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An Investigation of Sex Differences in Language Processes Before and After Temporal Lobe Epilepsy Surgery

A thesis submitted to the

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Abstract

Given mixed results of previous research in language function following anterior temporal lobectomy (ATL) for temporal lobe epilepsy (TLE) and literature suggesting sex-related differences in language, epileptogenic, and hypometabolic patterns, the present study sought to further our understanding of language outcome by introducing sex as an explanatory factor. Three aspects of language (object confrontation naming, verbal fluency, and auditory-verbal comprehension) were evaluated in 34 patients before and one year following surgery. No change in language ability was observed as a function of sex and no changes in language function occurred with respect to verbal fluency and auditory-verbal comprehension in any group. A significant decline in object confrontation naming was observed only in the left ATL group which corroborates previous research. Although ATL is an effective treatment for seizures, visually mediated pathways of word retrieval may be disrupted in cases of left TLE.

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CHAPTER I

INTRODUCTION

Epilepsy is the second most common neurological disorder, affecting people of all ages, ethnic groups, and socioeconomic backgrounds (Murray, Lopez, & Jamison, 1994) and is characterized by recurrent seizures, which are temporary abnormalities in brain electrical activity. Seizure activity involves either a portion of (i.e., partial seizures) or the entire brain (i.e., generalized seizures) (Loring, 1999). Partial seizures are generated from one part of the brain, known as the epileptogenic focus, and may or may not cause unconsciousness, resulting in a complex-partial or simple-partial seizure respectively. Generalized seizures result in a loss of consciousness and may arise from one or more brain regions simultaneously and quickly spread to encompass the entire brain (Kuzniecky & Jackson, 1995). While the use of anticonvulsant medications can reduce or eliminate seizure activity in the majority of cases, a subset of individuals will not find seizure relief from such medications and are said to have intractable epilepsy. An effective treatment for such cases when the epileptogenic focus can be localized to one of the temporal lobes is a surgical procedure known as the anterior temporal lobectomy (ATL) (Rausch, 1991; Wiebe, Blume, Girvin, & Eliasziw, 2001).

Many neurocognitive abilities are disrupted by chronic seizure activity in the syndrome of temporal lobe epilepsy (TLE) including memory, problem solving, and language (Engel, 1996). Furthermore, neurocognitive and neurobehavioral disturbances are not restricted to the period during the seizure, known as the ictus, but can also occur outside of seizure activity, during the interictal period (De Curtis & Avanzini, 2001; Privitera, Kohler, Cahill, & Yeh, 1996; Waxman & Geschwind, 1975). In addition to electroencephalographic (EEG) monitoring and magnetic resonance imaging (MRI) techniques, neuropsychological assessment provides important corroborative evidence for the lateralization of the epileptogenic focus in patients with complex-partial seizures which originate from the temporal lobes (Engel, Rausch, Leib, Kuhl, & Crandall, 1981; Loring & Meador, 1997; Milner, 1972). Such neurobehavioral measures are sensitive to slight neuroanatomical changes that can be difficult to detect using current imaging techniques or that may represent functional, rather than structural, abnormalities that result from epilepsy (Bigler, 2001; Jones-Gotman, 1991).

When the epileptogenic focus resides in the hemisphere of the brain that is dominant for the processing of language, deficits in this important function are often present prior to surgery (Bryden, Hecaen, & DeAgostini, 1983; Hermann, Wyler, & Somes, 1991; Mayeux, Brandt, Rosen, & Benson, 1980; Saykin, et al., 1995). Additionally, recurrent seizures will not only disrupt the neurocognitive abilities associated with the brain structures encompassed by the epileptogenic foci, but also those that rely on adjacent and strongly interconnected brain regions (Engel, 1991; Luders & Awad, 1991). As surgery has been found to be effective for the treatment or elimination of seizure activity in most cases of intractable epilepsy, it is of interest to assess and better understand whether specific neurocognitive abilities, such as language, will improve due to the elimination of recurrent seizures as a result of surgery. It is possible that seizure-related destabilization of neurocognitive functions supported by brain regions outside of the epileptogenic foci would be resolved, permitting an improvement from baseline evaluation in these cognitive domains, and perhaps normalization.

Past research has yielded contradictory results as to whether language improves or worsens post-surgically. Even among studies that report either a significant improvement or worsening of language function following surgery, there generally exists a subset of participants who show a drastic change in language function that is opposite to the direction of the results of the study (e.g., Hermann & Wyler, 1988; Langfitt & Rausch, 1996). One important factor that has been absent from consideration within this body of research is whether there is a differential change in language ability following surgery in males and females. Research has long suggested the existence of neuroanatomical and neurophysiological differences in men and women including differences in neuronal connectivity and density, metabolism, and brain region volume (McGlone, 1980). In epilepsy, several recent reports have suggested that the pattern of glucose metabolism and epileptogenic activity may differ between males and females, thus exerting a differential diaschiatic effect where one or more brain regions outside of the epileptogenic focus will experience an arrest or deceleration of function. It is therefore reasonable to hypothesize that following surgery, a resolution of diaschisis may lead to a differential rate of improvement in language function in males and females.

The current study may lead to a better understanding of human cognitive sex differences in general and recovery of language processes following ATL in men and women specifically. Such knowledge could benefit the patient who is status post-ATL by informing rehabilitative efforts toward emphasis of specific components of language ability (e.g. verbal fluency, comprehension, word-finding) that may be compromised following surgery. Furthermore, the clinician may use such information to more fully discuss the risks and benefits of surgery, particularly in regard to language function.

Background and Literature Review

Previous Studies Investigating Post-ATL Language Function

Language demands the function of a distributed network of cerebral structures (Binder, et al., 1997; Ojemann, 1991; Penfield & Roberts, 1958; Price, 2000) and can be subdivided into several linguistic domains, including naming, auditory-verbal comprehension, fluency, repetition, reading, spelling, articulation, prosody, and writing (Benson & Geschwind, 1985; Price, 2000). Auditory-verbal comprehension, object naming, and verbal fluency are three of the most critical linguistic abilities and are often the most disturbed in individuals with epilepsy (Mayeux et al., 1980).

To date there remains no definitive understanding of the status of language ability following surgery as results fall into one of three categories: those that find improvements in language ability following surgery, those that find no change, and those that find post-surgical decline. Perhaps a reason for the incongruous results is the way in which researchers have defined and studied language. The majority of studies in this area over the last 10 years have tended to utilize measures of visual confrontation naming as the sole measure of linguistic ability before and after ATL. While the ability to relate names to objects is a critical function of the linguistic system and part of word finding, it is not the only means by which humans communicate. In order to adequately understand the condition of language function before and after ATL, it is important to include the assessment of several of linguistic domains in the pre- and post-operative assessment.

Several studies have found significant improvement in specific areas of language function following ATL. For example, Hermann and Wyler (1988) found improvements in verbal fluency and auditory-verbal comprehension six months following surgery with no significant decline in naming ability in cases of left ATL (LATL). Although Loring, Meador, and Lee (1994) found an acute, transient decline in all areas of linguistic performance a few days following LATL, at one year follow-up, a significant improvement in verbal fluency and a return to baseline levels of naming and auditory-verbal comprehension were observed. Similarly, Martin and colleagues (Martin, et al., 2000) found improvements in verbal fluency one year following surgery in both right ATL (RATL) and LATL patients. A study by Langfitt and Rausch (1996) found post-surgical improvements in word-finding in cases of RATL, but not LATL.

In addition to the above mentioned studies which report a combination of improvement and no change within the same group of patients across different linguistic domains, others have reported not finding any significant change from pre-to post-surgical assessment in any linguistic domain. For example, Davies and colleagues (Davies, 1994; Davies, Maxwell, Beniak, Destafney, & Fiol, 1995) have found that verbal fluency ability in patients with LATL remains unchanged from pre-surgical status and confrontation naming abilities, although not significantly, do decline. This same group also found that post-RATL patients experienced no change in confrontation naming and slight, yet non-significant, improvements in verbal fluency.

Another cluster of studies has reported a significant decline in linguistic ability following surgery. Penfield and Roberts (1959) reported that nearly 60% of patients undergoing LATL presented with acute and transient post-surgical aphasia and Stafiniak and colleagues reported that patients have word-finding deficits at two weeks post-LATL (Stafiniak, et al., 1990). Similarly, Saykin and colleagues (1995) found that patients with LATL performed much worse on a measure of confrontation naming at three weeks following surgery. Hermann, Davies, Foley, and Bell (1999) showed that LATL patients experienced a significant decline in confrontation naming ability up to eight months following surgery after controlling for surgical procedure, surgical center, and amount of tissue resected during surgery, with those patients with a later age of seizure onset experiencing the most dramatic decline. Also, Langfitt and Rausch (1996) found that 30% of their sample of LATL and only 3% of the RATL patients experienced a decline in word finding or naming ability following surgery. Although both LATL groups declined significantly, Davies and colleagues (Davies, et al., 1998) found that those patients with a high degree of hippocampal sclerosis exhibited less pre- to post-operative decline in confrontation naming ability than those with a lesser degree of hippocampal sclerosis.

Based on a review of this literature, it would seem as though a short time interval between surgery and the follow-up neuropsychological assessment is generally associated with an acute aphasia and a post-surgical decline in language ability from baseline (e.g., Penfield and Roberts, 1959; Loring et al., 1994; Saykin, et al., 1995). It is possible that this decline could be related to acute physiological changes following surgery such as edema or alterations in ischemic patterns and that a longer time period to reassessment of language ability would permit recovery from such side effects. The majority of these studies would suggest that confrontation naming does not improve following surgery, as some investigators have reported declines (e.g., Davies, et al., 1998; Hermann, et al., 1999) while others have reported a return to baseline function (Loring et al., 1994). The majority of previous research suggests that auditory-verbal comprehension and word fluency abilities will either return to baseline or improve significantly following surgery in cases of both RATL and LATL.

<u>Sex-Related Differences in Language</u>

Although reported in the post-ATL memory literature (Geckler, Chelune, Trenerry, & Ivnik, 1993; Trennery, Jack, Cascino, Sharbrough, So, & Lagerlund, 1995) sex-related neuroanatomical and neuropsychological differences have not been reported in regards to language function following ATL. The existence of sexually dimorphic characteristics in the anatomy and functionality of the human brain is a controversial issue with many studies supporting (Azari, Rapoport, Grady, & DeCarli, 1992; Harasty, Double, Halliday, Kril, & McRitchie, 1997; McGlone, 1980; McKeown, et al., 1998; Nobre, et al., 1997; Waber, 1976; Wada, Clarke, & Hamm, 1975; Witelson, 1989) and others failing to support this contention (Aboitiz, Scheibel, & Zaidel, 1992; Damasio, Tranel, Spradling, & Alliger, 1989; DeRenzi, Faglioni, & Ferrari, 1980; Habib, et al., 1991; Jancke, Staiger, Schlaug, Huang, & Steinmetz, 1997; Warrington, James, & Maciejewski, 1986).

Research from many sources seems to support the notion that women have more well developed verbal abilities than men and that these verbal differences are the first to appear developmentally. It has been found that young females talk about one month earlier than boys (Moore, 1967; Gazzaniga, Ivry, & Mangun, 1998), are more fluent, articulate, grammatically correct, and spell and read better at an earlier age than males (Kramer, Delis, Kaplan, O'Donnell, & Prifitera, 1997; MacCoby, 1966; McGuiness, 1976; Smolak, 1986). MacCoby & Jacklin (1974) reported that females score better on tasks that require both receptive and productive language, such as analogy and reading comprehension as well as fluency. In adulthood, research has shown that fluency, spelling, and grammatical usage remain superior in the female (Butler, 1984; Hyde & Linn, 1988; Kramer et al., 1997; Martin & Hoover, 1987), while verbal intelligence, articulation, and reading are equivalent in males and females (Feingold, 1988).

A current theory for superior female verbal abilities is that the female brain is more functionally symmetric for language than the male. Both males and females may be, in most cases, left hemisphere dominant for language, however, the female brain may draw on neural resources from both hemispheres in a way that the male does not. Ojemann and Mateer (1979) found more "language areas" in the male than in the female brain through electrical stimulation of the cortex during neurosurgery. Given the general finding of superior verbal abilities in females, this would seem to imply that a smaller language area may be inversely related to ability. However, it may also imply that the female brain has additional language areas on the opposing hemisphere which were not manipulated during these experiments (which were performed during surgery). Indeed, a more recent investigation (Shaywitz, et al., 1995) used a functional magnetic resonance imaging (fMRI) paradigm to study language laterality in males and females which showed that during phonological tasks, brain activation is lateralized to the left inferior frontal gyrus in males, whereas in females the pattern of brain activity engages a more diffuse neural system involving the inferior frontal gyrus of both hemispheres. Their conclusion was that males are more strongly lateralized for language than females. This finding was later corroborated through a PET study by Jaeger and colleagues who demonstrated that males had a more left-lateralized pattern of activation while women showed bilateral activation during a verb generation task, while reaction time, error rates, and overall brain activation was similar for both sexes (Jaeger, et al., 1998). An additional study by Vikingstad, George, Johnson, and Cao (2000) further supports this notion as their participants (as a group) were left-hemisphere dominant for language, however, individually, the lateralization of language varied from left-hemisphere dominant to bilateral representation. In males, the trend was clearly left-hemisphere dominant, whereas in females the trend was approximately half left-lateralization, and half bilateral representation of language.

Sex related differences in language function have also been reported following brain injury and disease. Males tend to require a longer period of time to recover following brain damage that results in aphasia and they also experience more impairment than females (Basso, Capitani, & Moraschini, 1982; Pizzamiglio & Mammucari, 1985; Witelson, 1976). The finding that aphasia is less likely to occur in females after left-hemisphere damage has been taken as evidence that the female language system may be represented more bilaterally than the male (Kimura, 2000). However, there is no data to suggest that females suffer more from aphasia after right hemisphere lesions than males. Such findings have lead to hypotheses suggesting that the male and female language system may be differently organized intrahemispherically. There is some research to support this notion as females are more likely to be aphasic if a lesion occurs in the anterior region of the left hemisphere, whereas males are more likely to be aphasic if the damage occurs in the posterior region of the left-hemisphere (Kimura, 1983, 1993).

In further support of the hypothesis that female language representation is symmetric, it has been found that males perform more poorly on measures of verbal intelligence after lesions restricted to the left-hemisphere, whereas verbal intelligence deficits were found in females whether the damage was in the left or right hemisphere (Kimura & Harshman, 1984). However, an earlier study by Inglis and Lawson (1982) showed that damage to the left hemisphere in males led to declines on measures of verbal intelligence, whereas damage to the right hemisphere resulted in declines on measures of nonverbal intelligence. In females, damage to the left hemisphere resulted in a decline in both measures of verbal and nonverbal intelligence, whereas damage to the right hemisphere did not affect verbal or nonverbal intelligence.

Verbal fluency is more negatively affected by damage to the left than to the right hemisphere. The specific region of the brain that is essential for this ability is the anterior portion of the left hemisphere (Milner, 1964; Stuss, et al., 1998). On measures of verbal fluency, males perform much worse than females after damage to the left anterior region of the brain and also worse than both males and females with damage to the corresponding area in the right hemisphere. Interestingly, damage to either the left or right anterior region in females has been shown to result in poorer verbal fluency performance than damage to the right anterior region in males (Kimura, 2000). McGlone (1980) found that females showed a significant drop in verbal fluency with an injection of sodium amytal to either the left or right hemisphere while males showed a drop only after left hemisphere injection. This evidence would again suggest a female bilateral representation of language, in this case verbal fluency.

It has been widely reported that the number of neurons connecting the two hemispheres is greater in the female brain and thus it is possible that stronger or faster interhemispheric communication is occurring (Jancke, Schlaug, Huang, & Steinmetz, 1994). Indeed, research on callosum size has demonstrated that a greater number of neurons are present in a larger callosal area (Aboitiz et al., 1992). It would seem logical that neurocognitive functions which are dominant for a particular hemisphere are more likely to be shared by the other hemisphere if there are more interhemispheric connections, thus leading to superiority on specific neurocognitive tasks. For instance, one study, using only females, found that those with a larger corpus callosum had better performance on a task of verbal fluency (Hines, Chiu, McAdams, Bentler, & Lipcamon, 1992).

The previously mentioned findings support the notion that there are sex-related differences in interhemispheric and intrahemispheric cerebral connections that give rise to a differential representation of language function in males and females. In regards to language function following ATL, it is possible that the mixed results following surgery (discussed earlier) could be due, in part, to sex differences in language function. For instance, if females are more likely to experience aphasia following a dominant hemisphere anterior lesion, perhaps following ATL females will experience a greater disturbance in language function than the male. Or conversely, as females are more likely to have bilateral representation of language, perhaps language functions in females will remain intact, only decline slightly, or even improve when compared to the male following surgery.

Sex-Related Differences in Hypometabolism

Another important factor in epilepsy that may have a bearing on post-surgical language function and potentially lead to differences in outcome between males and females is decreased interictal rates in cerebral metabolism of glucose, more commonly known as hypometabolism. The exact mechanism of hypometabolism is unknown, however, it can be observed via PET imaging (Semah, et al., 1995). During hypometabolic periods brain regions which are part of the epileptogenic focus as well as surrounding areas effectively "switch off" or become immobilized indefinitely. This is much like the freezing of one or more computer programs to prevent a crash in and subsequent damage to the entire hard drive of a personal computer. The amount of brain volume encompassed by hypometabolism is much larger than the epileptogenic region, encompassing the entire temporal lobe (including polar, lateral, and mesial regions) and can often extend frontally and contralaterally (Azari et al., 1992; Jokeit, et al., 1997; Koutroumanidis, Hennessy, & Elwes, 1998; Koutroumanidis, et al., 2000). Approximately 70-95% of patients with epilepsy experience interictal hypometabolism (Engel, 1989; Hajek, Antonini, Leenders, & Wieser, 1993).

A result of temporal and extra-temporal hypometabolism is neurocognitive deficits that are related to brain regions well outside of the epileptogenic focus (Henry, Mazziotta, & Engel, 1993; Nagarajan, et al, 1996). Hypometabolism in the left hemisphere has been shown to be associated with poorer performance on measures of verbal IQ, verbal memory, verbal fluency, and recall of stories (Arnold, et al., 1996; Rausch, Henry, Ary, Engel, & Mazziotta, 1994). Hypometabolic spread to the ipsilateral frontal lobe is very common in cases of left TLE (Jokeit et al., 1997) and is hypothesized to be due to the strong neuroanatomical connections between the temporal and frontal lobes and the frequent spread of temporal lobe seizures to the frontal regions (Lieb, Dasheiff, & Engel, 1991). Following ATL, hypometabolic temporal as well as ipsilateral sites remote to the epileptogenic foci experience improved glucose metabolism, with the most improvement observed in the frontal lobes (Akimura, et al., 1999; Newberg, Alavi, Berlin, Mozley, O'Connor, & Sperling, 2000).

A recent paper by Savic and Engel (1998) demonstrated sexually dimorphic patterns of extra-temporal interictal hypometabolism. In males, a pattern emerged where both epileptiform activity and hypometabolism extend to the frontal (orbitofrontal and frontopolar) cortex ipsilateral to the seizure focus. From the same report, females showed a pattern of hypometabolism in the contralateral (mesial) temporal lobe as well as a spread of epileptiform activity to this region. No sex differences were found in the frontal lobe contralateral to the seizure focus, which was presumably not related to the epileptogenic process. Such findings may be related to sexual dimorphism in cerebral connectivity mentioned earlier as well as to the finding that healthy women have a higher number of interhemispheric correlations in glucose metabolism while healthy men have more intrahemispherically (Azari et al., 1992).

Aims and Hypotheses

The findings from the preceding literature review would suggest that the definitive status of language function following ATL is not known. As the language system is more symmetrically distributed in the female brain and hypometabolic patterns differ between the sexes, it is possible that sex differences may lead to different outcomes on measures of language following ATL. For example, following ATL it is possible that in females hypometabolism may resolve contralateral to the foci, thus allowing improved language function following ATL, perhaps more so in cases of post-RATL females. In post-ATL males, a resolution of hypometabolism ipsilateral and frontal to the foci may lead to improved performance on measures of verbal fluency. A resolution of hypometabolism in the temporal lobe may lead to improved auditory-verbal comprehension and verbal-intellectual functioning in both sexes. As there are no reports of sex differences in measures of confrontation naming it is unclear whether sex-related differences would have a differential effect on this ability following surgery. Perhaps females with a RATL would improve in naming ability following surgery and males would be more aphasic, but it has also been found that females are more likely to experience aphasia following anterior localized lesions, whereas aphasia in males is more likely following posterior lesions.

The following questions result: Do language processes change following surgery as a result of improved glucose metabolism in extra-temporal brain regions? If so, which language processes change and does the pattern of change in language function after surgery differ for males and females as a consequence of neuroanatomical and/or functional brain differences? To address these questions a set of pre- to post-surgical hypotheses are put forth for each specific language ability (groups are based on sex and side of surgery: MLATL = male left ATL, FLATL = female left ATL, MRATL = male right ATL, and FRATL = female right ATL):

I. Visual Confrontation Naming: 1) MLATL: significant decline in naming ability following surgery as males are more strongly lateralized to the dominant hemisphere. 2) FLATL: significant decline in naming ability following surgery as anterior lesions in females are more likely to lead to aphasia. 3) MRATL: no change is expected as language function is lateralized to the left. 4) FRATL: significant improvement due to the bilateral resolution of interictal hypometabolism across the temporal lobes.

II. Verbal Fluency: 1) MLATL: significant improvement as normal metabolism returns in the frontal regions of the dominant hemisphere after seizure activity is eliminated. 2) FLATL and FRATL: no change as there are no reports of sex differences with respect to epileptogenesis or hypometabolism in females in the frontal lobes. 3) MRATL: no change is expected as language function is lateralized to the left.

III. Auditory-verbal Comprehension: 1) MLATL and FLATL: Improvement as a result of increased glucose uptake in the temporal lobes including primary and secondary auditory cortices. 2) MRATL: no change is expected as language function is lateralized to the left. 4) FRATL: significant improvement due to a resolution of hypometabolism contralateral to the epilepstogenic foci.

The results of this study will contribute to our understanding of the degree to which language processes change post-surgically in the absence of epileptogenic activity and hypometabolism. Examining the role of sex differences will potentially provide a clearer picture of the individual differences that contribute to post-surgical language outcome. This study has implications for the quality of life of the epileptic patient who is considering surgery as a treatment for intractable TLE.

CHAPTER II

METHOD

Participants

Data from a convenience sample of 53 patients who underwent ATL at University Hospital, Cincinnati, Ohio, for relief of medically intractable partial or secondarily generalized seizures were evaluated for inclusion in this study. Inclusion criteria consisted of participation in the both pre-operative and post-operative neuropsychological evaluation that included a baseline measure of psychometric intelligence not indicative of mental retardation (Wechsler Adult Intelligence Scale-Revised Full Scale IQ (WAIS-R FSIQ > 69; Wechsler, 1981), the 60-item Boston Naming Test (BNT) (Kaplan, Goodglass, & Weintraub, 1983), and both the Controlled Oral Word Association Test (COWAT) and the Token Test of the Multilingual Aphasia Examination (MAE; Benton, Hamsher, Rey, & Sivan, 1994). At pre-surgical evaluation, participants had to be at least 16 years of age, have a minimum of eight years of education, be a native speaker of English, have an onset of seizures at least two years prior to the first neuropsychological assessment, have at least one partial seizure per month, have no previous history of brain surgery, and not have suffered from significant neurologic disorders other than epilepsy (e.g., Parkinson's disease, have a normal MRI apart from epilepsy-related causes [e.g., arterial venous malformation, tumor] or changes [e.g., mesial temporal sclerosis]) or major psychiatric disorders (e.g., schizophrenia). See Table 1 for sample demographic and Table 2 for participant seizure characteristics. Additionally, participants had to receive the follow-up neuropsychological evaluation between five and 24 months following surgery (See Table 3). Participants were excluded if the results of the WADA test indicated right hemisphere or in cases of bilateral language representation, right

Table 1

Sample Demographic Characteristics

	n	M	SD	Median	Minimum – Maximum
Age Pre-surgery					
MLATL	9	31.78_a	12.53	33.00	17 – 50
FLATL	6	25.00_a	9.06	22.00	16 – 37
MRATL	9	42.00_b	8.06	44.00	28 – 53
FRATL	10	29.90_a	11.00	25.00	18 – 47
Education Pre-surgery					
MLATL	9	11.89_a	1.76	12.00	10 – 16
FLATL	6	11.83_a	1.72	12.00	9 – 14
MRATL	9	13.11_a	2.80	13.00	8 – 18
FRATL	10	13.00_a	2.00	13.00	9 – 16
Handedness (Left/Right)					
MLATL	$(3/6)_a$				
FLATL	$(0/6)_a$				
MRATL	$(1/8)_a$				
FRATL	$(1/9)_a$				

Note. MLATL = Male, left anterior temporal lobectomy; FLATAL = Female, left anterior temporal lobectomy; MRATL = Male, right anterior temporal lobectomy; FRATL = Female, right anterior temporal lobectomy. [a]Group means of the same variable that do not share subscripts differ at $p < .05$ in the Tukey honestly significant difference comparison.

Table 2

Sample Seizure Characteristics

	n	M	SD	Median	Minimum – Maximum	
Age at Seizure Onset						
MLATL	9	15.17_b	8.16	15.00	.50 – 30	
FLATL	6	13.67_b	10.78	9.00	3 – 32	
MRATL	9	17.11_b	8.72	13.00	5 – 29	
FRATL	10	15.50_b	10.72	13.50	4 – 38	
Seizure Duration (years)						
MLATL	9	16.56_b	13.95	13.00	2 – 42	
FLATL	6	12.33_b	9.59	11.00	3 – 29	
MRATL	9	23.78_b	9.43	20.00	11 – 40	
FRATL	10	14.50_b	6.69	13.00	5 – 28	
Seizure Frequency/Month						Outcome[a]
MLATL	9	52.61_b	95.46	17.00	2.50 – 300	(6/1/1/1)
FLATL	6	15.33_b	13.11	11.50	2 – 32.50	(5/1/0/0)
MRATL	9	46.46_b	81.62	4.10	1 – 200	(7/1/1/0)
FRATL	10	79.95_b	235.46	5.75	1 – 750	(8/1/1/0)

Note. [a]Outcome = Engel Outcome (Engel, 1987): number of participants per post-surgical seizure status class (I/II/III/IV): I = Seizure (Sz.) free following surgery, II = Sz. improvement of 80%, III = Sz. improvement of 50%, IV = Sz. improvement of less than 50% (includes no improvement or increased seizure frequency following surgery). [b]Group means of the same variable that do not share subscripts differ at $p < .05$ in the Tukey honestly significant difference comparison.

Table 3

Epilepsy Etiology and Pathology by Group

Etiology	MLATL (n = 9)	FLATL (n = 6)	MRATL (n = 9)	FRATL (n = 10)
Idiopathic	2	2	2	2
Cryptogenic	0	0	3	1
Traumatic Brain Injury	2	2	0	0
Tumor	3	1	2	2
Febrile Seizures	1	0	1	2
Encephalitis/Meningitis	1	0	1	3
Cerebral Vascular Accident	0	1	0	0
Pathology				
Cases with MTS only	1	2	1	2
Cases with Gliosis only	1	2	4	2
Cases with both MTS & Gliosis	4	0	3	3

Note. MTS = Mesial temporal sclerosis.

Table 4

Neuropsychological Test Interval

	n	M	SD	Median	Minimum – Maximum
Surgical Interval[a] (Days)					
MLATL	9	332.22[c]	99.03	333.00	206 – 518
FLATL	6	321.33[c]	134.10	320.00	181 – 549
MRATL	9	334.22[c]	149.67	283.00	188 – 624
FRATL	10	234.10[c]	72.36	207.50	163 – 374
Test Interval[b] (Days)					
MLATL	9	399.56[c]	132.06	373.00	253 – 621
FLATL	6	600.50[c]	578.73	405.00	193 – 1736
MRATL	9	383.44[c]	166.43	360.00	202 – 668
FRATL	10	318.70[c]	119.03	290.50	198 – 584

Note. [a]Surgical Interval = Time between surgery and post-surgical neuropsychological assessment in days; [b]Test Interval = Time between 1st and 2nd neuropsychological assessment in days. [c]Group means of the same variable that do not share subscripts differ at $p < .05$ in the Tukey honestly significant difference comparison.

greater than left dominant for language. The results of the neuropsychological assessment were discussed with all participants.

The final sample included 34 post-ATL participants (9 MLATL, 6 FLATL, 9 MRATL, and 10 FRATL). All of the participants in this sample were Caucasian with the exception of one Asian American female in the FLATL group who was born and raised in the United States. Five participants in the final sample were left-handed but were included because their WADA results showed clear evidence of left-hemisphere speech-language dominance.

Procedure

All participants underwent prolonged video/EEG monitoring pre-surgically to determine seizure laterality and each had at least three seizures recorded. Laterality of seizure onset was determined by evaluation of multiple behavioral and ictal video/EEG recordings obtained using scalp/sphenoidal or scalp/intracerebral depth electrodes. The pre-surgical neuropsychological assessment took place in the participant's hospital room and the follow-up neuropsychological evaluation took place in an outpatient office. Non-neuropsychological data (e.g., medical and seizure history, surgical report) were procured with permission from the participant's medical file. All participants were undergoing maintenance therapy with anticonvulsant drugs at the time of both neuropsychological evaluations. At the time of each assessment all participants were oriented to personal, place, and time information and no patient was assessed status post-ictus or when there was clinical evidence of toxic effects of anticonvulsant therapy.

Instruments

Neuropsychological evaluation was undertaken before and at least five months following surgery. A comprehensive battery of tests was administered, including tests of language, memory, problem solving, attention, and intelligence. The following measures were administered according to standardized procedures to assess language function both pre- and post-operatively:

1. The BNT (Kaplan et al., 1983) was used as a measure of visual confrontation naming and consists of 60 line drawings ranging from simple (e.g., pencil) to rare words (e.g., abacus) that are presented one at a time from a small booklet. Two prompting cues (stimulus cue [e.g., "It's used for writing"] and phonemic cue [e.g., "It's used for counting"]) are given if the patient does not spontaneously produce the correct word. The primary purpose of the test is to assess the capacity to apply semantically correct verbal labels to visually presented stimuli, independent of defects in recognition or speech articulation.
2. COWAT (or Word Fluency) subtest of the MAE (Benton et al., 1994) was used as a measure of verbal fluency. The examinee is required to make verbal associations with a letter of the alphabet by saying all the words that he or she can think of beginning with that letter. Three letters of progressively increasing associative difficulty are presented successively as stimuli, and the subject is given one minute per letter in which to respond without using proper nouns or repeating the same word with different suffixes. The letters C, F, and L were used following Benton et al.
3. The Token Test of the MAE (Benton et al., 1994) was used as a measure of auditory-verbal comprehension which assesses the examinee's ability to

comprehend and carry out 22 commands of increasing length. The stimuli consist of 20 plastic tokens in five colors (red, white, yellow, blue, green), two sizes (large and small), and two shapes (either circle or square).

4. An estimate of the Verbal Intelligence Quotient (VIQ) was computed from a seven-subtest short-form of the WAIS-R (using the Information, Similarities, Arithmetic, and Digit Span subtests) to assess basic verbal intellectual abilities.

Raw were converted to standardized z-scores (mean = 0, standard deviation = 1) by use of the mean and SD of the normative sample to allow comparison across measures. As groups differed with respect to age of participant, the correction for age was performed on the raw COWAT scores and the normative sample based on age was used in standardizing the BNT and COWAT scores (Ross, Lictenberg, & Christensen, 1995, Tombaugh & Hubley, 1997). No correction for age or education was available for the Token Test. For nine participants entered into this study, only the age-corrected scaled scores, rather than the raw scores, were available for each measure. In these cases, the scaled scores were transformed into standardized scores.

Surgery

Shortly after the pre-surgical neuropsychological assessment (M = 60 days, SD = 63.89 days) all participants underwent partial resection of the anterior temporal lobe according to standard procedure to excise the seizure focus. After routine exposure of the temporal lobe via corticotomy, 3-6 cm of the anterior temporal neocortex was resected en bloc under local anesthesia. The same neurosurgeon performed all surgeries for the sample under study.

Approval from Human Subjects Committee

This study is part of a larger "Neuropsychology of Epilepsy" protocol for which full IRB approval has been obtained. IRB#_01022301.

CHAPTER III

RESULTS

Groups did not differ with respect to demographic and seizure characteristics with the exception of participant age ($F(3, 30) = 3.73$, $p < .05$) where the MRATL group (M = 42 years) was significantly older than the FLATL group (M = 25 years) (see Table 1)[1]. The length of time between the two neuropsychological assessments as well as between surgery and the second neuropsychological assessment did not differ between groups. See Tables 4 through 7 for pre- and post-operative performance on the neuropsychological measures, Figures 1 and 2 for a graphical representation of performance by each group by language variable, and appendix A for a display of performance on each language measure by each subgroup on a case-by-case basis. Data analysis was performed using the SPSS, NPSTAT, and NPFACT statistical programs.

Prior to analysis the characteristics of the data were evaluated to assess the degree to which assumptions of the statistical tests used were appropriately met. This was particularly a concern because of the small sample size utilized in this study. Leverage values as well as Cook's and Mahalanobis distances indicated no (multivariate) influential data points. Assumptions of normality were assessed through use of the Shapiro-Wilks test, the Q-Q plot, and the detrended normal probability plot by subgroup (see appendices B through E for output, histograms, and plots related to the assessment of normality and homogeneity of variance for participant group by dependent variable).

The results of this evaluation suggested that the distributions of the dependent variables for nearly one half of the participant groups were not normally distributed.

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[1] This result was also corroborated by both the Kruskal-Wallis nonparametric procedure ($p = .027$) and an exact permutation test that produced an exact p-value of .02.

Table 5

Pre- and Post-Surgical Performance on a Measure of Verbal Intellectual Ability (WAIS-R VIQ)

Group	Time	n	M	SD	Median	Range
MLATL	Pre	9	-0.75	0.54	-0.87	1.73
	Post	9	-0.79	0.91	-1.00	2.47
FLATL	Pre	6	-0.83	0.85	-1.07	2.33
	Post	6	-0.81	0.66	-0.93	1.87
MRATL	Pre	9	-0.31	1.16	-1.00	3.00
	Post	7	-0.11	1.06	0.13	3.13
FRATL	Pre	10	-0.47	0.44	-0.57	1.20
	Post	10	-0.45	0.60	-0.43	2.00

Note. Values represent z-scores. VIQ = WAIS-R Verbal Intelligence Quotient; MLATL = Male, left anterior temporal lobectomy; FLATAL = Female, left anterior temporal lobectomy; MRATL = Male, right anterior temporal lobectomy; FRATL = Female, right anterior temporal lobectomy.

Table 6

Pre- and Post-Surgical Performance on a Measure of Confrontation Naming (BNT)

Group	Time	n	M	SD	Median	Range
MLATL	Pre	9	-4.47	4.40	-5.55	13.06
	Post	9	-6.72	5.78	-5.54	17.17
FLATL	Pre	6	-6.18	3.78	-5.20	10.92
	Post	6	-9.24	3.74	-8.34	10.14
MRATL	Pre	9	-1.84	2.86	-0.31	7.49
	Post	9	-1.73	2.76	-0.12	7.21
FRATL	Pre	10	-1.77	2.03	-1.87	5.82
	Post	10	-1.30	1.92	-1.00	6.29

Note. Values represent z-scores. BNT = Boston Naming Test; MLATL = Male, left anterior temporal lobectomy; FLATAL = Female, left anterior temporal lobectomy; MRATL = Male, right anterior temporal lobectomy; FRATL = Female, right anterior temporal lobectomy.

Table 7

Pre- and Post-Surgical Performance on a Measure of Verbal Fluency (COWAT)

Group	Time	n	M	SD	Median	Range
MLATL	Pre	9	-1.23	1.27	-1.88	2.83
	Post	9	-1.18	1.05	-1.75	2.77
FLATL	Pre	6	-1.32	0.71	-1.21	2.06
	Post	6	-1.01	0.83	-1.08	2.08
MRATL	Pre	9	-0.63	1.35	-0.08	3.37
	Post	9	-0.61	0.95	-0.81	3.00
FRATL	Pre	10	-0.62	1.19	-0.20	3.10
	Post	10	-0.40	1.26	0.00	3.46

Note. Values represent z-scores. COWAT = Controlled Oral Word Association Test; MLATL = Male, left anterior temporal lobectomy; FLATAL = Female, left anterior temporal lobectomy; MRATL = Male, right anterior temporal lobectomy; FRATL = Female, right anterior temporal lobectomy.

Table 8

Pre- and Post-Surgical Performance on a Measure of Auditory-Verbal Comprehension (Token Test)

Group	Time	n	M	SD	Median	Range
MLATL	Pre	9	-0.15	0.67	0.00	2.00
	Post	9	-0.07	0.72	0.00	2.00
FLATL	Pre	6	0.28	0.49	0.50	1.00
	Post	6	0.06	1.18	0.50	3.00
MRATL	Pre	9	0.11	0.37	0.00	1.33
	Post	9	0.37	0.35	0.67	0.67
FRATL	Pre	10	0.20	0.61	0.50	1.67
	Post	10	0.13	0.67	0.33	2.00

Note. Values represent z-scores. COWAT = Controlled Oral Word Association Test; MLATL = Male, left anterior temporal lobectomy; FLATAL = Female, left anterior temporal lobectomy; MRATL = Male, right anterior temporal lobectomy; FRATL = Female, right anterior temporal lobectomy.

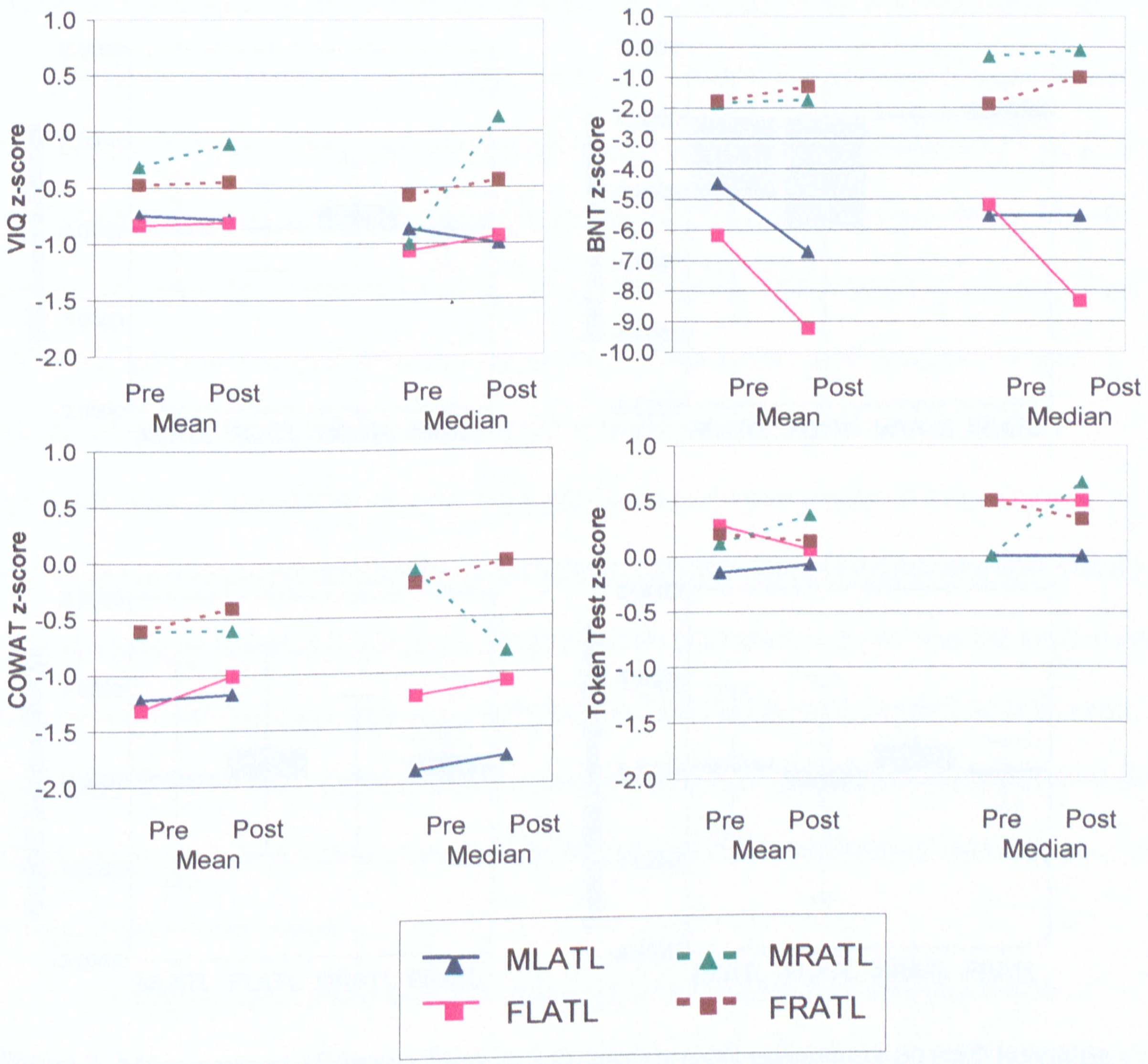

Figure 1. Mean and median pre- and post-surgical performance on each language measure by group.

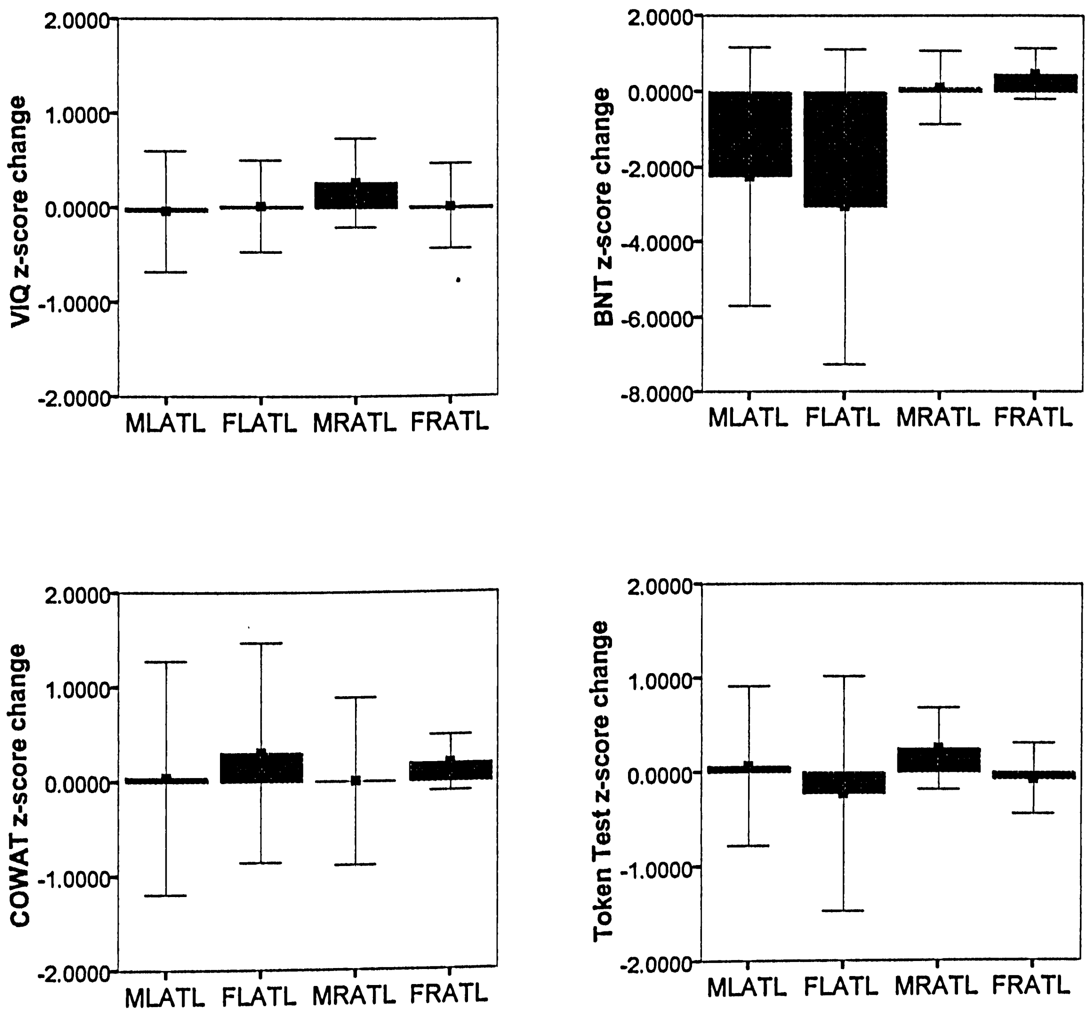

Figure 2. Mean amount of change from pre- to post-surgical assessment on each language measure by group. Error bars represent one standard deviation.

Although the Shapiro-Wilk statistic only showed that one-fifth of the distributions under consideration were non-normal (see appendix A), the Pearson skewness coefficient showed that the distributions of each dependent variable were moderately to highly skewed for at least three of the four participant groups (appendix B). The Levene statistic demonstrated that for several of the distributions of the dependent variable (pre-surgical VIQ, pre-surgical COWAT, and Post-Surgical BNT) the assumption of homogeneity of variance was not supported (appendix A). Visual inspection of the histograms, Q-Q plots, and the Q-Q detrended normal probability plots for each distribution of scores on the pre- and post-dependent measures demonstrated variable departures from normality (appendices C and D). Due to a general departure from many of the requisite assumptions it was decided to perform the necessary analyses using traditional parametric statistical procedures, followed by exact and nonparametric tests. As this study is essentially exploratory in nature, the alpha-level for rejection of null hypotheses was set to .10 so that the potential for clinically interesting results could be maximized.

Change in measures of language ability was analyzed with an omnibus mixed-factorial multivariate analysis of variance (MANOVA) with surgery (Pre- and Post-Surgery) and language function (VIQ, BNT, COWAT, and Token Test) serving as the within-subjects factors, and sex (Male and Female) and laterality (Left and Right) serving as between-subjects factors. A significant language function x surgery x laterality interaction was obtained (Wilk's $F(3, 26) = 3.94$, $p = .02$; $\eta^2 = .31$; observed power = .77). Sex did not significantly interact with any other factor. Follow-up univariate tests of the simple effects on each of the dependent variables revealed that the only dependent variable for which the two-way interaction of surgery x laterality was significant was BNT performance ($F(1,32) =$

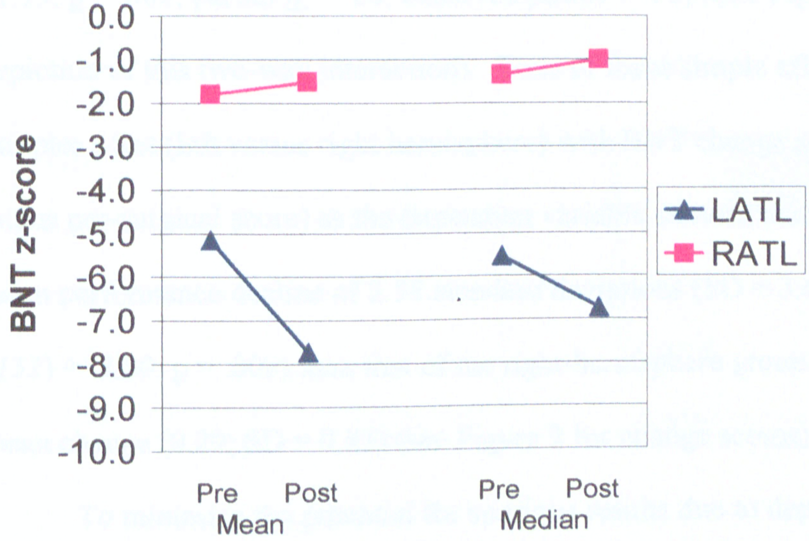

Figure 3. Mean and median time x laterality interaction on a measure of confrontation naming by hemispheric group.

11.19, p = .002; partial η^2 = .26; observed power = .90) (See Figure 3 for a graphical depiction of this two-way interaction). Tests of these simple effects using an independent-samples t-test (left versus right hemisphere) with BNT change scores (post-surgical score minus pre-surgical score) as the dependent variable showed that the left-hemisphere group mean performance decline of 2.58 standard deviations (SD = 3.64) was significantly different ($t(32) = -3.00$, $p = .009$) than that of the right-hemisphere group which showed virtually no mean change (0.29; SD = 0.83) (see Figure 2 for change scores).

To minimize the potential for spurious results due to departure from the parametric assumptions, a mixed factorial randomization (exact) test was performed on each of the dependent variables. Again, sex and laterality served as between-subjects factors and surgery served as the within-subjects factor. No significant three-way interaction emerged for any of the dependent variables and the only dependent variable to show a significant two-way interaction (Laterality x Surgery) was the BNT ($p = .09$). To test the simple effects an exact randomization independent-samples test was performed on the change scores for the BNT. Results showed a significant decline in BNT scores from pre- to post-surgery for the left-hemisphere group and no significant change for the right-hemisphere group ($p = .0005$). See Figure 4 for a representation of change scores for each language variable by hemispheric group.

A Pearson product moment correlation coefficient showed a statistically significant positive relationship between days from surgery to the follow-up neuropsychological assessment and change scores only for the MRATL group for the BNT ($r = .68$, $p < .05$) and the COWAT ($r = .70$, $p < .05$)[2]. Although the correlation only approached significance for

[2] Spearman's rho = .77 for the BNT and .75 for the COWAT; both at $p < .05$.

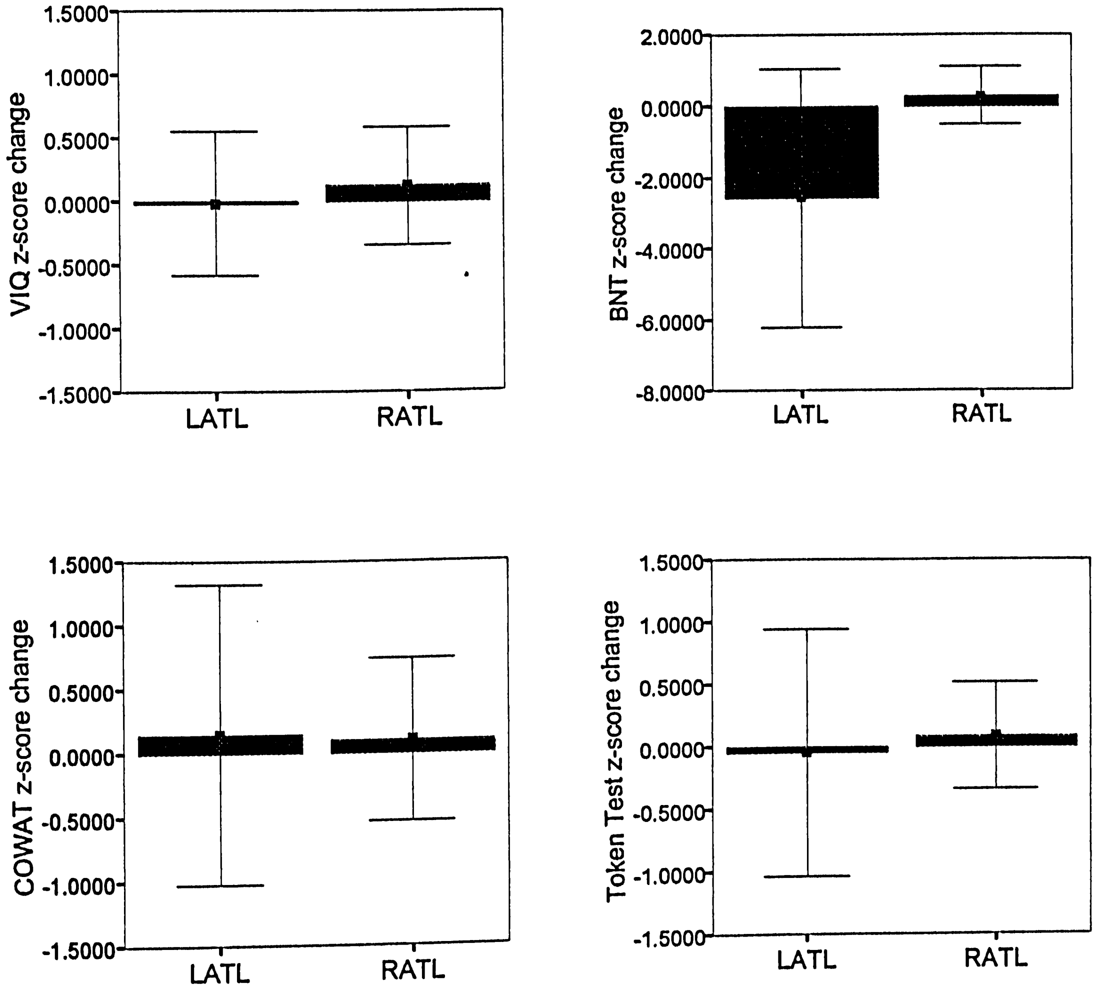

Figure 4. Mean change scores from pre- to post-surgical assessment on each language measure by seizure focus laterality group. Error bars represent one standard deviation.

the Token Test ($r = .65$, $p > .05$), use of Spearman's rank correlation demonstrated a significant association (Spearman's rho = .71).

CHAPTER IV

DISCUSSION

Summary

The purpose of this study was to evaluate changes in language function following anterior temporal lobectomy (ATL) for intractable temporal lobe epilepsy (TLE). Given mixed results from previous research, and previous literature suggesting sex related differences in language ability as well as hypometabolic and epileptogenic patterns, the present study sought to elucidate our understanding of language outcome following surgery by introducing sex as a possible explanatory factor. It was predicted that certain groups, based on a combination of their sex and laterality of seizure focus, would experience a differential change in specific language abilities following surgery and possible resolution of hypometabolism. Three specific domains of language function were investigated: object confrontation naming, verbal fluency, and auditory-verbal comprehension.

In the case of visual confrontation naming ability, it was predicted that MLATL and FLATL participants would experience a significant decline following surgery as neuroanatomical language regions are hypothesized to be more strongly lateralized to the dominant hemisphere of the brain in males and females are more likely to experience aphasia after anterior temporal lesions. These hypotheses were supported in that confrontation naming performance did significantly decline in both LATL groups, however, it is unclear whether this was due to sex related differences or some other factor. A significant improvement in confrontation naming performance was predicted in the FRATL group based on findings in the hypometabolic literature suggestive of bilateral resolution of interictal hypometabolism across the temporal lobes. However, no significant change following surgery was demonstrated in either the MRATL or FRATL groups.

In the case of verbal fluency, it was predicted that the MLATL group would experience significant improvement as normal metabolism returned to the frontal region of the dominant hemisphere following surgery. The results indicated that there was no significant change in verbal fluency from pre-surgical assessment for any group. The prediction that significant improvement in verbal-auditory comprehension following surgery would occur in the FRATL group due to the potential resolution of bilateral hypometabolism was also not supported. Further, general verbal-intellectual functioning did not change from pre- to post-surgery in any group.

Interpretation

As there was no effect of sex on any change in language performance on any variable of interest, this study failed to find support for the general hypothesis that differential changes in language function following ATL could be explained by sex differences. Only laterality of seizure focus was useful in determining change following ATL and then only in the case of confrontation naming. Although sex-related neuroanatomical differences may exist between males and females, no sex differences were observed in performance on measures of language function employed in the present study.

Work by others (e.g., Frost et al., 1999) has suggested that language processing is strongly left-lateralized in both males and females using large samples of healthy individuals in imaging-paradigm tasks. It is possible that sex differences do exist, but within-gender differences may be far greater than between-gender differences in the case of language function in the adult epilepsy population. Perhaps the neurophysiologic effects of epilepsy outweigh or distort neurocognitive sex differences reported elsewhere. Given the disagreement within the literature as to the existence of sex related differences both anatomical and cognitive, perhaps sex is only a proxy variable that does not yield consistent results in neuro-scientific research. For instance, there are virtually no studies that measure hormonal levels which are responsible for neuroanatomic variation and perhaps neurocognitive variation. In research regarding sex differences, it should be kept in mind that males and females share more commonalities than differences. In fact, after reviewing much of the then current literature on cerebral asymmetry, McGlone (1980) stated "the most basic conclusion is that basic patterns of male and female brain asymmetry seem to be more similar than they are different" (p. 226).

The results of the present study are in agreement with the findings of Davies and colleagues (Davies, et al., 1994; Davies et al., 1995) who reported that verbal fluency performance in participants with LATL remains unchanged from pre-surgical status. Additionally, their finding that post-RATL participants experienced no change in confrontation naming and slight, yet non-significant, improvements in verbal fluency was also replicated. However, rather than a stabilization in confrontation naming performance from pre- to post-surgery in patients with LATL, the present study found a statistically significant decline. With respect to confrontation naming, the present findings are most consistent with the results presented by Langfitt and Rausch (1996) and Hermann, et al. (1999) which showed LATL patients experiencing a significant decline following surgery.

The results of the present study differ from those of previous reports which demonstrated significant improvements in language function following surgery. For example, the finding that verbal fluency improved post-surgically (Hermann and Wyler, 1988; Loring et al., 1994; Martin et al., 2000) was not supported. Also not replicated was the finding of improvement in auditory comprehension (Hermann and Wyler, 1988) or confrontation naming ability following RATL (Langfitt and Rausch, 1996).

Decline in Confrontation Naming Following ATL

A decline in confrontation naming performance following ATL does not infer that naming functions are localized in the anterior temporal lobe. Confrontation naming is represented by a distributed system which includes visual recognition (Ungerleider & Mishkin, 1982), selection and retrieval processes, and productive speech. A disruption at any localized "node" of this system may lead to anomia.

Functional imaging techniques have helped to identify brain regions implicated in object naming tasks (Carbeza & Nyberg, 2000). The extreme ventral location the temporal pole (BA 38) is often beyond the brain region covered by many imaging scans. This is unfortunate as this area has an important role in frontotemporal connectivity and is the brain region resected during ATL (Markowitsch, 1995). However, many regions of the dominant hemisphere involved in confrontation naming have been identified by using imaging techniques such as components of the ventral visual processing stream (large portions of the left fusiform gyrus of the ventral occipital-temporal region, left inferior temporal lobe), the left inferior frontal-insular cortex (Zelkowicz, Herbster, Nebes, Mintun, & Becker, 1998), the left lateral temporal lobe, and the left posterior parietal lobe (Mummery, Patterson, Hodges, & Price, 1998). From studies using electrical stimulation mapping, naming errors or arrest are most likely to occur following stimulation of the superior temporal gyrus, compared with the middle or inferior gyri (Ojemann, G., Ojemann, J., Lettich, & Berger, 1989).

The process of confrontation object naming involves retrieval of a word from memory. The decline in naming performance following surgery may be related to a disruption in the retrieval process. As the hippocampus is often resected as part of the ATL procedure, this could interfere with retrieval or represent a disconnection between visual input and the hippocampus, disrupting the "what" visual pathway (Ungerleider & Mishkin, 1982) which then could lead to anomia. As the majority of the sample in the present study had both the hippocampus and the lateral anterior temporal cortex removed it was not able to separate the effects and study the removal of each region alone.

Others have hypothesized that the decline in confrontation naming following ATL is due in part to the nature of the words one is asked to name. For instance, Bell and colleagues (Bell, Davies, Hermann, & Walters, 2000) found that object names learned late in childhood were the most vulnerable following ATL. They also showed that there was no difference between naming living versus non-living things, words of different phonemic length, or words of different usage frequency following ATL. The deficit in naming objects whose names are acquired later in life is hypothesized to be related to impairment at either the phonological or semantic level of processing. From the phonological perspective, words learned early in life are most likely well-established and stored in complete form. Words acquired later in life may not be as well-established and only partially represented. When required, words learned later in life may demand regeneration of the unstored information. This more complicated process may be more vulnerable to brain injury. In regard to the role of semantic processes, later-learned object names may be more susceptible to disruption by brain insult as their associative connections may be low in number and strength (Johnson, Paivio, & Clark, 1996). In the present study a record of the type of naming error made on

BNT items was not available for all patients, thus an assessment of phonemic and semantic retrieval difficulties could not be performed.

Although the study by Bell et al. (Bell, 2000) showed no difference in difficulty naming living and non-living things following ATL it should be kept in mind that only 14 of 60 items represent living things on the BNT. A separate analysis was performed among the minority of individuals who had an effect for the living/nonliving variable. It was shown that individuals had more difficulty naming living things following ATL. These results were not consistent with others (Luckhurst & Lloyd-Jones, 2001; Tippett, Glosser, & Farah, 1996) who reported more difficulty with nonliving items following ATL. The living and nonliving items presented by Tippet et al. were matched on frequency, familiarity, and visual complexity, but they were not matched at age at acquisition. The poor performance in naming nonliving items in the Tippet et al. study may be explained by the fact that the mean age at acquisition for the nonliving items was significantly higher.

If seizures begin before the age of five, there is a high probability of cerebral reorganization. Such changes could range from a transfer of language function to the right hemisphere to atypical language representation in the dominant hemisphere. Rasmussen and Milner (1977) and later Devinsky and colleagues discussed the displacement of language functions as dependent not on early damage to the dominant temporal lobe, but following insult to the dominant frontal or parietal regions (Devinsky, Perrine, Llinas, Luciano, & Dogali, 1993). Early damage to the sensorimotor regions of the left frontoparietal lobes leads to a transfer of motor dominance in the right hemisphere which is strongly associated with the development of language function. The effect of early onset dominant temporal lobe epilepsy differs as motor dominance does not shift contralaterally, and consequently, nor does language. However, language sites could still be displaced within the hemisphere, either anteriorly (Devinsky et al., 1993) or into parietal regions (Ojemann & Whitaker, 1978).

Stable performance on measures of confrontation naming following ATL has been associated with individuals who had.an earlier age of seizure onset, while individuals with later age of onset experience greater declines (Davies, et al., 1996). This could indicate a system of distributed semantic stores which are less likely to be impacted by a localized resection (Saykin et al., 1995). In fact, Devinsky and colleagues have reported an association between early onset dominant temporal lobe epilepsy and a greater number of anterior temporal naming and reading sites (Devinsky, et al., 1993; Devinsky, et al., 2000). However, contrary to the findings of Davies et al., the post-surgical group investigated by Devinsky et al. were shown to have declines in confrontation naming function following surgery regardless of whether they had anterior temporal naming areas. Those with anterior temporal naming areas displayed poorer neurocognitive functioning (including language) and had fewer years of education than those with a normal language distribution. Due to the small sample size and focus on sex-related differences in the present study, age at seizure onset was not taken into account in the present study.

Stabilization of Verbal Fluency, Auditory-Verbal Comprehension, & Verbal-Intellectual Function

As there was no improvement observed in auditory-verbal comprehension and verbal fluency for any group it may be reasonable to hypothesize that a trade-off occurred between a reduction in "neural noise" due to seizures and possible post-ATL disturbances in language function due to resection of brain regions employed by the language system. In the case of auditory-verbal comprehension, the lack of improvement may simply represent a low psychometric ceiling effect and thus limited sensitivity to changes in this neurocognitive ability. Verbal fluency and confrontation naming may represent different aspects of a similar ability in that they are both means of retrieval from a lexical store. As performance on the verbal fluency task is not visually mediated, it may be somewhat more immune from the effects of ATL than is visual confrontation naming. As frontal regions are likely to experience improved glucose metabolism following ATL, verbal fluency should improve. However, if there is damage to the lexical store or the pathways that lead to its resources, verbal fluency performance may not improve. If the disturbances to confrontation naming and verbal fluency prior to surgery involved primarily phonological retrieval problems, the increased deficits experienced following surgery may be due to the removal of functional neurons within the hippocampus and may involve additional semantic retrieval difficulties. Verbal-intellectual functioning represents crystallized intelligence which is generally robust to most brain insults.

Limitations

The results of this study may only be generalizable to those individuals with TLE who meet inclusion criteria similar to that utilized in the present study. The results may also not generalize to other racial or geographic groups as the sample employed for this study was entirely Caucasian (with the exception of one Asian American) and from a U.S. Midwestern locale. Although the methods used by the neurosurgery team were not compared to those used at other hospital centers, they may differ and thus potentially lead to different neurolinguistic outcomes following surgery.

As this study is non-experimental and observational in nature, chief among methodological limitations is the lack of randomization to treatment groups or the manipulation of those treatments as the sample utilized was one of convenience. Also, no delayed-surgery control group was used to demonstrate whether language functions remain stable or worsen as a result of prolonged seizure activity. The small sample size utilized in this study was similar to those used in previous studies on this topic. However, this may lead to an increased chance of Type II error because of low power. Using exact statistics, an attempt was made to corroborate the results of the traditional parametric statistics and in each analysis the results were upheld.

Another potential limitation inherent with any pre/post design is the possibility of practice effects. Several studies (Chelune, Naugle, Luders, & Awad, 1991; Hermann, et al., 1996; Sawrie, Chelune, Naugle, & Luders, 1996) have attempted to remedy potential neuropsychometric carry-over effects through use of repeated testing of patients who do not undergo surgery. From these efforts reliable change indices (RCI) were developed to take into account the reliability of each measure and practice effects. As such, these scores provide a method for determining whether a participant's performance at retest is significantly changed from baseline. However, the RCI scores were developed using raw scores which were not available for all participants in the present study. Further, the interval between testing sessions in the studies from which the RCI scores were developed ranged from six to nine months and the post-surgical interval was six months, whereas the testing interval in the present study ranged from 11 to 20 months and the post-surgical interval was nearly 12 months. Although these differences in time may not be drastic, the language measures employed in the present study are among some of the most reliable neuropsychological measures used in a test-retest situation with an extended retest period (Hermann, et al., 1996). Therefore, it is doubtful if significant practice effects are a confound in this study.

Groups also differed with respect to age as the FLATL group was significantly younger than the MRATL group. However, the correction for age of participant was used in the computation of raw scores for three of the four measures utilized in the present study. The age difference may still lead to different levels of performance as those with a longer duration of seizures may have more impoverished neurocognitive function as a result of long-term seizure activity (Jokeit & Ebner, 1999). As age at surgery or any other age-related variable (e.g., age at seizure onset, duration of seizure activity) was not under consideration in the present study, these variables may be relevant for future research. Although not significantly different, a years of education difference between hemispheric groups of a little more than one year (LTAL 11.86 years, RATL 13.05 years) bridges the time period between high school and the 1st year of college. In part, this may explain the vast performance difference between hemispheric groups on the measure of confrontation naming ability. Those who complete high school and go on to college may have an educational/experiential advantage on such a verbal-semantic task.

A major factor which guided the hypotheses of the present study was that epilepsy-related hypometabolism differed between the sexes. Unfortunately, there was no way to quantitatively measure this variable as PET results were only available for a small portion of the sample utilized in the present study. It is possible that in this sample there was no significant resolution of hypometabolism. However, in order to maximize the likelihood of investigating the effects of normalization in glucose metabolism, a follow-up analysis that included only those participants who were seizure free following surgery yielded identical results.

Future Research

This study was able to corroborative the results of other studies in this area. However, future research should include other seizure and sex-related variables which could further our understanding of epilepsy and human sex-related neuropsychological differences. Although it is difficult to follow participants longitudinally for a year or more, perhaps alternative means, such as inter-site pooling of data would be possible. Use of a larger sample size would permit inclusion of other variables of interest such as age at seizure onset, hormonal levels, and hypometabolic measurements.

Conclusions

With the exception of visual confrontation naming, the results of this study would indicate that no significant change occurs in language functioning following surgery in cases of LATL or RATL in both males and females. In other words, this study provides no evidence for significant improvement and, perhaps more importantly, no significant decline in language functions following ATL with the exception of confrontation naming in the case of individuals with LATL. This information can be relayed to the individual considering surgery for TLE so that the benefit of seizure relief and the stabilization of many verbal functions, as well as the risk to word-finding abilities following surgery, can be understood.

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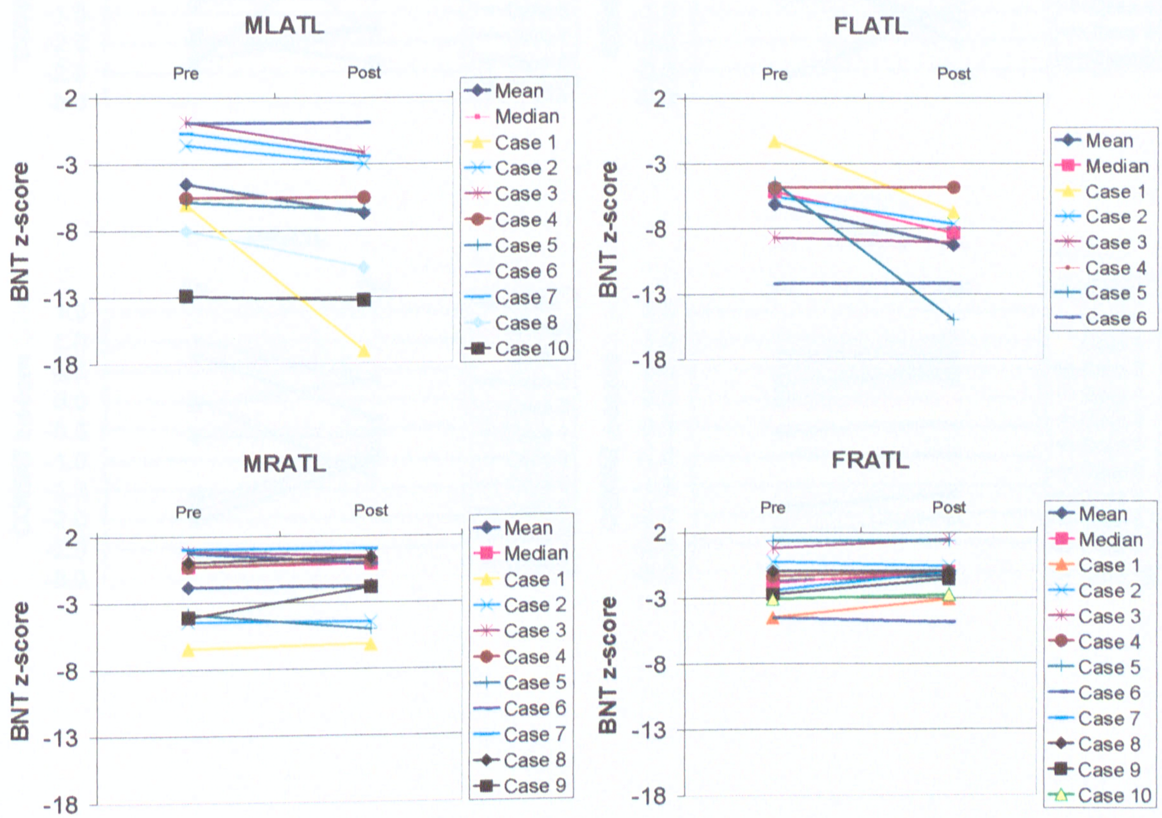
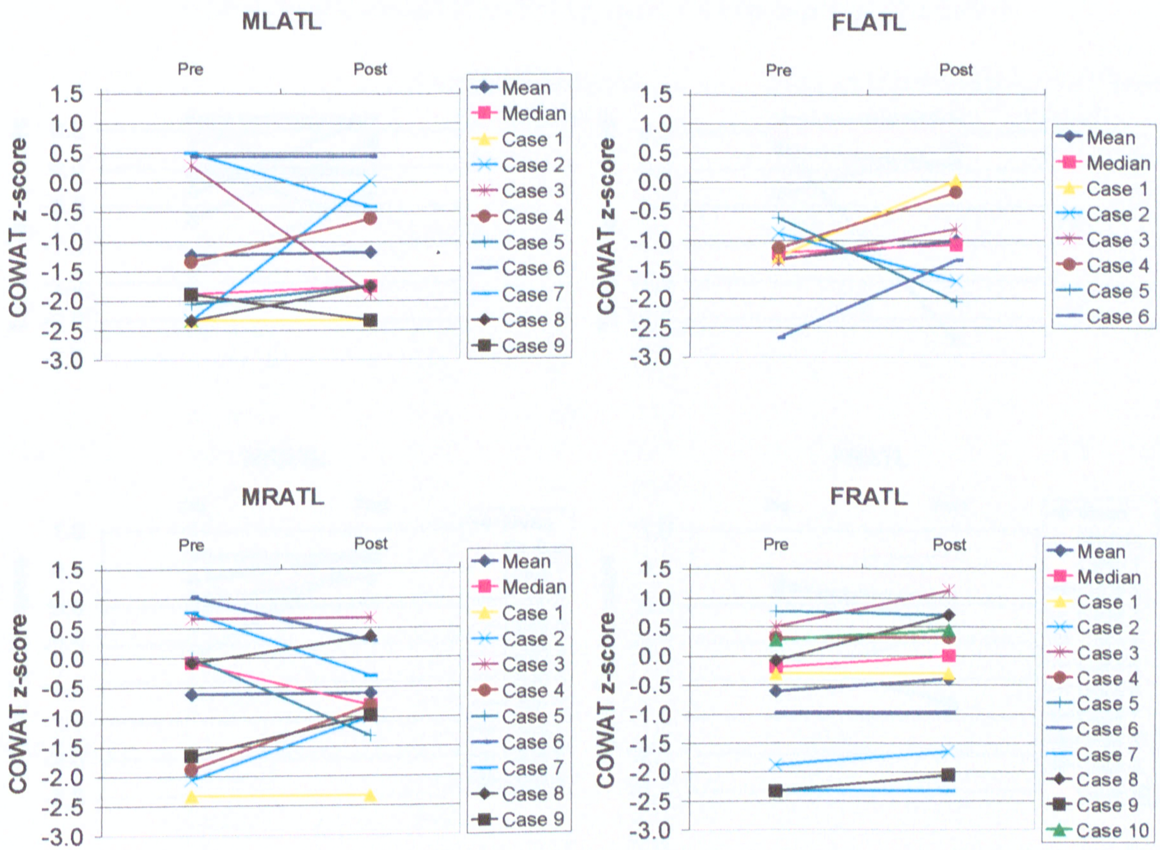
APPENDIX A

Pre- to Post-Surgical Change on each Language Variable by Group on a Case by Case Basis

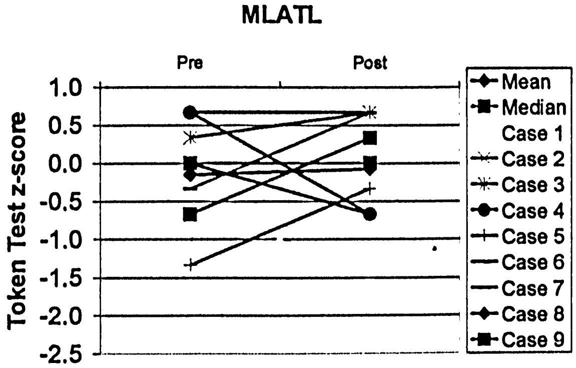
Visual Confrontation Naming (BNT)

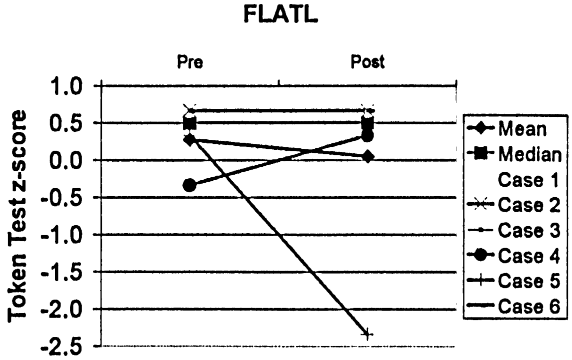


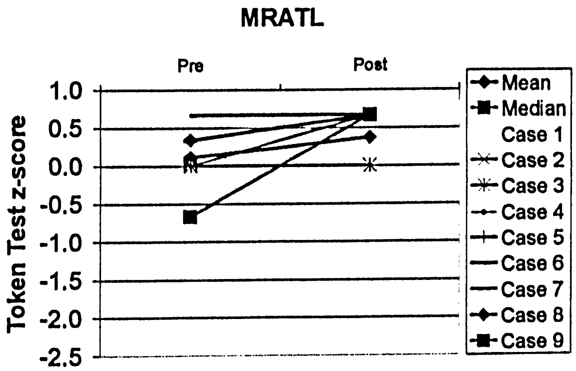
Verbal Fluency (COWAT)

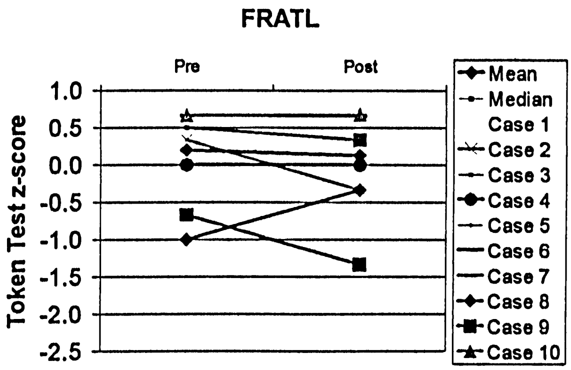


Verbal-Auditory Comprehension (Token Test)









APPENDIX B

Univariate Tests of Normality and Homogeneity of Variance

		Test of Normality Shapiro-Wilk			Test of Homogeneity of Variance Levene's Statistic[a]			
Variable	Group	Statistic	df	p	Statistic	df1	df2	p
Pre-VIQ	MLATL	.924	9	.441	5.26	3	28	.005*
	FLATL	.938	6	.590				
	MRATL	.870	7	.242				
	FRATL	.916	10	.373				
Post-VIQ	MLATL	.930	9	.475	1.79	3	28	.172
	FLATL	.935	6	.569				
	MRATL	.943	7	.633				
	FRATL	.981	10	.970				
Pre-BNT	MLATL	.902	9	.324	2.15	3	30	.114
	FLATL	.956	6	.747				
	MRATL	.859	7	.194				
	FRATL	.955	10	.706				
Post-BNT	MLATL	.923	9	.437	4.43	3	30	.011*
	FLATL	.950	6	.696				
	MRATL	.860	7	.198				
	FRATL	.945	10	.579				
Pre-COWAT	MLATL	.779	9	.016*	3.12	3	30	.041*
	FLATL	.852	6	.202				
	MRATL	.846	7	.134				
	FRATL	.877	10	.147				
Post-COWAT	MLATL	.893	9	.277	1.17	3	30	.338
	FLATL	.928	6	.505				
	MRATL	.918	7	.458				
	FRATL	.905	10	.311				
Pre-Token Test	MLATL	.947	9	.630	1.41	3	30	.258
	FLATL	.734	6	.017*				
	MRATL	.890	7	.332				
	FRATL	.792	10	.014*				
Post-Token Test	MLATL	.902	9	.329	1.56	3	30	.220
	FLATL	.614	6	.010*				
	MRATL	.598	7	.010*				
	FRATL	.802	10	.018*				

Note. [a]Levene statistic is based on the mean.

*$p < .05$.

APPENDIX C

Analysis of Skewness and Kurtosis

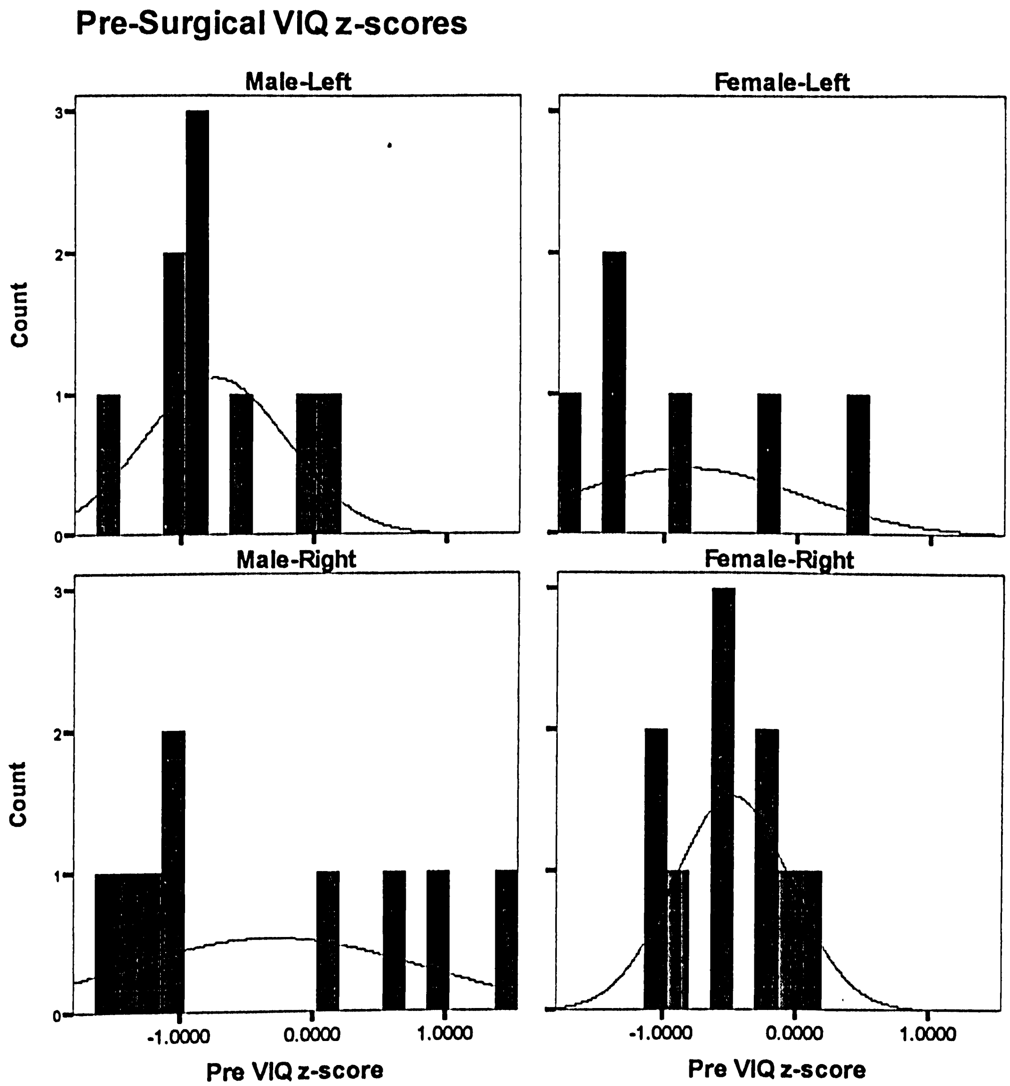
	Group	SE of Kurtosis	Kurtosis	SE of Skewness	Skewness	SK_p[a]	Fisher Kurtosis Coefficient[b]
Pre-VIQ	MLATL	0.1582	1.3997	0.4507	0.7171	0.6631*	0.1130
	FLATL	-0.1355	1.7408	0.7687	0.8452	0.8222*	-0.0779
	MRATL	-1.5039	1.3997	0.5451	0.7171	1.8227*	-1.0745
	FRATL	-1.4296	1.3342	0.1611	0.6870	0.6422*	-1.0714
Post-VIQ	MLATL	-1.6844	1.3997	0.1655	0.7171	0.7099*	-1.2034
	FLATL	1.4304	1.7408	1.1051	0.8452	0.5585*	0.8217
	MRATL	0.1968	1.5875	0.5961	0.7937	-0.6719*	0.1240
	FRATL	-0.0213	1.3342	0.0266	0.6870	-0.0672	-0.0160
Pre-BNT	MLATL	0.0091	1.3997	-0.7013	0.7171	0.7340*	0.0065
	FLATL	0.3850	1.7408	-0.6093	0.8452	-0.7788*	0.2212
	MRATL	-1.6574	1.3997	-0.4559	0.7171	-1.6005*	-1.1841
	FRATL	-1.0783	1.3342	0.0953	0.6870	0.1566	-0.8082
Post-BNT	MLATL	-0.5905	1.3997	-0.7428	0.7171	-0.6091*	-0.4219
	FLATL	-0.5803	1.7408	-0.6338	0.8452	-0.7229*	-0.3334
	MRATL	-1.4284	1.3997	-0.6959	0.7171	-1.7612*	-1.0205
	FRATL	0.1095	1.3342	-0.2703	0.6870	-0.4741	0.0821
Pre-COWAT	MLATL	-1.7620	1.3997	0.6616	0.7171	1.5496*	-1.2588
	FLATL	3.4435	1.7408	-1.6559	0.8452	-0.4740	1.98**
	MRATL	-2.1131	1.3997	-0.1011	0.7171	-1.1813*	-1.5097
	FRATL	-1.4493	1.3342	-0.5571	0.6870	-1.0309*	-1.0863
Post-COWAT	MLATL	-1.5992	1.3997	0.3937	0.7171	1.6408*	-1.1425
	FLATL	-1.8308	1.7408	0.1024	0.8452	0.2398	-1.0517
	MRATL	-0.2505	1.3997	-0.3634	0.7171	0.6400*	-0.1790
	FRATL	-1.5052	1.3342	-0.4470	0.6870	-0.9607*	-1.1281
Pre-Token Test	MLATL	-0.4855	1.3997	-0.4025	0.7171	-0.6644*	-0.3469
	FLATL	-2.0521	1.7408	-0.7107	0.8452	-1.3587*	-1.1788
	MRATL	1.9429	1.3997	-0.8433	0.7171	0.8944*	1.3880
	FRATL	0.1208	1.3342	-1.1383	0.6870	-1.4691*	0.0905
Post-Token Test	MLATL	-0.9322	1.3997	-0.4877	0.7171	-0.3077	-0.6660
	FLATL	5.5975	1.7408	-2.3465	0.8452	-1.1284*	3.22**
	MRATL	-2.5714	1.3997	-0.2711	0.7171	-2.5298*	-1.8371
	FRATL	1.2021	1.3342	-1.2008	0.6870	-0.8950*	0.9010

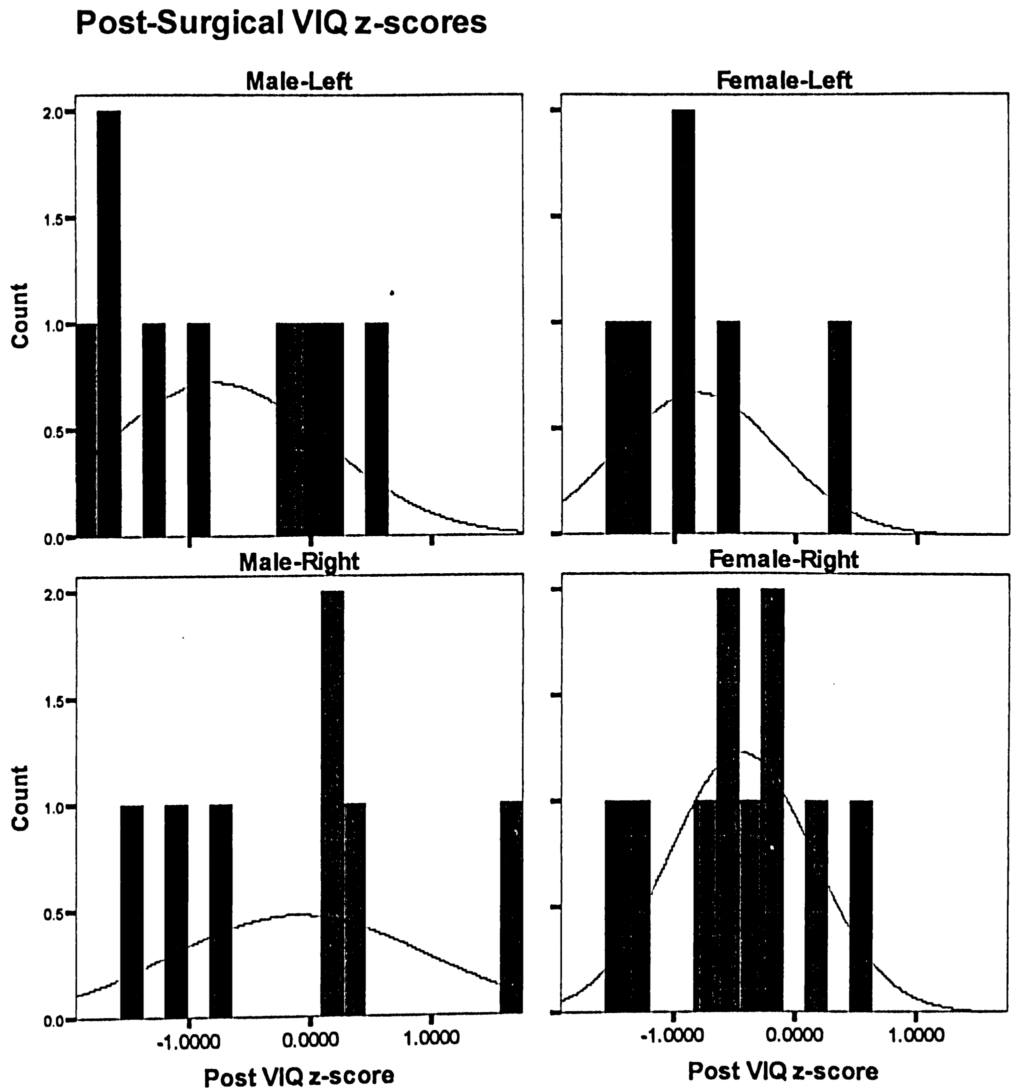
Note. [a]SK_p = Pearson skewness coefficient; *Skewness beyond +/- .50 (Lehman, 1991).

[b]Fisher Kurtosis Coefficient = Kurtosis/SE of Kurtosis; ** non-mesokurtic beyond +/- 1.96.

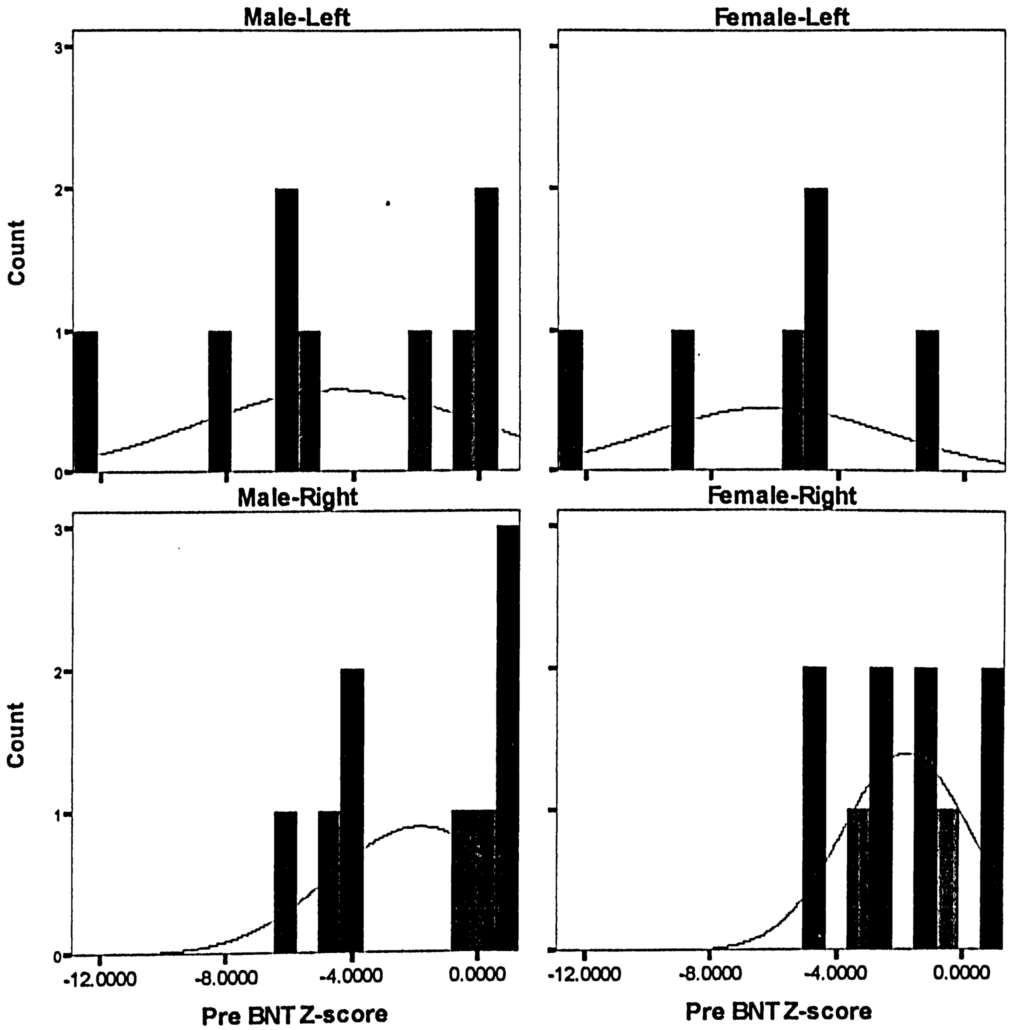
APPENDIX D

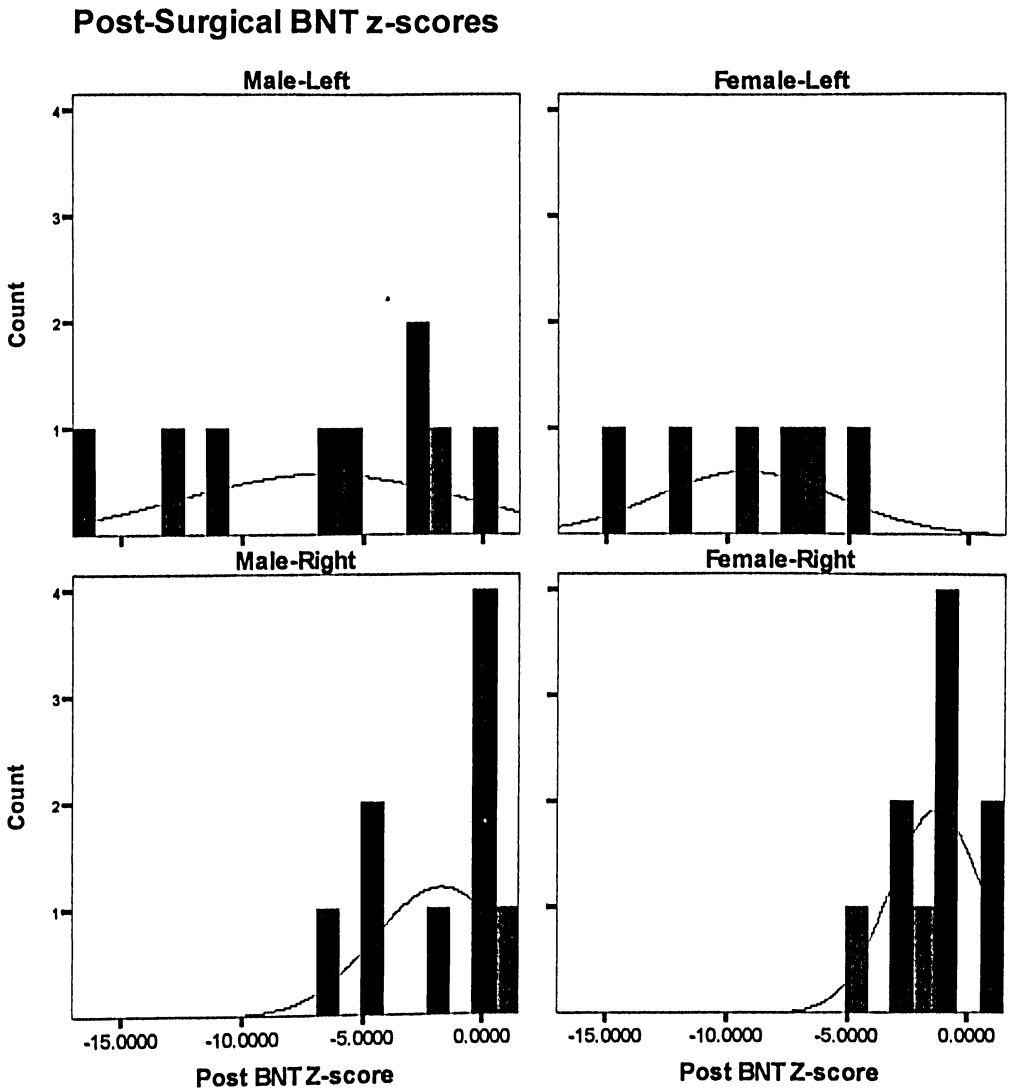
Histograms of Dependent Variables Both Pre- and Post-Surgically by Subgroup



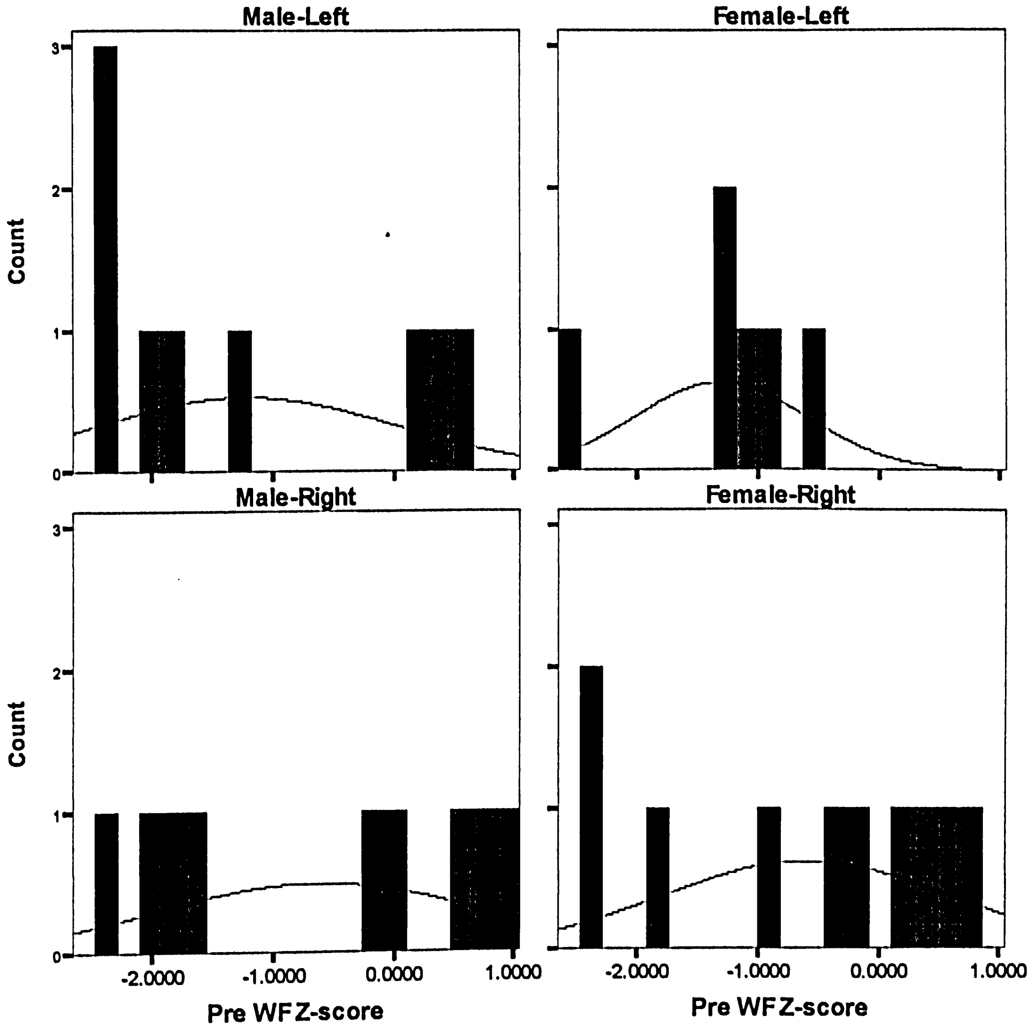

Post-Surgical VIQ z-scores
Male-Left
Female-Left
Male-Right
Female-Right
Count
2.0
1.5
1.0
0.5
0.0
-1.0000
0.0000
1.0000
Post VIQ z-score

Pre-Surgical BNT z-scores

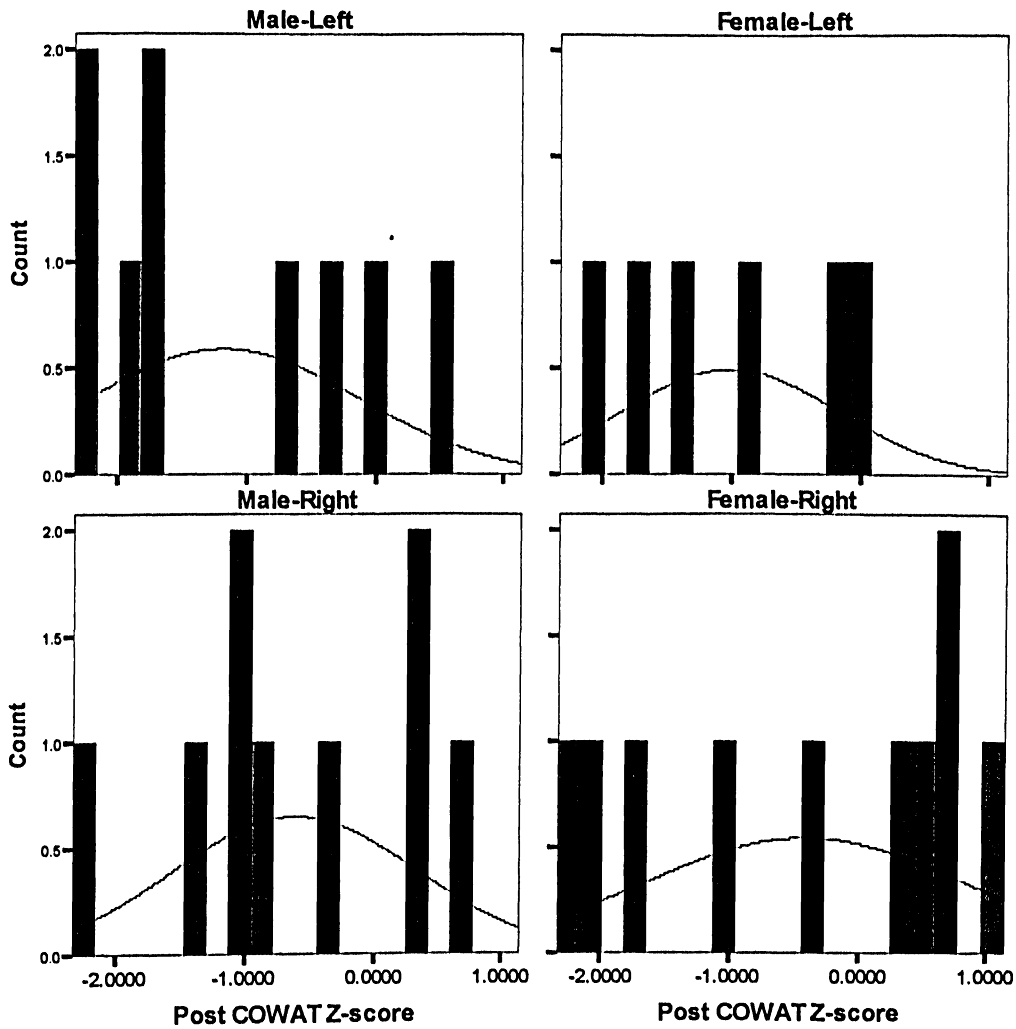


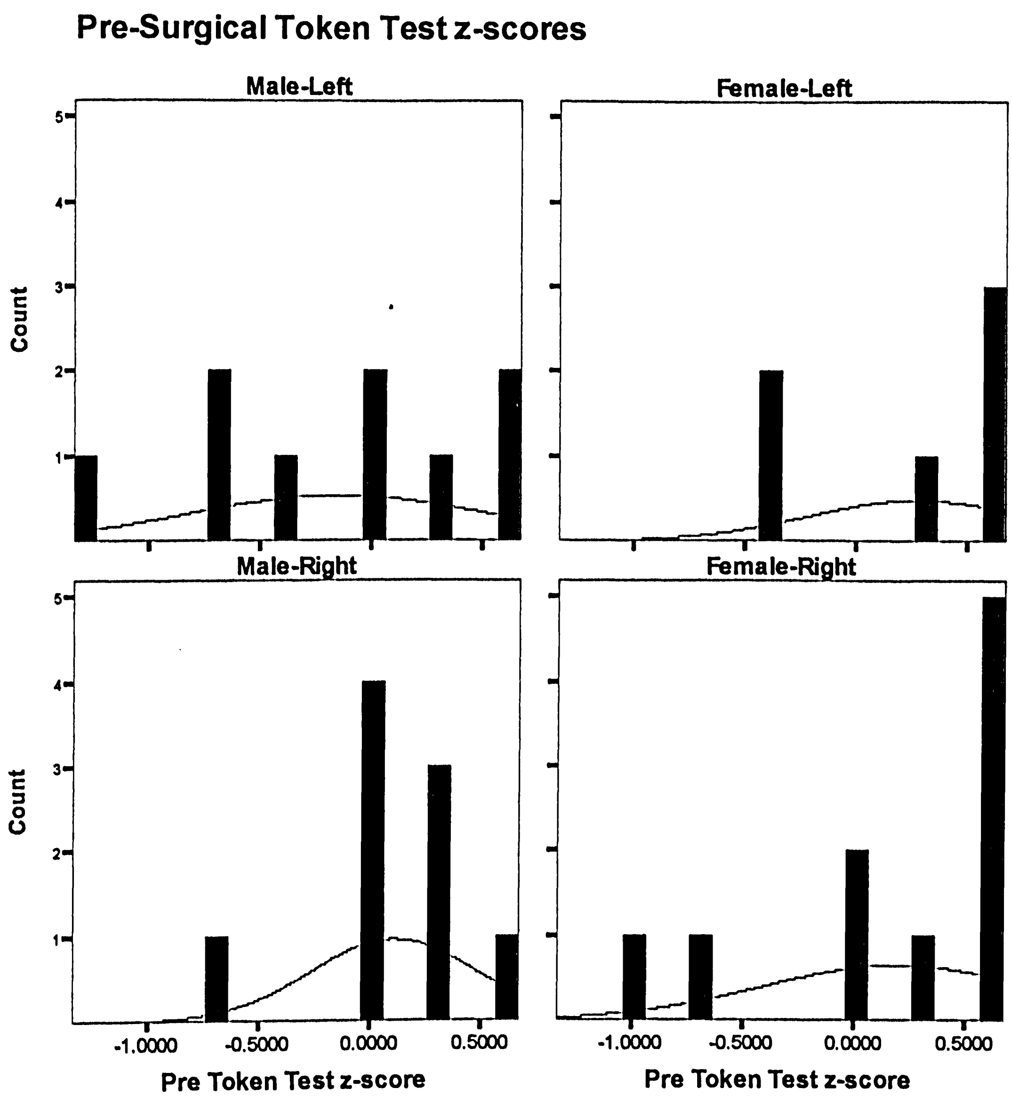

Post-Surgical BNT z-scores
Male-Left
Female-Left
Male-Right
Female-Right
Count
Count
4
3
2
1
4
3
2
1
-15.0000
-10.0000
-5.0000
0.0000
-15.0000
-10.0000
-5.0000
0.0000
Post BNT Z-score
Post BNT Z-score

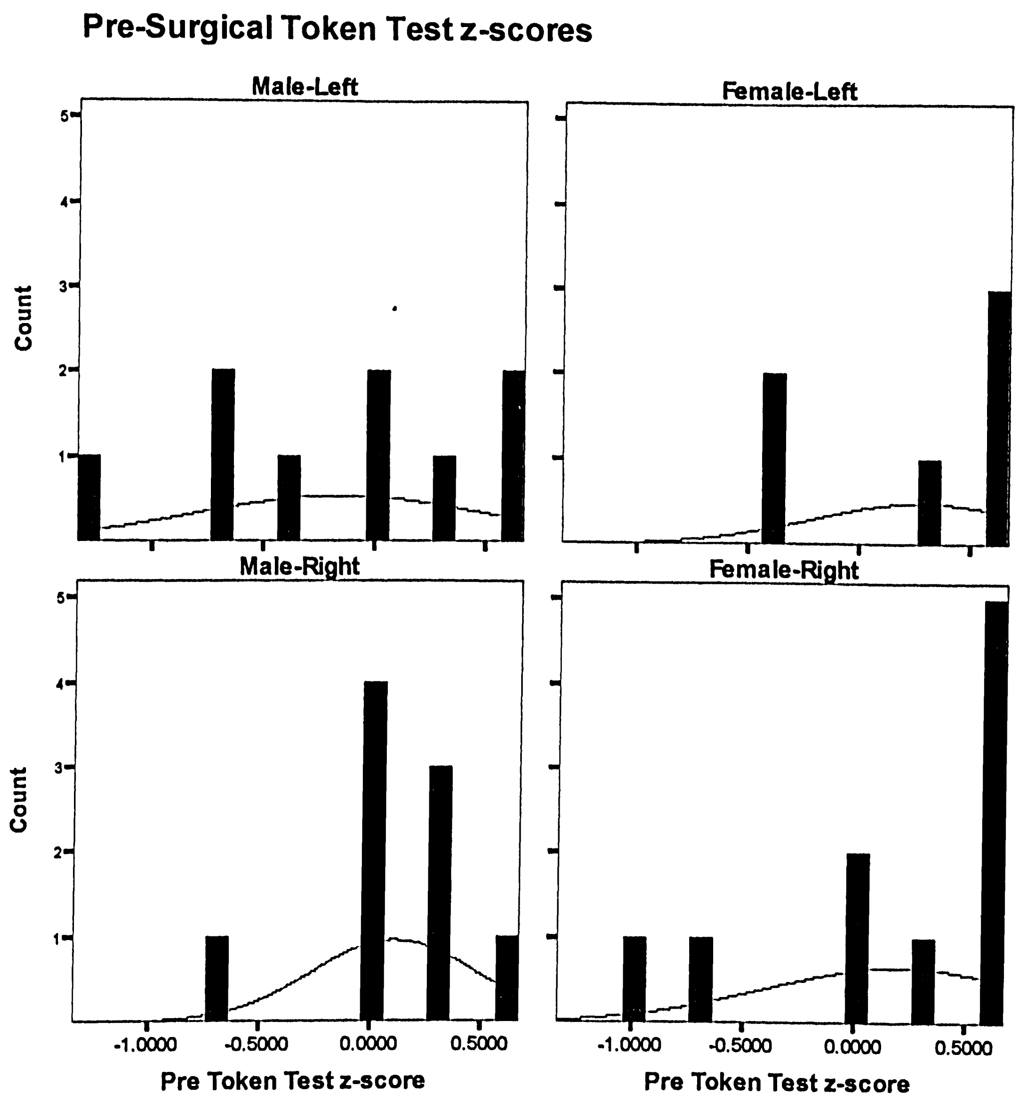
Pre-Surgical COWAT z-scores



Post-Surgical COWAT z-scores




Pre-Surgical Token Test z-scores
Male-Left
Female-Left
Male-Right
Female-Right
Count
Count
5
4
3
2
1
-1.0000
-0.5000
0.0000
0.5000
Pre Token Test z-score
Pre Token Test z-score



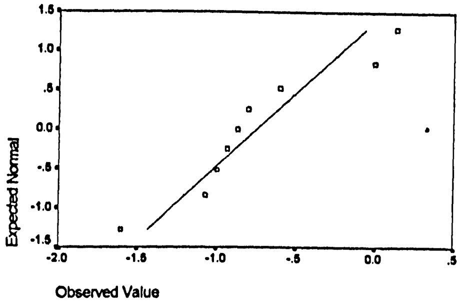
Pre-Surgical Token Test z-scores
Male-Left
Female-Left
Male-Right
Female-Right
Count
Count
5
4
3
2
1
-1.0000
-0.5000
0.0000
0.5000
Pre Token Test z-score
Pre Token Test z-score

APPENDIX E

Q-Q and Detrended Normal Q-Q Plots for Each Language Variable

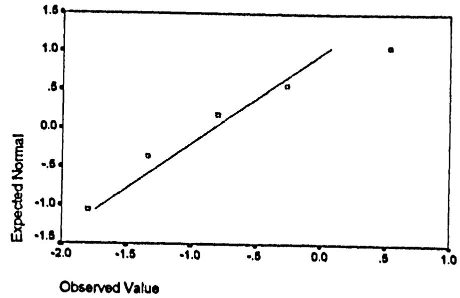
Normal Q-Q Plot of Pre VIQ z-score

For GPID= Male-Left



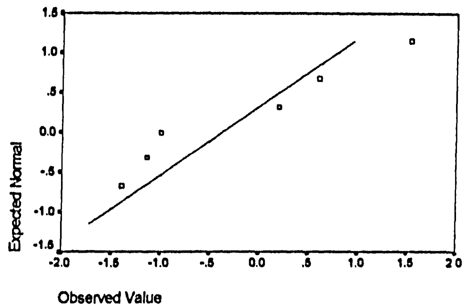
Normal Q-Q Plot of Pre VIQ z-score

For GPID= Female-Left



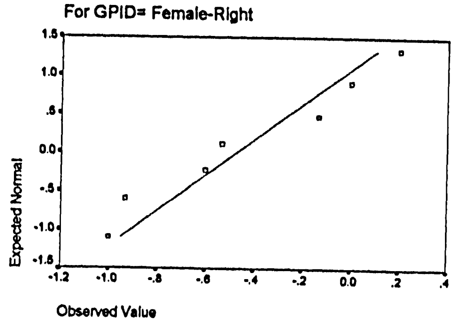
Normal Q-Q Plot of Pre VIQ z-score

For GPID= Male-Right



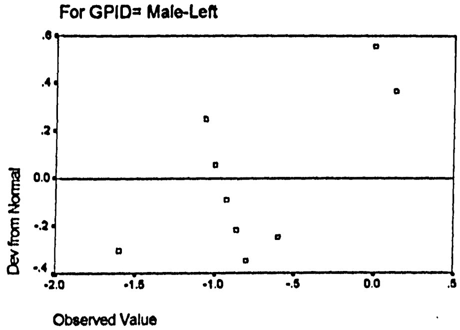
Normal Q-Q Plot of Pre VIQ z-score

For GPID= Female-Right



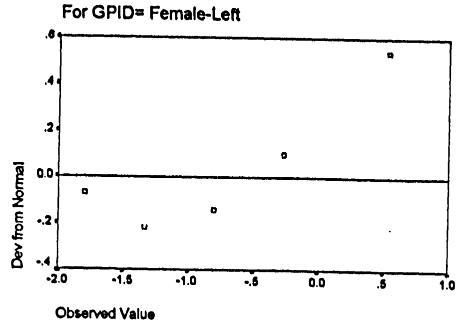
Detrended Normal Q-Q Plot of Pre VIQ z-score

For GPID= Male-Left



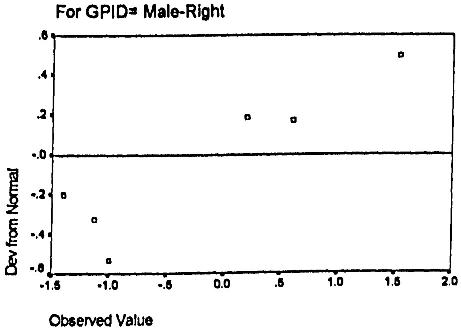
Detrended Normal Q-Q Plot of Pre VIQ z-scoı

For GPID= Female-Left



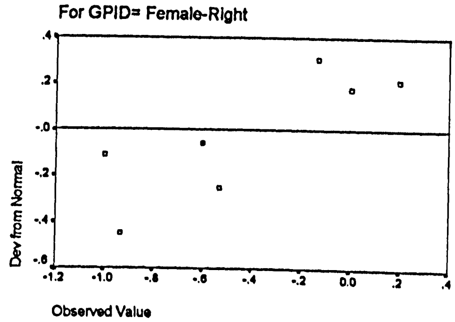
Detrended Normal Q-Q Plot of Pre VIQ z-score

For GPID= Male-Right



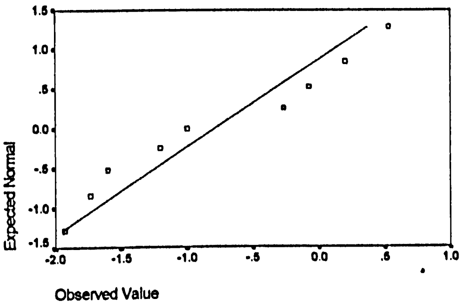
Detrended Normal Q-Q Plot of Pre VIQ z-score

For GPID= Female-Right



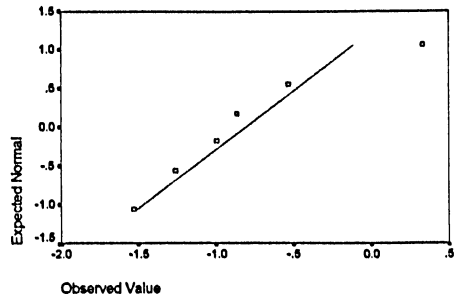
Normal Q-Q Plot of Post VIQ z-score

For GPID= Male-Left



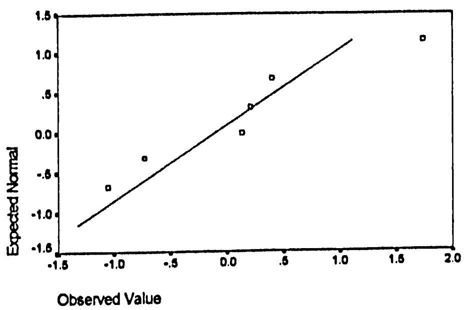
Normal Q-Q Plot of Post VIQ z-score

For GPID= Female-Left



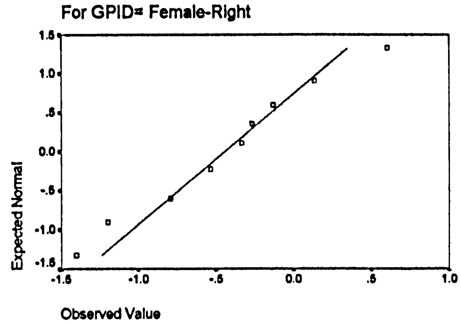
Normal Q-Q Plot of Post VIQ z-score

For GPID= Male-Right



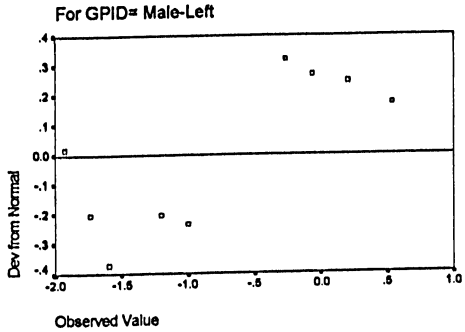
Normal Q-Q Plot of Post VIQ z-score

For GPID= Female-Right



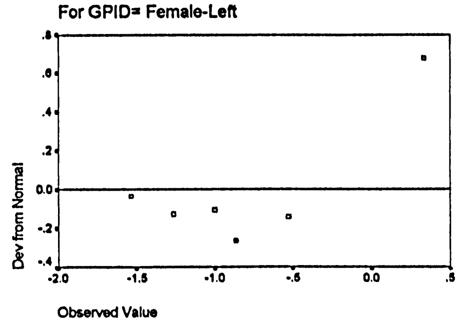
Detrended Normal Q-Q Plot of Post VIQ z-scoı

For GPID= Male-Left



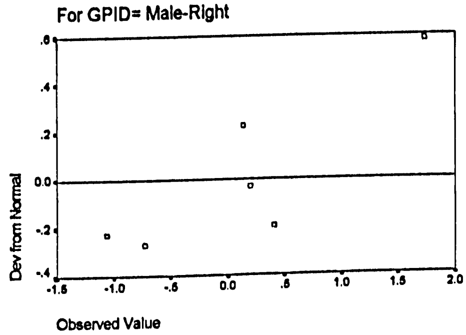
Detrended Normal Q-Q Plot of Post VIQ z-scı

For GPID= Female-Left



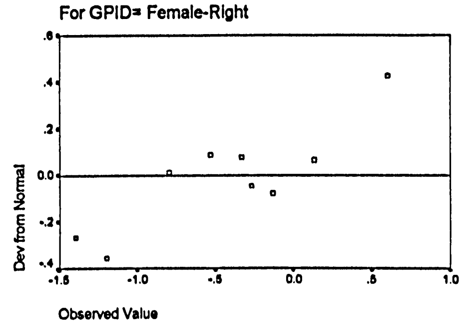
Detrended Normal Q-Q Plot of Post VIQ z-scoı

For GPID= Male-Right



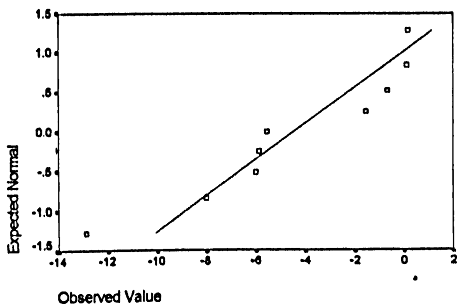
Detrended Normal Q-Q Plot of Post VIQ z-scı

For GPID= Female-Right



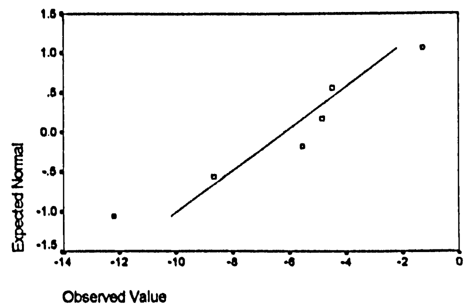
Normal Q-Q Plot of Pre BNT Z-score (age)

For GPID= Male-Left



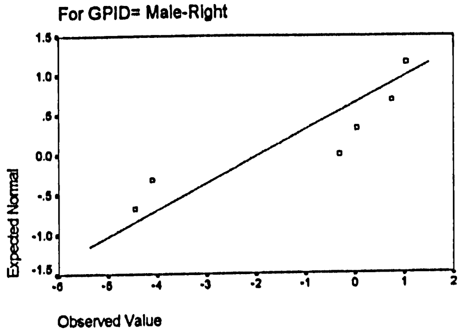
Normal Q-Q Plot of Pre BNT Z-score (age)

For GPID= Female-Left



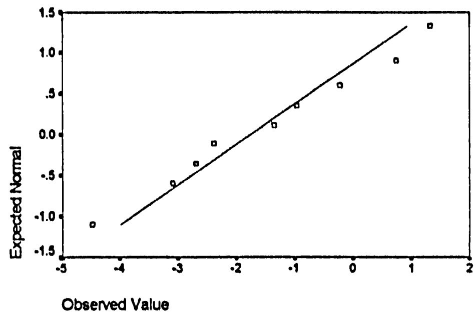
Normal Q-Q Plot of Pre BNT Z-score (age)

For GPID= Male-Right



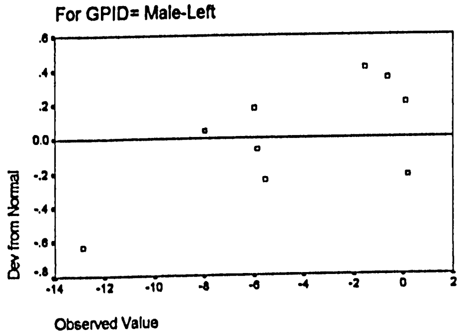
Normal Q-Q Plot of Pre BNT Z-score (age)

For GPID= Female-Right



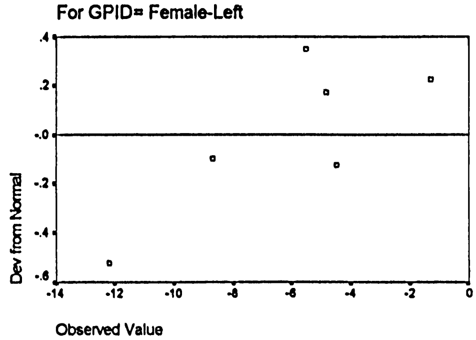
Detrended Normal Q-Q Plot of Pre BNT Z-scor

For GPID= Male-Left



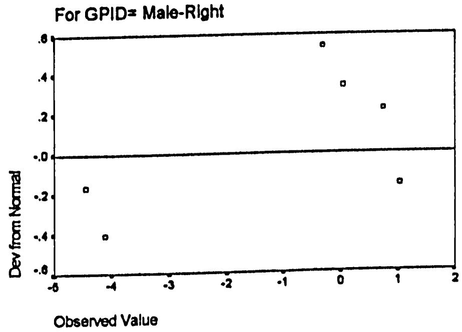
Detrended Normal Q-Q Plot of Pre BNT Z-scor

For GPID= Female-Left



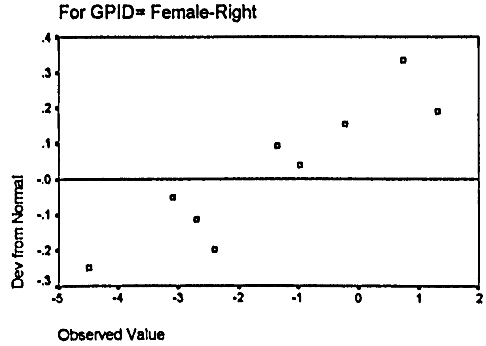
Detrended Normal Q-Q Plot of Pre BNT Z-scor

For GPID= Male-Right



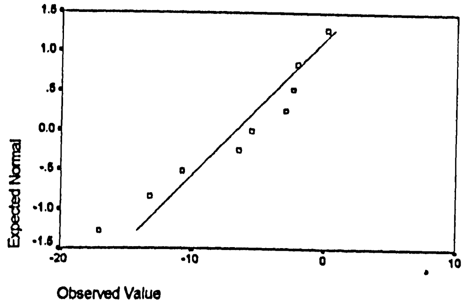
Detrended Normal Q-Q Plot of Pre BNT Z-scor

For GPID= Female-Right



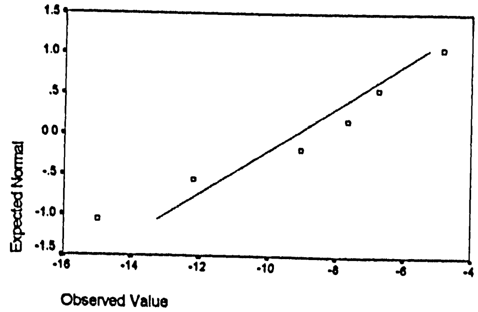
Normal Q-Q Plot of Post BNT Z-score (age)

For GPID= Male-Left



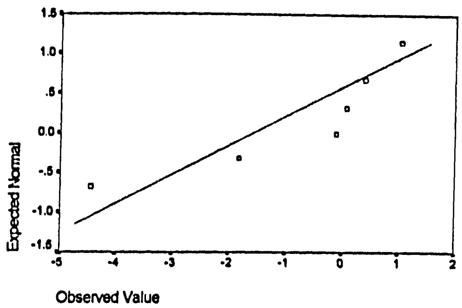
Normal Q-Q Plot of Post BNT Z-score (age)

For GPID= Female-Left



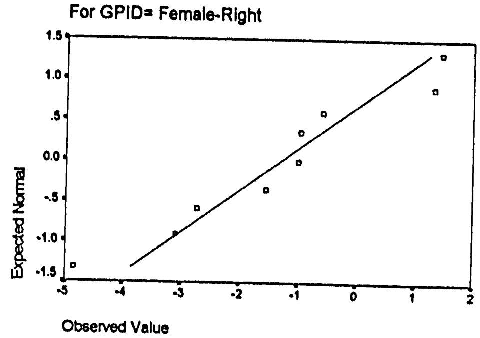
Normal Q-Q Plot of Post BNT Z-score (age)

For GPID= Male-Right



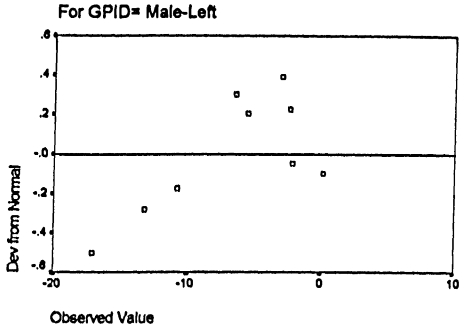
Normal Q-Q Plot of Post BNT Z-score (age)

For GPID= Female-Right



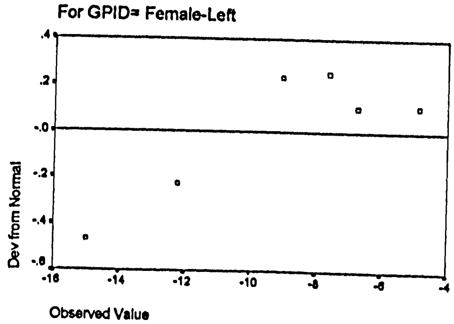
Detrended Normal Q-Q Plot of Post BNT Z-scc

For GPID= Male-Left



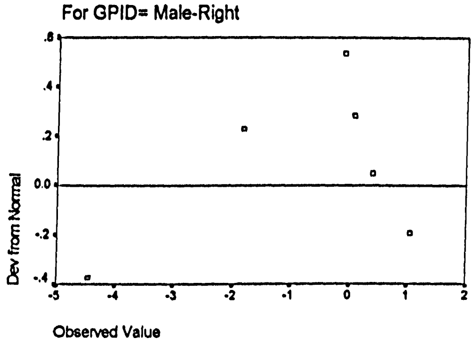
Detrended Normal Q-Q Plot of Post BNT Z-sc

For GPID= Female-Left



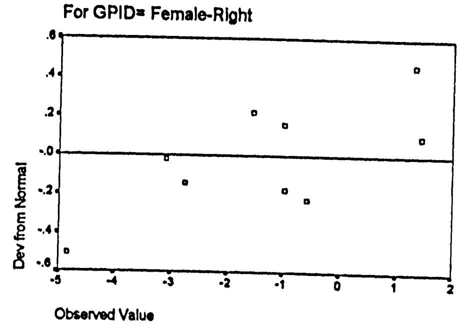
Detrended Normal Q-Q Plot of Post BNT Z-scc

For GPID= Male-Right



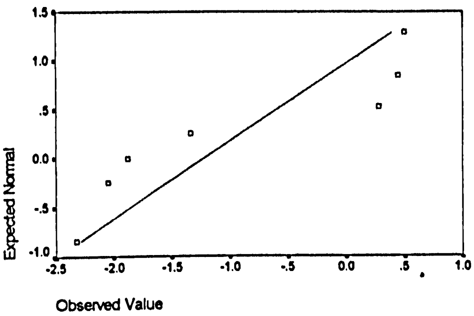
Detrended Normal Q-Q Plot of Post BNT Z-sc

For GPID= Female-Right



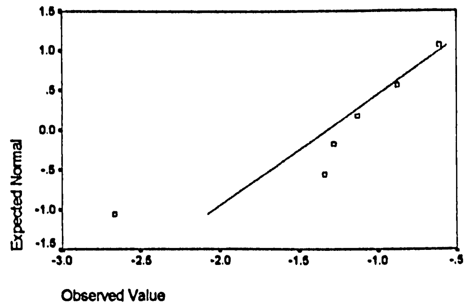
Normal Q-Q Plot of Pre WF Z-score (T-score)

For GPID= Male-Left



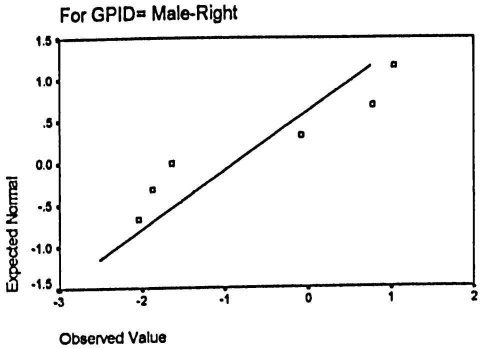
Normal Q-Q Plot of Pre WF Z-score (T-score)

For GPID= Female-Left



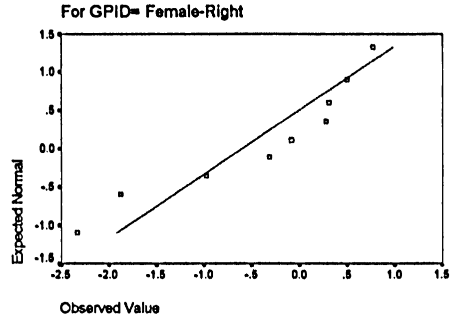
Normal Q-Q Plot of Pre WF Z-score (T-score)

For GPID= Male-Right



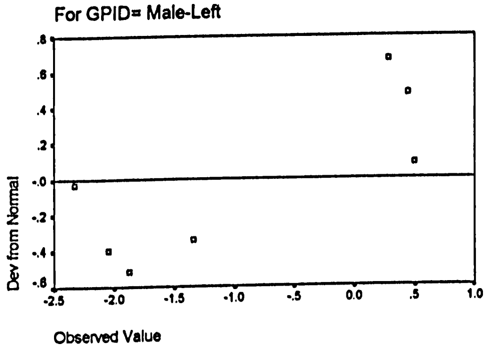
Normal Q-Q Plot of Pre WF Z-score (T-score)

For GPID= Female-Right



Detrended Normal Q-Q Plot of Pre WF Z-score

For GPID= Male-Left

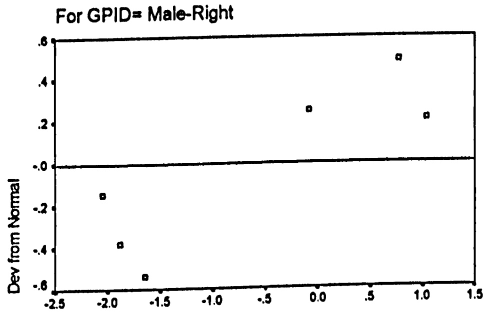


Detrended Normal Q-Q Plot of Pre WF Z-scor

For GPID= Female-Left

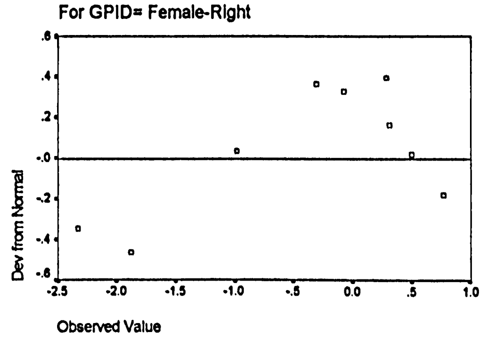
Detrended Normal Q-Q Plot of Pre WF Z-score

For GPID= Male-Right



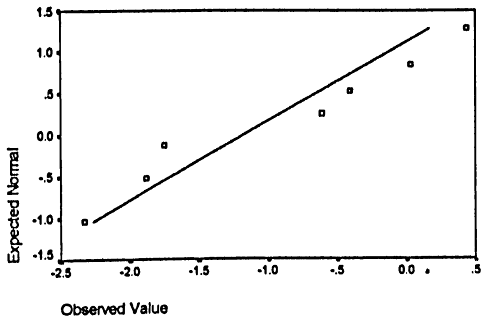
Detrended Normal Q-Q Plot of Pre WF Z-score

For GPID= Female-Right



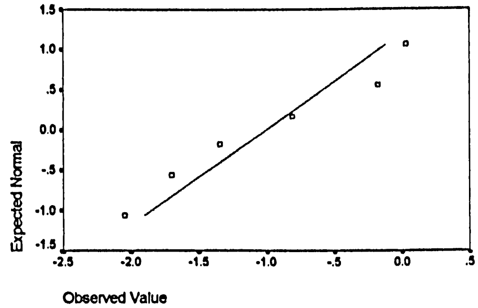
Normal Q-Q Plot of Post WF Z-score (T-score)

For GPID= Male-Left



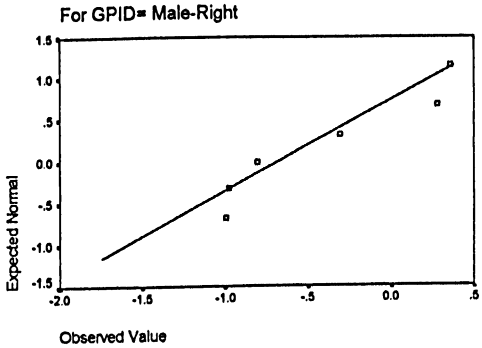
Normal Q-Q Plot of Post WF Z-score (T-score

For GPID= Female-Left



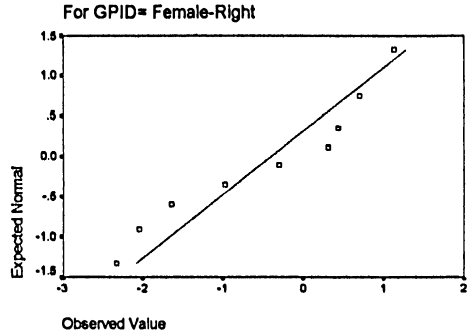
Normal Q-Q Plot of Post WF Z-score (T-score)

For GPID= Male-Right



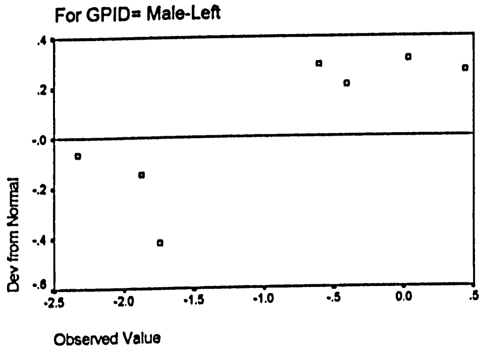
Normal Q-Q Plot of Post WF Z-score (T-score

For GPID= Female-Right



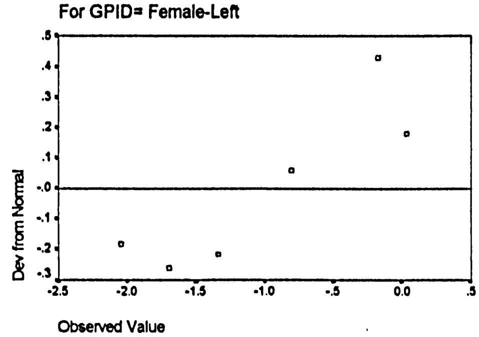
Detrended Normal Q-Q Plot of Post WF Z-scor

For GPID= Male-Left



Detrended Normal Q-Q Plot of Post WF Z-sco

For GPID= Female-Left

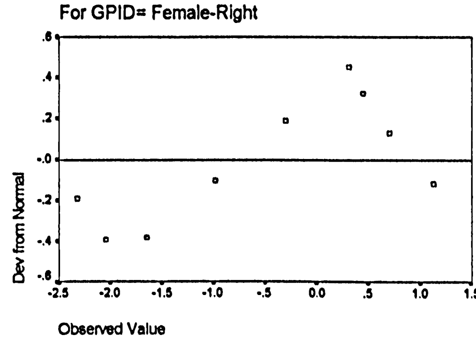


Detrended Normal Q-Q Plot of Post WF Z-scor

For GPID= Male-Right

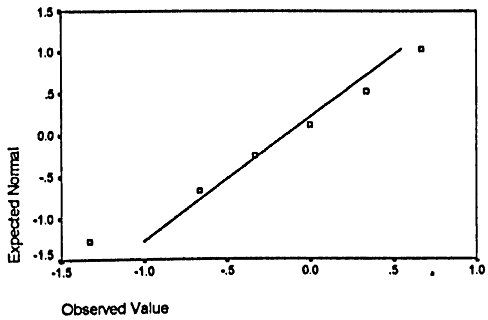
Detrended Normal Q-Q Plot of Post WF Z-sco

For GPID= Female-Right



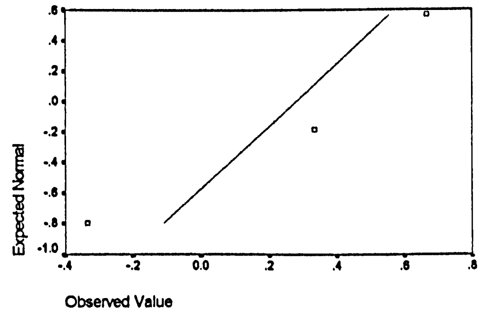
Normal Q-Q Plot of Pre TT z-score

For GPID= Male-Left



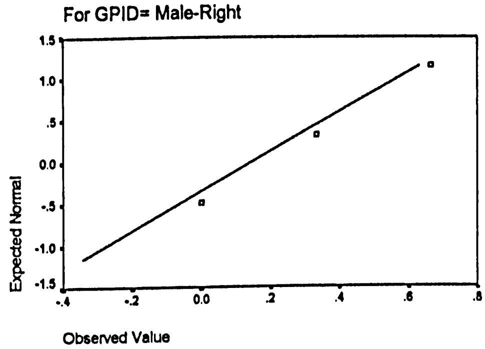
Normal Q-Q Plot of Pre TT z-score

For GPID= Female-Left



Normal Q-Q Plot of Pre TT z-score

For GPID= Male-Right

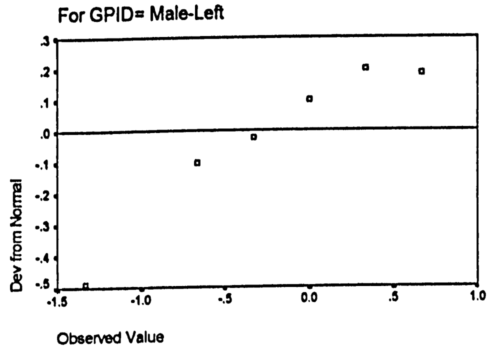


Normal Q-Q Plot of Pre TT z-score

For GPID= Female-Right

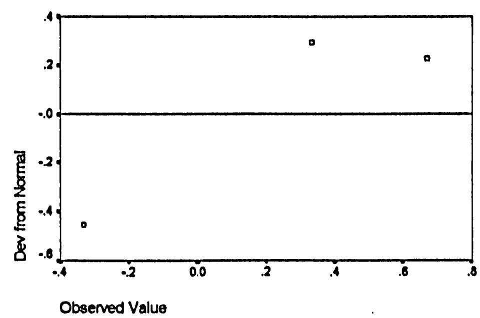
Detrended Normal Q-Q Plot of Pre TT z-score

For GPID= Male-Left



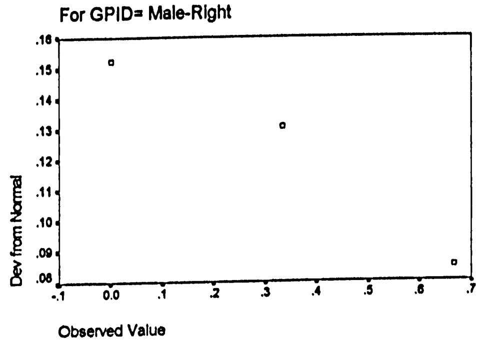
Detrended Normal Q-Q Plot of Pre TT z-score

For GPID= Female-Left



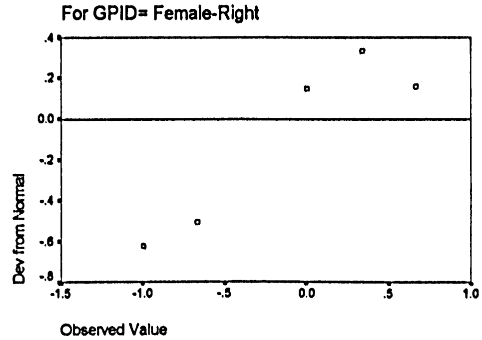
Detrended Normal Q-Q Plot of Pre TT z-score

For GPID= Male-Right



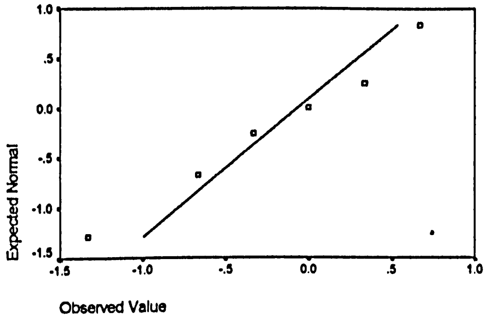
Detrended Normal Q-Q Plot of Pre TT z-score

For GPID= Female-Right



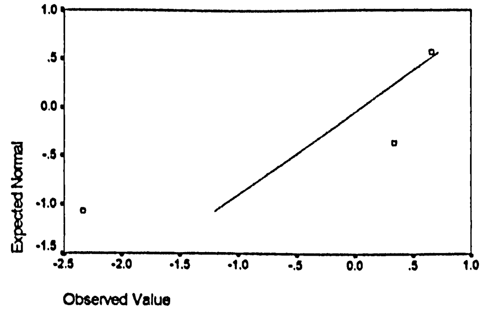
Normal Q-Q Plot of Post TT z-score

For GPID= Male-Left



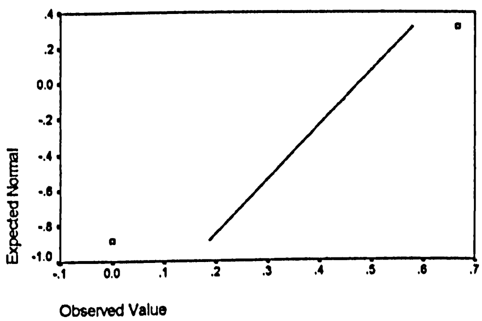
Normal Q-Q Plot of Post TT z-score

For GPID= Female-Left



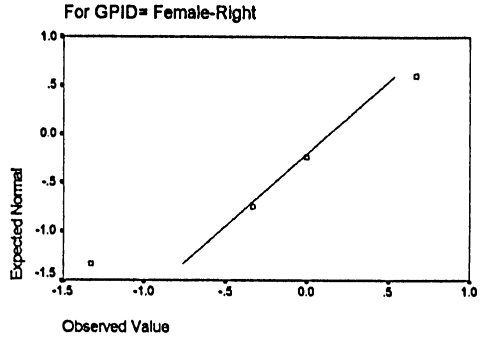
Normal Q-Q Plot of Post TT z-score

For GPID= Male-Right



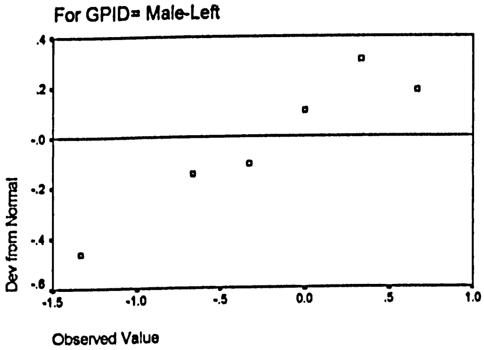
Normal Q-Q Plot of Post TT z-score

For GPID= Female-Right



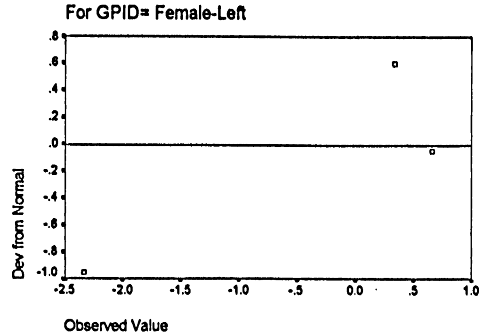
Detrended Normal Q-Q Plot of Post TT z-score

For GPID= Male-Left



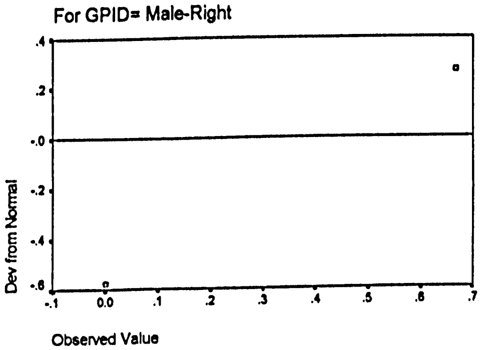
Detrended Normal Q-Q Plot of Post TT z-scor

For GPID= Female-Left



Detrended Normal Q-Q Plot of Post TT z-score

For GPID= Male-Right



Detrended Normal Q-Q Plot of Post TT z-scor

For GPID= Female-Right