

THE DIAGNOSTIC UTILITY OF A MULTI-TASK VERBAL FLUENCY PARADIGM IN
FRONTAL AND TEMPORAL LOBE EPILEPSY: AN ANALYSIS OF FLUENCY TYPE AND
QUALITATIVE PERFORMANCE

By

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To my chair, Dr. Russell M. Bauer, and all of my other mentors who have helped me navigate
the world of neuropsychology

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Abstract of Dissertation Presented to the Graduate School
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Epilepsy is a chronic, disabling condition affecting roughly 50 out of every 100,000 Americans. The most common site for seizure onset is in either the frontal (FLE) or temporal lobes (TLE) of the brain. Identification of the onset of seizures is important, and partly determined by cognitive test scores. Elucidating a pattern of neuropsychological test performance in FLE and TLE is complicated, but allows for more accurate identification of seizure onset, which is essential in treatment planning. Presently, these cognitive patterns are poorly defined and overlapping, partly due to the lack of specificity of our cognitive tests. The purpose of this study was to evaluate the utility of multiple measures of verbal fluency in the differential diagnosis of intractable FL and TL epilepsy.

Patients in the study included pre- and post-surgical refractory epilepsy patients with either temporal (N=14) or frontal lobe epilepsy (N=7) and healthy age and education matched controls (N=20). Patients completed a battery of neuropsychological tests thought to be sensitive to FL and TL functioning, including standard semantic and phonemic fluencies and novel action and name fluencies.

We found significant differences between patients and controls for action and name fluency. Patient groups were not statistically different on fluency measures, though effect sizes indicated FL patients outperformed TL patients on name fluency. A qualitative analysis of fluency (clusters and switches) only differed for patient groups on name fluency as well. Only name and semantic fluency were adequate predictors of patient group membership. We found support for the notion that all fluency measures were related to overall intellectual ability and verbal/semantic factors. However, measures of semantic and name fluency were more related to semantic abilities and phonemic and action fluency were also related to measures of executive functioning.

Results of the study indicate that in a mixed pre- and post-surgical epilepsy population, phonemic, action, and semantic fluency were not specific to frontal and temporal lobe functioning. Further, qualitative assessments of fluency did not offer significant information about seizure foci. Name fluency differentiated well between patient groups and appears to be a novel measure sensitive to the integrity of the left temporal lobe.

CHAPTER 1 BACKGROUND AND SIGNIFICANCE

The purpose of this study was to evaluate the utility of multiple measures of verbal fluency in the differential diagnosis of intractable epilepsy of temporal versus frontal lobe origin. The following sections in the present chapter provide background on the diseases of frontal and temporal lobe epilepsy, and the types of cognitive and neuropsychological deficits that are most common in these populations. The standard neuropsychological assessments used to detect these impairments are also reviewed, including the limitations of these measures in patients with focal epilepsy. Subsequently, the literature positing material-specific impairments in the production of “action words” and “proper names” in patients with frontal and temporal lobe disease is reviewed in order to substantiate the incorporation of these features into traditional neuropsychological assessment. Finally, specific aims and hypotheses for this study are presented.

Frontal and Temporal Lobe Epilepsy

Epilepsy is a chronic, often disabling disorder affecting between 30 and 60 persons per 100,000 in the United States (Hauser, Annegers, Rocca, 1996). In other countries, prevalence ranges between 30 and 100 cases per 100,000 individuals (Forsgren, Beghi, Oun, & Sillanpaa, 2005). While epilepsy accounts for only 5-10% of all disabilities in the United States, the consequences of the disorder can be quite severe, including impairments in quality of life, inability to drive and associated loss of independence, less frequent social interaction and lower marriage rates (Sperling, 2004). Further, uncontrolled seizures can lead to neuronal death and physiological dysfunction. While many individuals with epilepsy are diagnosed at a young age, epilepsy can begin at any point in the lifespan (Paradowski & Zagradjek, 2005; Hauser, Annegers, Rocca, 1996). Often, the etiology of the disorder is unknown. In some cases, however,

its development has been linked to neoplasm, head injury, family history of seizures, or severe illnesses such as meningitis or encephalitis (Chin, Neville, & Scott, 2005; Wakamoto, et al., 2004; Annegers, Hauser, Coan, et al., 1998; Davies, Hermann, Dohan & Wyler, 1996).

In recent years, there have been great advances in treatment options for individuals suffering from this disorder. Currently, there are dozens of pharmacological agents that can be used to prevent seizures, or to help lessen the frequency or intensity of the epileptic events (see Perucca, 2005 for a review). While drug therapies are often effective in managing epilepsy, many cases remain refractory to pharmacologic interventions. Individuals with medication refractory epilepsy, many of whom have complex-partial (or focal) epilepsy, often suffer from years of debilitating and dangerous seizures.

The most common types of focal epilepsies arise from either the temporal lobe or frontal lobe (Engel, 1996). Despite the relative number of patients with frontal lobe epilepsy (FLE), temporal lobe epilepsy (TLE) patients may become candidates for seizure surgery more frequently due to the difficulty in diagnosing and localizing frontal lobe epilepsy. This challenge is accounted for by several different reasons: FLE may be associated with diverse seizure semiologies and EEG recordings in FLE often show widespread epileptic activity, and neuropsychological profiles of patients with suspected FLE are often not distinct from patients with other epilepsies, including the most common variety, TLE (Exner et al., 2002; Hermann, Wyler, & Richey, 1988; Helmstaedter, 1996).

Although no signature pattern of impairment exists and much controversy exists around the “executive functions” of the frontal lobes, behavioral and cognitive characteristics of frontal lobe epilepsy, and frontal lobe damage in general, have been described in the literature. While executive functions are complex and multi-faceted, most of the literature concerning executive

dysfunction does implicate frontal lobe damage as etiologic. The heterogeneous term, “executive function” refers to both the notion of cognitive control over mental abilities, and the ability to be adaptive and flexible in novel or unpredictable situations, which is clearly important for everyday functioning. Generally, executive functions can be thought of as behaviors that include problem solving, planning, abstraction, response inhibition, self-awareness, cognitive flexibility, cognitive control and hypothesis generation (Risberg & Grafman, 2006; Lezak et al., 2004). Patients with frontal damage can exhibit various types of executive dysfunction on neuropsychological tests, depending on which sector of the frontal lobe is involved. Deficits include impairments in planning, initiative, inhibition, behavioral control, emotional regulation and working memory (Helmstaedter, 2001).

In addition to cognitive deficits, patients with lesions to the frontal lobe can exhibit a variety of characteristic personality, behavioral, and emotional changes. Damage to the orbitofrontal region, for instance, can cause behavioral disinhibition, emotional lability, impulsivity, altered social conduct (so-called “acquired sociopathy”), and changes in personality, whereas damage to the lateral prefrontal cortex can cause a decline in working memory abilities, impairments in abstract reasoning, mental inflexibility, and difficulties with decision making (Bechara, Damasio, & Damasio, 2000; Tranel, 1992). Many patients with damage to the frontal lobe display unique characteristics on neuropsychological and behavioral tests including perseverations (i.e. the inability to stop a behavior/response), intrusions, motor impersistence (i.e. an inability to sustain a motor gesture or action over a period of time), and poor self-regulation (Alvarez & Emory, 2006; Helmstaedter, 2001). In addition, depending on the site of the frontal lobe lesion, patients can also display difficulties with expressive speech, motor weakness or incoordination, apathy, or problems with abstract thinking.

While many of these characteristics are unique to persons with damage to the frontal lobes, others are found commonly in other patient groups. This is certainly the case when studying patients with frontal and temporal lobe epilepsy. Typically, patients with TLE localized to the left hemisphere (LTLE) display robust reliable neuropsychological impairments that are generally replicated across studies. These include deficits on tests on object and person naming, verbal comprehension, and learning and memory for both simple and complex forms of verbal material (Hermann, Seidenberg, Schoenfeld, & Davies, 1997; Hermann et al., 1999). However, LTLE patients commonly exhibit difficulty not only with verbal learning and memory, but also with response inhibition, impulsivity, set loss, and difficulties with mental flexibility and abstract thinking. These overlapping patterns of impairments on neuropsychological tests are likely due to a variety of factors, including the fact that patients with TLE often have propagation of abnormal electrical activity from the temporal to frontal regions, thereby causing potential impairment (Hermann & Seidenberg, 1995). Further, patients with TLE can exhibit reductions in white matter volume in frontal cortex, in addition to a reduction in overall cerebral volume and gray matter changes (Hermann et al., 2003; McMillan et al., 2004; Oyegbile et al., 2006). In addition, patients with longstanding seizure disorders may exhibit depressed cognitive profiles on multiple cognitive domains due to the cumulative effect of uncontrolled seizures (Jokeit & Ebner, 2002). Further, this lack of differentiation between frontal and temporal lobe epilepsy patients may also reflect the relatively poor specificity of our assessments for localized brain dysfunction. Given the relative overlap of these cognitive profiles, identification of seizure localization is at best a complicated and ambiguous task for neuropsychologists.

Measurement of Neuropsychological Functioning In FLE and TLE

As previously mentioned, patients with frontal and temporal lobe epilepsy may present with overlapping neuropsychological profiles. This may result, in part, from overlapping neural

pathology, and in part because of relatively poor ability of clinical tests to discriminate frontal from temporal lobe epilepsy. A pre-surgical neuropsychological test battery for epilepsy patients includes tests of overall cognitive functioning, expressive and receptive language, verbal and nonverbal memory, processing speed, visuoconstructional ability, attention, “executive function”, and mood. Tests routinely used to assess for “executive” or frontal lobe dysfunction usually include measures such as the Wisconsin Card Sorting Test (WCST), Stroop Color-Word Test (Stroop), Trail Making Test (TMT), and measures of verbal fluency, including phonemic and semantic fluency tests (Lezak et al., 2004). Additional measures such as Luria’s Motor Sequencing Tests (Luria, 1966) may also be administered in some clinics (Stuss & Levine, 2002). Combined results on these measures is then used to determine whether or not a patient displays significant executive dysfunction and, in combination with other test results, whether or not the patient displays a localizing pattern of deficits. The difficulty in clinical decision-making lies in the fact that these tests are sensitive to the presence of brain disease or damage, but may not be sufficiently specific to damage in a particular region of the brain.

A body of evidence supports the notion that impairment on measures of “executive function” are not specific to damage of the frontal lobe, and do not discriminate frontal patients from those with temporal or other types of damage. In epilepsy populations, Hermann, Wyler, and Richey (1988) initially documented significant errors in planning and problem-solving on the Wisconsin Card Sorting Test (WCST) in a small group of left and right TLE patients compared to generalized seizure patients and controls. The finding of poor performance on the WCST in TLE, as measured largely by the number of perseverative errors, has been confirmed by others (Martin et al., 2000; Trennery & Jack, 1994; Corcoran & Upton, 1993). A recent meta-analytic review (Emory & Alvarez, 2006) found that out of twenty-five lesion studies, twelve

found that adults with frontal lobe lesions performed more poorly on the WCST than healthy controls, and 10/16 studies suggested that frontal lobe lesioned persons performed worse than those with extrafrontal lesions. However, they also reported that two studies found no differences between frontal lobe patients when compared to normative data, and nine studies found no significant differences between groups with frontal cortical lesions and those with lesions elsewhere in the brain (i.e. basal ganglia, diffuse lesions).

Additional studies using the Stroop paradigm have found that non-frontal epilepsy patients perform poorly on this measure. One recent study by McDonald and colleagues (McDonald et al., 2005) found that patients with left lateralized TLE were significantly impaired on measures of switching and inhibition on the Color-Word Interference Test (McDonald et al., 2005). Despite the frequency of use by neuropsychologists, few lesion studies have employed the Stroop paradigm to examine its specificity to frontal lobe lesions. Of those that have, only two studies found that persons with lesions to the frontal lobes performed worse than controls (Stuss et al., 2001; Vendrell et al., 1995), and two studies reported those with frontal lesions perform worse than nonfrontal controls on the interference trial (Perret, 1974; Stuss et al., 2001). On the other hand, studies have found the opposite pattern; frontal lobe and temporal lobe lesioned patients performed equally poorly on this measure (Blenner, 1993).

Demakis (2004) conducted a meta-analysis of studies which have employed the TMT and Category Test to determine the relative utility of these instruments in detecting frontal lobe damage or dysfunction. Based on the studies included, 321 participants were included in the overall meta-analysis, although sample size varied slightly by test examined. Surprisingly, the results of the study indicated that frontal patients performed significantly worse than non-frontal patients on Trails A (thought to assess mainly psychomotor speed), but did not perform worse on

the Category Test or Trails B. Exner and colleagues (Exner et al., 2002) found that patients with frontal and temporal lobe epilepsy had inferior Trails A and B performance compared to controls, but did not significantly differ from each other on these measures.

In sum, these results and others indicate that tests commonly thought to assess the integrity of the frontal lobe are in many cases, sensitive to frontal dysfunction. However, many studies have failed to find such effects, and other studies have found that, while some of the tests may be sensitive to frontal lobe damage, they are nonspecifically impaired in damage to the temporal lobe and elsewhere in the brain. These results raise questions about the utility of many so-called “frontal-executive” tests, and at best, indicate that such tests may be sufficiently sensitive but insufficiently specific. These findings suggest the need to further develop neuropsychological methods with greater specificity for frontal lobe disturbance in clinical populations.

Verbal Fluency

Verbal fluency measures are amongst the most common measures administered in traditional neuropsychological assessment (Stuss & Levine, 2002), as more than 50% of neuropsychologists report using these measures in standard clinical practice (Butler et al., 1991). Fluency measures are quickly administered, easily scored, and readily available. Further, adequate norms exist for these measures making their use in clinical practice even more prevalent. These measures require “time-restricted generation of multiple response alternatives under constrained search conditions and involves associate exploration and retrieval of words” (Henry & Crawford, 2004). Although a variety of fluency measures exist (i.e. written fluency, figural fluency) the most common varieties of fluency tests are oral in nature, and assess word generation to either a phonemic or semantic cue. Phonemic fluency requires generation of words

that begin with a particular letter (i.e. F, A, S, or C, F, L), whereas semantic fluency assesses word production to a given category (i.e. animals, items in a supermarket, fruits and vegetables).

Semantic Fluency

Presently, there is disagreement in the literature as to the extent to which semantic fluency is sensitive to the integrity of the frontal lobes. Some evidence suggests that phonemic and semantic fluency may impose differing demands on frontal-executive processes; searching for semantic items within a larger superordinate category places demands on well-established search mechanisms that are congruent with organizational structures in our environment (e.g. generating items that can all be found in a supermarket, as opposed to generating items by letter, which contain no inherent semantic relationships). Perret (1974) has argued that because the search criteria for semantic fluency are consistent with the natural organization of the human lexicon, the demands of this task rely less on the executive processes, and more on the integrity and organization of semantic memory stores. Others argue, however, that patients with executive dysfunction are unable to perform effective and strategic searches through memory, irrespective of whether the search is semantically or phonemically driven (Baldo et al., 2006; Baldo & Shimamura, 1998; Troyer et al., 1998), and as such, would be equally impaired on semantic and phonemic fluency tests.

Empirical data provides some clarity to the theoretical debate, although the body of literature is not entirely consistent. For instance, Drane et al. (2006) found that patients with frontal lobe epilepsy were more impaired than a group with temporal lobe epilepsy on measures of semantic fluency. A study comparing patients with focal anterior and posterior lesions found that both types of lesions produced impairments on semantic, or category, fluency (Stuss et al., 1998). Additional studies employing a variety of populations have found similar impairments in semantic fluency in frontal-lobe patients (Baldo & Shimamura, 1998; Costello & Warrington,

1989; Owen et al., 1990; Randolph et al., 1993). Conversely, studies report spared semantic fluency in patients with frontal lesions (Corcoran & Upton, 1993; Joanet & Goulet, 1986; Jurado et al., 2000, Vilkki & Holst, 1994). In addition, secondary interference tasks though to disrupt frontal lobe functioning have not been successful in disrupting category fluency performance (Mack, 1994; Martin et al., 1994).

Functional imaging studies have attempted to delineate brain regions associated with successful category fluency performance. Mummery (Mummery et al., 1996) reported significant left temporal lobe activation in the inferior and anteromedial regions while patients performed category fluency tasks, but did not find significant frontal lobe activation for this task. Using voxel-based lesion mapping, Baldo and colleagues (2006) found that category fluency performance was associated with lesions in the left temporal lobe, post-central gyrus, parietal cortex, and putamen. When examining areas specific to category fluency, the most important regions of interest were in the temporal (Brodmann's Areas (BA) 22, 37, 38, 41, and 43) and parietal cortices (BA 7, 39). No significant regions in the frontal lobe were noted (Baldo et al., 2006). These findings have been replicated by other functional imaging studies (Gourovitch et al., 2001), but additional areas of activation have been found for category fluency, namely the left hippocampus and medial frontal cortex.

It is commonly believed that semantic fluency performance relies heavily on the integrity of intact semantic memory networks, or the modules of long-term memory that contain knowledge about objects, concepts, facts, as well as the meanings of words, largely localized to the temporal structures of the language dominant hemisphere (Butters et al., 1987; Monsch et al., 1992). Consistent with this perspective, lesion studies examining patients with temporal lobe involvement are generally impaired on tests of semantic fluency, compared to other patient

groups and controls. Compared to healthy controls, Troster and colleagues demonstrated that patients with left TLE generated fewer words on a semantic fluency test (supermarket fluency) (Troster et al., 1995). This pattern of worse semantic fluency performance in LTLE compared to controls has been replicated by others (Gleissner & Elger, 2001; N'Kaoua, 2001; Martin, Loring, Meador, & Lee, 1990). A pattern of impaired semantic fluency performance has also been reported in other clinical samples with temporal lobe involvement, including Alzheimer's Disease (Randolph et al., 1993; Diaz et al., 2004). A recent meta-analysis of 995 patients (Henry & Crawford, 2002) with a wide range of lesion etiologies found that temporal patients were more impaired on semantic than phonemic fluency, and that those with left lateralized temporal lesions were more impaired than those with right temporal lesions. Results on the aforementioned neuroimaging, dual-performance, and voxel-based lesion mapping studies also confirm the crucial role the left temporal lobe plays in retrieval of words from superordinate semantic categories.

These findings indicate adequate performance on semantic fluency tasks is multi-determined. It is clear that semantic fluency relies heavily upon access to the semantic memory stores of the temporal lobe, and that damage or disease processes involving this region impairs successful performance on semantic fluency. The role that the frontal lobes play in the controlled search process necessary to complete the task appears to be less critical, although damage to the frontal cortex can also impair semantic fluency to a lesser degree.

Phonemic Fluency

Phonemic fluency measures commonly consist of three trials, which require generation of words beginning with a particular letter (Lezak, 2004). While phonemic fluency performance is obviously dependent on the integrity of language systems as well, this measure has traditionally been conceptualized as a measure of executive function because of the unusual demand of word

generation based on orthographic criteria. Further, the task requires the creation of nonhabitual strategies of word retrieval based on lexical representations, and the suppression of responses based on their meaning (Perret, 1974). Effective performance on this measure also requires efficient organization of verbal recall, retrieval, and output, in addition to self-monitoring, effortful self-initiation, an inhibition of previously given responses (Henry & Crawford, 2004; Ruff et al., 1997).

Research supports the assertion that there is a relationship between the integrity of the frontal lobes and performance on phonemic fluency. The finding of decreased phonemic fluency in frontal-lobe patients has been reported in patients with traumatic brain injury (Jurado, et al., 2000), left frontal and bi-frontal epilepsy (Troyer et al., 1998), dementias involving the frontal lobes (Rosser & Hodges, 1994), and a variety of patient groups of mixed frontal-lobe pathology (Stuss et al., 2000; Janowsky et al., 1989). In their meta-analysis, Emory and Alvarez (2006) found that the majority of studies of frontal-lobe lesion patients reported significantly poorer phonemic fluency scores compared to controls, although a smaller percentage found this same difference compared to non-frontal lobe lesions patients. Another meta-analysis reported large effect sizes ($r=.52$) for deficits of their frontal lobe group compared to their non-frontal group, and deficits were largest with left frontal lesions, although patients with left focal non-frontal lesions also showed significant impairment on phonemic fluency tests (Henry & Crawford, 2006). While the sensitivity of this measure has been demonstrated in lesion studies, its specificity has not yet been established because a number of studies demonstrate no significant differences between frontal patients and those with either non-frontal cortical or diffuse lesions (Stuss et al., 1998; Miller, 1984; Pendelton et al., 1982; Perret, 1974). Further, some authors suggest that while phonemic fluency does indeed tap an “executive” factor, the contribution of

verbal abilities to overall performance are equally important. Indeed, Ramier and Hécaen (1970) argued that successful performance on phonemic fluency is determined by an “executive” factor located within the frontal lobes and a “verbal” factor mediated more generally by the left hemisphere function (presumably the language dominant hemisphere).

Neuroimaging studies of healthy controls confirm the critical role of the frontal lobes in phonemic fluency performance, despite significant variability in task procedure and imaging parameters. Studies have found specific areas of increased activation in the left inferior frontal gyrus (IFG), anterior cingulate (AC), and left dorsolateral prefrontal cortex (DLPFC) (Paulesu et al., 1997; Frith et al, 1995; Frith et al., 1991). Other studies report activations in these areas while also finding significant increases in blood/glucose to more widespread areas of the frontal lobes (Parks et al., 1988).

In sum, evidence from lesion and neuroimaging studies suggests that phonemic fluency relies upon the integrity of the frontal lobes, much more so than semantic fluency. Semantic fluency on the other hand, appears to be more sensitive to the integrity of the temporal lobes and places a larger demand on semantic memory stores. Nonetheless, contradictory reports in the literature draw the specificity of these measures into question, as it is clear that both frontal and temporal lobe patients can exhibit impairment on either, or both tasks. At this point in time, the scientific literature does not provide definitive support for the notion that frontal lesions necessarily produce disproportionate impairment on phonemic fluency, and temporal lesions disproportionately affect semantic fluency performance. It may be that further refinements in fluency tasks, or in ways in which fluency performance is measured, might improve the ability to provide such a double dissociation. Providing such refinements is one purpose of the current research.

Novel Techniques for Dissociating Frontal and Temporal Lobe Impairment

Many previous studies have attempted to differentiate frontal from nonfrontal lesions on the basis of performance on experimental tasks designed to isolate particular aspects of frontal-executive dysfunction. These include assessments of set shifting (McDonald et al., 2005a), figural fluency (McDonald et al., 2005b), directed forgetting (McDonald et al., 2006), priming (Alexander et al., 2005; Stuss et al., 1999), self-ordered pointing (Lamar & Resnick, 2004; Petrides & Milner, 1982), source memory (Thaiss & Petrides, 2003), and structured semantic cueing paradigms (Drane et al., 2006; Randolph et al., 1993).

This general tradition has also led to refinements of traditional oral fluency paradigms. One such paradigm is based on the literature that posits distinct neural regions for the processing of words that denote concrete entities, such as objects, and words that denote action or motion, verbs.

Action/Verb Retrieval

Although a fair amount is known about the neural representation for words denoting concrete entities (“objects”) less is known about the neural basis of action word retrieval. However, a growing body of literature across many fields, including linguistics, cognitive and experimental psychology, neurology, and clinical psychology lends support to the idea that distinct neural regions are involved in more highly specialized in processing information that relates to action or movement.

Why should actions and objects have different neural bases? One theory posits that knowledge about objects and actions is stored in association cortices adjacent to the primary cortical regions that process these classes of stimuli (Damasio & Tranel, 1993). According to this theory, object knowledge is stored in cortical regions adjacent to the occipito-temporal visual stream, while action knowledge is stored adjacent to motor structures in the frontal lobe

including the prefrontal cortex, premotor cortex, and supplementary motor area (Lu et al., 2002) that process skilled movement and action. As such, it is suspected that the frontal lobes likely serve as a storehouse for knowledge related to movement/action, and to the extent that the major semantic features of an object include implications for motion, a substantial portion of its' neural network will reside within the frontal lobes. In contrast, object knowledge, based as it is on structural representations of object form, is more dependent on the occipitotemporal visual stream, which normally process object qualities.

Another theory posits that words are segregated based on how they were learned, thus emphasizing the distinction between objects, which are highly visual, and actions that have salient functional components (Warrington & Shallice, 1984). Alternatively, because actions are captured by grammatically-rich verbs, it is possible that difficulty recognizing and producing action words is related primarily deficits in grammatical processing (McCarthy & Warrington, 1985). Still another view holds that the deficit is largely executive in nature, and relates to the difficulty of “mentally coordinating and manipulating the large amount of information related to action-words” (White-Devine et al., 1996). Although the outcome of this debate remains unclear at this point, it may be possible that several of these theories will eventually contribute to our understanding of the mechanism underlying category-specific deficits. Further, regardless of which theory is correct, all posit separate neural substrates for objects and actions.

The literature is beginning to draw a clear picture that category-specific deficits for action words (verbs) do exist. The strongest support for this claim is from the lesion literature, in which a variety of studies have demonstrated this category specific deficit. This finding was first noted in agrammatic aphasics who demonstrated notable deficits in verb production, whereas anomia aphasics had greater impairment in the retrieval of nouns (Miceli et al., 1984). Damasio & Tranel

(1993) present three compelling case studies; two of their patients had damage to the anterior and middle temporal cortices and the third in the left premotor cortex. Results revealed a double dissociation in which their first two patients had difficulty naming common nouns (pictures of objects) whereas the third patient was unable to name actions depicted in line drawings. A similar category-specific noun/verb effect has been shown in other groups of patients with damage to various regions within the frontal cortex (Caramazza & Hillis, 1991; Daniele et al., 1994; Hillis & Caramazza, 1995; Miceli et al., 1984; Rapp & Caramazza, 1998). Exploiting the known neuropathology of various dementia types, researchers have also demonstrated action naming impairments in groups with frontal lobe pathology, and the lack of impairment in patients with an absence of this pathology. Although both Alzheimer's (AD) and fronto-temporal dementia (FTD) patients displayed impairments in object and action naming compared to controls, the discrepancy between object and action naming performance was significantly larger for FTD than AD patients regardless of dementia severity (Cappa et al., 1998). The same group later found that impaired action naming was not only present in FTD, but also in other patient groups with frontal-subcortical disease, including those with supranuclear palsy and corticobasal degeneration (Cotelli et al., 2006). Another study comparing action and object fluency in AD and FTD confirmed Cappa's results, but further elucidated the nature of the action naming disorder. In FTD the naming disorder was found mostly to be due to a dysexecutive deficit whereas in AD, it was due largely to linguistic difficulties (Silveri et al., 2003). Although the possibility of a selective verb deficit has not been explored in frontal lobe epilepsy, one study did find that verb naming was spared in patients who had undergone LATL; a finding that is consistent with the view that action naming is not localized to the temporal lobes (Glosser & Donofrio, 2001).

Functional imaging studies in both patients and healthy volunteers further confirm the role of the frontal lobes in the retrieval of action words. In fact, one of the earliest tasks used in PET and fMRI studies was a task in which participants were shown a picture of an object (“ball”) and asked to generate a verb (“kick”) for the object. These early imaging studies found that the left inferior frontal gyrus (IFG) was activated during these tasks (Petersen et al., 1989; Petersen, Fox, Snyder & Raichle, 1990; Raichle et al., 1994). More recent studies have confirmed the role of the frontal cortices in naming and generating action words. Thompson-Schill found that patients with damage to the left IFG not only had more difficulty generating semantically appropriate verbs, but also made more errors on their task than did patient or elderly control groups (Thompson-Schill, 1998). Other fMRI findings using varying task demands found similar activations in the left inferior prefrontal cortex (Perani et al., 1999; Shapiro, Moo & Caramazza, 2006; Tyler et al, 2004). One recent PET study found that naming actions was correlated with increased glucose utilization in the left frontal operculum, left posterior middle frontal gyrus, and left and right parietal lobule (Damasio et al., 2001).

Until recently, the assessment of verb retrieval abilities has been limited to action naming paradigms, similar to an “action” analog of traditional naming tests, such as the Boston Naming Test (BNT). While these paradigms are useful in assessing verb naming impairments, they all require identification of a verb associated with a graphically depicted image (Oblor & Albert, 1979) as opposed to free generation of action-related words. Over the past several years, however, a small body of literature using action fluency paradigms has emerged. Action fluency paradigms assess the spontaneous production of verbs, with the instructions “tell me as many different things as you can think of that people do” (Piatt, Fields, Paolo, & Troster, 1999).

Preliminary evidence from action fluency studies suggests that performance on this task is indeed sensitive to frontal lobe dysfunction. Patients with known frontal-subcortical damage were significantly impaired on action fluency when compared to healthy controls. Patients with frontal-subcortical pathology secondary to HIV-1 infection performed similarly to healthy controls on measures of semantic fluency, but were significantly impaired on the action fluency measure (Woods et al., 2005). When Parkinson's patients with (PDD) and without dementia (PDND) and healthy controls were compared on action, phonemic, and semantic fluency tasks, PDD patients performed worse on all three measures. However, performance on the action fluency task was differentially more difficult for the PDD group than semantic or phonemic fluency, relative to the control and non-dementia groups (Piatt et al., 1999b). The authors conclude that the measure was both sensitive and specific to frontal-subcortical disease.

Three studies have examined the construct validity of the action fluency test as a measure of frontal lobe functioning and/or executive function. Piatt Fields, Paolo & Troster (1999) demonstrated the convergent validity in a sample of healthy older adults. They found that action fluency performance was significantly related to several measures of executive function (i.e. TMT-B, WCST) but not with common measures of temporal lobe functioning (i.e. BNT, Logical Memory from the Wechsler Memory Scale). While action fluency shared common variance with other measures of executive function, the test also seemed to measure a component of executive functioning not tapped by more traditional tasks. Woods et al (2005) found similar relationships with putative measures of executive function in healthy young volunteers, but found no relationship with measures traditionally associated with the posterior cortex. In sum, there is support for dissociation between action and object naming, with the naming of actions being dependent on anterior brain structures, namely the frontal lobes. Further, preliminary findings

indicate that action fluency is a novel paradigm that may not only be sensitive, but also specific to frontal lobe functioning. To our knowledge, this paradigm has been applied only to patients with HIV and Parkinson's Disease and normal older and younger controls, and has not been used in patients with focal epilepsy.

Proper Name Retrieval

The difficulty in isolating patients with frontal lobe damage lies not only in identifying tasks sensitive to frontal lobe dysfunction, but also in designing equivalent tasks sensitive only to temporal lobe damage in order to doubly dissociate performance on neuropsychological tests. While the mesial temporal lobe is critically important in episodic memory, the lateral (cortical) aspects of the temporal lobes are likely critical in the storage and maintenance of semantic memory, or knowledge of objects, facts, and names. Patients with damage to the anterior and lateral portions of the temporal lobes often have difficulty on tasks tapping semantic memory stores. This is particularly true in the case of proper names. The specific difficulty in producing proper names has generally been attributed to their semantic uniqueness, or the fact that these names refer to unique entities (Semenza & Zettin, 1989; Grabowski et al., 2001). While common names refer to concepts, or a set of attributes that are shared by multiple entities within the same concept, proper names do not inherently contain attributes in and of themselves and are merely expressions by which we refer to an individual person or item. Because of this, it is thought that widespread neural networks support the representation of common nouns, while proper nouns are thought to hold rather fragile "associations" with their unique reference (Martins & Farrajota, 2007). In addition, difficulty in retrieval of common nouns is often abated by the fact that they can often be substituted with synonyms, whereas this is not usually possible with proper names (Bredart, 1993).

Regarding the neural representation of proper names, several cases studies have shown that lesions to the left anterior temporal and temporal polar regions selectively disrupt the retrieval and production of proper names (Damasio et al., 1996; Harris & Kay, 1995; McKenna & Warrington, 1980). Two lesion studies demonstrated this effect across naming paradigms (naming to pictures, naming to description), and name generation tasks (actors, sports figures). The dissociation of common and proper name impairments was also demonstrated in a stroke patient (ACB) who suffered an ischemic lesion that involved that temporal neocortex and temporal pole (Martins & Farrajota, 2007). Subsequently, he was unable to recall proper names (particularly those that referred to well-known figures, such as politicians) while his ability to produce common names of objects was relatively spared. Similar deficits in proper naming abilities were documented in a patient who underwent left ATL surgery for refractory epilepsy (Fukatsu, et al., 1999). This patient was able to accurately perceive pictures of faces, but was able to name only 25% of his acquaintances from photos, and even fewer from verbal description (24%). He named only 4 out of 25 famous faces correctly. He was able to name 90/100 pictures of common items, however (animals, furniture, tools, insects). Further, his fluency for common names was double his fluency for proper names. Similar, though less dramatic findings of proper name impairment have been reported in patients who underwent LATL for epilepsy relief (Barr, Goldberg, Wasserstein & Novelly, 1990; Tsukiura et al., 2002; Seidenberg et al., 2002; Glosser, Salvucci, Chiaravalloti, 2003). In these studies, many of the LATL patients had impaired naming of famous faces compared to controls, but were able to recognize or subsequently provide semantic information about them, apart from their actual name.

Because the majority of these studies involve the naming of persons in response to visual representation, it raises the question of whether this impairment is related to the specificity of the

task (i.e. retrieving unique names) or to preferential processing of facial stimuli by the anterior temporal lobe. Several neuroimaging studies have tried to address this question. Regardless of presentation format (printed names versus photo) or presentation modality (visual versus auditory), similar areas of activation are noted (Tempini et al., 1998; Tranel, Grabowski, Lyon & Damasio, 2005). In addition, this question has been addressed directly by comparing retrieval of names of other unique entities (landmarks and buildings) to retrieval of proper names of persons. The results of these studies (Milders, 2000; Tranel, 2006; Grabowski et al., 2001) confirm the hypothesis that portions of the left temporal lobe (anterior temporal lobe, temporal pole) are in fact specialized for the retrieval of unique entities as a whole, not only entities that contain human features.

Apart from a limited number of lesion studies that have used the design experimentally, the assessment of unique (or proper) naming abilities has been limited to paradigms that require identification of a name associated with pictures or photographs. Although there is sufficient evidence to support the idea that the retrieval of proper names depends on the integrity of anterior portions of the temporal lobe, and taps a unique aspect of semantic processes, these hypotheses have not been directly tested in this format in clinical populations, and the ability to generate proper names without corresponding visual stimuli has not been examined.

Qualitative Analysis

Tests of verbal fluency, regardless of type, are generally scored by tallying the total number of words generated, minus errors or repetitions. While this score is an accurate measurement of fluency output, it provides minimal information about how the task is completed, and as previously discussed, may be limited in accurately characterizing performances by different groups of patients because the same score can be obtained in qualitatively different ways. Because fluency score is likely multi-determined, and affected by

difficulty initiating or maintaining performance, faulty search and retrieval strategies, degraded semantic memory stores, failure to maintain set, and self-monitoring failures, a more thorough analysis of the cognitive processes involved in task performance is warranted.

Aspects of fluency performance, including perseverations and intrusions, have been assessed in a variety of clinical and healthy populations (Reverberi, Laiacona, & Capitani, 2006; Warrington, 2000; Martin & Fedio, 1983; Troster et al., 1989) and recently, Troyer, Moscovitch, & Wincour (1997) developed a methodology for examining organizational retrieval processes involved in word generation. They suggest that optimal fluency performance is composed of the production of semantic (i.e. apples, bananas, grapes) or phonemically-related (i.e. far, fat, fast) “clusters” of words, and when one cluster is exhausted, a switch is made to another cluster. As such, they envision two important aspects of fluency performance; *clustering*, which is the production appropriate words within the subcategories, and *switching*, the ability to shift between said subcategories. Clustering is thought to rely heavily upon organized access of semantic memory stores (more strongly localized in the temporal lobe), while switching is thought to rely more heavily upon cognitive flexibility, ability to shift set, disengagement from previous responses, and strategic search (more strongly localized in the frontal lobe; Troyer & Moscovitch, 2006). Some evidence suggests that while clustering relies on relatively automatic cognitive process, switching is thought to involve effortful processing (Rende, Ramsberger, & Miyake, 2002).

Data from healthy young and old volunteers has suggested that clustering and switching are indeed dissociable processes. Clustering and switching scores were both related to total fluency score on semantic fluency measures, but the switching score was more uniquely related to overall phonemic fluency, consistent with the view that both rely more heavily on frontal-

executive processes (Troyer, Moscovitch & Wincoeur, 1997). The finding that divided-attention tasks (concurrent finger-tapping) disrupted switching but not clustering also supports this assertion.

Given that these processes have been identified as dissociable in healthy volunteers and have shown differential relationships with overall fluency scores, others examined whether they would be differentially affected by neurological disorders. As predicted, patients with temporal lobe epilepsy showed decreased clustering on semantic fluency tests, while patients with frontal lobe epilepsy exhibited decreased switches on both phonemic and semantic fluency tests. Troyer et al. (1998a) determined that the best indices for discriminating these patients were phonemic-switching and semantic-clustering scores. Early AD patients, who have known temporal lobe pathology, showed reduced cluster size on both types of fluency (Troyer et al., 1998b). Patients with frontal and/or subcortical disease demonstrated the expected pattern of relatively intact semantic cluster size, but decreased switching (Demakis et al., 2003; Ho et al., 2002; Troster et al., 1998) as did patients with psychiatric disease known to affect frontal-lobe functioning (Fossati et al., 2003; Robert et al., 1998).

Quantitative fluency scores are certainly sensitive to frank pathologies such as those underlying Alzheimer's Disease and aphasia, and can be also be sensitive to milder forms of pathology in some cases. However, impairment of this score can be due to heterogeneous causes, which greatly limits or precludes interpretation about the underlying cognitive processes responsible for the deficit. A qualitative analysis of fluency performance, however, helps to elucidate the mechanisms by which the task is completed and may shed light on the nature of fluency impairment. This qualitative analysis appears to be most helpful in identifying components of fluency performance due to frontal and temporal lobe impairment.

Summary

Elucidating a pattern of neuropsychological test performance characteristic of frontal and temporal lobe epilepsy is complicated at best, but remains important for a number of reasons. First, identification of patterned impairments allows for better and more accurate identification of seizure onset, which is essential in treatment planning. Beyond the clinical and practical importance, a more thorough understanding of these cognitive impairments further extends our scientific knowledge about the neural substrate of these cognitive processes. Presently, these cognitive patterns are poorly defined and overlapping, partly due to the lack of specificity of many of our tests.

In particular, many of our tests thought to identify frontal lobe dysfunction appear sensitive, but not specific. These include tests thought to assess mental flexibility, set-shifting, response inhibition, and working memory. Traditional measures of fluency are commonly used to identify patterns of performance of frontal and temporal lobe epilepsy patients, however, both patient groups may exhibit deficits on both types of tests, affording them minimal discriminative validity.

Despite the relative lack of specific standardized assessments, the scientific literature provides insight into the type of impairments that may exist with damage to either the frontal or temporal cortices. Specifically, damage to the language dominant temporal lobe produces deficits in the retrieval of names of unique entities (people or places), whereas damage to the frontal cortex, particularly left lateralized damage, produces impairments in the retrieval of words denoting actions. In conjunction with the test content, a qualitative examination of the cognitive strategy involved may also have useful predictive value.

The current study seeks to incorporate this material-specific content into traditional test paradigms in order to further explore the unique cognitive deficits associated with localized

neural dysfunction. By manipulating the retrieval demands involved and examining the cognitive strategies employed, we hope to more accurately discriminate between patient groups and to advance our understanding about the neural specificity of these brain regions. Specific aims of the study are listed below.

CHAPTER 2
SPECIFIC AIMS & HYPOTHESES OF CURRENT STUDY

Aim 1

The first aim of the study was to characterize performance of patients with either frontal or left temporal lobe epilepsy, and matched healthy controls on a panel of verbal fluency tests, that includes both traditional measures of semantic and phonemic fluency, and experimental measures of action and proper name fluency. We hypothesized that overall fluency score on action and proper noun fluency would doubly dissociate patients with frontal and temporal lobe epilepsy, with frontal lobe patients performing worse on action fluency and temporal lobe patients exhibiting comparative deficits on tests of proper name fluency. We also suspected that patients with temporal lobe epilepsy would also evidence impaired semantic fluency (but not phonemic fluency), while patients with frontal lobe would demonstrate impairments on phonemic fluency (but not semantic fluency). All patient groups were predicted to generate fewer total words than controls due to the overall effect of their neurological disorder.

Aim 2

The second aim of the study was to compare the clinical utility and predictive validity of experimental versus traditional fluency measures in identifying seizure location and lateralization, and in discriminating between temporal and frontal groups. We predicted that the experimental fluency measures would have similar, and possibly more favorable operating characteristics (sensitivity, specificity, positive and negative predictive value) than traditional measures of fluency, and that our panel of fluency measures would be effective in accurately discriminating frontal and temporal lobe patients.

Aim 3

The third aim was to establish the psychometric properties of the experimental fluency measures (convergent and discriminant validity) using traditional measures of frontal and temporal lobe dysfunction and to compare the predictive power of various fluency tests with more traditional neuropsychological measures. We hypothesized that performance on tests of common and proper noun fluency would be related to measures of language and semantic/episodic memory (Wechsler Memory Scale-Logical Memory, Boston Naming Test), while action and phonemic fluency scores will exhibit moderate relationships with traditional measures of executive function (Wisconsin Card Sorting Test, Trail Making Test B). However, as these tests tap varied aspects of cognitive functioning whose neural instantiations exist within the frontal lobe, we thought that this fluency measure may comprise a new dimension of executive function not assessed by other measures.

Aim 4

The fourth aim was to determine whether a qualitative analysis of fluency performance (i.e., clustering and switching performance) would dissociate performance of patients with FLE, TLE, and healthy controls. Consistent with previous lesion studies, we expected that patients with TLE would exhibit an average number of switches, but reduced cluster size, particularly on tests that rely more heavily on semantic memory (proper name fluency, common noun fluency). Conversely, we thought that patients with FLE would display the reverse pattern of spared semantic cluster size, but reduced number of switches, predominantly on tests of phonemic and action fluency.

CHAPTER 3 SUBJECTS & METHODS

Study Participants

Participants in this study included patients with documented epilepsy localized either to the frontal or temporal lobes. A healthy control group with no current or past history of neurological disease was also recruited for participation in the study. Initial power analyses, computed from data provided in Troyer et al. (1997), indicated that with an evenly distributed sample of 30 (10 patients with left frontal lobe epilepsy, 10 patients with left temporal lobe epilepsy, and 10 healthy controls), our study would be powered adequately (Critical $F = 3.55$, Actual power = .975, α error probability = .05) to detect overall group differences in fluency score, our primary aim of the study. However, additional analyses computed from data in Troyer et al. (1997) also suggested that as few as six participants were needed per group (Critical $F = 3.88$, Actual power = .955, α error probability = .05).

Initial investigation of pre-surgical patient flow over the past several years suggested our patient recruitment goals were feasible in a pre-surgical population over a ten to twelve month recruitment period. While the initial goal of the study was to recruit pre-surgical patients with either language-dominant temporal lobe epilepsy (i.e., left-hemisphere) or patients with left frontal epilepsy, this goal could not be achieved even with extended recruitment over a period of eighteen months. In eighteen months, we were successful at recruiting only five presurgical patients with left temporal lobe epilepsy who met all inclusion/exclusion criteria and four patients with frontal lobe epilepsy (one right, two left, one bifrontal).

Because of the significant difficulty recruiting patients pre-surgically, post-surgical patient data was collected concurrently. Combining both pre-surgical and post-surgical patients, we were able to collect data on fourteen patients with left temporal lobe epilepsy, seven patients

with frontal lobe epilepsy, as well as eighteen patients with right temporal lobe epilepsy. By combining both pre-and post-surgical data, we were able to meet our sample size requirements in our left temporal lobe group. However, even when combining pre- and post-surgical data we were not able to obtain ten patients with left frontal epilepsy, which was our initial goal. Because of this, we combined patients with left frontal, right frontal, or bifrontal epilepsy to compose our “frontal lobe” group, for a total of seven frontal lobe epilepsy patients (Table 3-1).

Participants included in the final study were fourteen patients (pre- and post-surgical) who had epilepsy localized by EEG to the left temporal lobe, seven patients (pre- and post-surgical) with EEG documented epilepsy of the frontal lobes (left, right, or bilateral) and twenty healthy controls. Lateralization and localization of seizure foci was determined by consensus diagnosis using data from Phase I EEG monitoring, MRI, patient history, and cognitive test results. At the present time, six of the nine pre-surgical patients have proceeded to surgery. Differences in demographic and clinical characteristics were assessed using one-way analysis of variance (ANOVA) and chi-square tests. Patients and control groups were well matched for age ($F(2, 40) = .08, p > .05$), education ($F(2, 40) = 3.1, p > .05$), gender ($X^2(2) = .03, p > .05$), handedness ($X^2(2) = 4.09, p > .05$), race ($X^2(2) = 3.51, p > .05$), and WASI full scale IQ ($F(2, 40) = 2.62, p > .05$) (Table 3-2). On average, our patient and control groups were around forty years of age, had slightly more than a high school education, and were composed largely of Caucasians. While controls had slightly higher full-scale IQ's, patients and controls did not differ significantly and overall intellectual functioning for all three groups was in the average range. The groups were predominantly right handed ($X^2(2) = 4.09, p > .05$), and were composed of slightly more women than men. Patient demographics are summarized in Tables 3-1 and 3-2.

Patient groups did not differ significantly on language dominance ($t(20) = .80, p > .05$) or age of seizure onset ($t(20) = .28, p > .05$). In general, temporal lobe and frontal lobe patients first developed seizures during their teenage years, though there was a wide range in the age of seizure onset amongst the patients (LTL $M=16.9, SD=15.2$; FL $M=13.5, SD=11.7$) (Table 3-2). Four of our TL patients and two of our FL patients had a history of psychiatric illness or diagnosis ($X^2(1) = .04, p > .05$). With regard to risk factors for epilepsy, thirty-five and twenty-eight percent of TL and FL patients had a family history of epilepsy, respectively ($X^2(1) = .10, p > .05$). Four TL patients had suffered a mild-to-moderate traumatic brain injury (TBI) and three of the FL patients experienced a mild-to-moderate TBI ($X^2(1) = .214, p > .05$). Slightly more TL patients had a history of child illness, though this was not statistically significant ($X^2(1) = 3.28, p = .07$). In general, the patients in this study did not have a history of febrile seizures ($X^2(1) = 2.14, p > .05$). Results of magnetic resonance imaging scans (MRI) revealed that ten of the TL patients had lesions consistent with mesial temporal sclerosis (MTS), and four of our FL patients had lesions or other neural anomalies ($X^2(1) = 5.57, p = .06$).

Epilepsy Patients

Pre-surgical patients

All pre-surgical patients selected for inclusion in this study had medication refractory epilepsy, documented by a board-certified neurologist at the University of Florida Comprehensive Epilepsy Program (UFCEP), and had experienced uncontrolled seizures under at least two medication regimens for at least an 18-month period. Participants were identified and recruited from the Neurology and Psychology Clinics at Shands Hospital and were screened to determine if they met inclusion criteria for the study, as approved by the Institutional Review Board (IRB) at the University of Florida. Inclusion criteria for all patients were: 1) 18 years of age or older, 2) documented epilepsy of either the temporal or frontal lobes, and 3) English as a

first language. Exclusion criteria were: 1) history of severe developmental disorder, or mental retardation resulting in $IQ \leq 69$, 2) history of Axis I psychiatric disturbance that resulted in inpatient hospitalization, 3) history of substance abuse/dependence, using DSM-IV criteria, 4) first language other than English, 5) lesional temporal-lobe epilepsy, or 6) presence of neurological disease in addition to epilepsy (e.g., radiation or chemotherapy for brain cancer in the past year; head trauma resulting in moderate to severe brain injury).

Patients were approached during either their Phase I (inpatient) video-EEG hospital stay or during their outpatient appointment in Neuropsychology, were presented with information about the study, and were asked if they would like to participate. Patients who agreed to participate gave informed consent and were tested in their hospital room as an inpatient in Shands hospital, or arranged testing on another day as an outpatient. In a few instances, testing could not be completed in one session and the patient was seen twice. Relevant demographic and medical information was also gathered from the participant's medical record. Relevant demographic information collected included age, gender, educational and occupational attainment, reported handedness, and ethnicity. Medical and seizure related variables were also recorded, and included age of first seizure, current medications regimen, seizure frequency and duration, and Wada memory and language dominance.

Over the course of eighteen months, approximately 150 pre-surgical patients were screened for the study via medical record review. Of the patients screened, we recruited 37 patients for the study, and of those patients, nine met full inclusion criteria for the present study; five were determined to have clearly lateralized left temporal lobe seizures and four were determined to have frontal lobe seizures (one right, two left, one bilateral). The remaining patients were determined to have non-epileptic seizures, seizures originating from another foci,

had right or mixed language dominance, were unable to be classified based on EEG recordings, or did not meet inclusion/exclusion criteria. Classification of seizure onset was determined by a board-certified neurologist who reviewed EEG recordings, clinical notes, and patient history. A summary of pre-surgical patient characteristics is included in Table 3-1 and Table 3-2.

Post-surgical patients

Post-surgical epilepsy patients were patients who had undergone surgery between 2000 and 2007, and had undergone either an anterior temporal lobectomy or a frontal cortical resection. These patients were recruited from the Departments of Neurosurgery and Neuropsychology at the University of Florida. Patients were identified through clinical databases and were selected for recruitment based on surgery type, medical record review, and date of surgery. Patients were recruited throughout the entire state of Florida.

Eligible patients were contacted via letter and provided with information about the purpose of the study, and its potential benefits and risks. They were provided with a self-addressed stamped postcard so they could indicate a desire to participate in the study, decline participation, or inquire further about study details. Patients who returned the postcard and were interested in participating or wanted more information were then contacted and given the opportunity to inquire further or schedule an appointment for cognitive testing. They were also screened briefly over the phone, after which the cognitive testing was arranged. Testing took place either at Shands Hospital, or if the patient was unable to travel to Gainesville, at the patient's home.

We screened approximately 1,000 patients who had undergone epilepsy-related neurosurgery (i.e., grids, resections, vagus nerve stimulator placement) between the years 2000 and 2007, and attempted to recruit approximately 125 by letter. The 125 persons contacted met

criteria for study enrollment and had current mailing addresses. Of the 125 contacted, approximately 50 responded with an interest in the study. Of the 50 who expressed interest, 30 were enrolled in the study. The remaining 20 patients either declined participation, were unable to be scheduled due to distance (> 5 hours away), or had travel, family, or work conflicts. Patients who participated in the study included nine patients with left temporal lobe resections, eighteen patients with right temporal lobe resections, and three patients who had undergone right frontal cortical resections. A summary of post-surgical patient characteristics is presented in Tables 3-1 and 3-2.

Healthy controls

We attempted to recruit family members of patients to serve as healthy volunteer (i.e. control) participants. When patients were recruited into the study, family members who were present were also informed about the study and given the option to be screened and participate as a member of the healthy control group. Post-surgical patients were informed on the phone about the option of family members participating. These individuals were often tested the same day as their family member, in a quiet room in Shands hospital, although several were tested on alternative dates. The remainder of our healthy controls were recruited in Gainesville, Florida through the use of fliers. When interested persons called to inquire about the study, they were informed of its purpose and procedures. They were also given a brief screening measure over the phone, consistent with IRB protocol, to determine if they were eligible to participate. Volunteers who were eligible and interested in participating engaged in a single testing session in a quiet testing room on the ground floor of Shands Hospital. During this session, volunteers first gave informed consent in person, and displayed an understanding of the testing procedures.

We attempted to match this group on age and education variables with our patient groups. Exclusion criteria for our controls were: 1) Age younger than 18, 2) history of severe developmental disability or mental retardation resulting in $IQ \leq 69$, 3) history of significant Axis I psychiatric disturbance that resulted in inpatient hospitalization, 4) history of substance abuse or dependence, 5) neurological illness (e.g., epilepsy, cerebrovascular disease, brain tumor, or head trauma resulting moderate to severe head injury), 6) current radiation or chemotherapy treatment (within 1 year), or 7) English as a second language.

We recruited twenty healthy controls to serve as volunteers in our study, eight of whom were family members of patients. A summary of control characteristics is included in Table 3-2.

Measures

Pre-surgical Patients

Typically, pre-surgical epilepsy patients are routinely administered a standard neuropsychological test battery (SNB) as part of their Phase I evaluation through the UFCEP. Most patients in our study were administered the SNB, though some were still in the process of their pre-surgical evaluation, and had not yet undergone clinical neuropsychological testing. As part of the SNB evaluation, subjects were administered tests of verbal and non-verbal memory, naming, fluency, “executive function”, visuoconstructional and visuospatial ability, attention, mood, and intellectual functioning. A list of measures traditionally administered is listed in Appendix A. Because many measures of interest are routinely administered to patients, and because re-testing patients on the same tests may have produced biased results, data for selected tests from the SNB was used in the current study. Measures of particular interest from the SNB included assessments of verbal memory (Logical Memory Stories from the Wechsler Memory Test-III [WMS-III]), language (Boston Naming Test [BNT]), and measures of “executive

function” (Wisconsin Card Sorting Test [WCST], Trail Making Test B [TMT B], and WAIS-III Digit Span. As a detailed description of many of these tests has been provided elsewhere (Lezak et al., 2004; Spreen & Strauss, 2006) and are reviewed briefly in Appendix A, they will not be described in further detail here.

The study measures were administered during a separate experimental testing session. These measures included a standard assessment of phonemic fluency, using three 60-second trials of word generation beginning with the letters “C”, “F”, and “L”. These phonemic probes were chosen to be distinct from the phonemic fluency trial (FAS) given during the SNB. Analyses were computed using the letter “C” only so that overall score would be comparable to that of other fluency measures (i.e., a single trial) although analyses with overall phonemic fluency score (i.e., C+F+L) were computed as well. The semantic fluency category (i.e. Supermarket items) was also chosen for its non-overlap with category, “Animals”, used in the SNB. As a hierarchically organized “supercategory”, supermarket items also permit an analysis of how patients’ fluency performance reflects retrieval from multiple semantic subcategories within a trial. Total score for this was also the number of correct words generated within 60 seconds. Clustering and switching was also evaluated, as described below.

Two experimental measures of fluency were administered. These measures are similar in administration time and scoring format to the previous measures, but differ in content. For the Action Fluency Test, participants were instructed to “List as many different things that [you] can think of that people can do”. The total score for this task is the number of correct target words, minus words denoting actions not performed by people (e.g., “molt” or “photosynthesize”). Questionable answers (homonyms, i.e. bear-bare), or words with ambiguous grammatical roles (e.g., table) were queried by the examiner to determine if the word was an intrusion, and was

scored accordingly. For the Famous Name Fluency Test, patients were instructed to “List as many different names of famous or well-known people that you can think of”, within a minute. Total score for this measure represented the number of correct names generated, minus names that could not be verified as famous persons, or intrusions or repetitions. As the format for these tests is similar, the administration of these four trials were counterbalanced across participants to account for any practice effect related to familiarity with test administration procedures (i.e. ABCD, DCBA, BDAC, CADB).

Qualitative analysis of the fluency protocols was completed in accordance with procedures described elsewhere (Troyer & Moscovitch, 2006). Briefly, clusters on phonemic fluency were defined as “successively generated words that begin with the first two letters, differ only by a vowel sound, rhyme, or are homonyms”. Semantic clusters were successively generated words that belong to a semantic subcategory, such as fruits, vegetables, meat, dried goods, and dairy, on supermarket fluency. Pilot data for our study revealed several naturally occurring clusters for action and name fluency. Clusters that emerged for action fluency were actions with the hands, feet/legs, facial gestures, grooming, household actions, work actions, emotional actions, actions involving language, and actions involving rest/relaxation. Clusters on famous name fluency were actors/actresses, politicians, sports figures, TV personalities, and musicians/singers. Additionally, on this test clusters could be defined temporally (TV personalities from the 1980’s) or by relationships (either personal or professional). As is customary, the cluster size was counted beginning with the second word within each cluster. See Appendix B for examples.

Switching scores were defined as transitions between clusters. Although some controversy exists around this scoring procedure, the raw number of switches is used as the score, rather than a score corrected for total words produced. Because switching is in part, responsible for overall

score, “adjusting switches according to the total words generated would be akin to correcting a cause for its effect” (Troyer & Moscovitch, 2006). To further emphasize this point, only raw switching score has been shown to produce meaningful data (Troyer et al., 1998b). Errors and intrusions were also included in scoring clusters and switches, as they are thought to provide useful information about the underlying cognitive strategy, but are always excluded from total overall fluency score. All fluency measures were double-scored to ensure accuracy in calculation of total score, errors, clusters, and switches.

Finally, apart from measures of cognitive functioning, all study participants were administered a brief questionnaire assessing demographic variables and the Edinburgh Handedness Inventory (Oldfield, 1971).

Additional Measures

In addition to the SNB and experimental measures listed above, two additional measures were given to study participants, The Action Naming Test (Obler & Albert, 1979), and a modified version of the Famous Faces Naming Test (Seidenberg et al., 2002). While these measures were not related directly to the primary aims of the study, they were administered to study participants for several reasons.

First, the experimental fluency paradigms proposed for this study were based in part on the naming literature which provides evidence for the category-specific deficits for actions and proper nouns/names. This body of naming literature posits distinct neural substrates for action naming (i.e. the frontal cortices) and person naming (i.e. the anterior temporal cortices of the left hemisphere). While there is similar (but preliminary) support for a comparable substrate for action fluency, this paradigm has not been used extensively in the literature, and has not been used in epilepsy populations. Further, the name fluency paradigm has not been used widely either in clinical or research arenas, apart from its use in an isolated number of case studies.

While we hypothesized these deficits would be apparent in a fluency paradigm, this extension has not yet been documented empirically. As such, the administration of naming analogues to our fluency paradigms allowed us to examine the pattern of deficits across naming and fluency tests in order to determine whether these unique category-specific deficits were isolated to naming, or are in fact, present in a fluency format as well.

Further, to our knowledge, the discrepancy between action and proper noun naming has not been explored in clinical epilepsy. The addition of these tests to our battery not only allowed for comparisons between naming and fluency paradigms, but also provided interesting information about various category-specific naming deficits which have been relatively unexplored in this population. Additionally, these naming tests were examined in conjunction with performance on a common object naming test, the BNT. A brief summary of these tests follows:

Action Naming: The Action Naming Test (ANT; Obler & Albert, 1979) contains a series of 55 black-and-white line drawings and was modeled after the Boston Naming Test (BNT). The items in this test, however, are a series of line drawings depicting actions. Sample actions include running, swimming, reading, curtsyng, and exercising. Test items range in difficulty in ascending order. Study participants were shown one picture at a time and were instructed to “tell what is happening in the picture”, preferably with one word responses. Similarly to the BNT, phonemic cues were given if the participant could not name the action, although successful naming of these items are scored as incorrect. Total score was the number of correct answers.

Famous Face Naming: The Famous Face Naming Test (Seidenberg et al., 2002) is a test that contains 100 black-and-white photographs of famous or well-known persons. A shortened version, containing 48 stimuli, was used for this study. The sub-set of stimuli was selected in

order to shorten test administration time, and make it comparable in length to our other naming tests. Stimuli were excluded from the study if they contained features that aided in identification (i.e. shirts with sports logos, war uniforms) or if the picture quality was deemed unsatisfactory. The stimuli are head-shots of famous persons sampled across decades since the 1960's, and contain images of athletes, presidents, actors, singers, politicians, and other newsworthy individuals. Sample faces include Kobe Bryant, Peter Jennings, Bob Barker, and Sting. Participants were initially asked if they recognized the person pictured and asked to provide any descriptive information about them (i.e., a comedian; the boxer who bit someone's ear off; the guy who hosts the New Year's Eve celebration in Times Square). They were then instructed to provide the name of the person in the picture if able. No cues were given. Because recognition of test items varied across participants, the total score was corrected for the number of famous faces recognized (i.e., correct names produced/recognized multiplied by 100; Drane et al., 2008).

Post-surgical Patients and Healthy Controls

Healthy volunteers and post-surgical patients were administered identical measures. This included four fluency tests (phonemic, semantic, action, and proper name), and two naming tests (action and famous faces). Because healthy controls and post-surgical patients had not been administered the SNB, additional testing was completed in order to obtain scores on measures of language, verbal memory, and executive function. Accordingly, they were administered the WASI, WMS-III LM, WCST, TMT-B, Digit Span from the WAIS-III, and BNT.

Pre-surgical, post-surgical and control participants were all compensated \$10.00 per hour of time and given a \$3.00 parking voucher. Average time spent in completion of this study was an hour for pre-surgical patients and two-and-a-half hours for post-surgical and control participants.

Table 3-1. Patient seizure characteristics

	EEG Interpretation/Resection Site	Surgery?
<u>Temporal</u>		
Pre	left temporal lobe and NES	No
Pre	bilateral (left > right) temporal	Yes
Pre	left temporal lobe	Yes
Pre	predominantly left temporal; 1 bilateral onset	Yes
Pre	left temporal lobe	Yes
Post	LATL	2001
Post	LATL	2006
Post	LATL	2004
Post	LATL	2003
Post	LATL	2002
Post	LATL	2003
Post	LATL	2006
Post	LATL	2003
Post	LATL	2005
<u>Frontal</u>		
Pre	left frontal lobe	Yes
Pre	right frontal lobe	Yes
Pre	bilateral frontal (left > right)	No
Pre	left frontal lobe	No
Post	Right Frontal Cortical Resection	2007
Post	Right Frontal Cortical Resection	2006
Post	Right Frontal Cortical Resection	2005

Table 3-2. Demographic and clinical characteristics

	LTL	FL	Controls
N	14	7	20
Age (years)	41.1 (13.2)	39.4 (12.9)	40.9 (15.7)
Education (years)	13.5 (2.6)	12.7 (2.5)	15.3 (2.7)
Gender (M/F)	6/8	3/4	8/12
Handedness (R/L)	12/1	6/1	11/1
Race (Cau./AA/His.)	12/1	7/0/0	16/3/1
Full-Scale IQ	96.1 (12.3)	94.0(14.6)	104.1 (9.8)
Language Dom. (L/R)	14/0	5/1	-
Age of Seizure Onset	16.9 (15.2)	13.5 (11.7)	-

Note: Means are presented, standard deviations in parenthesis.

CHAPTER 4 RESULTS

The results of our analyses are presented below as they relate to the specific aims of the study:

Aim 1

The first aim of our study was to characterize performance of patients with either frontal or temporal lobe epilepsy, and matched healthy controls on a panel of verbal fluency measures, including traditional measures of semantic and phonemic fluency, and experimental measures including action and proper name fluency.

Because we were interested in determining whether a panel of fluency tests incorporating traditional and experimental measures would detect group differences in our patient groups, we first computed separate multivariate analysis of variance tests (MANOVA's) for the tests we hypothesized would be sensitive to TL pathology (semantic and name fluency tests) and the tests hypothesized to be sensitive to FL pathology (action and phonemic fluency tests). Using Pillai's trace, there was not an overall group difference for our patients in fluency performance on phonemic and action tests ($V=.02$, $F(2, 18) = .135$, $p>.05$, $\eta^2=.015$). There was, however, an overall significant group difference for the semantic and name fluency panel ($V=.28$, $F(2, 18) = 3.54$, $p=.05$, $\eta^2=.28$). Results of the omnibus MANOVA's are presented in Table 4-2. Univariate test results are presented below.

When comparing patients and controls, healthy controls outperformed patients on all measures of fluency including standard measures of semantic (supermarket) and phonemic (letter fluency) fluency, as well as experimental measures of fluency, including action and famous name tests. Overall univariate tests of analysis of variance (ANOVA's) revealed significant main group effects for action ($F(2, 38) = 7.90$, $p=.001$, $\eta^2=.54$) and name fluency ($F(2, 38) = 17.02$

$p=.000$, $\eta^2=.68$) tests, and there were trends for significance for the semantic ($F(2, 38) = 2.94$, $p=.065$, $\eta^2=.36$) and phonemic fluency ($F(2, 38) = 2.73$, $p=.07$, $\eta^2=.35$) measures. Planned post-hoc contrasts revealed significant group differences between controls and both patient groups on action fluency (LTL < Control, $p<.005$; FL < Control, $p<.05$) and name fluency (LTL < Control, $p<.0001$; FL < Control, $p<.01$). When combining scores across phonemic fluency trials (“C” plus “F” and “L” trials), healthy controls outperformed TL patients ($F(2, 38) = 5.08$, $p=.011$, $\eta^2=.45$), but the difference in score was not significant for controls compared to FL patients. Contrary to our hypothesis, performance differences between frontal and temporal groups were not statistically significant on any of the four fluency measures. However, there was a large effect size for group differences between TL and FL patients on name fluency ($d=.75$), with FL patients generating more names than TL patients. Means and standard deviations for patients and control groups are presented in Table and Figure 4-1.

Repeated-measures ANOVA revealed that both FL ($F(3, 18) = 12.37$, $p<.001$) and TL ($F(3, 39) = 30.72$, $p<.001$) patients performed best on semantic fluency, followed by action fluency, phonemic fluency, and name fluency. FL patients performed significantly better on semantic fluency as compared to phonemic ($p=.005$) and name fluency ($p=.009$). TL patients performed significantly better on semantic fluency compared to action ($p=.002$), phonemic ($p=.001$), and name fluencies ($p=.001$). TL patients also performed worse on name fluency compared to action fluency ($p=.01$). There was a trend for significant differences between name and phonemic fluency ($p=.06$) though this finding did not reach statistical significance (Figure 4-1).

Aim 2

The second aim of the study was to examine the clinical utility and predictive validity of experimental fluency measures in identifying seizure location and discriminating between patient groups.

Before attempting to dissociate patients groups, we sought to determine how well performance on our panel of fluency measures would dissociate patients from controls. Because our variables were not significantly collinear (Supermarket: Tolerance=.771, $VIF=1.29$, Action: Tolerance=.46, $VIF=2.13$, Name: Tolerance=.48, $VIF=2.10$, Phonemic: Tolerance=.51, $VIF=1.95$) we used forward-entry logistic regression with all four fluency measures included to predict patient status. This overall model was significant, and a good fit for the data ($X^2(4) = 27.9, p < .001$). This model correctly classified seventeen healthy controls as controls, and classified eighteen patients as patients. The model incorrectly classified three controls as patients and three patients as controls, resulting in an overall classification accuracy of 85%. Sensitivity and specificity were both 85%.

We then calculated multiple logistic regressions to determine how well differences in fluency performance predicted patient group membership. Again, we initially used forward-entry logistic regression with all four fluency measures included as predictors. Entry of all four fluency variables into the model revealed a non-significant overall effect ($X^2(4) = 7.66, p = .10$) and a poorly fitted model. This model correctly classified twelve patients with TLE as TLE patients, but incorrectly classified two TLE patients as having FLE. This model also correctly classified three FLE patients as FLE patients, though incorrectly classified four FLE patients as TLE patients. Overall, 86% of TLE patients were accurately classified, whereas 43% of FLE patients were accurately classified, resulting in a total correct classification accuracy of 71% (Table 4-3). Because of the poor fit of the model, we subsequently used backwards entry logistic

regression to determine suitability of the variables for the model. Results of this analysis provided two additional models. The first model included action, name, and semantic fluency, and showed a trend for significance ($X^2(3) = 7.66, p=.053$). The final model fit the data well ($X^2(2) = 7.66, p=.02$), and included only semantic ($p=.07$) and name fluency ($p=.053$), removing the non-significant action ($p=.91$) and phonemic fluencies ($p=.97$). This final model correctly classified twelve TLE patients as having TLE, and incorrectly classified two as having FLE. This model also correctly classified five patients with FLE as having FLE, and incorrectly classified two as having TLE, resulting in an overall correct classification rate of 81%. This model correctly classified 86% of patients with TLE as having TLE, and 71% of patients with FLE as having FLE. Classification statistics for both models are presented in Tables 4-3 and 4-4.

The predicted probabilities from this final model were subsequently used to predict a receiver operating characteristic (ROC) curve (Figure 4-2). Using the final predictors in our model (semantic and name fluency tests only), the overall predicted area under the curve was .806.

Aim 3

The third aim of the study was to examine the convergent and discriminant validity of the experimental fluency tests with other tests sensitive to frontal and temporal lobe dysfunction, and to examine the relationship amongst fluency measures.

We first examined the relationship amongst fluency measures for patient groups only and then for patients and controls combined. When patients and controls were combined, there were positive, statistically significant correlations amongst all fluency measures. Semantic fluency was significantly correlated with name fluency ($r=.407, p=.008$), action fluency ($r=.446, p=.003$), and phonemic fluency ($r=.382, p=.01$). Name fluency was also significantly positively correlated with action ($r=.662, p<.001$) and phonemic fluency ($r=.628, p<.001$). Performance on

action fluency was also correlated with phonemic fluency performance ($r=.637, p<.001$). The correlation matrix for patients and controls is presented in Table 4-6.

When we examined patients alone, there were no statistically significant correlations between semantic and phonemic fluency ($r=.076, p>.05$), name and phonemic fluency ($r=.144, p>.05$), semantic and action fluency ($r=.210, p>.05$), or name and action fluency ($r=.285, p>.05$). However, there were trends for significance for some correlations. As predicted, semantic and name fluencies were positively correlated with a moderate effect size ($r=.415, p=.06$). There was also a positive correlation of moderate effect between action and phonemic fluencies ($r=.390, p=.08$). These results are presented in Table 4-5.

We also examined the relationship between performance on fluency tests and performance on traditional neuropsychological measures thought to be sensitive to the presence of language-dominant TL and FL dysfunction. These included the Boston Naming Test (BNT) and Logical Memory (LM) I and II (WMS-III), and Digit Span (DS) (WAIS-III), Wisconsin Card Sorting Test (WCST), and Trails B (TMT-B), respectively. Measures of particular interest included the number of categories correctly completed and number of perseverative responses on the WCST, and total time to completion and total errors on the TMT-B.

We examined these relationships separately for patients, and then for patients and controls combined. When patients and controls were combined, there were statistically significant positive correlations between semantic and name fluency and scores on the BNT, LM-I, and LM-II, such that better performance on fluency tests was associated with better performance on these measures ((semantic and BNT: $r=.449, p<.01$; semantic and LM-I: $r=.542, p<.001$; semantic and LM-II: $r=.601, p<.001$) and (name and BNT: $r=.582, p<.001$; name and LM-I: $r=.624, p<.001$; name and LM-II: $r=.638, p<.001$)). Semantic fluency performance was negatively correlated

with TMT-B time ($r=-.382, p<.05$) and TMT-B errors ($r=-.455, p<.01$). Finally, better name fluency was significantly associated with better performance on DS ($r=-.401, p<.01$).

Action and phonemic fluency were also positively correlated with performance on the BNT, LM-I, and LM-II. Action fluency performance was significantly positively correlated with DS total score ($r=.493, p<.01$) and WCST-Categories ($r=.429, p=.01$). Action fluency was significantly negatively correlated with TMT-B time ($r=-.485, p<.01$) and WCST-perseverations ($r=-.381, p<.05$), such that persons who performed worse on this test had more perseverations on the WCST and took longer to complete TMT-B. Phonemic fluency scores exhibited a similar pattern; significant correlations were found between phonemic fluency and DS total score ($r=.527, p=.001$), TMT-B time ($r=-.430, p<.01$), and WCST-perseverations ($r=-.392, p<.05$).

When examining patients separately, semantic fluency remained positively correlated with LM-II ($r=.467, p=.05$), and there was a moderate positive correlation and trend for significance with LM-I ($r=.416, p=.08$). There was also a moderate negative correlation and trend for significance with TMT-B errors ($r=-.424, p=.07$). Additionally, action fluency remained negatively correlated with TMT-B time ($r=-.453, p<.05$), and positively correlated with BNT ($r=.543, p<.05$) and LM-II ($r=.476, p<.05$). There was a trend relationship between action fluency and WCST-categories ($r=.448, p=.07$). Scores on phonemic fluency were positively correlated with DS total score ($r=.494, p<.05$), negatively correlated with TMT-B time ($r=-.510, p<.05$), and there was a trend for significance for WCST-perseverations ($r=-.408, p=.12$) and BNT ($r=.415, p=.08$). There were no significant correlations with name fluency. Correlation matrices are presented in Tables 4-7 and 4-8.

Aim 4

The fourth aim of our study was to determine whether a qualitative analysis of fluency performance, including the number of clusters, cluster size, and switches, would dissociate

performance of FL and TL patients. Additionally, we sought to ascertain whether TL and FL patients displayed fewer clusters and switches on fluency tests thought to most sensitive to temporal and frontal lobe dysfunction, respectively.

We examined the number of clusters, switches, and mean cluster size for each individual fluency measure separately. On the semantic fluency task, controls, TL patients, and FL patients generated a similar number of clusters ($F(2, 36) = .574, p = .56, \eta^2 = .17$) and switches ($F(2, 36) = 3.14, p = .06, \eta^2 = .38$), and did not differ significantly on the size of clusters generated ($F(2, 36) = .57, p = .57, \eta^2 = .17$). Controls and patients also performed similarly on measures of phonemic fluency, with no significant group differences on number of clusters ($F(2, 38) = .05, p = .94, \eta^2 = .06$), switches ($F(2, 38) = 2.87, p = .07, \eta^2 = .36$), or cluster size ($F(2, 38) = .40, p = .67, \eta^2 = .14$). On action fluency clusters, significant group differences were found, ($F(2, 36) = 4.1, p = .025, \eta^2 = .43$) and planned contrasts revealed that controls generated significantly more clusters than TL patients ($p = .05$), but not FL patients. Controls also switched between clusters more frequently than patients ($F(2, 36) = 4.9, p = .01, \eta^2 = .45$), with planned contrasts revealing controls switched more frequently than TL patients ($p = .01$). There were no significant group differences in action fluency cluster size ($F(2, 36) = 2.25, p = .12, \eta^2 = .33$). On name fluency, there were significant group differences for total number of clusters ($F(2, 36) = 3.1, p = .05, \eta^2 = .38$) and switches ($F(2, 36) = 7.75, p < .01, \eta^2 = .54$), and a trend towards significance for mean cluster size ($F(2, 36) = 2.45, p = .10, \eta^2 = .34$). Planned contrasts revealed that TL patients generated significantly fewer name clusters than controls ($p = .05$), and that both TL ($p < .01$) and FL ($p < .05$) patients switched less frequently than controls. While not statistically significant, there was a large effect ($p = .16, d = .71$) showing that TL patients also generated fewer clusters than FL patients on name fluency. Despite the non-significant finding for group differences in

cluster size, there were also large effect sizes for between-group differences for TL and FL patients ($d=.88$), and TL patients and controls ($d=.73$), with TL patients generating smaller clusters than both groups. Data for clusters, switches, and mean cluster size across fluency type are presented in Figures 4-3 through 4-5.

Additional Study Aims

While not the primary aims of our study, we were interested in examining the relationship amongst performances on naming analogues of our fluency paradigms, and between naming and fluency performance.

Because scores on naming tests were not normally distributed, we used non-parametric tests (Kruskal-Wallis and planned Mann-Whitney contrasts) to assess for group differences in naming performance. Number of actions correctly named on the Action Naming Test differed significantly by group ($H(2) = 19.54, p < .001$), with controls correctly naming more actions than both TL patients ($U=21, z=-4.19, p < .001$) and FL patients ($U=21, z=-2.74, p < .01$). Contrary to our hypotheses, the two patient groups did not differ significantly in their ability to name actions ($U=46, z=-.225, p > .05$).

Performance on the Famous Face Naming Test was assessed by computing a “percent correct” score, which was the total number of items correctly named out of the items correctly recognized, multiplied by 100. There were significant group differences in the ability to name famous faces ($H(2) = 18.95, p < .001$). TL patients were able to accurately name only 33% of the faces they recognized, as compared to 53% for FL patients and 71% for controls. As expected, both TL and FL patients performed significantly worse than controls on this test (TL: $U=22, z=-4.13, p < .001$; FL: $U=32.5, z=-2.07, p < .05$) and consistent with our hypotheses, patients with TLE performed significantly worse than patients with FLE ($U=22.5, z=-1.97, p < .05$).

On a test of common object naming (Boston Naming Test), controls were able to correctly name more items without cueing than both FL and TL patients ($H(2)=17.48, p<.001$; TL: $U=16, z=-3.97, p<.001$; FL: $U=15, z=-2.16, p<.05$). On average, controls correctly named 55/60 items, FL patients named 49/60, and TL patients named 43/60. Naming differences between FLE and TLE patients were not statistically significant ($U=18, z=-1.44, p>.05$), but a moderate effect size ($r=.33$) suggests FL patients performed better than TL patients.

Spearman rho non-parametric correlations were conducted to examine the relationship amongst naming measures and between fluency and naming performance. When combining patients and controls, performance on the three naming tests was highly positively correlated. Performance on the ANT and BNT was also highly correlated with fluency test performance regardless of fluency type. Famous faces naming score was significantly correlated with scores on semantic fluency, name fluency, and action fluency. When we examined patients alone, BNT score was significantly correlated with ANT ($r=.542, p<.01$) and FFNT ($r=.508, p=.01$) scores, but there was only a trend relationship between ANT and FFNT scores ($r=.314, p=.08$). Neither BNT nor FFNT score was significantly associated with performance on fluency measures. Performance on the ANT was significantly positively associated with phonemic fluency ($r=.505, p=.01$) and name fluency ($r=.372, p<.05$) scores. Correlations are presented in Tables 4-10 and 4-11.

Table 4-1. Performance on fluency measures

	LTL	FL	Controls
N	14	7	20
Phonemic (C)	10.1 (4.3)	9.60 (2.6)	13.3 (5.4)
C+F+L	27.7 (11.3)	28.7 (4.7)	38.4 (11.1)*
Semantic	18.1 (5.4)	16.5 (4.2)	22.5 (6.5)
Action	11.7 (4.5)	12.7 (2.9)	18.3 (5.8)**
Name	6.1 (3.5)	8.8 (2.3)	14.5 (4.7)**

Note: Means are presented, standard deviations in parenthesis.

** $p \leq .01$ for controls versus LTL and FL

* $p < .05$ for controls vs LTL

Table 4-2. Multivariate analysis of fluency performance in patients

	Pillai's Trace	<i>F</i>	<i>p</i>	Partial Eta-Squared
Phonemic + Action Model	.015	0.14	.87	.015
Semantic + Name Model	.280	3.54	.05	.282

Table 4-3. Four fluencies predicting patient group membership

	LTL (predicted)	FL (predicted)	% correct
LTL (actual)	12	2	85.7
FL (actual)	4	3	42.9
			71.4

Table 4-4. Semantic and name fluencies predicting patient group membership

	LTL (predicted)	FL (predicted)	% correct
LTL (actual)	12	2	85.7
FL (actual)	2	5	71.4
			81.0

Table 4-5. Correlations coefficients for fluency measures (patients only)

	(1)	(2)	(3)	(4)
(1) Phonemic Fluency	1.00			
(2) Semantic Fluency	.076 .74	1.00		
(3) Name Fluency	.144 .54	.415 .06	1.00	
(4) Action Fluency	.390 .08	.210 .36	.285 .21	1.00

Pearson correlation coefficients are presented followed by significance values.

Table 4-6. Correlations coefficients for fluency measures (patients and controls)

	(1)	(2)	(3)	(4)
(1) Phonemic Fluency	1.00			
(2) Semantic Fluency	.388 .01*	1.00		
(3) Name Fluency	.628 .00*	.407 .01*	1.00	
(4) Action Fluency	.637 .00*	.446 .00*	.662 .00*	1.00

Pearson correlation coefficients are presented followed by significance values.

* $p \leq .01$

Table 4-7. Correlations amongst neuropsychological measures (patients only)

	DS	TMT-B	TMT-B Err.	WCST- Cat.	WCST- Pers.	BNT	LM-I	LM-II
Semantic	-.108 .64	-.311 .18	-.424 .07	.034 .89	-.095 .73	.143 .78	.416 .08	.467 .05*
Action	.365 .11	-.453 .04*	-.285 .24	.448 .07	-.363 .17	.543 .02*	.326 .19	.476 .04*
Name	.103 .66	.066 .78	-.157 .52	-.171 .51	.077 .78	.124 .62	.233 .35	.240 .33
Phonemic	.494 .02*	-.510 .02*	-.282 .24	.231 .37	-.408 .12	.415 .08	-.290 .24	.095 .70

DS=Digit Span total score; TMT-B=Trail Making Test-B time; WCST=Wisconsin Card Sorting Test;

BNT=Boston Naming Test, LM=Logical Memory

Pearson correlation coefficients are presented followed by significance values.

* $p \leq .05$

Table 4-8. Correlations amongst neuropsychological measures (patients & controls)

	DS	TMT-B	TMT-B Err.	WCST- Cat.	WCST- Pers.	BNT	LM-I	LM-II
Semantic	.194 .243	-.382 .028	-.455 .01**	.191 .27	-.212 .23	.449 .01**	.542 .00**	.601 .00**
Action	.493 .00**	-.485 .00**	-.260 .13	.429 .01**	-.381 .02*	.683 .00*	.638 .00*	.602 .00*
Name	.407 .01**	-.253 .13	-.224 .20	.161 .36	-.242 .17	.582 .00**	.624 .00**	.638 .00**
Phonemic	.527 .00**	-.430 .01**	-.285 .10	.222 .21	-.392 .02*	.566 .00**	.328 .05*	.453 .01**

DS=Digit Span total score; TMT-B=Trail Making Test-B; WCST=Wisconsin Card Sorting Test; BNT=Boston Naming Test, LM=Logical Memory

Pearson correlation coefficients are presented followed by significance values.

** $p \leq .01$

* $p \leq .05$

Table 4-9. Performance on naming measures

	LTL	FL	Controls
BNT	43.4 (6.7)	48.6 (5.0)	54.9 (4.7) ^a
ANT	47.4 (3.7)	48.0 (4.1)	53.1 (1.9) ^a
FFNT	33.3 (21.1)	53.9 (20.4) ^b	71.9 (16.9) ^a

Note: Means are presented, standard deviations in parenthesis for ANT and BNT. FFNT is presented as % correct x 100.

^a Controls >TL and FL

^b FL > TL

Table 4-10. Correlations between naming and fluency measures (patients and controls)

	FFNT	ANT	BNT	Phonemic Fluency	Semantic Fluency	Name Fluency	Action Fluency
FFNT	1.00	.651 .00*	.664 .00*	.234 .07	.368 .01*	.433 .00*	.350 .01*
ANT	.651 .00*	1.00	.853 .00*	.413 .00*	.513 .00*	.565 .00*	.489 .00*
BNT	.664 .00*	.853 .00*	1.00	.403 .01*	.456 .00*	.596 .00*	.628 .00*

Pearson correlation coefficients are presented followed by significance values.

* $p \leq .01$

Table 4-11. Correlations between naming and fluency measures (patients only)

	FFNT	ANT	BNT	Phonemic Fluency	Semantic Fluency	Name Fluency	Action Fluency
FFNT	1.00	.314	.508	.136	.177	.003	.116
	.	.08	.01**	.27	.22	.49	.30
ANT	.314	1.00	.542	.505	.283	.372	.191
	.08	.	.01**	.01**	.10	.04*	.20
BNT	.508	.542	1.00	.265	.056	.013	.363
	.01**	.01**	.	.14	.41	.47	.06

Pearson correlation coefficients are presented followed by significance values.

** $p \leq .01$

* $p \leq .05$

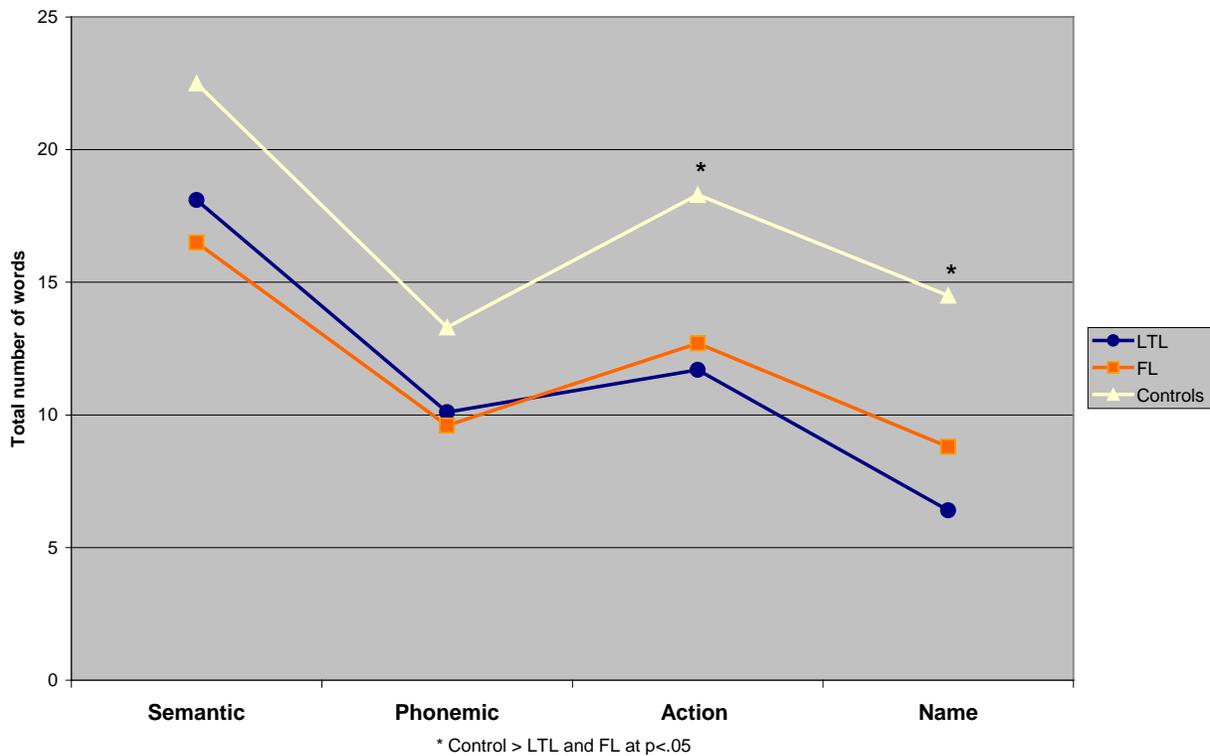


Figure 4-1. Overall fluency performance across groups

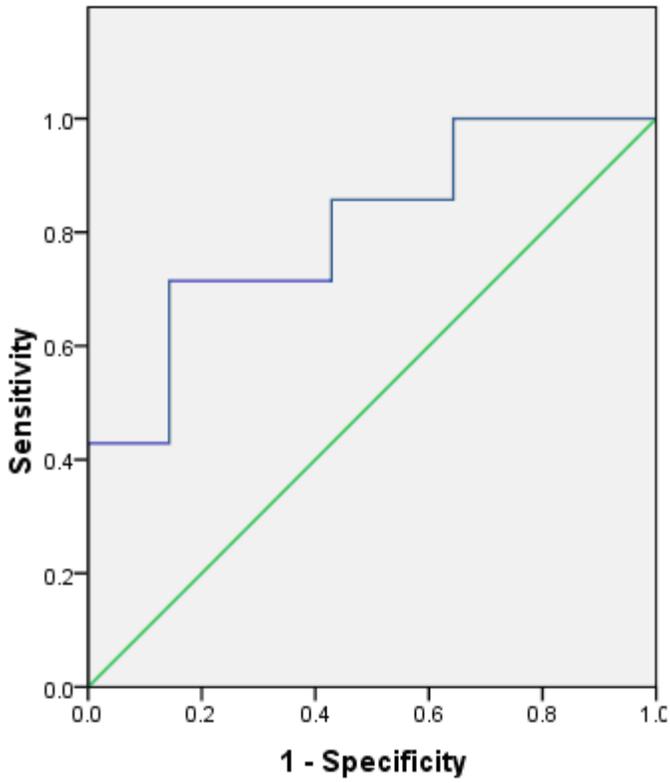


Figure 4-2. Receiver operating characteristic (ROC) curve for semantic and name fluencies predicting patient group

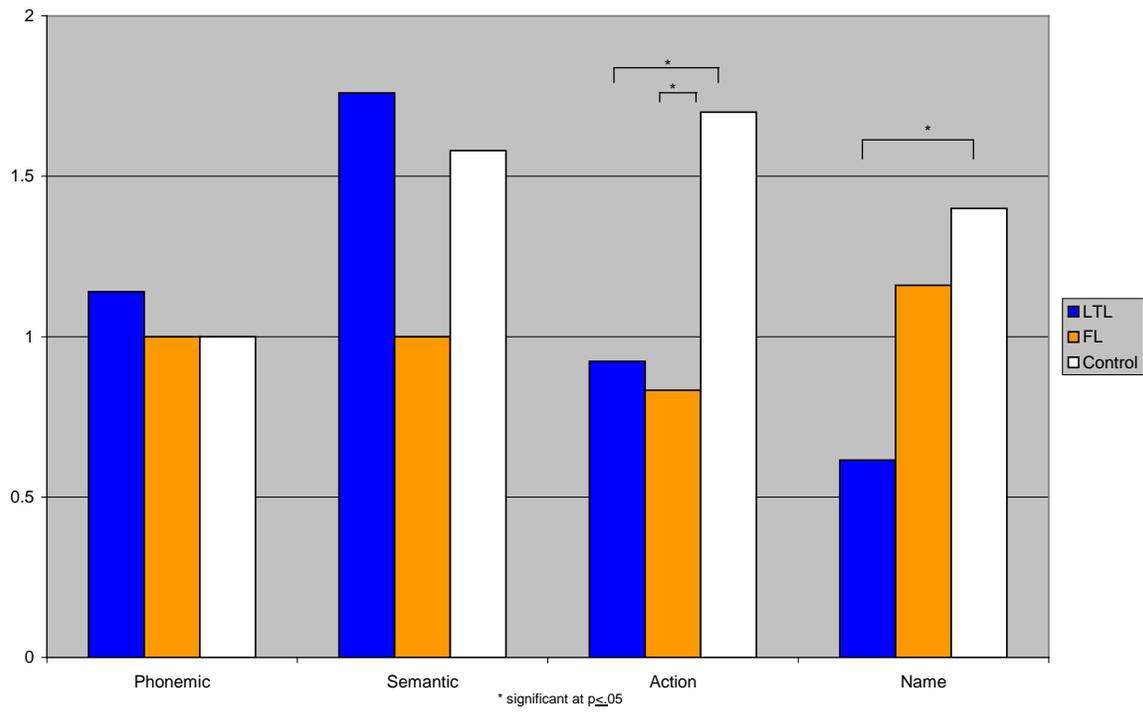


Figure 4-3. Mean number of clusters by group

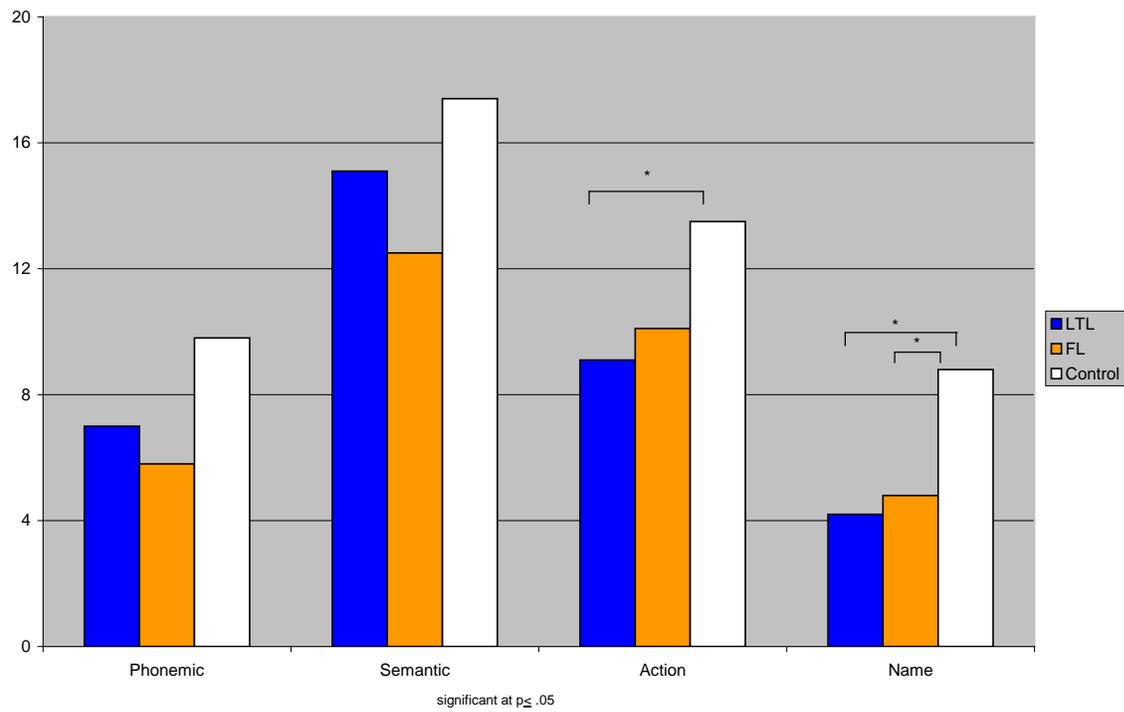


Figure 4-4. Mean number of switches by group

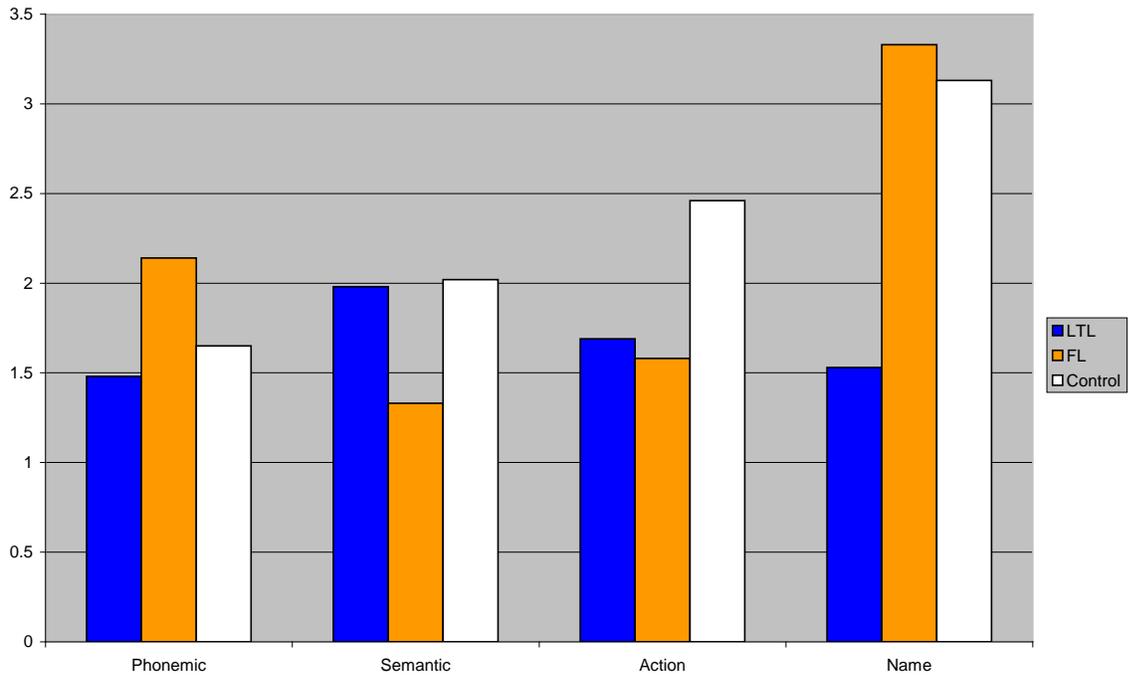


Figure 4-5. Mean cluster size by group

CHAPTER 5 DISCUSSION

Summary of Findings

The current study was undertaken to help understand differences in cognitive impairment in patients with left temporal lobe epilepsy versus epilepsy localized to the frontal lobes. More specifically, we sought to elucidate a distinct pattern of fluency test performance that would discriminate between these two patients groups. We were interested in examining differences in both traditional semantic and phonemic fluency performance, as well as performance on two experimental fluency tests, action and name fluency. Scientific literature positing different neural networks for retrieval of action words and proper names suggested that incorporation of this material-specific content into traditional fluency test paradigms would improve measurement of the unique cognitive deficits associated with localized neural dysfunction. Furthermore, we hoped that an examination of fluency strategy, including generation of clusters, cluster size, and switches between clusters, would provide useful diagnostic information about our patients. In other words, by manipulating the fluency retrieval demands involved and examining the cognitive strategies employed, we hoped to more accurately discriminate between patient groups, in addition to advancing our understanding about the neural specificity of the brain regions involved.

The first primary aim of this study was to characterize performance of patients with frontal or left temporal lobe epilepsy, and matched healthy controls on a panel of verbal fluency tests that included clinical measures of semantic and phonemic fluency, and experimental measures of action and proper name fluency. We hypothesized that patients with epilepsy would perform worse on all of these measures than would our healthy controls. We also believed that patients with temporal lobe epilepsy would evidence impaired semantic fluency (but not phonemic

fluency), while patients with frontal lobe epilepsy would demonstrate impairments on phonemic fluency (but not semantic fluency). With regard to our experimental fluency measures, we believed that overall fluency score on action and proper noun fluency would doubly dissociate patients with frontal and temporal lobe epilepsy, with frontal lobe patients performing worse on action fluency and temporal lobe patients exhibiting comparative deficits on tests of proper name fluency. These hypotheses were only partially confirmed. As expected, controls generated more words across fluency tests than both patient groups. Interestingly, however, the findings were statistically significant only for the experimental action and name fluency tests, with controls outperforming patients with both types of epilepsy. While there were trends for significance and moderate effect sizes for patient and control group differences on semantic and phonemic fluency, these effects did not reach a level of statistical significance. Contrary to our predictions, there were no statistically significant differences between the two epilepsy groups on any of the fluency measures. However, there was a moderate effect size for name fluency, with TL patients generating fewer proper names than FL patients, suggesting meaningful group differences that could not be adequately detected because of our sample size. In both patient groups, participants generated the most words for supermarket fluency, followed by action, phonemic, and name fluency, a finding consistent with past literature (Piatt et al., 1999).

Our second aim was to determine the predictive validity of traditional and experimental fluency measures in predicting patient group membership. We predicted that both traditional and experimental fluency measures would adequately discriminate between patients with frontal and temporal lobe epilepsy, and that the multivariate combination of our four fluency measures would have superior predictive ability above and beyond either traditional or experimental fluency measures alone. These hypotheses were not confirmed in our study population. We

found that our fluency panel did an inadequate job of accurately predicting patient group membership. Our four-fluency model better predicted temporal lobe than frontal lobe involvement, but was still a poor fit for our data. Our final model, which fit the data well, included only semantic and name fluency and accurately predicted 86% and 71% of our TL and FL patients, respectively. This suggests that the tests removed from the model (action and phonemic fluency) did not offer additional predictive value beyond the variables in our final two-predictor model.

The third aim was to examine the convergent and discriminant validity of our experimental fluency measures using traditional neuropsychological measures of frontal and temporal lobe functioning as criterion variables. We hypothesized that performance on tests of common and proper noun fluency would be more related to measures also sensitive to the integrity of the temporal lobe (i.e., related to semantic stores), while action and phonemic fluency scores would exhibit small to moderate relationships with traditional measures of executive function. When examining performance for controls and patients combined, we found strong positive correlations amongst all four fluency measures, suggesting the presence of a common source of variance in fluency performance regardless of the retrieval demands. When only patients were included in the analysis, phonemic and action fluency were moderately positively correlated, as were name and semantic fluency. Name and semantic fluency were uncorrelated with both action and phonemic fluency, suggesting that in patients with localized neuronal dysfunction, fluency performance was differentially impaired based on the category-specificity of the material to be retrieved.

When we examined relationships between our fluency measures and other measures of neuropsychological functioning for our patients and controls, there were significant positive

correlations between all four measures and scores on tests of language and verbal memory (BNT, LM-I and LM-II). This was consistent with our predictions for name and semantic fluency, but not action and phonemic fluency. As predicted, action and phonemic fluency were correlated with measures of executive function (Digit Span number correct, TMT-B time, and WCST-perseverations). Contrary to our prediction, semantic fluency was correlated with performance on TMT-B (time and errors) and name fluency was related to performance on Digit Span.

The fourth aim of the present study was to determine whether a qualitative analysis of fluency performance, including number of clusters, switches, and cluster size, would dissociate performance of patients with FLE, TLE, and healthy controls. Based on existing literature, we hypothesized that patients with TLE would exhibit reduced cluster size, particularly on tests that carry a heavier semantic burden (name fluency, semantic fluency) and that patients with FLE would evidence a reduced number of switches, primarily on tests of phonemic and action fluency. These hypotheses were only partially confirmed. There were no significant group differences for clusters, switches, or cluster size for phonemic or semantic fluencies. On action fluency clusters, controls generated more clusters than did either patient group, though this was statistically significant for only for the control versus TL comparison. Controls also switched more frequently than TL patients. There were no significant group differences in action fluency cluster size. On name fluency, TL patients generated significantly fewer name clusters than controls, and both TL and FL patients switched less frequently than controls. There was a large effect indicating TL patients also generated fewer clusters than FL patients. Large effect sizes also revealed that TL patients generated smaller clusters than FL and controls on name fluency, which is consistent with our a priori hypothesis.

The body of naming literature posits distinct neural substrates for action naming (i.e. the frontal cortices) and person naming (i.e. the anterior temporal cortices of the left hemisphere), and while there is preliminary support for a comparable fluency substrate, these paradigm have not been used extensively in the literature. Because of this, we were interested in examining the relationship between our fluency measures and related naming measures, including the Boston Naming Test, Action Naming Test, and Famous Faces Naming Test. We hypothesized TL patients would exhibit more prominent naming deficits than FL patients and controls on measures of common object naming and famous faces naming, but that patients with FLE would exhibit deficits on our measure of action naming. Our naming hypotheses were also only partially confirmed. As expected, controls were able to correctly name more items on all three naming measures than both FL and TL patients. On the BNT, no statistical differences were found between patient groups, but a moderate effect size suggested that TL patients were more impaired at naming common objects than FL patients. TL patients were also worse at naming familiar famous faces as compared to patients with FL epilepsy; in fact, they named 20% less than patients in the FL group. Contrary to our predicted results, FL and TL patients did not differ in their ability to name actions on the ANT.

When examining the relationship amongst naming measures, performance was highly correlated for patient and controls. Performance on the ANT, BNT, and FFNT was also highly correlated with fluency test performance regardless of fluency type, except for FFNT and phonemic fluency. When we examined patients alone, BNT score was significantly correlated with ANT and FFNT, but no significant relationship was established between ANT and FFNT. Neither BNT nor FFNT score was significantly associated with performance on fluency measures. Performance on the ANT was associated with phonemic and name fluencies.

In sum, while many of our hypotheses were confirmed in the present study, a significant portion were also disconfirmed, particularly as it relates to performance on traditional measures of fluency, action fluency, and our qualitative analysis of fluency performance. Interpretations of our study findings are presented below.

Interpretation of Findings

Semantic and Phonemic Fluency

We found that our patient groups did not show differential phonemic and semantic fluency performance and that neither measure was a good predictor of patient group membership. These findings were inconsistent with our hypotheses, but not entirely surprising, and part of the reason we undertook the present study comparing our experimental tests to these traditional measures. While there are many studies that show successful semantic fluency performance relies more on the integrity of the left temporal lobe and phonemic fluency is sensitive to the presence of frontal lobe pathology, there are numerous studies that fail to show this effect. Thus, the current results are in good company.

Studies have shown equivalent test performance on semantic fluency in patients with anterior and posterior lesions. In an epilepsy population, Drane et al. (2006) found that patients with frontal lobe seizure foci were more impaired than a group with temporal lobe epilepsy on measures of semantic fluency, contrary to their hypotheses that predicted more impairment in the temporal lobe group. Another study comparing patients with focal anterior and posterior lesions found that both types of lesions produced impairments on semantic, or category, fluency (Stuss et al., 1998). Additional studies employing a variety of populations have found a similar pattern of equivalently impaired semantic fluency in frontal and temporal lobe patients (Baldo & Shimamura, 1998; Costello & Warrington, 1989; Owen et al., 1990; Randolph et al., 1993). These authors have argued that rapid word generation, regardless of retrieval demand, can be

impaired by frontal lobe lesions. These studies purport that patients with executive dysfunction are unable to perform effective, strategic, and efficient searches for words, irrespective of whether the search is semantically or phonemically driven (Baldo et al., 2006; Baldo & Shimamura, 1998; Troyer et al., 1998).

A similar pattern has also been established for phonemic fluency tests (Stuss et al., 1998; Miller, 1984; Pendelton et al., 1982; Perret, 1974). Emory and Alvarez (2006) found that the bulk of studies in their meta-analysis of frontal-lobe lesion patients reported significantly poorer phonemic fluency scores compared to controls, however, a significant percentage found similar impairment on phonemic fluency in patients with non-frontal lobe lesions. Henry and Crawford (2006) found that phonemic fluency deficits were largest in patients with left frontal lesions, but that patients with non-frontal left hemisphere lesions were often similarly impaired, suggesting phonemic fluency performance may be determined both by an executive factor *and* a verbal component. In fact, this theory was put forth decades ago by Ramier and Hécaen (1970), who hypothesized that successful performance on phonemic fluency is determined by an “executive” factor located within the frontal lobes and a “verbal” factor mediated more generally by the language-dominant hemisphere.

Equivalently impaired performance on semantic and phonemic fluency in patients with frontal and temporal lesions suggests that these tests are sensitive to the presence of frontotemporal damage, but not specific to more localized impairment within this region. Adequate performance on semantic and phonemic fluency tasks is likely multi-factorial, and may depend on verbal contributions from the language dominant hemisphere, efficient search and retrieval strategies dependent on frontal lobe functioning, and a general cognitive factor, or “g”. This was reflected in our study; semantic and phonemic fluency performance was significantly

correlated with measures of verbal/semantic ability but was also related to measures thought to tap an executive component. Further, WASI Full-Scale IQ was a strong predictor of fluency score ($R^2=.26$, and $.30$ for semantic and phonemic fluency) suggesting that fluency performance, regardless of the retrieval demands, could also be nonspecifically depressed in both groups due to an overall cognitive impairment associated with chronic, uncontrolled seizures (Jokeit & Ebner, 2002).

That being said, intact verbal and semantic memory abilities and efficient search/retrieval strategies likely contribute in different ways to performance on these measures, with the former being more important to semantic fluency performance and the latter to phonemic fluency (Butters et al., 1987; Gleissner & Elger, 2000; Janowsky et al., 1989; Jurado, et al., 2000; Martin, Loring, Meador, & Lee, 1990; Monsch et al., 1992; N’Kaoua, 2001; Rosser & Hodges, 1994; Stuss et al., 2000; Troster et al., 1995; Troyer et al., 1998). This implies that the original hypotheses pertaining to our patient groups may be valid, but due to the nature of our study population, were unable to be borne out within the constraints of our current study. Power analyses based on data from Troyer and colleagues (1998) suggested that between-group differences could be detected on semantic and phonemic fluency with a sample of seven-to-ten patients with left-lateralized frontal and temporal lesions. While studies do not provide conclusive evidence that phonemic and semantic fluency performance can be doubly-dissociated, the discrepancy between our findings and those projected are most likely due to differences in our sample populations. Many studies that have found group differences in TL versus FL populations, including Troyer et al. (1998), included patients with circumscribed lesions from stroke and tumors, in addition to etiologies such as traumatic brain injury and seizure surgery. Similar to our study, her study included a mixed population of relatively acute (i.e., post-stroke)

and chronic patients (i.e., post-surgical intractable epilepsy). Contrary to ours, however, her patients all had stable (> 3months post-injury) and focal (dorsolateral prefrontal cortex; superior medial frontal; inferior medial frontal) lesions. Our study population was different from this in many regards. A pre-surgical epilepsy population likely suffers from both diffuse (e.g., a history of intractable seizures with propagation to surrounding brain regions) and focal (e.g., localized onset) impairments, and can experience overall cognitive depression due to epilepsy medications or the duration of their disease (Jokeit & Ebner, 2002; Loring, Marino, & Meador, 2007; Nichols, Meador & Loring, 1993). Additionally, most of the pre-surgical patients in our study were actively experiencing seizures, which contributed to the chronicity and pervasiveness of their cognitive dysfunction, making their pattern of neuronal damage dramatically different than patients who experience an acute injury such as a stroke.

Furthermore, due to recruitment constraints, our study included both pre- and post-surgical epilepsy patients and patients with both right and left frontal lesions, both of which are factors that could explain our lack of predicted group differences. By including both pre- and post-surgical patients, some of whom had circumscribed, defined, and stable lesions and some of whom did not, we introduced more variance into our study sample. The inability to include only left frontal patients in our study was possibly the single biggest explanatory factor for our non-significant findings. The left frontal lobe, particularly the dorsolateral prefrontal region (DLPFC), has been shown to be the most critical region to phonemic fluency performance (Milner, 1964; Pendelton et al., 1982; Perret, 1974; Stuss & Levine, 1998), while the right DLPFC appears to be a less important region. Patients with right DLPFC damage (Miceli et al., 1981; Miller, 1984; Ramier & Hacean, 1970; Troyer et al., 1998) display impaired phonemic fluency, but to a lesser degree than their left hemisphere counterparts. There is some evidence

that the right DLPFC contributes to “on-task” behavior important to fluency performance, such as monitoring, retrieval success, and inhibition of extraneous information (Cabeza and Nyberg, 2001). However, the left dorsolateral prefrontal regions are also thought to play a key role in these same processes in addition, perhaps, to its preferred access to the lexicon. Imaging data supports primary involvement of the left DLPFC, and secondary involvement of right frontal structures, in phonemic fluency performance (Frith et al., 1995; Parks et al., 1988). Damage to the superior medial frontal regions in both the right and left hemisphere can impair fluency performance (Stuss & Levine, 2002; Troyer et al., 1998) but are again thought to play a secondary role to the DLPFC. Unfortunately, the nature of our patient group did not allow for more precise localization of pathology within particular sectors of the frontal lobe. However, because of our mixed sample of left and right frontal lobe epilepsy patients, the demands of phonemic fluency tests (i.e., search and retrieval, organization of unstructured orthographic information, flexibility) may not have been as taxing as they might have been in a more pure sample of left-lateralized patients, thereby reducing the extent to which impairments were found.

Action Fluency

Action fluency is a relatively new test construct that grew out of the naming literature in agrammatic aphasics showing impaired retrieval of words denoting actions in the presence of spared object naming (Miceli, 1984). The lesion literature also supports deficits in action naming associated with damage to the frontal cortices. For instance, Damasio & Tranel (1993) demonstrated a double dissociation in the performance of patients with anterior temporal cortex damage (who had difficulty naming pictures of objects) compared to another patient with left premotor damage (who was unable to name actions depicted in line drawings). Deficits in action naming have been inconsistently demonstrated in patients with fronto-temporal dementia and

various other lesions (Damasio & Tranel, 1993; Monsch et al., 1992; Ostberg et al., 2005; Silveri et al., 2003).

Action *fluency*, on the other hand, has been relatively unstudied until recently. Preliminary studies with HIV and Parkinson's dementia patients have demonstrated impairments in action fluency compared to semantic and phonemic fluency. These studies have also supported the idea that action fluency is a construct of executive functioning (Piatt et al., 1999a and 1999b; Woods et al., 2005a and 2005b). These findings were only partially replicated in our patients with frontal epilepsy. We found that frontal and temporal lobe epilepsy patients performed similarly on both action word naming and action fluency. As a result, action fluency score was a poor predictor of patient group membership. We did find support for the notion that, at best, action fluency may indeed be a construct sensitive to "executive functioning", or that it at least had some relationship with other measures purported to be sensitive to executive function. Action fluency, more so than phonemic fluency, was strongly related to performance on the WCST-Categories, WCST-Perseveration, Digit Span, and Trails B time, providing evidence of convergent validity amongst measures of executive functioning. Also noteworthy, however, is the fact that action fluency scores were moderately correlated with measures of verbal/semantic ability, including the BNT and WMS-LM II. This has not been found previously in the literature, but has also not been explored fully as Woods et al. (2005) did not include measures of naming or verbal retrieval in their analysis of correlates of action fluency. Our findings, in conjunction with previous findings of Woods and Piatt, indicate that adequate performance on this test is multi-determined, related both to executive functioning abilities and to verbal abilities. Neuroimaging studies also support the notion that both anterior (frontal operculum, left premotor, left prefrontal, left insula) and posterior (left mesial occipital cortex, left supramarginal and posterior

temporal regions) cortices may play a role in the retrieval of words denoting actions (Damasio et al., 2001; Tranel et al., 2001).

Impaired action fluency performance in our temporal lobe group may be in part, attributed to this factor. Another possible explanatory factor is that temporal lobe epilepsy patients commonly exhibit difficulty with components of executive functioning (response disinhibition, impulsivity, set loss, and difficulties with mental flexibility and abstract thinking) secondary to propagation of seizure related ‘neural noise’ from temporal to frontal regions via the medial and lateral limbic circuits (Hermann & Seidenberg, 1995). Moreover, a growing body of literature suggests that structural and functional abnormalities in TLE patients exist not only within TL structures, but also in regions outside of the temporal lobes. For instance, significant white matter changes have been demonstrated in extratemporal cortex, including the frontal lobes (Hermann et al., 2003; Oyegbile et al., 2006). This pattern of impaired executive functions has been well documented on the WCST, TMT, and Stroop paradigms, amongst others (Hermann, Wyler, and Richey, 1988; Martin et al., 2000; McDonald et al., 2005; Trennery & Jack, 1994; Corcoran & Upton, 1993). In fact, many of these studies have found patients with language dominant temporal lobe epilepsy to be equally or even more impaired than those with frontally mediated seizures. This explanation has also been used in part to explain similarly impaired performance on phonemic fluency tests, and may also extend to our tests of action fluency. Again, the possibility remains that our temporal lobe patients with longstanding seizure disorders may also have exhibited depressed cognitive profiles on multiple cognitive domains due to the cumulative effect of uncontrolled seizures (Jokeit & Ebner, 2002).

Additional differences in our study population and those of Woods and Piatt may help to explain our discrepant findings. The action fluency construct has been used only in studies of

patients with frontal and subcortical disease, namely HIV and Parkinson's Disease. Both populations can exhibit significant executive dysfunction, but also deficits in motor and cognitive processing speed, which are not necessarily hallmarks of focal seizure disorders. The impact of cognitive slowing on fluency performance was not accounted for in studies by Piatt or Woods, despite significant relationships between action fluency scores and scores on measures of cognitive and motor processing (Woods et al., 2005). It may be the case that the combination of executive dysfunction and cognitive slowing in these populations differentially affected action fluency performance compared to semantic fluency, for instance, which could help explain the intact performance of our frontal lobe epilepsy patients. This could be the case for action fluency in particular given the hypothesized "executive" burden of the test. Finally, as with semantic and phonemic fluency performance, our mixed sample of left and right frontal patients probably reduced our ability to find a significant effect that may have otherwise been present in a solely left-frontal sample.

With regard to the two predominant theories that exist to explain the discrepancy between retrieval of action versus object words, the first states that knowledge about objects and actions is stored in association cortices adjacent to the primary cortical regions that process these classes of stimuli (Damasio & Tranel, 1993; Perani et al., 2009). As such, object knowledge is stored in cortical regions adjacent to the occipito-temporal visual stream, while action knowledge is stored adjacent to structures in the frontal lobe including the prefrontal cortex, premotor cortex, and supplementary motor area and focal lesions to these areas can disrupt successful retrieval of action words. The second theory holds that the deficit is largely executive in nature, and relates to the difficulty of "mentally coordinating and manipulating the large amount of information related to action-words" (de Nóbrega, Nieto, Barroso, & Montón, 2007; Grossman, 1998; Silveri

et al., 2003; White-Devine et al., 1996). This latter theory also posits that as with all fluency paradigms, verbal ability may mediate overall fluency score regardless of executive capacity.

In reality, these theories are not mutually exclusive and the scientific literature provides support for both. It is likely the case that while acute lesions to premotor or association motor cortices disrupt successful retrieval of action words, insult to other neuronal regions or pathways is also sufficient to impair this ability. The current study provides greater support for the second theory, though the former cannot be tested fully because our group was not comprised of patients with focal lesions in the aforementioned regions.

Name Fluency

Generally speaking, our findings with regard to performance on tests of proper name generation were consistent with our hypotheses. Name fluency proved to be the most demanding fluency measure for all patients and controls, but TL patients were differentially impaired on this test, suggesting a true deficit in this ability rather than a main effect of task difficulty. Patients with left-temporal lobe epilepsy, both pre- and post-surgical, showed the weakest performance on this measure, generating on average only six accurate responses in the span of a minute, which was statistically different than controls, and different from FL patients based on measures of effect size. Indeed, name fluency was the strongest predictor of group membership in our regression analysis. In fact, classification accuracy statistics for name fluency alone were rather comparable to the model that additionally included semantic fluency, with the two-predictor model correctly classifying only two additional TL patients.

As we expected, in our patient groups, name fluency was related to the traditional measure of semantic fluency, but not to measures of action or phonemic fluency, providing evidence for the convergent and discriminant validity of the measure as closely allied with semantic retrieval. When we examined patients and controls combined, our correlations show that this measure is

strongly related to other tests assessing verbal and/or semantic abilities such as the BNT, LMI and LMII, reflecting good external validity for a measure thought to be sensitive to temporal lobe functioning. However, for patients alone, no significant relationships with measures of language or memory, both largely mediated by language-dominant temporal structures, were seen. While surprising initially, this finding is consistent with studies showing that deficits on famous face naming tests may be dissociated from deficits on measures of common object naming (Drane et al., 2008). In other words, this test construct may be mediated less by general verbal abilities than most fluency tests, and may rely more upon a unique “semantic” factor not tapped by other assessment instruments. This feature may make famous face naming particularly sensitive and specific to anterior temporal lobe functioning. A roughly equivalent pattern of results was exhibited when we embedded this test construct in a confrontation naming paradigm, lending further support to our hypothesis that generation of proper names is dependent on the integrity of temporal lobe structures. For patients and controls, significant relationships were found amongst the FFNT and all other fluency and naming tests, but when we examined patients alone, the relationship with the BNT emerged as the only significant relationship, followed by the weak correlation with the ANT. On this famous faces naming measure, temporal lobe epilepsy patients were able to correctly generate names for only 1/3rd of the familiar faces, compared to roughly 1/2 and 3/4 for the frontal lobe patients and controls, respectively.

Our findings provide support for the notion that the anterior portion of the left temporal lobe plays a critical role in the ability to generate names or apply labels to people or objects, and is particularly important in the case of proper names. Existing lesion studies (Fukatsu et al., 1999; Glosser, Salvucci, & Chiaravalloti, 2003; Martins & Farrajota, 2007) and functional imaging data (Gorno-Tempini et al., 1998; Grabowski et al., 2001; Tranel, 2006; Tranel,

Grabowski, Lyon, & Damasio, 2005; Tsukiura et al., 2002) provide support for this hypothesis. This area has been deemed a “convergence zone” by Damasio, Tranel, and colleagues (Damasio, et al., 1996; Damasio et al., 2004; Tranel, Damasio, & Damasio, 1997; Tranel et al., 2003). These authors propose that the anterior temporal lobe serves as a region that helps bind multi-modal sensory and motor input from our surroundings, leading to the development of amodal concepts. Since names are arbitrary labels that denote members of conceptual categories, damage to this area can produce category-specific deficits in word retrieval.

Specific deficits have been shown for animals and “unique entities” such as people and landmarks (Damasio, 1996; Fukatsu et al., 2000; Glosser, Salvucci, & Chiaravalloti, 2003; Gorno-Tempini et al., 1998; Grabowski et al., 2001; Milders, 2000; Tranel, 2006). The apparent difficulty with retrieval of the latter has to do with the “semantic uniqueness” of the object or person (Semenza & Zettin, 1989; Glosser, Salvucci, & Chiaravalloti, 2003; Grabowski et al., 2001; Tranel, 2006). Whereas common names refer to concepts, or a set of attributes that are shared by multiple entities within the same concept, proper names do not inherently contain attributes in and of themselves and are merely expressions by which we refer to an individual person or item. Because of this, it is thought that widespread neural networks support the representation of common nouns, while proper nouns are thought to hold rather fragile “associations” with their unique reference (Gorno-Tempini & Price, 2001; Martins & Farrajota, 2007). This distinction is particularly salient when contrasting between generation of common versus proper names on fluency and naming tests, and may explain why the latter are emerging as particularly sensitive to anterior temporal lobe damage. For instance, the semantic representation for the word “dog” (an appropriate response for the semantic fluency category “Animals”) is likely much more substantial, perhaps encompassing the words “beagle”, “pug”,

“dalmation”, “poodle”, and the like, whereas “Bob Dole”, “Marilyn Manson”, “Hulk Hogan”, and “Mother Theresa” all refer to singular, unique entities, not linked in cohesive semantic networks.

Our findings suggest that a name fluency paradigm may offer particular value in detecting the type of impairment that is common in both pre- and post-surgical language-dominant temporal lobe epilepsy patients. Name fluency score appears to be less affected by frontal lobe fluency processes such as efficient monitoring/searching/flexibility than are other measures of fluency, including semantic fluency, and are more contingent upon adequate functioning of the temporal lobe semantic networks. It may also be the case that a name fluency paradigm could reveal impairments that are not evident on other types of neuropsychological tests. Drane and colleagues (2008) have described patients with subjective complaints of post-surgical naming deficits who perform at expectation on measures of common object naming but show impairment on their famous-faces naming test. This suggests that traditional clinical measures, which focus only on object naming, may not adequately tap the type of abilities commonly disrupted by TLE or anterior-temporal lobectomy.

Qualitative Analysis of Fluency Performance

Unfortunately, we did not find that an analysis of qualitative fluency performance provided much additional useful information about the patient groups in our study. In general, the pattern of qualitative fluency performance echoed the quantitative analysis of performance; no significant group differences were found on measures of semantic and phonemic fluency. TL patients generated fewer clusters and switches on action fluency than controls, and fewer and smaller clusters than controls and FL patients on name fluency. Both patient groups switched less frequently than controls on name fluency; all results that mirror the quantitative impairments just discussed.

This raises the following question: are number of clusters, cluster size, and switches actually proxies for overall fluency performance or are they independent measures of the functional integrity of the temporal and frontal structures? There is evidence to support the former (proxy) view, as qualitative measures of fluency have been shown to be highly tied to overall fluency score in an Alzheimer's and Parkinson's sample (Troyer et al., 1997). This pattern was replicated in our data; measures of qualitative performance, across group and fluency task, were correlated with overall number of words generated. Most studies of clustering and switching as measures of temporal and frontal lobe functioning have found a similar pattern (Troyer et al., 1998a, 1998b; N'Kaoua et al., 2001). When studies have found overall group differences in fluency score, they also have reported differences in clustering and switching across tasks. When group differences were not found for overall total score, differences did not tend to emerge on clustering and switching analyses. Troyer addresses this issue directly (1998a), and argues against this point, but does recognize that switching score and words generated may be correlated variables because the "number of words generated were always associated with group differences in switching." In earlier work, she provides direct evidence that decreased clustering does lead to an overall decrease in total words produced (Troyer et al., 2007). It is certainly plausible that two patients with the same overall fluency score of ten, for instance, could produce very different patterns of performance (i.e., *orange-grape-apple-cheese-yogurt-butter-paper towel-napkin-toilet paper* versus *orange-hot dog-paper towel-pencils-wine-beer-champagne-cat food-cheese-carrots*), thereby achieving differing scores on clustering and switching. However, the data from our study and others finds this scenario less likely when differences in overall score are not apparent.

An alternative explanation is that clusters and switches are not necessarily proxies of overall fluency score, but that clusters/switches and overall score are both proxies of temporal and frontal lobe functioning. Under this premise, the lack of significant findings across most of qualitative (and quantitative) measures has to do with the underlying level of localized neuronal dysfunction in our patient groups. Again, the heterogeneous nature of our sample, our frontal lobe group in particular, may have lessened our ability to replicate the effects found in other studies of patients with more circumscribed lesions of the left or bilateral frontal lobes. Troyer and colleagues (1998a) were able to compare performance across subgroups of frontal patients (i.e., left dorsolateral prefrontal cortex (LDLPFC), right dorsolateral prefrontal cortex (RDLPFC), superior medial frontal (SMF) cortex, inferior medial frontal (IMF) cortex) and found between-group differences that support this assertion; specifically, switching was impaired in the LDLPF and combined SMF groups, but not the RDLPF and IMF groups. This finding is consistent with other neuroimaging and cognitive studies showing impaired initiation of behavior, poor cognitive flexibility, and perseverations are most strongly related to the left dorsolateral frontal, inferior frontal, and anterior cingulate regions (Hirschorn & Thompson-Schill, 2006; Troster et al., 1998). Most likely, our sample included patients whose damage transcended these functional boundaries, muddying any profile that may have resembled those previously reported with regard to switches in particular.

Despite our non-significant findings between patient groups with regard to switches, and clusters on action, phonemic and semantic fluency, the reduced cluster number and size on name fluency in our temporal lobe group is an interesting finding, and consistent with our a priori hypothesis. Unfortunately, our small sample size kept these numbers from reaching statistical significance, but our large effect sizes suggest they are indeed meaningful findings. Our results

show that not only did patients with left temporal lobe epilepsy have difficulty generating proper names, they also had more difficulty than frontal lobe patients or controls in linking response items to each other in a semantically meaningful way. When they were able to successively generate semantically-related names, they tended to be able to generate fewer of these names before exhausting the semantic network in which they reside. These findings on name fluency are particularly interesting, as this was the measure we hypothesized to be most sensitive to impairment of semantic networks subserved within anterior temporal structures. Consistent with our hypotheses pertaining to overall name fluency performance, this reduced ability to generate semantically related proper names in particular may reflect the disruption or degradation of semantic memory stores within the temporal lobes. The finding of reduced clusters and cluster size on tests sensitive to temporal-lobe functioning has been reported frequently; Troyer has hypothesized that the best indices for discriminating patient groups were “phonemic-fluency switching...and semantic-fluency clustering” (Troyer et al., 1998a, 2000; Reverberi, Laiacona, and Capitani, 2006). This observation indicates that a combination of overall fluency score and an analysis of clustering and switching by fluency type may provide useful information about the underlying cognitive impairments in various patient groups.

Limitations of the Present Study

There were a number of factors that limited the present study and may have affected our ability to find the results we predicted. We have previously discussed most of these, but they will be reviewed herein. First and foremost, our small heterogeneous sample likely negatively impacted our study. Unfortunately, even with an extended recruitment time of eighteen months, we were unable to collect data on enough pre-surgical patients with left lateralized temporal and frontal lobe epilepsy. This may have been due to a number of factors, though the primary reason was decreased patient flow through Shands inpatient epilepsy monitoring unit. To supplement

patient flow, we concurrently recruited post-surgical epilepsy patients who had undergone surgery between 2000 and 2007. By employing this recruitment strategy, we were able to meet our expected sample size for our left-temporal group. However, we were still not able to recruit enough participants with left frontal epilepsy and in fact, no additional left frontal patients were able to be recruited through post-surgical mailings. The alternative to this solution was to include patients with frontally-localized epilepsy, regardless of laterality. Through this means, we were able to meet our projected sample size in both patient groups.

However, this likely limited our ability to test out our hypotheses as they pertained to left frontal-lobe functioning in particular. Many of our predictions with regard to tests of frontal-lobe functioning (i.e., phonemic and action fluency) were based on the notion that the left frontal region, the DLPFC specifically, plays a key role in successful fluency performance. This could not adequately be explored in our current sample because of the mixed nature of our group. While other areas of the frontal lobes, including the bilateral portions of the superior medial frontal lobe may also be involved in fluency performance, the lack of specificity in our sample prohibited us from testing the contribution of various regions to task behavior. Nonetheless, we did still find interesting differences related to some of our study hypotheses, largely related to tests sensitive to temporal-lobe functioning, which were less impacted by the heterogeneous nature of this sample. Many of these findings still only reached clinical, not statistical significance, implying our study may still have been slightly underpowered.

That being said, the pre-surgical patients we screened and recruited into our study were consecutive admissions to a clinical epilepsy center and are representative of the actual type of patients neuropsychologists are asked to assess for pre-surgical evaluations. Patients with epilepsy often do not have clearly localized seizures. They may have multiple seizure foci,

seizures that propagate from one brain region to another, a mixed pattern of focal and generalized events, or have a mixed profile of electrographic and non-epileptic seizures, all of which can complicate the localization/lateralization process. These patients also frequently present with psychiatric illness, past surgeries, significant head injury, and comorbid diagnoses of learning disability or mental retardation, and take multiple medications, all obscuring the diagnostic picture even farther. So in reality, the sample with which we tested our measures and hypotheses was not ideal, but in many ways, most representative of the type of patient on which these measures would be used clinically. While this limits our ability to make conclusions about the sensitivity and validity of our measures, it provides useful information about how a typical patient with frontally-mediated seizures might perform.

One of the initial points of the current study was to assess the utility of our standard fluency measures and develop new measures more sensitive to the presence of frontal or temporal lobe dysfunction. This is particularly important as it relates to our ability to provide useful information to epileptologists and epilepsy neurosurgeons about laterality and localization of seizure onset based on cognitive test patterns. Though we can make statements about the sensitivity and specificity of these measures as they relate to frontal and temporal functioning in general, we cannot decisively comment on their ability to predict seizure localization pre-surgically. All of the patients in our final sample had medication-refractory epilepsy, though a portion had undergone resective surgery to alleviate their seizures. Cortical resections for epilepsy tend to be rather focal removing only the epileptogenic foci if possible, though often surrounding tissue may also be removed or compromised. For our post-surgical patients, surgical intervention tended to be curative, as the majority were seizure free following their resections. This alleviation of seizures likely promoted overall brain health, but could have also introduced

more cortical damage than was initially caused by the seizures themselves. This could have obscured the true cognitive picture that may have been present in a strictly pre-surgical population, making conclusions about performance in that population difficult. Unfortunately, our samples of pre and post-surgical patients were too small to conduct any meaningful analyses to compare group differences with regard to demographic, medical, or cognitive variables for these patients.

Finally, our small sample size prohibited us from examining other factors of interest that may have impacted our fluency and naming results. This includes an analysis of the role of age of seizure onset, the absence/presence of lesions, propagation of seizure activity, and effects of anti-epileptic medication.

Directions for Future Research and Clinical Use

Phonemic and semantic fluency measures are two of the most commonly used tests by neuropsychologists. These tests have well established, demographically corrected norms, making them appropriate for Caucasians and African-Americans, and persons from their first through their ninth decade of life (Delis, Kaplan & Kramer, 2001; Heaton, Miller, Taylor & Grant, 2004). These tests have been used to characterize the cognitive performance of virtually every type of patient, including those with dementia, epilepsy, TBI, infection, and tumor. They obviously offer clinical value as part of neuropsychological assessments and will continue to be used in the future.

The current study suggests that used individually, they may not offer definitive localizing value with regard to clinical epilepsy patients. As previously mentioned, the sample of epilepsy patients in this study is thought to be representative of the overall population of patients who present for evaluation in surgical epilepsy centers. In our sample, scores on tests of phonemic and semantic fluency were overlapping, and did not distinguish between patient groups, which is

part of the usual question that motivates pre-surgical neuropsychological assessments. As such, configural interpretation of cognitive profiles should include fluency tests along with other tests sensitive to the presence of localized neuronal dysfunction.

Action fluency is a relatively new construct in the literature and has only been used in limited populations at the present time. These populations tend to have both frontal and subcortical disease involvement, making it difficult to pinpoint the exact underlying process that is impairing action fluency performance. Furthermore, no definitive theory has emerged in the literature that is sufficient to explain the neural underpinnings supporting this construct to the exclusion of other viewpoints. Complicating the theoretical debate is that fact that cognitive, neuroimaging, and lesion data exist that support both main theories, raising the possibility that they may not be mutually exclusive. Our findings do not provide significant clarity to this debate.

To our knowledge, there have been no published studies that have examined the action fluency construct in a surgical epilepsy population. Based on the current findings, there appears to be limited support for the use of an action fluency paradigm in clinical epilepsy at the present time. To the extent that our sample represents a real-life population, the test appears to have little predictive power and its' sensitivity to frontal-lobe functioning remains questionable. A significant amount of theory-driven research needs to be done to show the specificity of this test and its' construct validity before it is used clinically. More specifically, a series of well-designed studies contrasting patients with circumscribed premotor/supplementary motor and DLPFC lesions would shed light on the most important cortical regions subserving test performance. Additional neuroimaging studies employing an action fluency paradigm compared to generation of proper nouns, for instance, would also help elucidate brain regions critical to action word

generation in particular. Contrasting patients with isolated focal or subcortical disease would also provide clarification the relative role of these structures in action fluency performance. Finally, a more controlled study comparing patients with frontal lobe versus temporal lobe epilepsy would help to elucidate the contribution of these various structures to action fluency performance.

To the best of our knowledge, this is the first study that has used a proper noun generation paradigm embedded within a fluency test, as this construct has been studied specifically within a naming format to this point. The naming literature has offered preliminary support for this construct, possibly as more unique to anterior temporal functioning than tests employing naming of common objects. The results that we found are promising and provide converging evidence that this may indeed be a paradigm, both in the naming and fluency format, that shows great promise with a variety of clinical populations.

Additional research with this fluency and naming paradigm is absolutely warranted. First, further psychometric studies need to be undertaken to help establish the construct validity of these measures and show the convergent and discriminant validity with other tests in both clinically and normally-functioning populations. In order for the test to be used clinically, adequate normative studies need to establish performance in healthy controls on the fluency paradigm. Development of a standardized naming paradigm could prove to be more difficult due to stimulus selection, which is something that was carefully considered in the present study. Naming stimuli have to be free of identifying features (i.e., uniforms, for example), stratified across decade, and controlled for type and amount of fame (i.e., sports, news, politics, movies). As we found in the present study, familiarity with face stimuli will vary across person and must be accounted for. This should be then be contrasted with naming ability in order to gain an

accurate appreciation of true word-retrieval deficits. Additional complications with developing a clinical famous faces naming task include the fact that it must be updated over time to account for famous persons now obsolete, or new famous persons in popular media.

Nonetheless, the famous name paradigm, particularly the fluency format, should be studied in additional clinical epilepsy populations to document its utility with this sample. Preliminary studies could utilize post-ATL populations, patients with circumscribed lesions, to show the sensitivity and perhaps specificity to the anterior temporal lobe. The paradigm could then be advanced to pre-surgical populations to ascertain its ability to aid in the differential diagnosis of refractory seizure populations, the point of the present study. This paradigm could also offer significant value to other clinical populations apart from epilepsy. Similar to patients with left temporal lobe epilepsy, patients with Alzheimer's dementia evidence disease of temporal lobe structures and perform poorly on naming and semantic fluency paradigms. Name fluency may prove to be sensitive to degenerative disease of the temporal structures as well. Of more interest are patients with "pre-Alzheimer's", or mild cognitive impairment (MCI). Most of these patients evidence focal impairment in one domain, but later go on to progress to full blown dementia. As of late, the focus of research has turned to identifying these patients in a pre-clinical state so that early intervention may be undertaken. As many of these patients report that their earliest problem is difficulty retrieving names of people, this measure may provide a useful clinical tool in identifying early deficits not tapped by other assessment measures.

Finally, our findings with regard to qualitative fluency performance were discordant than most of those presented in the literature, but may be explained by overall lack of fluency differences across groups. As this finding of related qualitative-quantitative performance has been reported elsewhere, it is at least a likely possibility that these scores are dependent. Given

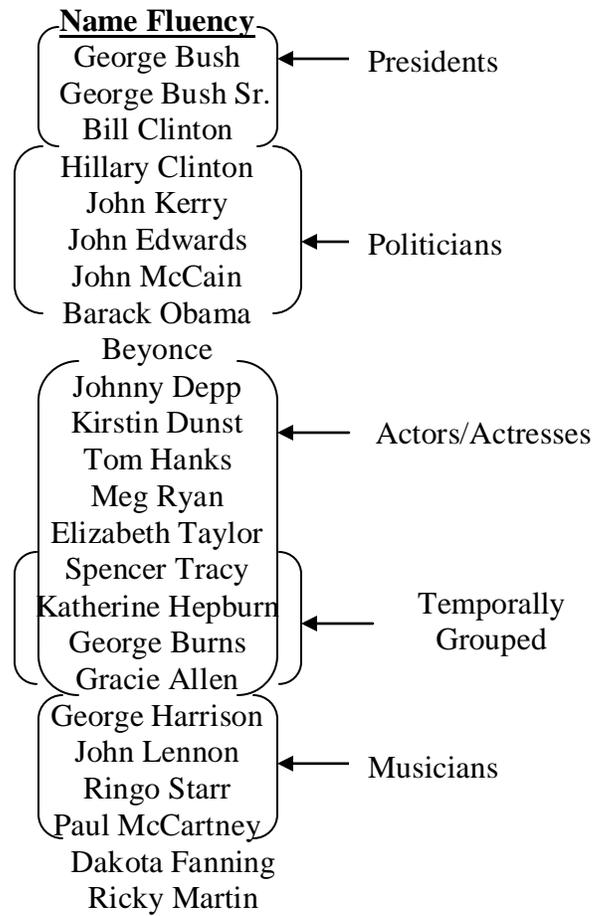
that, the clinical utility of clusters and switches necessarily depends on how sensitive fluency measures are at detecting the presence or absence of pathology.

Clustering and switching analyses are easy to compute and do not require significant additional work once familiarity with the scoring criteria has been established, making them relatively easy measures to consider clinically. However, additional work needs to be done to establish a normative basis for these measures before they are used in impaired populations. At the present time, only one study has attempted to norm these measures (Troyer, 2000). Should normative data be established, these measures could be used clinically in conjunction with overall fluency score to help provide useful information about localization of function.

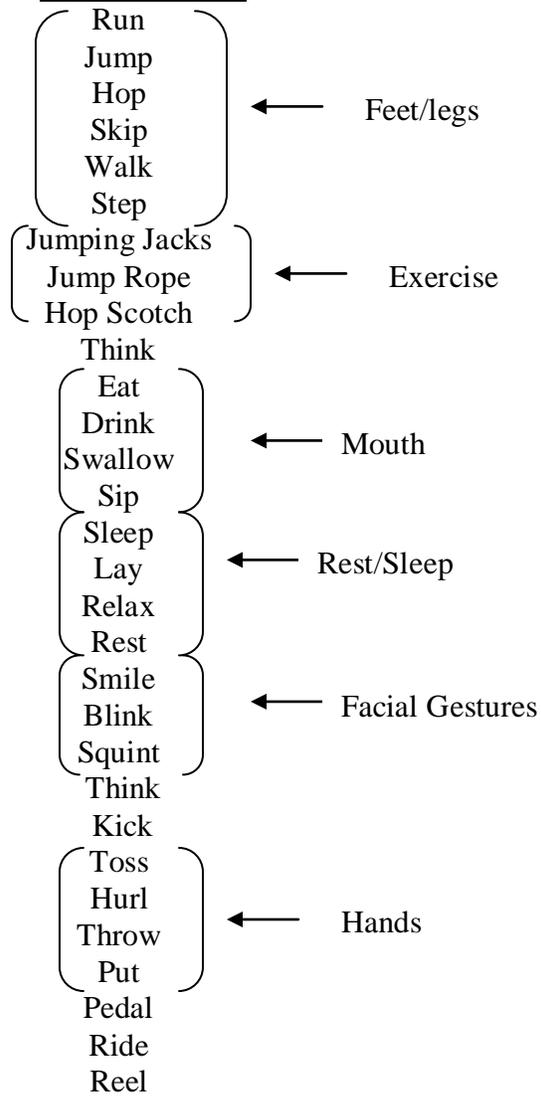
APPENDIX A
STANDARD NEUROPSYCHOLOGICAL TEST BATTERY (SNB)

<u>Construct</u>	<u>Test Name and Reference</u>	<u>Description of Test Measure</u>	<u>Dependent Variables; Time to Administer</u>
Intellectual Functioning	Wechsler Abbreviated Scale of Intelligence (WASI; Psychological Corporation, 1999)	Block Design, Matrix Reasoning, Vocabulary, and Similarities subtests	Verbal IQ, Performance IQ, Full Scale IQ; subtest T-scores Time=20-30'
Memory Functioning	Rey Complex Figure Test and Recognition Trial (Myers & Myers, 2004)	Measure of figural memory visuoconstruction that requires copy, immediate and delayed recall of a complex figure	Scores for Immediate and Delayed Recall Time=15'
	California Verbal Learning Test – 2nd Edition (Delis et al., 2000)	Verbal list learning; assesses learning strategy, immediate and delayed recall, recognition, and interference	Scores for Immediate and Delayed Free Recall Time=15'
	Wechsler Memory Scale-R; Logical Memory I & III (Wechsler, 1997)	Measure of verbal memory for stories and figural memory for geometric designs.	Scores for Immediate and Delayed Recall Time=15'
Language Functioning	Controlled Oral Word Association (COWA; Spreen & Benton, 1977)	Verbal fluency for alphabet letter (i.e. F,A,S)	Total correct exemplars Time=5'
	Semantic Fluency – Animals (Tombaugh et al., 1999)	Verbal fluency for a semantic category	Total correct exemplars Time=5'
	Boston Naming Test – II (Goodglass & Kaplan, 2000)	Confrontation naming using large ink drawings	Total Correct Time=10'
Visuo-perceptual / Visuo-constructional Functioning	WASI Block Design subtest (Wechsler, 1997)	Visuoconstructional measure requiring construction with blocks	Total score based on time limits Time=10'
Frontal / Executive Skills -- Attention, Psychomotor Speed, Abstract Thinking	Wisconsin Card Sorting Test (Heaton, 1981)	Measure of mental flexibility and problem solving.	Number of categories achieved; Number of errors; trials to finish first category Time=15'
	Trail Making Test (Reitan, 1958)	Measures visuomotor speed, set-shifting	Total time to complete; Number of errors Total time=5'
	WAIS-III Digit Span (Wechsler, 1997)	Memory for digit sequences; Requires attention span	Total correct score Time=10'
Sensory Perceptual and Motor	Finger Tapping (Halstead, 1947; Reitan & Wolfson, 1993)	Speeded fine motor movement for dominant and non-dominant hands	Average number of taps across five trials Time=5'
	Grooved Pegboard Test (Klove, 1963)	Speeded fine motor movement and dexterity	Total time; # of drops Time=5'
Mood and Affect	Beck Depression Inventory-II (Beck, Steer, & Brown, 1996)	21 item self-evaluation questionnaire assessing elements of depression	Total number of items endorsed Time=5'

APPENDIX B
SAMPLE RESPONSES FROM FLUENCY DATA



Action Fluency



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BIOGRAPHICAL SKETCH

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