes (including the hippocampi) in executive functions and to examine the impact of lesion side, gender, and modality (verbal vs. non-verbal) variables on executive function impairment. A number of neuropsychological tests known to be sensitive to executive deficits were administered. The following hypotheses were tested: 1) Patients with temporal lobe involvement will exhibit executive deficits both pre- and post-surgically. Reduction of executive deficits following surgery will support

the nociferous hypothesis. By contrast, the exacerbation of executive deficits following surgery will support the direct role of the temporal lobes (including the hippocampi) in executive functions. 2) There will be a distinct pattern of impairment relating side of lesion to the modality of executive function impairments. That is, patients with left-sided lesions will show greater impairment on verbally mediated executive tests, and patients with right-sided lesions will show greater impairment on visually mediated nonverbal executive tests. 3) The relationship between modality and side of lesion will be mediated by gender, with stronger associations in men than in women.

Participants

The data were obtained from a subject pool of patients scheduled to undergo surgery to control epilepsy. Patients were selected for the study using the following criteria: right-handed, native English speaker, and no history of mental retardation. There were 42 right-handed pre- and post-amygdalo-hippocampectomized temporal lobe epilepsy cases (20 men and 22 women) but due to participant dropout, only the data from participants that were administered a particular neuropsychological test were considered for statistical analysis for that test. As determined by the Wada procedure, all the patients were left-hemisphere dominant for language. Twenty patients (11 women and 9 men) underwent right temporal (RT) lobe resection, and 22 (11 women and 11 men) underwent left temporal (LT) lobe resection. Analysis of variance showed that RT and LT participants did not differ significantly in terms of gender (52% of the

participants were women and 48% of the participants were men), age (34.10 ± 10.92 years for RT participants and 36.05 ± 10.82 years for LT participants) and education (13.70 ± 2.25 years of education for RT participants and 13.13 ± 2.28 years of education for LT participants). In addition, analysis of variance showed that the four groups (RT women, LT women, RT men, LT men) did not differ significantly from each other in terms of age and education (see Tables 2 & 3). Patients were administered a battery of neuropsychological tests, known to be sensitive to executive functioning, prior to and one year following surgical intervention.

Neuropsychological Measures

The following measures of executive functioning were administered: the Wisconsin Card Sorting Test (WCST), the Controlled Oral Word Association Test (COWAT), the Ruff Figural Fluency Test (RFFT), and the Trail Making Test -- Parts A & B (TMT). All of these tests are simple, non-invasive paper-and-pencil tests (see Table 1).

The Wisconsin Card Sorting Test (WCST), originally developed in 1948 by Grant and Berg (1948), permits the assessment of the following executive functions: strategic planning, organized search, the ability to utilize environmental feedback to shift cognitive sets, directing behavior toward achieving a goal, and modulating impulsive responding (Lezak, 1995).

Normed for individuals aged 6.5 through 89 years, the WCST tests the ability to develop and maintain an appropriate problem-solving strategy across

changing stimulus conditions in order to achieve a future goal. The four stimulus cards incorporate three stimulus parameters (Color, Form, and Number). Respondents are required to sort the cards according to different principles during test administration. For the purpose of this study, the number of categories achieved (a measure of guiding behavior according to a mental representation) and the number of perseverative errors (the ability to shift according to environmental contingencies) will be analyzed. These two measures are among the most often used measures of executive functioning (Lezak, 1995).

The Controlled Oral Word Association Test (COWAT) is a measure of verbal fluency (Benton, Hamsher, & Sivan, 1994). Individuals with executive deficits are known to be impaired on verbal generation tasks (Lezak, 1995). The COWAT requires participants to generate as many unique words starting with a particular letter (C, F, and L) as possible within 60 seconds. For the purpose of this study, the most commonly used clinical measure - number of words generated will be analyzed.

The Ruff Figural Fluency Test (RFFT) was designed by Ronald M. Ruff (Lezak, 1995; Ruff, 1996; Ruff, Allen, Farrow, Niemann, & Wylie, 1994) to evaluate an individual's nonverbal capacity for divergent thinking, ability to shift cognitive set, and planning strategies. The RFFT was designed as a nonverbal counterpart to frequently administered verbal fluency tests that require respondents to generate as many words as possible starting with a specific letter. The RFFT requires that draws as many unique designs as possible within 60 seconds by connecting the dots in different patterns. Similar to the different

alphabetical letters that are used in the verbal fluency tests, the 5-dot stimulus configurations are different in three parts of the test. The most commonly used measure is the total number of unique designs drawn in three parts of the test. For the purpose of the current study, the number of unique designs generated will be analyzed.

The Trail Making Test (TMT) test assesses visuomotor tracking. Part B requires divided attention, planning and working memory, and this measure is widely used to assess executive system functions in clinical populations. Part A is used as a baseline measure. The TMT has been used for clinical diagnostic purposes, especially as part of the Halstead-Reitan Battery (Lezak, 1995; Reitan, 1958). The TMT is a set of two visual search and sequencing tasks that challenge attention, concentration, the ability to guide behavior by internal representation, and cognitive flexibility. More specifically, it detects problems with sequencing and impairments in set-shifting. The TMT is normed for individuals ranging in age from 11 years through 74 years. Administration is timed and takes approximately 10 minutes. The task of here is to connect a series of stimuli (numbers and letters) in a specified order as fast as possible. The score derived for each trail is the number of seconds required to complete the task. On Trail A, the examinee draws a line to connect the numbers 1 through 25 in order. On Trail B, the examinee draws a line to connect, in alternating sequence, the numbers 1 through 13 and the letters A through L. The examinee begins with 1 and then draws a line to A, then proceeds to 2, then B, and so on until all the numbers and letters are connected. Both trials are preceded by a short practice trial. For the purpose of

the current study, the time to complete Trail B will be used.

The design consisted of both within- and between-group comparisons. All the raw data (in the pre- and post-surgical conditions) for each of the five dependent variables (DVs) were to be converted to z-scores according to age-, gender-, and education-appropriate norms from healthy adults. The 5 DVs were: categories achieved on the WCST; number of perseverative errors on the WCST; number of unique designs on the RFFT; number of unique words generated on the COWAT; and the time necessary to complete Trial B on the Trail Making Test. The normative sample mean was subtracted from each participant's raw score and divided by the normative sample standard deviation. To make sure that all z-scores would represent the same directionality of change, for all those neuropsychological DVs where the larger raw score represents a greater degree of impairment (i.e., time in seconds or number of errors), the negative value of calculated z-score was used. The mean z-score for each DV in the pre- and post-surgical condition was compared to a Z = 0 using one sample t-test (see Table 8). Additionally, the values of z-scores of the pre- and post-surgical condition were compared using 5 repeated measures ANOVAs (see Table 9). Generalized executive dysfunction was expected to be found in the pre-surgical group (Hermann et al., 1988; Horner, et al., 1996; Martin, Sawrie, Gilliam et al., 2000; Trenerry & Jack, 1994). If the comparison of the pre- and post-surgical groups yields the results that point toward an improvement of executive functioning, it will support the nociferous cortex hypothesis, which ascertains that the removal of epileptogenic regions which adversely affect extratemporal regions mediating

executive system abilities will improve executive functioning in general (Corkin, 2001; Hermann & Seidenberg, 1995). On the other hand, if the comparison of the pre- and post-surgical groups shows no improvement or worsening of executive functioning, the results will support the hippocampal hypothesis which suggests that executive impairments are due to the fact that the human hippocampi are directly involved in the mediation of certain executive functions and that performance deficits are therefore directly attributable to hippocampal pathology (Upton & Corcoran, 1995).

Additional statistical analysis of the data entailed carrying out a univariate analysis of variance (ANOVA). Five repeated-measure 2 x 2 x 2 ANOVAs with gender (male vs. female) and side of involvement/resection (left vs. right) as between-subjects factors and testing time (pre- vs. post-surgery) as the within-subjects variable were to be calculated separately for each dependent measure: categories achieved on the WCST; number of perseverative errors on the WCST; number of unique designs on the RFFT; number of unique words generated on the COWAT; and the time necessary to complete Trial B on the Trail Making Test. There were two between-subjects factors, lesion side (left vs. right) and gender (men vs. women), and one within-subjects factor, time of testing (pre- vs. post-surgery).

Furthermore, pending the outcome of the overall ANOVA results, four groups (LF, RF, LM, and RM) were to be compared with respect to their performance on the verbally mediated executive task (COWAT) versus non-verbally mediated executive task (RFFT). Provided that such analyses were

justified by the overall ANOVA results, it was expected that patients with left-sided lesions would be more impaired on the verbally mediated executive test (COWAT), whereas patients with right-sided lesions would show greater impairment on the non-verbally mediated tests (RFFT). Moreover, the interaction between the side of the lesion and performance on the verbal fluency test (COWAT) versus performance on the figural fluency test (RFFT) was to be related to gender. Provided that such analyses were justified by the overall ANOVA results, it was expected that men would show greater lateralization of verbally- and non-verbally mediated executive functioning supported by the hippocampus than women. In men, it was expected to have greater left hippocampal involvement in verbally mediated executive functions (as measured by the COWAT) (Trenerry, et al., 1995). Similarly, in men it was expected to have a greater right hippocampal involvement on non-verbally mediated executive functions (as measured by RFFT). By contrast, it was expected that in females the differential effects of lesion sides on verbal vs. non-verbal tasks would be less pronounced or altogether absent.

Results

All the raw data (in the pre- and post-surgical conditions) for each of the five dependent variables (DVs) were converted to z-scores according to age-, gender-, and education-appropriate norms from healthy adults. The 5 DVs were

categories achieved on the WCST, number of perseverative errors on the WCST, number of unique designs on the RFFT, number of unique words generated on the COWAT, and time necessary to complete Trial B on the Trail Making Test. The normative sample mean was subtracted from each participant's raw score and divided by the normative sample standard deviation. To make sure that all z-scores would represent the same directionality of change, for all those neuropsychological DVs where the larger raw score represents a greater degree of impairment (i.e., time in seconds or number of errors), the negative value of calculated z-score was used.

To determine whether there are executive impairments in patients with temporal lobe epilepsy, the mean z-score for each of the dependent measures in the pre- and post-surgical conditions was compared to the normative sample's expected mean score of 0 using a one-sample t-test. All of the z-scores were negative in value (see Table 8), meaning that they were all below the average that is expected from the normative sample. This was true both pre- and post-surgically.

On the WCST, patients achieved significantly fewer categories both pre- and post-surgically. The mean z-score for the pre-surgical condition was -0.54 ± 1.44, $t(41) = -2.42$; $p = 0.02$. The mean z-score for the post-surgical condition was -0.83 ± 1.86, $t(37) = -2.74$; $p = 0.009$. Additionally, on the WCST, patients committed a significant number of perseverative errors both pre- and post-surgically. The mean z-score for the pre-surgical condition was -0.74 ± 1.44, $t(41) = -3.03$; $p = 0.002$. The mean z-score for the post-surgical condition was

-1.38 ± 2.18, t (36) = -3.84; p < 0.001.

On the RFFT, patients generated significantly less unique designs both pre- and post-surgically relative to normative data. The mean z-score for the pre-surgical condition was –1.19 ± 1.11, t (30) = -5.99; p < 0.001. The mean z-score for the post-surgical condition was –0.78 ± 1.18, t (36) = -4.04; p < 0.001.

On the COWAT, patients generated significantly fewer words relative to normative data only in the post-surgical condition. The mean z-score for the post-surgical condition was -0.48 ± 1.18, t (38) = -2.56; p = 0.014. The mean z-score for the pre-surgical condition was –0.31 ± 1.35, t (41) = -1.50; p = 0.14.

On the TMT, patients were significantly slower relative to normative data in completing the task only pre-surgically. The mean z-score for the pre-surgical condition was –1.58 ± 3.16, t (41) = -3.22; p = 0.003. The mean z-score for the post-surgical condition was -0.64 ± 2.41, t (37) = -1.62; p = 0.112.

To further assess possible changes in executive functioning after temporal lobe resection, a repeated-measures 2 x 2 x 2 ANOVA was conducted for each dependent variable with gender (male vs. female) and side of involvement/resection (left vs. right) as between-subjects factors and testing time (pre- vs. post-surgery) as a within-subjects factor. The prediction was that after removing the seizure focus or achieving better seizure control, there would be an improvement in executive functioning. (For a summary of all of the p-values for all the ANOVAs conducted, see Table 9)

There were no significant findings with respect to Testing Time for any of the 5 ANOVAs, meaning that, overall, patients did not perform significantly

differently after surgery as opposed to before surgery. However, for the Trail Making Test, a significant two-way interaction (time of testing by side of involvement/resection) was obtained, F (1, 33) = 4.14, p = 0.05. Patients with right-hemispheric involvement performed better on the TMT after surgery (mean z-score and standard deviation of 0.00 ± 1.22) as opposed to before surgery (mean z-score and standard deviation of -1.03 ± 1.50), whereas patients with left-hemispheric involvement performed better on the TMT before surgery (mean z-score and standard deviation of -0.85 ± 1.77) as opposed to after surgery (mean z-score and standard deviation of -1.40 ± 1.50) (see Table 10).

In addition, a trend for a three-way interaction (Time x Gender x Side) was obtained for the RFFT, F (1, 23) = 3.28, p = 0.083. Interestingly, when performances for the right-sided patients vs. the left-sided patients were compared across the subject groups (women before surgery, women after surgery, men before surgery, and men after surgery), in 3 out of 4 comparisons, patients with right-sided involvement/resection were more impaired than those with left-sided involvement/resection, providing some support for the notion that the RFFT is more dependent on right hemispheric structures than left-hemispheric structures (see Table 11).

Review of between-subjects effects yielded an unexpected finding. There was a significant difference in the performance of women versus men on the WCST as measured by categories achieved, F (1, 33) = 4.02, p = 0.053. Overall, women achieved significantly fewer categories than men. Estimated marginal mean z-scores and standard errors for the WCST categories completed were

-0.98 ± 0.28 for women and -0.25 ± 0.30 for men. This finding was further supported by an exploratory investigation of an observed trend of a between-subjects effect of gender on performance on the WCST as measured by the number of perseverative errors committed, F (1, 32) = 3.03, p = 0.091. There was a trend for women to commit more perseverative errors than men. Estimated marginal mean z-scores and standard errors for the WCST number of perseverative errors were -1.50 ± 0.36 for women and -0.62 ± 0.38 for men (see Table 12). For both WCST variables, male patients performed at a relatively higher level than did female patients.

Based on follow-up clinical reports, complete seizure elimination following surgery was noted in approximately 80% of the patients, and significant seizure reduction was observed in an additional 10%. The data for the remaining 10% were inconclusive.

Discussion

The current study demonstrated the presence of executive impairment in patients with temporal lobe epilepsy. This is consistent with reports in the literature (Hermann et al., 1988; Horner, et al., 1996; Martin, Sawrie, Gilliam et al., 2000; Trenerry & Jack, 1994). While it is the case that executive deficit was noted both pre- and post-surgically, and no significant improvement was noted as a result of surgery, there was also no significant decline in any of the measures of

executive functioning after surgery. Thus, we can conclude that the overall temporal lobe resection does not cause any deterioration of the executive functions. The fact that executive impairment remains after surgery may represent the irreversible changes in the distant brain regions including the frontal lobes changes associated with the life long history of temporal lobe epilepsy. Had it been shown that executive deficits are related to structural damage and not to seizures by demonstrating performance deterioration after temporal lobe resection, this study would have lent support to the hypothesis that the temporal lobe contribute directly to executive functions.

Alternatively, practice effects on the tests administered might have masked performance deterioration. For example, some test-retest improvement on the Trail Making Test has been reported in the literature (Leininger, Gramling, Farrell, Kreutzer, & Peck, 1990; Lezak, 1982). However, this improvement only reaches significance for the Trail Making Test, Part A, whereas no such improvement has been demonstrated for Part B. Furthermore, one study showed that no practice effect was present even on Part A when the second administration occurred after a year or later (Basso, Bornstein, & Lang, 1999). In a similar vein, no significant practice effects were reported when re-testing was done more than a year after the initial administration for the RFFT, COWAT, and WCST.

The previous work in this area suggests that there is some impairment of executive functioning in TLE patients but that this impairment is likely to be related to the effects that epileptogenic regions exert on distant brain regions, more specifically, on the fronto-striatal system. While partially supporting this previous

line of work (Hermann et al., 1988; Horner, et al., 1996; Martin, Sawrie, Gilliam, et al., 2000; Trenerry & Jack, 1994), the current study cannot specify more precisely whether executive deficits in TLE patients are attributable to the nociferous effects of the temporal lobe on the fronto-striatal system or whether the temporal lobe contributes directly to the executive functions and such deficits result from the abnormal functioning or structural damage of the temporal lobe. Even a finding of a very high rate of seizure improvement (complete seizure elimination following surgery was noted in approximately 80% of the patients, and significant seizure reduction was observed in an additional 10%) does not permit us to distinguish between the nociferous hypothesis (which predicts improvement in performance due to seizure reduction) and the hippocampal hypothesis (which predicts decrement in performance due to hippocampal resection), since no changes in performance after surgery were observed.

On the other hand, seizure severity has been reported to predict performance deficits on the WCST (Martin, Sawrie, Gilliam, et al., 2000) and seizure elimination has been shown to improve performance on the COWAT (Martin, Sawrie, Edwards, et al., 2000). Perhaps, additional statistical analysis where seizure severity is correlated with performance on the tests of executive functions woul further elucidate the role of the hippocampus in the executive functions system.

The study yielded a somewhat surprising finding of a relatively poor performance of women on the WCST in comparison to men, both with respect to categories achieved and number of perseverative errors. While most published

normative studies (Heaton, Chelune, & Talley, 1993; Yeudall, Fromm, Reddon, & Stefanyk, 1986) do not report gender differences in WCST performance, one study (Boone, Ghaffarian, Lesser, Hill-Gutierrez, & Berman, 1993) found that in older non-impaired adults, women do better on the WCST than men. The findings of this study point in the opposite direction. The fact that normative data do not show gender difference and that the data from the current study do, may suggest that the data reflects gender-specific effects of brain damage. Possibly, this finding reflects a well-documented greater equipotentiality of the two hemispheres with respect to a wide range of cognitive functions in women. It has been proposed that, due to greater inter-hemispheric connectivity, representation of cognitive processes is more bilaterally distributed in women than in men. This has been demonstrated for the neural structures involved in normal processing of linguistic functions (Harasty, 2000; Harasty, Double, Halliday, Kril, & McRitchie, 1997; Shaywitz et al., 1995). In addition, according to this view, any disruption of cerebral functioning is more likely to produce cognitive impairment in women than in men. In language impairment, it has been commonly reported that a well-defined stroke in either hemisphere is more likely to produce aphasia in women than in men (Hier, Yoon, Mohr, Price, & Wolf, 1994). Subsequently, women have better prognosis for recovery due to the fact that through greater distribution of cognitive functions, they are likely to have additional unaffected language areas in the brain that can assume a compensatory role. By extension, since the complexity of executive function system is at least comparable to that of language function system, it is plausible that such greater functional distribution in women is

also characteristic of the representation of the executive function system in the brain. Moreover, in contrast to the rest of the neuropsychological tests administered, the WCST is the most complex, multifactorial task. In that regard, performance on this test is more likely to involve a vast array of distinct cortical areas.

Additionally, one study (Strauss, Hunter, & Wada, 1993) reported that perseverative errors in women with temporal lobe epilepsy are strongly associated with early structural damage to the left temporal lobe and that this relationship is less significant in patients with right temporal lobe epilepsy. One way to further clarify these findings would be to relate the WCST performance in women to the age of epilepsy onset and to the side of epileptic focus.

In addition, a trend for a three-way interaction (Time x Gender x Side) was noticed for the RFFT. When performance for right-sided patients vs. left-sided patients was compared across the 4 groups (women before surgery, women after surgery, men before surgery, and men after surgery), in 3 out of 4 cases, patients with right-sided involvement/resection were more impaired than those with left-sided involvement/resection, providing some support for the notion that the RFFT is more dependent on right hemispheric than on left-hemispheric structures (Ruff, Allen, Farrow, Niemann, & Wylie, 1994). Interestingly, the group that did not show more impairment on the RFFT in terms of right-sided involvement/resection as opposed to left-sided involvement/resection was the group that consisted of women before surgery. This finding can be considered in keeping with an explanation provided earlier regarding gender differences in performance on the

WCST. Greater equipotentiality of the two hemispheres with respect to a wide range of cognitive functions has been documented in women. It has been proposed that, due to greater inter-hemispheric connectivity, representation of cognitive processes is more bilaterally distributed in women than in men. Consistent with this notion, women are more likely to perform poorly on the RFFT when either the left or right temporal lobe is impaired, whereas men are expected to perform poorly only when the right temporal lobe is impaired.

On a different note, it is important to indicate that in any major surgery both patients and surgeons assume certain risks that the side effects inherent in surgical complications may outweigh the benefits of desired treatment effects. The cost-benefit ratio for major surgeries quite often may be marginal at best. In addition, it is not uncommon that a major surgical intervention might affect a distant part or a seemingly unrelated function of the human organism. In fact, residual cognitive deficits have been demonstrated for procedures that do not involve direct neurosurgical intervention, for example, cardiac bypass surgery (Browne, Halligan, Wade, & Taggart, 2003; Kilo et al., 2001), chemotherapy (Kingma et al., 2001; Tannock, Ahles, Ganz, & Van Dam, 2004), and radiation treatment (Appleton, Farrell, Zaide, & Rogers, 1990; Cull et al., 1994) in cancer patients.

Such cautionary considerations apply even more to neurosurgery. Given the critical role that the brain has in the human body and the fact that it is extremely vulnerable to adverse conditions, patients and surgeons are exceptionally cautious when discussing neurosurgery as a treatment option and

often utilize it only as the last possibility.

The risks inherent in brain surgery are characterized by certain peculiarities unique to neurosurgery. The brain functions as a whole are exercised by interrelating its component parts, each endowed with its own function, yet, interdependent with other brain structures. It is safe to assume that interference with, removal of, or dysfunction of certain anatomical structures of the brain may result in the disruption of functions that are not necessarily thought to be dependent on those particular brain structures. One of the hypotheses entertained in the current study examines precisely this "remote effect" possibility – that interictal temporal lobe discharges might interfere with the frontal lobe function.

There are also general risks associated with any brain surgery. Some of the most common risks are developing an infection of the surrounding structures, or bleeding and hematomas, a clotted collection of blood outside the vessels. In the case of brain surgery, this localized mass can cause swelling which in turn produces pressure on surrounding brain structures, as a result of which necrotic changes may take place in the brain. Extreme precision during brain surgery is also necessary to avoid accidental injury to surrounding brain regions and consequent loss of function that is mediated by that specific part of the brain (e.g. memory, language production, or auditory comprehension).

In brain surgery, the resulting side effects can produce pervasive behavioral deficits disabling individuals to the point of not being capable of functioning independently in society. This issue becomes even more important when one considers that surgery might produce deficits in the executive function

system - a system that is thought to be responsible for planning and goal-directed behavior, the cognitive abilities which are among the most critical functions of purposeful human behavior. This is an important consideration when choosing a treatment option. In this respect, the absence of decrement on all of the examined tests of executive function (i.e., the WCST, TMT, RFFT, and COWAT) suggests that temporal lobe surgery does not produce pervasive cognitive deficits, at least with respect to executive functions. On a practical level, our findings provide important evidence that temporal lobectomy or partial temporal lobe resection is relatively free of cognitive side effects. This amplifies the role of surgical intervention as a viable alternative to treat intractable seizures, where the benefits of being seizure-free significantly outweigh the risks of a major invasive procedure.

One of the pitfalls of the current study is a relatively small number of cases in the overall analysis, in general, and especially when the four different subgroups (RF, LF, RM, and LM) are created. Many of the studies cited relevant to the role of temporal lobes in executive functions used samples at least 2-3 times as large as in the current study. The absence of a normal control group is also a limitation of the current study. Since performing sham temporal lobe surgeries on humans does not represent a humanely viable solution, this issue was attempted to be addressed by using pre-existing published normative data as the point of comparison. Another limitation of this study is that no non-executive measurement has been evaluated. It is possible that the TLE patients in the current study would have deficits in other cognitive domains, in addition to the

above-described executive deficits -- deficits that are not traditionally thought to be directly related to temporal lobe function.

In such cases, post-surgical improvement of these functions would have strengthened the claim that the executive deficits in TLE patients can be explained through the nociferous cortex hypothesis. In other words, it would have supported the possibility that epileptogenic regions in the temporal lobes exert a nociferous effect on additional non-frontal structures and that by removing this effect, one might expect an improvement in these non-executive functions. Due to the fact that the current study cannot provide any definitive support to either hypothesis, this pitfall is not critical. However, any future studies in the nature of executive impairments in TLE patients should include non-executive neuropsychological measures.

This study clarified an important issue that temporal lobectomy in epilepsy patients does not cause decrement in executive functioning. What, then, accounts for the presence of impairment in executive functioning before and after surgery? One possibility is that anticonvulsant medications may have an iatrogenic effect on executive functions.

Indeed, it has been shown that antiepileptic medication does cause cognitive impairment (Aldenkamp et al., 2000; Armon et al., 1996; Binnie, 1994; Forsythe, Butler, Berg, & McGuire, 1991; O'Dougherty, Wright, Cox, & Walson, 1987). For example, O'Dougherty and colleagues (1987) reported an adverse effect of carbamazepine on learning new information. Forsythe and colleagues (1991) found supporting evidence that carbamazepine impairs learning and

memory. Aldenkamp et al. (2000) reported adverse effects of topiramate on verbal learning. In light of the information that antiepileptic pharmacology causes cognitive impairment and in light of the executive deficits demonstrated in the current study, it would be prudent to investigate the possible role that anticonvulsant medications may have on executive functioning in temporal lobe epilepsy patients.

Conclusions

In summary, the current study suggests that there is no change in executive functioning after resection of the temporal lobe containing an epileptogenic focus, despite significant seizure reduction observed after surgery. Therefore, the current study cannot provide support for either the nociferous cortex hypothesis, which states that the executive impairments in patients suffering from temporal-lobe seizure disorder is caused by the pathophysiological process within the temporal lobes exerting remote disruptive effects on frontal lobe functions, or for the hippocampal hypothesis, which states that executive impairments in TLE patients are directly related to hippocampal dysfunction. Moreover, the fact that no significant deterioration was noted in any of the executive functions provides further evidence that temporal lobe resection is safe from at least one cognitive standpoint as a viable option to treat intractable seizures.

The finding of gender differences in performance on the WCST most likely reflects different expressions of the epileptic disorder in the context of normal

gender differences in brain structure and function. One plausible explanation is that greater functional distribution and hemispheric equipotentiality in women is also characteristic of the representation of the executive function system in the brain. By extension, according to this view, the disruption of cerebral functioning in either hemisphere is more likely to produce cognitive impairment, in general, and executive functions specifically in women than in men. Additionally, patients with the right temporal involvement performed more poorly on the RFFT as opposed to patients with the left temporal involvement. It also appears that this dichotomy is more characteristic for male than female patients, this further supporting the hypothesis of greater functional distribution of cognitive functions in women.

Future research may be directed to investigate the possible role that anticonvulsant medications may have on executive functioning in temporal lobe epilepsy patients.

Appendix

Table 1

Brief Description of Neuropsychological Tests and Dependent Variables

Neuropsychological Test	Dependent Variable	Purported Underlying Cognitive Function
Wisconsin Card Sorting Test (WCST)	Number of categories achieved	Strategic planning, organized search, the ability to utilize environmental feedback to shift cognitive sets, directing behavior toward achieving a goal
Wisconsin Card Sorting Test (WCST)	Number of perseverative errors	Ability to utilize environmental feedback to shift cognitive sets and modulating impulsive responding
Controlled Oral Word Association Test (COWAT)	Number of unique words generated	Verbal capacity for divergent thinking, ability to shift cognitive set
Ruff Figural Fluency Test (RFFT)	Number of unique designs generated	Nonverbal capacity for divergent thinking, ability to shift cognitive set
Trail Making Test, Part B (TMT B)	Time to complete in seconds	Attention, parallel processing, ability to guide behavior by internal representation, and cognitive flexibility

Table 2

Demographic Information for Pre-surgical Condition

		RF (n = 11)	LF (n = 11)	RM (n = 9)	LM (n = 11)	Combined (n = 42)
Age	*M*	34.82	36.09	33.22	36.00	35.12
	SD	11.67	10.77	10.57	11.40	10.78
Education	*M*	13.09	13.27	14.44	13.09	13.43
	SD	1.58	2.00	2.79	2.70	2.27

Note. RF = females with right temporal involvement; LF = females with left temporal involvement; RM = males with right temporal involvement; LM males with left temporal involvement. Age and education are in years.

Table 3

Demographic Information for Post-surgical Condition

		RF (n = 11)	LF (n = 10)	RM (n = 9)	LM (n = 8)	Combined (n = 38)
Age	*M*	36.45	36.80	35.11	33.37	35.58
	SD	11.50	10.98	10.17	8.52	10.14

Note. RF = females with right temporal resection; LF = females with left temporal resection; RM = males with right temporal resection; LM males with left temporal resection. Age is in years. Education is unchanged from pre-surgical condition.

Table 4

Mean Raw Scores for Each Dependent Variable Before Surgery

		RF	LF	RM	LM	Combined
WCST (categories)	*M*	4.73	4.54	5.33	5.63	5.02
	SD	2.10	1.69	1.12	0.67	1.54
WCST (perseverative err.)	*M*	17.27	19.18	12.00	11.64	15.17
	SD	12.81	11.69	8.99	9.16	10.98
COWAT (words generated)	*M*	39.91	35.00	37.22	31.82	35.92
	SD	18.90	11.44	13.86	8.41	13.53
RFFT (designs generated)	*M*	68.17	71.25	72.29	69.10	70.19
	SD	25.45	17.55	11.48	23.79	19.46
Trail B (completion time)	*M*	84.73	84.82	107.56	95.91	92.57
	SD	30.90	40.60	78.66	70.70	56.09

Note. RF = females with right temporal involvement; LF = females with left temporal involvement; RM = males with right temporal involvement; LM males with left temporal involvement.

Table 5

Mean Raw Scores for Each Dependent Variable After Surgery

		RF	LF	RM	LM	Combined
WCST (categories)	*M*	3.82	4.89	5.56	5.12	4.78
	SD	2.64	.78	1.33	1.81	1.89
WCST (perseverative err.)	*M*	22.54	21.50	15.00	16.37	19.05
	SD	20.48	6.89	14.76	12.87	14.94
COWAT (words generated)	*M*	34.09	35.20	36.56	31.25	34.37
	SD	13.46	12.37	13.68	10.47	12.28
RFFT (designs generated)	*M*	72.36	80.56	84.75	76.50	78.08
	SD	23.80	35.43	26.92	20.20	26.42
Trail B (completion time)	*M*	63.73	109.40	69.50	67.87	78.22
	SD	21.25	71.41	27.21	17.69	44.50

Note. RF = females with right temporal resection; LF = females with left temporal resection; RM = males with right temporal resection; LM males with left temporal resection.

Table 6

Mean Z-scores for Each Dependent Variable Before Surgery

		RF	LF	RM	LM	Combined
WCST (categories)	*M*	-0.69	-1.13	-.31	.03	-.54
	SD	1.71	1.73	1.31	.57	1.44
WCST (perseverative err.)	*M*	-1.02	-1.27	-.36	-.22	-.74
	SD	1.75	1.67	1.10	0.96	1.44
COWAT (words generated)	*M*	0.08	-0.37	-0.25	-0.70	-0.31
	SD	1.70	1.31	1.45	0.90	1.35
RFFT (designs generated)	*M*	-.85	-1.10	-1.6	-1.18	-1.09
	SD	1.65	0.85	1.07	1.02	1.11
Trail B (completion time)	*M*	-1.11	-1.25	-2.73	-1.39	-1.58
	SD	1.80	2.11	5.49	2.73	3.16

Note. RF = females with right temporal involvement; LF = females with left temporal involvement; RM = males with right temporal involvement; LM males with left temporal involvement.

Table 7

Mean Z-scores for Each Dependent Variable After Surgery

		RF	LF	RM	LM	Combined
WCST (categories)	*M*	-1.72	-0.72	-0.22	-0.55	-0.83
	SD	2.51	0.86	1.22	1.76	1.86
WCST (perseverative err.)	*M*	-1.89	-1.79	-0.83	-1.01	-1.38
	SD	3.00	1.27	2.17	1.84	2.18
COWAT (words generated)	*M*	-0.41	-0.40	-0.32	-0.75	-0.48
	SD	1.10	1.26	1.41	1.23	1.18
RFFT (designs generated)	*M*	-1.05	-0.43	-0.97	-0.69	-0.78
	SD	1.06	1.45	1.39	0.91	1.18
Trail B (completion time)	*M*	0.15	-2.25	-0.20	-0.36	-0.64
	SD	1.06	3.97	1.46	1.15	2.41

Note. RF = females with right temporal resection; LF = females with left temporal resection; RM = males with right temporal resection; LM males with left temporal resection.

Table 8

T-test Results for Pre- and Post-surgical Conditions

Dependent Variable	*N*	*M*	*SD*	*t*	*df*	*p*
WCST Categories (before surgery)	42	-0.54	1.44	-2.42	41	0.02
WCST Perseverative Errors (before surgery)	42	-0.74	1.44	-3.03	41	0.002
RFFT (before surgery)	31	-1.19	1.11	-5.99	30	<0.001
COWAT (before surgery)	42	-0.31	1.35	-1.50	41	0.14
TMT (before surgery)	42	-1.58	3.16	-3.22	41	0.003
WCST Categories (after surgery)	38	-0.83	1.86	-2.74	37	0.009
WCST Perseverative Errors (after surgery)	37	-1.38	2.18	-3.84	36	<0.001
RFFT (after surgery)	37	-0.78	1.18	-4.04	36	< 0.001
COWAT (after surgery)	39	-0.48	1.18	-2.56	38	0.014
TMT (after surgery)	38	-0.64	2.41	-1.62	37	0.112

Table 9

Probability Values for 5 ANOVAs

	Gender	Side	Time	G x S	G x T	S x T	G x S x T
WCST (categories) N=37	0.053	0.483	0.360	0.473	0.722	0.965	0.223
WCST (per err.) N = 36	0.091	0.903	0.147	0.997	0.973	0.912	0.639
COWAT N = 38	0.643	0.418	0.258	0.664	0.556	0.554	0.426
RFFT N = 27	0.825	0.360	0.136	0.151	0.939	0.327	0.083
TMT N = 37	0.162	0.465	0.780	0.119	0.591	0.050	0.276

Table 10

Mean Z-scores and Standard Deviations for the TMT for Patients with Right Temporal Involvement Versus Patients with Left Temporal Involvement Before and After Surgery

Side of Involvement	Before Surgery	After Surgery
Right	-1.03 ± 1.50	0.00 ± 1.22
Left	-0.85 ± 1.77	-1.40 ± 1.50

Table 11

Mean Z-scores and Standard Deviations for the RFFT for Men and Women with Right Temporal Involvement Versus Left Temporal Involvement Before and After Surgery

	Before Surgery		After Surgery	
Side of Involvement	Men	Women	Men	Women
Right	-1.6 ± 1.07	-0.85 ± 1.65	-1.06 ± 1.48	-1.10 ± 1.04
Left	-0.98 ± 0.94	-1.12 ± 0.92	-0.80 ± 0.92	0.11 ± 1.11
Right - Left	-0.62	0.27	-0.26	-1.21

Table 12

Estimated Marginal Mean Z-scores for the WCST Measures by Gender

		F	M
WCST (categories)	*M*	-0.98	-0.25
	SE	0.28	0.30
WCST (perseverative err.)	*M*	-1.50	-0.62
	SE	0.36	0.38

Note. F = females patients; M = males patients.

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