The Prediction of IQ and Cognitive Impairment in Temporal Lobe Epilepsy: The Findings of a Multi-Center Study.

by

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Abstract

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The literature suggests that seizure disorders are associated with an increased likelihood of intellectual problems. Investigators have explored many potential risk factors. One common predictor variable identified in the literature is age of onset. The relative strength of other seizure-related variables in the prediction of intellectual and cognitive outcome is less clear. The analyses presented in this thesis examine the unique and combined contribution of specific factors (age of seizure onset, duration of illness, laterality of seizure focus, gender and education) to intellectual and cognitive outcome in chronic, unilateral, medication refractory Temporal Lobe Epilepsy (TLE). Adult subjects were selected from a number of epilepsy centers (Cleveland Clinic, Long Island Jewish Medical Center, Mayo Clinic, Epi-Care Center, Yale University, New York University, Medical College of Georgia and University of British Columbia and University of Victoria).

The results indicate that a small portion of the variance in intellectual functioning is accounted for by seizure-related variables, but a much larger amount of the variance is accounted for by the secondary consequences of these factors on the level of education achieved. The combination of seizure-related variables and level of education accounted for a modest amount of the variance in performance on tasks of verbal retrieval and verbal memory. Results are discussed within a developmental context and application to future studies of TLE and other childhood chronic disorders.

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Finally, I thank Jonah. Jonah you reminded me that dreams do come true, you just have to have a little faith and work really hard. I thank you for the support, the flowers, and your love. I'm glad you are here to cheer me through this finish line, I look forward to the rest of the starting gates that we will enter and go through together.

Ultimately, this work is dedicated to Jeremy, my son, my love, my favorite person. Jeremy has been a constant source of joy, love and life.

Together we have met challenges in the past few years that others could not begin to imagine. Jeremy, I am in awe of your strength and ability to maneuver through the challenges of life. I am forever thankful for your love, your smile, and for the wonderful person that you are.

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Chapter 1

Introduction

A. Statement of the Problem

Many potential seizure-related risk factors (e.g., age of onset, duration of disorder, etiology, and seizure type) have been associated with the intellectual outcome of individuals with chronic seizure disorders (Ossetin, 1988). The literature that deals with intellectual and cognitive outcome in chronic epilepsy can be characterized by three schools of thought. There are investigations that have dealt primarily with the issue of laterality of seizure focus and differences between group performance (Camfield et al., 1984; Delaney et al., 1980; Dikmen, 1980; Fedio and Mirsky, 1969; Hermann et al., 1987; 1992; Loring et al., 1986; Mungas et al., 1985). There have been investigations that explored seizure-related variables in isolation and the association between seizure-related factors (e.g., age of onset, duration of illness) and performance on intelligence tests (Dodrill, 1992; Dodrill and Matthews, 1992). Recently, there have been investigations that examined both the unique and combined contributions of seizure-related variables on intellectual and cognitive outcome (Strauss, Hunter and Wada, 1995).

This dissertation examined the unique and combined contributions of seizure-related (primary) variables in conjunction with the investigation of the secondary consequences of seizure-related variables on educational attainment (e.g., the relation between age of onset and education). The primary and secondary factors were both employed in the prediction of intellectual and cognitive outcome. In this context, the term "primary" refers to the amount of variance in performance that a seizure-related variable accounts for (e.g., the relation between age of onset and performance on measures of intelligence). The term "secondary" refers to the variance accounted for in performance by a related subsequent consequence associated with seizure-related variables (e.g., the impact of age of onset on psycho-educational factors). For example, the secondary effect of age of onset on education (a secondary variable) was examined in a large sample of individuals with chronic, medication refractory temporal lobe epilepsy (TLE), of unknown etiology.

The primary aim of this project was to investigate the interactions that occurred between seizure-related factors, as well as the secondary consequence of these primary variables on subsequent level of education achieved. The prediction of intellectual and cognitive outcome was attempted within this hierarchy of factors.

Specifically, seizure-related factors and the factor of education were employed in the construction of hierarchical regression models in the prediction of intellectual outcome, verbal retrieval, verbal learning, and delayed verbal recall. The amount of variance accounted for by knowledge of these factors was assessed.

This investigation examined the performance of individuals who have acquired chronic, medication-refractory TLE from a developmental perspective and argues that the variable of age of onset can be viewed as a potential modulating factor associated with the prediction of a differential risk to intellectual and cognitive outcome that is related to education. The independent variables that were investigated included: age of onset, duration of disorder, laterality of temporal lobe seizure focus (etiology and location of seizure focus were controlled via subject selection criteria), gender and level of education achieved. The dependent measures included Intelligence Quotient scores (IQ), performance on confrontation naming and phonemic fluency tasks, and verbal list-learning performance. Finally, this project was designed to remove many of the methodological and statistical problems that are discussed in the literature review. These problems have made it difficult to predict intellectual and cognitive outcome in chronic medication-refractory

TLE.

The variable of age of onset has been discussed in detail in the literature, because age of seizure onset has often been identified as a key variable in predicting intellectual and cognitive outcome (Huttenlocher & Hapke,1990; Loiseau, Strube, Broustet, Battellochi, Gomeni & Morselli,1983; O'Leary, Seidenberg, Berent and Boll,1981; Saykin, Gur, Sussman, O'Connor & Gur,1989). While many have explored this variable in relation to intellectual functioning, to date none have examined the secondary consequences of age of onset on education in relation to subsequent intellectual and cognitive outcome. This is an important oversight in the literature on TLE because performance on measures of intelligence are correlated with educational achievement in standardization samples (Anatasi, 1988); this is not surprising given that the original purpose of these measures was to predict academic success.

There are some reports in the literature that when considered together support a more detailed exploration of primary factors in conjunction with their secondary consequences, especially in the case of age of onset and educational attainment. For instance, it has been discussed that greater intellectual impairment is associated with early onset seizure disorders (Holmes, 1991), but the relation of this finding to early psycho-educational factors is unknown. A schematic diagram of this view of age of onset and IQ, looked at in isolation of other variables might look like that shown in Figure 1.

Age of Onset → IQ

Figure 1: Schematic Representation of the Relationship Between Age of Onset and IQ in Isolation of Other Variables

Prevalence studies have shown that learning difficulties are more prevalent in children with epilepsy than in the general population (Pazzaglia and Pazzaglia, 1976; Seidenberg et al., 1986). Some reports have discussed that not only are children with chronic epilepsy at risk for developing learning problems (Rutter et al., 1970; Stores, 1978,1987; Thompson, 1987), but that approximately one third receive some form of special education services (Holmes, 1991; Thompson, 1987). It has also been demonstrated that diminished educational attainment is associated with seizure disorders that begin prior to the age of eighteen (Berent et al., 1984). In fact, Berent et al. (1984) reported that the effect of age of onset on IQ was not significant when education was co-factored into the equation. The depiction of this view of age of onset might look like that shown in

Figure 2.

Age of Onset → Education → IQ

Figure 2: Schematic Representation of the Relation Between Age of Onset and Education, and Education and IQ

From the depiction shown in figure 2, one might expect that age of onset would be positively correlated with education, and that education would be positively correlated with IQ, but there would be no correlation between age of onset and IQ when education was partialled-out of the equation.

Another way that these factors may be related is that age of onset impacts both education and IQ, and that education also impacts IQ. This method of examining the unique and combined effect of factors on IQ is depicted in Figure 3a and a variation of it is depicted in 3b. In this view, one would expect that both education and IQ would be positively correlated with age of onset, and that education would be positively correlated with IQ even when age of onset was partialled out.

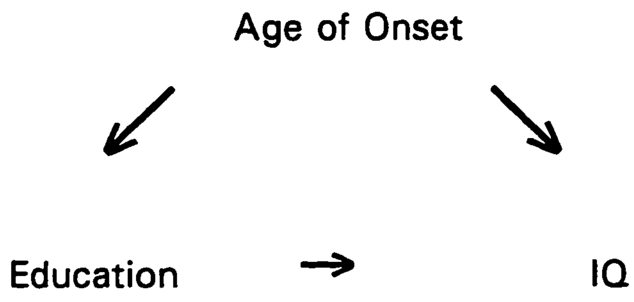

Figure 3a: Schematic Representation of the Secondary Consequences of Age of Onset on Education and IQ

A variant of this view of age of onset is depicted in Figure 3b; in this view age of onset is viewed as impacting both education and IQ, and education and IQ are seen as reciprocally impacting each other.

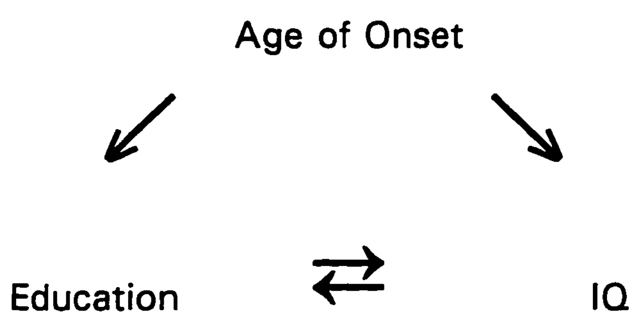

Figure 3b: A Variant Schematic Representation of the Secondary Consequences of Age of Onset on Education and IQ, with Recognition of the Two-sided Interplay between Education and IQ

There are other secondary factors related to age of onset. For instance, the medications often employed with early onset seizures have been reported to have adverse cognitive and behavioral effects (e.g., phenobarbital) (Ransom and Elmore, 1991). The possibility of accumulating of a larger number of seizures throughout life is also more likely with early onset (Dodrill and Matthews, 1992; Farwell, Dodrill and Batzel, 1985). These statements underscore two issues. The first issue is the need to further investigate the primary seizure-related variables in combination, because they are intimately related and difficult to tease apart (e.g., age of onset, duration of illness, and age at time of testing). The second issue is the need to consider that there may be secondary consequences of these factors that need to be considered when attempting to predict intellectual and cognitive outcome in chronic TLE. The decision to focus on a psycho-educational factor rather than also include these other secondary factors was based on the quality and quantity of data available from patient records regarding level of education achieved relative to information on these other secondary factors.

The background and rationale for this investigation are presented as follows. First, operational definitions are provided and the literature related to the potential seizure-related risk factors (primary variables) associated with performance on intelligence tests and select cognitive tasks are discussed. Second, to characterize different profiles of cognitive impairments associated with seizure disorders and age of onset and age at time of testing the neuropsychological data from pediatric and adult patients with seizure disorders are examined. Finally, the earlier sections are discussed as a rationale for the current investigation.

Definitions: In this dissertation, age of onset was operationally defined as the age at which a chronic seizure disorder was initially treated with medication. A related factor is the duration of the disorder. In this dissertation, duration of disorder was operationally defined as the length of time that has passed since onset of chronicity to the time of testing. Subjects included in this research underwent neuropsychological testing as presurgical candidates for temporal lobe resection for relief from medically intractable seizure disorders. In the sample of adult TLE patients studied[1] in this dissertation the duration of disorder was characterized in a number of ways, in some cases it was: 1) early onset of illness with a long duration of illness, 2) late onset of illness with a short duration of illness, and 3) late onset of illness with a long duration of illness.

Another important factor that must be defined is the etiology of a seizure disorder. Individuals with symptomatic epilepsy (when

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[1] It is important to note that all subjects in this dissertation sample ultimately where evaluated as pre-surgical candidates for temporal lobe resection for the relief of intractable seizures.

seizures occur as symptoms of structural cerebral pathology) have been reported to perform more poorly on cognitive tests than those with idiopathic epilepsy (cryptogenic, of unknown etiology) (e.g., Bourgeois, Prensky, Palkes, Talent and Busch, 1983; Klove and Matthews, 1966). Subjects investigated in this study consisted only of those with idiopathic epilepsy, to avoid possible confounding effects on performance related to brain tumor, stoke, or vascular malformations.

In this dissertation, the discussion of the location of a seizure focus was restricted to the temporal lobe and laterality of seizure focus (left or right). The variable of seizure type must also be mentioned, because it has often been reported that the risk of cognitive impairment is greater in individuals with generalized seizures[2] (Matthews & Klove, 1967; Farwell et al., 1985); in contrast to the risk of memory impairments associated with complex partial seizures[3] (Pedersen & Dam, 1986). Dodrill (1986) noted that decreased mental abilities were associated with lifetime histories of more than 100

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[2] According to the International Classification of Epileptic Seizures, the term generalized seizures refers to ictal events in which the first clinical changes indicate involvement of both hemispheres.

[3] According to the International Classification of Epileptic Seizures, complex partial seizures refer to ictal events in which the first clinical and electroencephalographic changes indicate initial activation of a systems of neurons limited to part of one cerebral hemisphere associated with impaired consciousness.

generalized tonic-clonic[4] seizures or with even one episode of status epilepticus[5]. Thus, according to Dodrill (1986) not only are the number of seizures important, but the type of seizures and their temporal pattern are also relevant as they might impact mental abilities and performance on measures of intelligence.

B. Literature Review

Impairment of cognitive abilities and lower intellectual function in individuals with epilepsy has been discussed in the literature for many years (Lennox, 1942) and discussed in several review articles (Addy, 1987; Besag, 1989; Brown and Reynolds, 1981; Dodrill, 1983; Harrison and Taylor, 1976; Lesser et al., 1986). There are many seizure-related variables that have been discussed in the literature with reference to their impact on intellectual functioning (Ossetin, 1988). The factors discussed in the literature have generally been investigated in isolation and assessed for their unique contribution to the intellectual outcome of individuals with chronic epilepsy. There

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[4] According to the International Classification of Epileptic Seizures, tonic-clonic seizures consist of an initial increase in tone of certain muscles followed by bilateral symmetrical jerking of extremities.

[5] The operational definition of status epilepticus which is accepted by most neurologists is two or more seizures without full recovery of consciousness between seizures or recurrent epileptic seizures for more than 30 minutes.

are a number of issues that must be pointed out with reference to the literature that encompasses studies that investigate seizure-related variables in isolation. Specifically, it has been demonstrated that the effect of age of onset did not remain statistically significant when secondary variables, such as level of education, were co-factored into the analyses (Berent et al. 1984). This raises the question as to whether the effect often associated with age of onset on intelligence is related to the effect of age of onset on level of education achieved and the impact of education on IQ scores. It could be the case that age of onset is a credible variable, but the magnitude of its effect is decreased in the presence of other variables. Either other variables have more potency or the interactions between variables are important. To date, no one has investigated the long term consequence of age of onset on ultimate level of education achieved. In this dissertation, this question was examined using a database from multiple epilepsy centers.

The need to investigate the interactions between seizure-related variables in addition to the main effects exerted by these factors was alluded to in the previous paragraph and can be demonstrated by the following series of studies, reported by Dodrill (1992), Dodrill and Matthews (1992), and Berent et al. (1984). Each of these studies investigated the variable of age of onset in relation to intellectual outcome. Dodrill (1992) observed that Full Scale Intelligence Quotient (FSIQ) scores increased linearly with age of seizure onset. In a study of 410 adults with heterogeneous seizure disorders, he reported that the mean FSIQ was 90.6 with age onset 0-5 years verses 100.8 with age onset between 19-28 years (Dodrill, 1992). These findings were replicated by Dodrill and Matthews (1992) in a sample that was composed of 676 subjects with epilepsy (338 female; 338 male), aged 16-66 years, with a mean of 11.68 years of education.

In a similar vein, Berent and colleagues (1984) also reported findings of significantly higher intellectual scores obtained by adults (n = 187) with idiopathic epilepsy[6] acquired in adulthood as compared to those with early childhood onset epilepsy. Individuals who acquired a seizure disorder after the age of 18 years performed better than those who acquired a seizure disorder between the following age groups : 0-5 years, 6-12 years, and 13-17 years. Examination of the interactions between variables revealed level of education achieved was a factor related to intelligence levels across groups. All subjects in the group of individuals with onset after the age of eighteen had completed high school, unlike the composition of the other age of

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6 In this study idiopathic epilepsy was defined as seizure disorders that were not secondary to structural cerebral pathology.

onset groups. When level of education was co-factored into the analyses, significant differences between the age of onset groups were not obtained. Thus, although the effect of age of onset initially appeared to be significant in these three studies, it's direct effect on IQ scores was no longer significant, when considered in the presence of a secondary factor such as level of education which has also been associated with intellectual outcome.

C. Age of Onset

In this dissertation, age of onset was defined as the age at which a chronic seizure disorder was initially treated with medication. The pediatric literature on focal brain injury and pediatric epilepsy suggests that intellectual functioning is more generally impaired in the first years of life than when focal brain injury or seizures are acquired in adulthood (e.g., Dodrill and Matthews, 1992; Hebb, 1942; Isaacson & Nonneman, 1973; Isaacson, 1975; O'Leary et al., 1983; Woods, 1980; Woods and Carey, 1979). One possible explanation for why children who develop epilepsy prior to the age of five perform more poorly as a group relative to children with later onset seizure disorders is that the early onset groups often include children impaired by birth asphyxia, intrauterine infections, brain malformations, and other congenital brain damage. Individuals in early onset groups are thus more likely to acquire symptomatic seizures. One of the questions that was addressed in this dissertation related to whether or not there was evidence to suggest that poorer performance on intelligence tests in early onset groups might somehow be related to the educational process. One way to consider this possibility is to posit that the educational process might be disrupted by the presence of an early onset seizure disorder of unknown etiology. The disruption might relate to episodic disruption of neural activity and/or to the problems associated with frequent absences from the classroom. The educational process could conceivably be hampered by limited expectations from parents and teachers, as well. Bear in mind that when seizures are present in childhood they exist within the context of a developmental process that relates to cognitive, psycho-educational, and psycho-social factors in addition to neurodynamic factors.

Some have argued that the age of an individual at the time in which a seizure disorder becomes chronic provides an important marker for long-term functioning (e.g., Dam, 1990; Dikman, 1980; Dodrill, 1992; Dodrill and Matthews, 1992; Trimble, 1990; for recent reviews). These reports suggest that the more time a system is able to develop in the absence of a chronic seizure disorder, the more competent the resulting system. The components that account for increased competency are not explicitly discussed, but appear to be related to some extent to the level of education achieved. For example, some investigators have reported that Full Scale Intelligence Quotient (FSIQ) scores increase linearly with age of seizure onset[7] (Dodrill, 1992); whereas others have demonstrated that the effect of age of onset may be related to other factors (such as duration of disorder and level of education achieved) which have been associated with intellectual outcome as well, (e.g., Berent et al., 1984; Dikman and Matthews, 1977; O'Leary, Seidenberg, Berent and Boll, 1983). Thus, the logic of exploring the effect of age of onset in isolation of other related variables needs to be re-examined. Not surprisingly, some have suggested that reports discussing age of onset as a unique predictor of cognitive outcome are actually dealing with the result of multiple factors which might be related to issues of neuronal development (Strauss, Satz and Wada, 1990; Strauss, Wada and Goldwater, 1992; Strauss, Wada and Hunter,1992), medication effects on cognition and behavior (Dodrill,1991; Ransom and Elmore,

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[7] The statistical significance of the effect of age of onset (e.g., the linear increases in FSIQ observed with later ages of onset) on intellectual outcome is not maintained when other variables (e.g., duration of disorder, level of education achieved, etiology) are considered simultaneously. This point has already been discussed via the work of Berent and colleagues (1984).

1991; Smith, 1981;1991), seizure frequency throughout life (Dodrill, 1986), level of education achieved (Berent et al., 1984) and the modulating influence of (secondary consequences of) the age of an individual at the time of acquiring a chronic seizure disorder. Age of seizure onset might be a factor in life that is not only a crucial determining variable at the time of its occurrence, but one that continues to influence and impact (moderate) secondary factors throughout life and particularly the educational process. The age at which a chronic seizure disorder begins might impact various aspects of functioning (e.g., level of intelligence, level of education achieved, and psycho-social functioning). It is even possible that seizure disorders beginning years before schooling begins may be less detrimental than those that occur immediately prior to introduction into the school system for a number of reasons. Specifically, seizures may alter levels of attention and consciousness and/or the frequency of seizures may interfere with school attendance; both of these situations are likely to disrupt the educational experience.

In the examination of intellectual functioning in individuals with childhood brain injury (which includes patients with childhood epilepsy) it is not only crucial to evaluate the age of onset (Huttenlocher & Hapke,1990; Loiseau, Strube, Broustet, Battellochi, Gomeni & Morselli,1983; O'Leary, Seidenberg, Berent and Boll,1981; Saykin, Gur, Sussman, O'Connor & Gur,1989) the duration of the disorder (Dodrill,1981), but also the age at time of testing. The developmental literature on children with and without cerebral injuries supports the supposition that injury can produce different cognitive outcomes during different phases of development (e.g., Ewing-Cobbs, Fletcher, Landry and Levin, 1985). It has been pointed out that there is a complex interaction between age at time of injury and the consequences to functions in brain damaged children (Teuber and Rudel,1962). Cerebral injury may have delayed effects, or deficits become more evident with age. Some cognitive systems may be more resilient to early focal insult while others may be more vulnerable. Poor performance on a task may reveal impairment at one age or simply a demonstration that the information needed to perform the task has not been provided to this subject yet due to their age at time of testing (e.g., knowledge of certain vocabulary words are required for confrontation naming tasks; an eight year old may not be familiar with the word "sphynx", but this lack of information does not imply a deficit).

It is important to recognize that the majority of literature on the effect of early brain injury in children generally describes the sequelae during the acute recovery stages and not the subsequent outcome, leaving issues related to neuro-development, duration of disorder, level of education achieved and intellectual outcome somewhat unexplored[8].

Age of Onset and Intellectual Outcome: The remainder of the literature review discusses seizure-related variables individually and in isolation, because that is the manner that they have been dealt with in the literature. With regard to the few reports that have considered variables in combination, it is pointed out. The variable of age of onset was stressed in this literature review, because most of the literature has concentrated on this variable and its effect on measures of intelligence.

The distribution of Intelligence Quotients (IQ) obtained by individuals with epilepsy reveal that there is a great deal of variability in performance profile. The profile of the distribution tends to be negatively skewed (Holmes, 1987;1991), although superior IQ scores have been reported in individuals with epilepsy (Collins and Lennox,

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[8] There are some reports which suggest that intact regions of the brain may eventually take over functions normally attributed to other brain regions, when the area that normally sub-serves the function is destroyed (Rothi & Horner, 1983) or dysfunctional (Strauss, Satz & Wada,1990). This type of plasticity of the brain varies with the age of the subject, but is generally associated with the immature brain (Kohn,1980; Leleux & Lebrun,1981).

1945; Harlin and Pullen, 1965). This dissertation investigated the variability in performance, via primary and secondary factors, to explore if it was possible to identify individuals at risk for intellectual impairment. If high risk factors can be identified then early intervention protocols can be developed and employed as part of the educational experience.

One possible explanation for the variability in the distribution of IQ scores obtained by individuals with epilepsy is that it is the result of varying selection criteria employed in the literature. There are discrepancies reported on the relationship between age of onset and IQ in the epilepsy literature (see Bourgeois et al., 1983; Ellenberg et al., 1984). In the early studies that selected patients from institutions, mean IQ scores were reported to be in the borderline or deficient range (see Barnes and Fetterman, 1938; Collins and Lennox, 1947; Kugelmass et al., 1938; Tenny, 1955). In contrast, reports that investigated outpatient samples have reported mean IQs in the low average range (see Klove and Matthews, 1966; Needham et al., 1969). Results of studies performed in tertiary care facilities may be distorted by selection bias.

Recent studies in the literature are generally composed of subjects treated in outpatient facilities by neurologists or from samples treated in comprehensive epilepsy centers. In many instances subjects have been evaluated as pre-surgical candidates for temporal lobe resection for relief from medication-refractory chronic seizures. The results reported in the most recent studies suggest a trend in which seizure disorders are associated with an increased risk of intellectual deficiencies (e.g., Bourgeois et al., 1983; Holmes, 1991; Rodin, 1968; Rutter et al., 1970; Seidenberg and Berent, 1992; Stores; 1978; 1981; Thompson, 1987; Trimble, 1990).

In the pediatric literature there are reports of overall decrement in intellectual functioning (e.g., Levine et al.,1987; Woods, 1980) that hint at the issue of a differential risk related to age of onset with early unilateral lesions. The role of education, however, is unclear in this body of literature. As mentioned previously, there are a number of ways that the process of education can be disrupted. For example, Woods (1980) reported IQs of children, followed as outpatients, with unilateral cerebral lesions sustained in the first year of life were below those of children who had sustained cerebral lesions later in life. In the Woods (1980) study very early lesions of either the left- or right-hemisphere were associated with generalized impairments in intellectual functioning, whereas later lesions of the right-hemisphere were significantly associated with decrements in Performance Intelligence Quotients (PIQ).

To investigate the interaction between age of onset and seizure type, O'Leary et al. (1983) examined children's performance (49 with partial seizures; 57 with generalized seizures) on measures of intelligence. Subjects were selected from a comprehensive epilepsy center. Subjects were divided into four groups based on seizure type[9] (partial, generalized) and age of onset. There was an Early Onset Partial group (n=27), a Late Onset Partial group (n=22), an Early Onset Generalized group (n=33), and a Late Onset Generalized group (n=24). The mean age of onset and mean duration of illness for each of the four groups are presented in Table 1.

Age at time of testing and duration of disorder were included as covariates in order to control for the effects of these variables. The effects of age of onset were significant on measures of VIQ and PIQ, with children in the early onset groups (partial and generalized)

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[9] Seizures are termed "partial" when behavioral or EEG evidence indicate that they originate in a part of the brain limited to one hemisphere. Seizures are termed "generalized" when they appear to begin bilaterally (Engel, 1989).

performing worse than those with later onset[10]. These results support previous reports that seizure disorders occurring early in life are associated with a relatively greater risk for intellectual impairment.

Table 1

Mean Age of Onset and Mean Duration of Illness for the Four Groups in the O'Leary et al. (1984) study.

Group	Mean Age of Onset (years)	Mean Duration of Illness (years)
Early Onset Partial (n=27)	2.4	9.4
Late Onset Partial (n=22)	9.0	4.0
Early Onset Generalized (n=33)	2.4	9.8
Late Onset Generalized (n=24)	8.4	4.0

There are some studies that do not report this profile (Bourgeois et al., 1983), but the discrepancy is likely related to methodological issues related to the definitions employed to group subjects into early onset groups and both the duration and severity of the seizure disorders of the subjects under study. Specifically, Bourgeois et al.

[10] Post hoc analysis revealed that for children with partial seizures only PIQ was significantly different between onset groups. The variable of laterality of seizure focus was not explored in this study. For children with generalized seizures, the early and late groups differed significantly on VIQ, but not PIQ.

(1983) examined 72 children ranging in age from 18 months to 16 years two weeks post initial diagnosis of epilepsy and prospectively followed them yearly for an average of four years. Eight of the 72 patients (11.1%) had a decrease in their IQ of 10 points or more. These eight patients had a higher incidence of drug toxicity and tended to present with earlier ages of onset (exact ages of subjects in this sub-group were not provided). The findings related to the eight patients with higher incidence of drug toxicity and earlier ages of onset bring up an interesting issue. The findings may indicate that disruption in the learning process, related to neurodynamic issues, severity of illness, and/or psychosocial difficulties could interfere with educational achievement which in turn could be associated with subsequent intellectual outcome. This line of speculation assumes that the effects often associated with age of onset might be the manifestation of the secondary consequences of the age of onset of any chronic illness on education. The epilepsy literature does not address whether the risk to intellectual outcome that is often related to age of onset is due to neurodynamic issues or rather due to the complications associated with any chronic disorder neurological or otherwise (e.g., the impact of the number of days absent from school due to illness related events). This gap in the literature underscores the necessity of investigating the longitudinal course of development and the importance of knowing not only the age of onset, but the severity of the illness and the length of time that has passed since onset (Rutter, 1982).

To review the material presented up to this point on the relation between age of onset and intellectual functioning, studies have reported that seizure onset in early childhood is associated with a higher risk of decrement to intellectual functioning than is onset during late childhood or adolescence (Dodrill,1992; Levine et al., 1987; O'Leary et al., 1981; Woods, 1980). One way to explore this subject further, is to investigate the impact of a seizure disorder on higher cognitive functions. If the effect often associated with age of onset and IQ is related to education then we should see impairment in other tasks that education has been associated with. For example, education has been correlated with performance on tasks associated with vocabulary skills (e.g., reading, confrontation naming, and phonemic fluency).

In this literature review and dissertation research the impact of primary and secondary variables on verbal as opposed to non-verbal material was explored. The decision to concentrate on verbal as opposed to non-verbal material was based on the results of factor analytical studies on commonly used tasks to assess memory which have failed to demonstrate the existence of an independent non-verbal memory factor (Larrabee & Curtiss, 1995; Larrabee, Kane, Schuck & Francis, 1985; Roid, Prifitera & Ledbetter, 1988; Smith, Malec & Ivnik, 1992). The dependent measures of verbal retrieval available in the multi-center database employed in this project consisted of confrontation naming and phonemic fluency. The reader is cautioned that the error variance associated with these tasks is greater than that associated with measures of IQ. Thus, the effect of age of onset may not be as robust due to the psychometric properties of these measures. This psychometric issue will be returned to in the Methods and Discussion Sections.

The literature related to age of onset and verbal measures will now be presented and discussed with reference to the developmental literature. The justification for presenting some of the developmental literature on cerebral injury in addition to the TLE literature was based on the frequent identification of age of onset as a key variable in both domains of study. In the developmental literature, the age at which a cerebral insult was acquired has often been reported to be a sensitive factor. Performance differences associated with age at the time of the insult have been observed on language measures. In the case of seizure disorders, it is unclear if the effect of age of onset is robust enough when examined in isolation, to observe differences in verbal retrieval performance. When performance differences have been observed they were generally evident in combination with other predictor variables (e.g., laterality of TLE focus).

Age of Onset and Verbal Retrieval: There is pediatric literature which has examined the relationship between age of onset and object naming performance (e.g., Aram, Ekelman and Whitaker, 1987; Kiessling, Denckla and Carlton, 1983; Vargha-Kahdem, O'Gorman and Watters, 1985; Woods and Carey, 1979). This literature revealed a trend in which children sustaining early left brain lesions were more likely to present with impaired naming performance. The impaired naming performance may indicate a word knowledge or vocabulary weakness as these measures have been reported to load highly on this type of factor in children (Halperin et al., 1989) comparative construct validity reports on adults have not been reported.

Woods and Carey (1979) looked for specific language deficits that persisted after left hemisphere lesions acquired during infancy or childhood (defined as prior to adolescence) in a sample followed in an out-patient clinic. They examined individuals who had sustained a single, unilateral, non-progressive cerebral lesion in the perinatal period, in infancy, or in childhood. Subjects were divided into two groups; an Early lesion group (n = 11) composed of subjects with lesions incurred prior to their first birthday and a Later lesion group (n = 16) comprised of subjects with lesions acquired after their first birthday. The group with early lesions were reported to have a mean age at time of testing of 17.8 years (range = 10.2-25.5 years); the mean age at time of testing for the later lesioned group was 15.3 years (range = 8.6-24.5 years).

The mean age of onset, mean age at time of testing, and mean FSIQ and VIQ scores for the two groups are presented in Table 2.

Table 2
Mean Age of Onset, Mean Age at Time of Testing, and Mean FSIQ and VIQ Scores for the Two Groups in the Woods and Carey (1979) study.

Group	Mean Age of Onset (years)	Mean Age at Testing (years)	FSIQ Mean (SD)	VIQ Mean (SD)
Early Lesion (n = 11) (range)	0 (not given)	17.8 (10.2-25.5)	86.5 (20.1) (not given)	90.3 (19.5) (not given)
Later Lesion (n = 16) (range)	5.7 (1.2-15.1)	15.3 (8.6-24.5)	89.5 (22.1) (not given)	90.1 (24.8) (not given)

The two groups were compared to 48 individuals of average intellectual ability who were in grades 5,7,9, and 11 at the time of testing. The Later Lesion group was significantly more impaired on six of eight measures of language performance (object naming, that-clause, sentence completion, token test, spelling, semantic/ syntactic relations) relative to the control group. The Early Lesion group performed significantly different from the control group only on a spelling task. There were not measures of VIQ, vocabulary/or reading employed in this study to further interpret the naming performance of the Later lesion group reported. It is not clear if this finding of a differential risk to naming ability in those individuals sustaining left-hemisphere injury after the first year of life is related to the concept of (time-limited) plasticity in the immature brain (Kohn, 1980; Leleux and Lebrun, 1981). It could be evidence of the secondary consequence of cerebral dysfunction as it occurs closer in time to the beginning of formal education, or it might be related to the younger mean age at the time of testing in the Later onset group relative to the other groups.

The work of Vargha-Kahdem, O'Gorman and Watters (1985) extended the findings of Woods and Carey (1979) by exploring object naming as a function of hemispheric side of injury and age at injury in children (left = 28; right = 25; control = 15) with congenital and acquired lesions. Although the patient groups were not matched for time post injury, they were investigated at least two years after the cerebral insult. The patient groups were further divided into three groups based on age at cerebral insult. There was a Prenatal[11] group, an Early Postnatal group (insult occurring from 2 months to 5 years), and a Late Postnatal group (insult occurring from 5-14 years). Subjects who comprised the control group were individually matched in age at time of testing and FSIQ with 15 of the patients in the Prenatal Left Hemisphere group. The mean FSIQ and age at time of testing for the groups are shown in Table 3.

The effects of hemispheric side of lesion (left, right) and age at injury (prenatal, early postnatal, late postnatal) on object naming were investigated. A significant main effect of side of lesion was obtained, the means of the Right hemisphere groups revealed higher accuracy on the naming task than those of the Left hemisphere groups.

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[11] The classification of the Prenatal group was based on the absence of evidence indicating perinatal or postnatal episodes which may have been responsible for the demonstration of hemiparesis.

Table 3
Mean FSIQ and Age at Time of Testing for the Seven Groups in the Vargha-Khadem et al. (1985) Study

Group	N	FSIQ	Mean Age at Time of Testing
Control	n=15	100.1	10.6 (3.07) years (range=6-16 years)
Prenatal	n=16	98.8	Right=10.9 years (range= 6-16 years)
	n=18	95.5	Left=10.6 years (range= 6-16 years)
Early Postnatal	n=5	90.8	Right= 8.9 years (range= 6-17 years)
	n=6	90.0	Left=10.4 years (range= 7-17 years)
Late Postnatal	n=5	94.8	Right=12.1 years (range= 10-14 years)
	n=4	84.0	Left=10.7 years (range= 7-14 years)

It should be noted that the mean FSIQs were higher in all Right hemisphere groups relative to their corresponding age of onset Left hemisphere groups. The Prenatal Right and the Late Postnatal Right groups were not significantly different from the controls, but the Early Postnatal Right group was significantly impaired relative to the control group on the naming task. It should also be noted that the mean VIQ of the Early Postnatal Right group was 95.2 and the mean VIQ for the control group was 96.3. The three Left groups (Prenatal, Early Postnatal, Late Postnatal) were significantly impaired relative to the control group. Furthermore, the Late Left Postnatal group was significantly impaired relative to all other groups. Significant positive correlations were reported, only in the Left hemisphere groups, between object naming scores and FSIQ and VIQ. There was also a significant negative correlation between object naming scores and age at injury in the Left hemisphere groups only. It is important to note that interpretation of these correlations should be done with caution due to the extremely small sample sizes of these groups.

Initially, the findings reported by Vargha-Kahdem and colleagues and those reported by Woods and Carey (1978) appear to support reports that left-hemisphere injury prior to the age of five may influence cerebral organization of language functions (Krashen, 1973; Luria, 1980; Milner, 1974;1975). These finding could also be interpreted in a number of other ways. In a broader sense they could be interpreted as the consequence of the secondary impact of age of injury on intellectual outcome that may be related to injury near or at the time of the beginning of formal education. Recall that in the Vargha-Kahdem sample, the mean age at time of testing was youngest and testing was performed during the earliest period of education in the Early Postnatal Right group relative to the other groups (mean age at time = 8.9 years; range =6-17 years). It could also be argued that the impaired performance of the Early Right Postnatal group relative to that of the control group was related to their younger age at the time of testing and may not be related to age at time of injury, but related to age at time of testing. Specifically, the data may represent the less developed lexicon of younger subjects relative to older subjects.

The reports just mentioned underscore the importance of examining the age of onset that a non-progressive injury or insult was acquired, as well as knowledge of when testing took place in relation to the date of injury, and age at time of testing. One issue related to research that has attempted to investigate the issue of a differential risk to cognitive outcome related to age of onset is the different "cut-offs/criteria employed between studies in the definition of "early onset". For instance, in the study reported by O'Leary et al. (1983) the early onset groups were characterized by group mean ages of onset of 2.4 years, whereas Woods and Carey (1979) defined their early onset group as those individuals who had acquired cerebral injury prior to 12 months of age. The subjects in the Bourgeois et al. (1983) study were not included if onset was prior to 18 months of age, whereas in the Vargha-Kahdem et al. (1985) study there was a Prenatal group and an Early Postnatal group composed of subjects with ages of onset that ranged from 2 months to 5 years of age (see Table 4 for a summary of the definitions employed to divide subjects into early onset groups).

Table 4
Summary of Various Defining Characteristics of Early Onset Groups Reported in the Literature

Study	Definitions of Early Onset Groups
O'Leary et al. (1983)	1) early partial group: Mean 2.4, SD (1.8) years 2) early generalized group: Mean 2.4, SD (1.6) years
Woods & Carey (1979)	acquisition of cerebral injury prior to 12 months of age
Bourgeois et al. (1983)	acquisition of cerebral injury subsequent to age 18 months
Vargha-Kahdem et al. (1985)	1) Prenatal group 2) Early Postnatal group 2 months to 5 years of age

In spite of the different cut-off criteria employed to group subjects the findings have been generally consistent between studies. The similarity in results between studies that employed different cut-off criteria suggests that age of onset is a viable factor and merits further investigation. The factor of age of onset appears to be robust enough to exert a differential effect even on tasks with higher error variance as in the case of naming tests[12] just as it does on more stable measures with higher reliability coefficients[13] like the WAIS-R.

Based on the studies that examined naming ability in children

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[12] Test-retest reliability data are not available on the Boston Naming Test.

[13] The average reliability coefficients across age groups for VIQ, PIQ, and FSIQ are .97,.93,and .97 respectively (Wechsler, 1981).

with either left- or right- lesions it can be surmised that there is some evidence suggesting that left- and right- lesions in children are associated with the risk of persistent naming deficits, up until the time of testing (Aram, Ekelman & Whitaker, 1985; Kiessling, Denckla & Carlton, 1983; Vargha-Khadem, O'Gorman & Watters, 1985). The research in this area may be used in making some predictions in relation to the age of onset and laterality interactions that might be evident in the area of TLE and performance on naming tasks. Based on the literature (which does not consider education as a factor) one might anticipate that as a group individuals with right-TLE would perform with higher accuracy on tasks of confrontation naming than would those with left-TLE. Individuals with early onset right-TLE might be predicted to perform with less accuracy on tasks of confrontation naming relative to those with later onset right-TLE. In contrast to those with left-TLE, in which case those with later onset left-TLE would be expected to be most impaired.

Generally, the literature on adults with TLE has explored confrontation naming in relation to laterality of TLE focus, rather than in relation to age of onset. In adults, the integrity of many regions in the left hemisphere are necessary for the naming process (see Mesulam, 1990; Wise, Chollet, Hadar, Friston, Hoffner & Frackowiak, 1991); however word retrieval processes have been associated primarily with structures of the left temporal lobe (Kremin and Koskas, 1983; McKenna & Warrington, 1980). Adults who have lesions with left temporal lobe involvement have been reported to perform significantly worse on naming tasks than those with left hemisphere lesions that spare the temporal lobe (Coughlan & Warrington, 1978; McKenna & Warrington, 1980).

Adults with left-TLE have been reported to present with naming impairments within the context of fluent spontaneous speech and intact comprehension (Blaxton and Bookheimer, 1993; Hermann et al., 1988; 1992; Mayeux et al.,1980). Generally, subjects with left-TLE have been reported to perform in a relatively more impaired fashion than those with right-TLE (Hermann et al., 1992; Howell et al.,1994; Saykin et al.,1995) or generalized epilepsy (Mayeux et al., 1980). Some investigators (Mayeux et al.,1980) have discussed the experienced word-finding impairments associated with TLE as a word-selection anomia[14] (Benson, 1979).

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[14] Word selection anomia may be characterized as the inability to produce a specific word in the absence of phonemic or contextual cuing. This suggests that there is some form of search strategy impairment or constriction within the semantic system.

Mayeux, Brandt, Rosen, and Benson (1980) studied a sample of 14 patients with left-TLE, 7 with right-TLE, and 8 with generalized epilepsy, all with onset of seizure disorders during adulthood. Groups were equated for age, education, IQ, duration of illness, seizure frequency, and medication. Subjects were examined with the Boston Naming Test (85 item). The Left-TLE group was significantly more impaired than the other groups on the naming task (Group Means on the $BNT_{85\ item}$: L-TLE=59.6; R-TLE=76.4; GE=71.4).

Hermann and colleagues (1992) attempted to explore the lateralized differences in naming performance initially observed by Mayeux et al. (1980). They examined the effect of laterality of seizure focus on the adequacy of select language functions in patients with idiopathic, unilateral left- (n=47) and right- (n=52) TLE. Group means did not differ in age at evaluation, education, age of onset (adolescence), or duration of disorder. Group performance was compared on the Multilingual Aphasia Examination (Benton and Hamsher, 1983). Consistent with the finding of Mayeux et al. (1980) the left-TLE group performed significantly more poorly than the right-TLE group on five[15] of the seven measures of the Multilingual Aphasia

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[15] The five subtests the Left-TLE subjects were significantly impaired on relative to the Right-TLE subjects consisted of Visual Naming, Sentence Repetition, Token Test, Reading Comprehension, and Aural Comprehension.

Battery. Further analysis revealed that patients with high naming scores tended to obtain higher WAIS-R IQs. This should be expected, because it is known that measures of general vocabulary level correlate highly with other measures of verbal and non-verbal intelligence (Wechsler, 1981).

Research on adult TLE samples has also demonstrated subtle lateralized (fewer productions associated with foci ipsilateral to the dominant vs non-dominant hemisphere) impairment in the performance on phonemic fluency tasks (Hermann, Wyler, and Somes, 1991; Howell et al., 1994; Martin et al., 1990). Productions on phonemic fluency tasks have been thought to be guided by phonemic and/or lexical cues (Butters et al., 1987; Martin and Fedio, 1983; Monsch et al., 1994) and require associative exploration and retrieval of particular categories for successful verbal production. In a factor analytic study with adults, desRosiers and Kavanagh (1987) reported that phonemic fluency loaded primarily on a verbal knowledge factor (loaded with VIQ and Vocabulary).

Saykin et al.(1992) and Martin et al. (1990) have reported that prior to surgery, adults with both right- and left-TLE were impaired in their performance on phonemic fluency tasks, and that subjects with left-TLE were more impaired relative to those with right-TLE. It is not clear if these findings are issues of laterality of seizure focus, age of onset, education or in some cases the interaction among these variables. To date this remains unanswered, but was explored in conjunction with confrontation naming performance in the Methods and Results Section of this dissertation.

A final note should be mentioned as to whether or not there is a gender effect in the epilepsy literature on verbal retrieval. This is a hard question to address, because language functioning in chronic TLE has been an area of relatively little research; furthermore few investigators have examined the role that gender may exert on verbal retrieval performance in epilepsy. This is likely due to the problems of sample sizes and not being able to further sub-divide groups by gender. There is some epilepsy literature (Seidenberg et al., 1986; Strauss, Hunter and Wada, 1995) which suggests that men and boys may be at greater risk for impairment in verbal abilities relative to girls and women. This issue of a differential risk related to gender was explored in the Results Section.

<u>Age of Onset and Verbal Memory</u>: In this portion of the dissertation, the discussion of the location of a seizure focus will be

restricted primarily to the temporal lobe and laterality of seizure focus (left or right) as that is the way it is generally dealt with in the literature. It is important to note that the secondary consequence of age of onset on education and how that might relate to verbal-learning and delayed recall are not dealt with in the literature.

The role of the temporal lobes and associated subcortical structures in memory functions has been well documented (Squire, 1987, for review). Specifically, research on adults with TLE and those who have undergone temporal lobectomy have generally supported the assumption that the dominant left temporal lobe is primarily involved with verbal/semantic memory, and the right non-dominant temporal lobe is involved in visual/figural memory (Delaney et al.,1980; Jones-Gotman, 1986; Saykin et al., 1989). There are only three comparable studies in the pediatric TLE literature (e.g., Camfield et al., 1984; Cohen, 1992; Fedio and Mirsky, 1969).

Fedio and Mirsky (1969) compared the performance of children with left- and right-TLE, children with generalized absence epilepsy, and a group of normal children, ages 6-14. Groups were compared on tests of intelligence and verbal/nonverbal tasks of learning and delayed memory. The results indicated that children with left-TLE were relatively impaired on Verbal IQ measures and delayed verbal memory measures. In contrast, children with right-TLE presented with deficits in Performance IQ and delayed nonverbal memory measures. These results appear to support the lateralized performance patterns often reported in the adult TLE literature of material-specific impairment (Delaney et al., 1980; Dikmen, 1980; Hermann et al., 1987; 1992; Loring et al., 1986; Mungas et al., 1985).

In contrast to the Fedio and Mirsky (1969) report, Camfield et al. (1984) failed to find significant differences in cognitive functioning between children with left- and right-TLE. Possible reasons for this failure may be related to the sample compositions in these two studies. The patients in the Fedio and Mirsky (1969) study were selected from a pediatric seizure clinic and may have suffered from more severe epilepsy than those in the Camfield et al. (1984) study who were selected from a broader spectrum of children with TLE treated at a tertiary pediatric center (although this comment is only speculation). It is difficult to know if the subjects treated at the seizure clinic presented with more severe seizure disorders. In fact, review of the literature makes it clear that some sort of severity index is needed in future research to better characterize samples on both primary and secondary consequences of seizure-related variables, this point will be returned to in the Discussion Section. It is likely that the inconsistencies between the Fedio and Mirsky (1969) and the Camfield et al. (1984) studies were also related to differing task demands. Specifically, the Fedio and Mirsky (1969) study included tasks with a delayed memory component, whereas Camfield et al. (1984) did not. Material-specific memory impairment, as a function of laterality of seizure focus, may not be evident until a delay is imposed between presentation and recall of material. When a delay is employed left-TLE adult patients tend to be impaired on delayed recall of verbal material such as prose (Delaney et al., 1980) and word list learning (Hermann et al., 1987; Mungas et al., 1985).

The third study in the pediatric literature evaluated auditory/verbal and visual/spatial memory in children with TLE (Cohen,1992). Each subject was administered the Comprehensive Children's Memory Scale[16]. Cohen compared two groups of children with TLE (left-TLE: n=12; right-TLE: n=12) selected from a comprehensive epilepsy center with a group of seventy normal

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[16] The auditory/verbal memory section of this test battery consists of digit span, sentence repetition, passage recall (immediate and delayed), verbal learning with selective reminding (immediate and delayed), and an auditory paired associate learning test. The visual/spatial memory section of this battery consists of a motor-free memory for designs subtest, visual sequential memory, sequential hand movements, sequential touch subtest, visual paired associate learning, and a delayed tactile/kinesthetic recall test.

children, ages 6-12 years. The results indicated that children with left-TLE were significantly more impaired than controls on the auditory/verbal memory tasks; whereas children with right-TLE were significantly more impaired than controls on the visual/spatial memory tasks. The left- and right-TLE groups did not differ significantly from each other, although performance for each group was in the expected direction. The results of this study offer some support for the conjecture of Fedio and Mirsky (1969) that children with TLE may present with material specific memory impairment, like many adults with TLE.

In regard to memory function in adults with TLE, material-specific memory deficits have been reported (Dikmen, 1980; Hermann et al. 1992; Mungus et al. 1985), but the effect appears to be more robust with regard to left-TLE and verbal memory impairment (Loring et al., 1986). The relatively higher frequency with which verbal memory impairments have been associated with left-TLE in the literature relative to non-verbal memory impairments being associated with right-TLE might be related to the clinical validity of the tasks that are employed to assess non-verbal memory. Evidence for this conjecture is based on the fact that most studies which have examined the factor structure of the Wechsler Memory Scale (WMS) and the Wechsler Memory Scale-Revised (WMS-R) have failed to demonstrate the existence of an independent non-verbal memory factor (Larrabee & Curtiss, 1995; Larrabee, Kane, Schuck & Francis, 1985; Roid, Prifitera & Ledbetter, 1988; Smith, Malec & Ivnik, 1992).

The pattern of lateralized memory impairment has been demonstrated in delayed recall of verbal list-learning tasks in the adult TLE literature (Hermann et al., 1988; 1992; Mungus et al., 1985), but group differences related to laterality of TLE focus have not been seen in the learning slope of these verbal lists. For instance, Mungas, Ehlers, Walton, and McCutchen (1985) examined the verbal learning abilities in 11 patients with left-TLE, 10 with right-TLE, and in 11 normal control subjects. The seizure groups did not differ in age of seizure onset (adult onset: Mean for left-TLE=36.3 (16.6), range=18-67; Mean for right-TLE= 27.3(16.5), range=7-56), age at testing or in educational level achieved. The learning slope on the Auditory Verbal Learning Test (AVLT)[17] was similar across all three groups. The left-TLE group did perform poorer than the other groups on the delayed recall of the first list, a pattern that is consistent with other

[17] The test consisted of 2 lists of 16 items each. There were 5 consecutive learning trials for List 1, List 2 was used as an interference learning trial, which was followed by delayed recall of List 1 and then List 2. Free recall trials were followed by phonemic and graphemic cued recall and semantic cued recall.

reports (e.g., Delaney et al., 1980; Hermann et al., 1987; 1988; 1992).

Other investigators have failed to find differential memory performance related to laterality in adult TLE subjects (Delaney et al., 1980; Mayeux et al., 1980). As in the case of the pediatric literature, this difference between reports may be related to methodological issues associated with task demands. It may also be related to the characteristics of the seizure disorders of the sample under investigation (e.g., age of onset, duration of disorder, medication-refractory seizure disorders). This possibility underscores, once again, the need for the construction of a severity index in future research endeavors. Another reason for the failure to observe differential memory performance may be related to the factor structure of the tests employed. Factor analytic studies of the California Verbal Learning Test (CVLT) have yielded six factors: a general learning factor, learning strategy, acquisition rate, serial position effect, discriminability, and learning interference (Delis et al., 1988). From the factor structure it is apparent that this test, often employed in the literature as a measure of verbal memory, does not examine rote verbal memory, but rather some level of interaction between verbal memory and conceptual ability.

The interrelationship between measures of expressive language functions and verbal learning/memory was examined in twenty-five adult pre-surgical left-TLE patients with complex partial seizures by Hermann, Wyler, Steenman and Richey (1988). The mean age of onset was during adolescence (14.1 years) which is younger [18] than the other samples discussed previously. One potential problematic issue with this sample was that only 36% of the patients included had seizures of idiopathic etiology, the remaining subjects were classified as having unspecified symptomatic etiologies. Recall that earlier in this document the potential confounding effects associated with symptomatic epilepsy were discussed. Specifically, individuals with symptomatic epilepsy have been reported to perform more poorly on cognitive tests than those with idiopathic epilepsy (e.g., Bourgeois, Prensky, Palkes, Talent and Busch, 1983; Klove and Matthews, 1966).

The Hermann et al. (1988) study was, however, noteworthy for many reasons and a number of issues are pointed out prior to presenting the details of the study. This study by Hermann et al.

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[18] The mean age of onset in the Mungas et al. (1985) study was 36.3 (16.6) for the left group and 27.3 (16.5) in the right group. In the Mayeux et al. (1980) study the mean age at testing in the left group was 45.78 (10.6) with the mean duration of illness being 22.71 (8.8); the mean age at testing for the right group was 41.9 (12.3) with the mean duration of illness being 18.28 (13.1).

(1988) underscored the necessity of assessing language function and VIQ when evaluating verbal learning/memory. The second issue of note related to this study, was that the mean age of onset for this adult sample was during adolescence which is a rare finding in the literature on this topic. The younger mean age of onset and the fact that only 36% of the sample had seizures of unknown etiology raises questions related to how variables such as age of onset (especially early in childhood) and etiology of seizure disorder can moderate VIQ, verbal retrieval and impact on verbal learning and delayed recall in TLE. This younger mean age of onset also raises questions as to the composition/pattern of the distribution of age of onset in this sample and begins to highlight the need to consider and examine the variable of age of onset in relation to its consequences on education further.

Hermann, Wyler, Steenman and Richey (1988) explored the interrelationship between measures of expressive language functions using the Multilingual Aphasia Examination (MAE) (Benton & Hamsher, 1983) and verbal learning/memory as assessed by the CVLT. They reported that the total number of words recalled across $Trials_{1-5}$ on the CVLT was positively correlated with VIQ ($r=.45$) while the total number of subtests on the MAE outside normal limits (defined as falling in the impaired range) was negatively correlated with total recall on $Trials_{1-5}$ ($r=-.68$). These findings were predictable and underscore the need to assess VIQ in studies of this kind. When both language impairment (predictor variables were MAE subtests in the impaired range) and VIQ were entered into a backward elimination regression analysis[19] using the total number of words recalled as the criterion measure, only language impairment remained significant not VIQ. The degree of retrieval difficulty[20] was negatively correlated with VIQ ($r=-.53$) and positively correlated with the number of subtests outside normal limits ($r=.48$). When entered into a backward elimination regression analysis VIQ remained significant using retrieval difficulty as the criterion measure, not language impairment predictor variables. The best predictors of CVLT performance in general were the visual naming and phonemic fluency subtests of the MAE which accounted for 46% of the variance.

Hermann and colleagues (1992) continued to explore the

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[19] Most regression techniques are based on a sequential movement in which regressor variables are added or deleted one at a time on how the change impacted the regression, or residual, sum of squares. Backward elimination regression begins with a full set of candidate variables. Variables are eliminated one at a time with termination coming when the candidate for elimination is statistically significant on the basis of a partial F (Myers,1986; p.10).

[20] Retrieval difficulty was defined as the difference between the number of words correctly identified on recognition testing minus the number of words free recalled on $Trial_5$. The larger the discrepancy the greater the difficulty in retrieval.

relation between adequacy of language function and verbal learning/memory performance in patients, but in this sample they included only subjects with idiopathic left-TLE (n=47) and right-TLE (n=52). Group means did not differ in age at evaluation, education, age of onset (adolescence), or duration of disorder. Using the same evaluation as in the study reported in 1988 they examined the effects of laterality of seizure onset and adequacy of language function on verbal learning performance.

The left-TLE group was significantly more impaired than the right-TLE group on five[21] of the seven measures of the Multilingual Aphasia Battery. Patients who obtained lower scores on the naming task relative to their respective (lateralized) group means performed significantly more impaired on the verbal learning task and tended to obtain lower WAIS-R IQs. The variable of age of seizure onset was not explored within the high and low naming groups, but in light of the lower IQ scores it may be that the low naming groups presented with earlier ages of onset. When compared in multiple regression[22] analyses to examine the unique variance associated with laterality of

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[21] The five measures included the following: Visual Naming, Sentence Repetition, Token Test, Reading Comprehension, and Aural Comprehension.

[22] Multiple linear regression extends bivariate regression by incorporating multiple independent variables.

TLE and language function (entered as a block), it was reported that language function[23] and not laterality was the best predictor of verbal learning on the CVLT.

A point that merits discussion related to this finding revolves around the appropriateness of using language functioning as a predetermining factor of performance (as in the case of the variable of laterality of seizure focus) on a task of verbal learning. This point is important, because it is known that measures of general vocabulary level correlate highly with other measures of verbal and non-verbal intelligence (Wechsler, 1981). Furthermore, results from the Hermann et al. (1988) study revealed that the total number of words recalled across $Trials_{1-5}$ on the CVLT was positively correlated with VIQ ($r=.45$) and degree of retrieval difficulty was negatively correlated with VIQ ($r=-.53$). It would be more prudent to perform a factor analysis first to explore the relation between IQ, naming, and CVLT performance to assess whether, in TLE, these tasks evaluate similar or different factors. Finally, it might have been more appropriate to perform Hierarchical Regression analyses on each of the standardized test scores with the seizure variables used as predictors. In light of

[23] Within the language block, better visual naming performance was significantly associated with better short delay recall, and fewer intrusion errors.

the fact that the entry order of predictor variables into the equation can have an effect on the outcome of a regression analysis, a hierarchical model would need to be constructed such that a seizure-related variable entered later in the list of predictor variables could not be the cause of an earlier variable, or that variables temporally preceding later ones would be entered into the equation first (Cohen and Cohen, 1983). For instance the predictor variable of age of onset should be entered into the regression equation prior to entering the predictor variable of duration of illness. A hierarchical method of regression is better suited to this type of analysis. In the Backward Elimination method, employed by Hermann and colleagues, the overall R^2 generated by putting all independent variables into the equation was initially generated. Then each variable was deleted, one at a time, to explore whether R^2 dropped significantly. Each variable was tested to see what would happen if it were the last one entered into the equation. The absence of a gender effect in the work of Hermann et al. (1988) on the CVLT was surprising, because it has been reported in the normative literature that women tend to outperform men on learning and recall indices of this test (Kramer, Delis, and Daniel, 1988) this issue was explored in the Results Section using the Hierarchical method of regression which allowed for the forced entry order of variables into the equation.

To recapitulate the literature presented up to this point, studies have reported that seizure onset in early childhood is associated with a higher risk of lower intellectual functioning than is onset during late childhood or adolescence (Dodrill,1992; Levine et al., 1987; O'Leary et al., 1981; Woods, 1980). The pediatric literature related to subsequent outcome of language suggests a trend in which children sustaining early left brain lesions are more likely to present with impaired naming performance (e.g., Aram, Ekelman and Whitaker, 1987; Kiessling, Denckla and Carlton, 1983; Vargha-Kahdem, O'Gorman and Watters, 1985; Woods and Carey, 1979), however early right-hemisphere lesions have also be associated with impaired naming performance (Vargha-Kahdem et al, 1985). Adults with left-TLE have been reported to present with language impairments (e.g., Blaxton and Bookheimer, 1993; Hermann et al., 1988; 1992; Howell et al.,1994; Mayeux et al.,1980; Saykin et al.,1995) and subtle impairments in the performance on fluency tasks (e.g.,Hermann, Wyler, and Somes, 1991; Howell et al., 1994; Martin et al., 1990; Troster et al., 1995) and the delayed recall of verbal lists (e.g., Delaney et al., 1980; Hermann et al., 1987; 1988; 1992; Loring et al., 1986; Mungus et al., 1985).

There were a number of methodological and demographic differences between studies on verbal memory discussed up to this point. The mean ages of onset varied between samples. For instance, the sample in the Hermann, Wyler, Steenman and Richey (1988) study consisted of 25 patients with a mean age of onset of 14.1 years which is younger than that mentioned in the sample discussed in the Mungas et al. (1985) study in which case the mean age of onset in the was 36.3 (16.6) for the left group and 27.3 (16.5) in the right group. Age of onset was not provided for the sample of the Mayeux et al. (1980) study, but the mean age at testing in the left group was 45.78 (10.6) with the mean duration of illness being 22.71 (8.8); the mean age at testing for the right group was 41.9 (12.3) with the mean duration of illness being 18.28 (13.1).

Some of the reports in the literature included subjects with TLE of symptomatic etiology as in the cases of Hermann et al. (1988) and Mungus et al (1985), whereas the sample in the Mayeux et al. (1980) study was composed of subjects with epilepsy of unknown etiology.

In regard to whether subjects were surgical candidates (which may indicate the severity of illness) and level of education, the samples reported on by Mayeux et al. (1980) and Mungus et al. (1985) were composed of patients with seizure disorders who were not surgical candidates for temporal lobectomy with relatively higher mean levels of education. The mean levels of education in the Mayeux et al. (1980) report were R-TLE = 13.5 (3.89); L-TLE = 12.1 (2.91). The mean levels of education in the Mungus et al. (1985) report were R-TLE = 13.1 (2.3); L-TLE = 13.4 (2.0). The mean levels of education in the Hermann et al. (1992) report were R-TLE = 12.5 (2.8); L-TLE = 12.5 (2.2). The samples in the Hermann et al. (1987; 1988; 1991; 1992) studies were composed of medication-refractory presurgical candidates with relatively lower mean levels of education.

In spite of the differences between studies, the outcome appears to be similar. There do not appear to be differences in the learning slope of left- and right- TLE groups, but there does appear to be a difference between left- and right- TLE groups on delayed recall of list learning tasks.

Thus far, factors associated with seizure disorders and performance on intelligence and select verbal and verbal list-learning tests have been discussed. There were three issues that have been emphasized. The first issue was that some variables are related to each other (e.g., age of onset and duration of disorder; age of onset and level of education; level of education and obtained IQ scores).

The second issue was that when age of onset occurs early in life it is enmeshed with development. The third issue of importance related to the effect that a chronic seizure disorder may have on education. It might be postulated that the ability to acquire and retain information is differentially affected in a child who is acquiring knowledge of the world in the presence of a seizure disorder, as opposed to an adult who acquires a seizure disorder after he/she has completed schooling.

In conclusion, the combined contributions of seizure-related variables to IQ scores, verbal retrieval, and verbal list-learning have not been adequately explored in the literature in relation to the secondary consequences associated with seizure-related variables. The nature of the impairments associated with TLE may reflect the broad developmental influence of a disruption in education programs that is subtly manifest later in life.

D. Rationale for the Series of Studies Performed in this Dissertation

The rationale for this dissertation centers on the need in the literature to identify primary variables that are associated with the greatest risk for intellectual impairment and cognitive deficiencies. Furthermore, review of the literature has made it evident that some deficits may be related to the secondary and even tertiary consequences of these primary factors.

The purpose of this research was to explore the primary seizure-related variables and some of the secondary consequences of these variables in relation to intellectual outcome and verbal retrieval and verbal learning outcomes. As discussed previously the concentration on verbal as opposed to non-verbal material was chosen due to the results of factor analytical studies on commonly used tasks to assess memory which have failed to demonstrate the existence of an independent non-verbal memory factor (Larrabee & Curtiss, 1995; Larrabee, Kane, Schuck & Francis, 1985; Roid, Prifitera & Ledbetter, 1988; Smith, Malec & Ivnik, 1992).

The present study was designed to remove many of the methodological and statistical problems/issues which have made it difficult to predict intellectual and cognitive outcome in TLE. This research explored the secondary consequences of age of onset in TLE in relation to intellectual and cognitive outcome.

E. Ex Post Facto Research Design

An ex post facto research design was required because the independent variables could not be experimentally controlled by randomization or manipulation. Subjects were studied because they possessed the seizure characteristics of interest.

Hierarchical regression techniques were employed to assess the relations between primary and secondary factors and task performance measures. Recognizing that the order of predictor variables may have an effect on the outcome of a regression analysis, a hierarchical model was constructed, so that a later variable could not be the cause of an earlier variable or that variables temporally preceding later ones would be entered into the equation first (Cohen and Cohen,1983).

This ex post facto research employed a retrospective method of investigation to explore the prediction of intellectual and cognitive outcome in chronic TLE with data on select primary and secondary factors. This ex post facto research examined a number of variables (age of onset, duration of illness, laterality of TLE focus, gender, and level of education) and the contribution they provide, uniquely and in combination, to the prediction of general intellectual and cognitive outcomes. The purpose of this ex post facto research was to describe the relationships between variables. Inferences about relations were made without direct intervention, from concomitant variation of independent and dependent variables.

This research was performed on the data collected from multiple epilepsy centers. There were a number of benefits to using a large sample selected from more than one epilepsy center. Specifically most of the literature consists of studies based on relatively small sample sizes (typically less than 50 cases) selected from a single institution. Thus, results may reflect sample specific fluctuations related to catchment area and demographics. A sample selected from multiple centers in various geographic locations allows for the generality of findings to other individuals who meet the criteria articulated in this research project. A larger sample size was also needed to address many of the questions and discrepancies related to small group sizes (the issue of error variance associated with task measures and how that might reduce the effect of an independent variable) and heterogeneity within samples (e.g., the inclusion of subjects with symptomatic epilepsy). The impact of variables such as age of onset and duration of disorder can be examined in relation to general intellectual functioning and specific aspects of verbal retrieval and verbal learning and verbal memory; large sample sizes are required for this endeavor to deal with the fluctuations in the age-specific incidence of seizure disorders (Ellenberg et al., 1984; Hauser, 1992). A large sample was needed to further our understanding of TLE and the interactions between primary seizure-related factors and the secondary consequences associated with them. Specifically, while the majority of the studies in the literature examined primary variables in isolation, none of the primary variables in isolation were terribly robust. The opportunity to examine the data from a larger sample provided a means of looking at the primary variables in isolation and in combination while dealing with issues related to error variance.

In this investigation, the neuropsychological test scores and demographic/historical information from the subject pool of the Bozeman Consortium, a collaboration of several epilepsy surgery centers (Cleveland Clinic, Long Island Jewish Medical Center, Mayo Clinic, Epi-Care Center, Yale University, New York University, Medical College of Georgia, and University of British Columbia and University of Victoria) that have allowed their databases to be merged were analyzed.

The ex post facto approach using retrospective data provided a means to examine the seizure-related variables and educational attainment in a large group of subjects with intractable TLE in an attempt to identify those factors associated with intellectual and cognitive outcome. This approach allowed for the investigation of potential risk factors that could be identified in relation to cognitive status at the time of testing. The major advantage of this approach was that it could be performed quickly, inexpensively, on existing data (hospital records and databases). Large numbers of cases that had been accumulated over long periods of time were studied for a very homogeneous sample, as in the case of the sample studied in this thesis (chronic, intractable, medication-refractory, uni-focal TLE of unknown etiology who are pre-surgical candidates).

The series of statistical analyses in this dissertation replicated and extended previous work in the area of general intellectual functioning, select verbal retrieval, verbal learning, and verbal memory abilities in chronic, medication-refractory, unilateral TLE. Initially, a set of analyses were performed that explored differences between and within epilepsy centers, exploring the characteristics of samples and seizure-related variables. This set of analyses was followed by descriptive statistics characterizing the two samples that were studied. The next set of analyses examined predictor variables and the strength of prediction in intellectual and cognitive outcome in TLE.

Predictions Related to Intellectual Outcome

Many potential seizure-related risk factors have been associated with the intellectual outcome of individuals with chronic seizure disorders (Ossetin, 1988). The relation between the factors of age of onset, education and IQ still remains unclear. Based on the literature reviewed the following predictions were advanced:

1) If age of onset is a key predictor of intellectual outcome then:

a) age of onset should be positively correlated with WAIS-R IQs when level of education is controlled in partial correlations.

b) age of onset should be positively correlated with WAIS-R IQs when duration of chronic TLE is controlled in partial correlations.

2) If a secondary consequence of the age at which a chronic seizure

disorder begins is related to level of education achieved, and we know that education is highly correlated with IQ indices (Weschler, 1981), then the combination of the primary and secondary variables should account for a greater amount of variance in performance on intelligence measures than when either the primary or the secondary factors are considered in isolation. Furthermore, we should expect that both age of onset and level of education achieved will be significant predictors of IQ indices when the variance accounted by other primary factors is held constant.

Predictions Related to Confrontation Naming, Phonemic Fluency and Delayed Verbal Recall

3) Based on the reports on the factor structure of these tasks and the literature of Hermann et al. (1987; 1988; 1992) proficiency in confrontation naming is expected to be positively correlated with VIQ, phonemic fluency, and delayed verbal recall performance.

a) if it is found that age of onset is a significant predictor of VIQ, and it is also found that VIQ is positively correlated with performance on tasks of confrontation naming and phonemic fluency then a greater amount of variance in performance on measures of confrontation naming and phonemic fluency should be accounted for when the primary and secondary variables are considered in combination than when assessed in isolation.

4) If the laterality of TLE focus is a key predictor of performance on confrontation naming performance and delayed verbal recall in TLE then:

a) individuals with right-TLE should perform with higher accuracy on the confrontation naming task than those with left-TLE. The possibility of an interaction between laterality of TLE focus and age of onset will have to be explored.

b) the reports of Seidenberg et al. (1986) and Strauss, Hunter and Wada (1995) suggest that a gender effect will be evident in performance on tasks of verbal retrieval (confrontation naming and phonemic fluency), with females outperforming males.

c) from the pediatric and adult literature (Fedio and

Mirsky, 1969, Hermann et al., 1992; Mungus et al., 1985) it should be anticipated that as a group: individuals with right-TLE will perform with higher accuracy on tasks of delayed verbal recall than will those with left-TLE. Lateralized group differences are not expected in the rate of learning over trials.

5) The normative literature (Kramer, Delis, and Daniel, 1988) and reports in the epilepsy literature (Seidenberg et al., 1986; Strauss, Hunter and Wada, 1995) suggest that a gender effect should be anticipated such that females will outperform males on tasks of delayed verbal recall. It is predicted that a greater amount of variance in performance on measures of verbal delayed recall would be accounted for when the primary and secondary variables were considered in combination than when assessed in isolation. Gender is expected to be a significant predictor when the variance accounted for by the other predictor variables is held constant.

Chapter 2

Method

Sample Selection

A. Selection Criteria

The subjects with medically-refractory uni-focal TLE that were studied in this dissertation research were from the Bozeman Epilepsy Consortium. The database of the consortium consisted of approximately 1500 adult patients ranging in age from 16-74 years, the majority with temporal lobe dysfunction, evaluated as pre-surgical candidates.

There were two samples studied in this dissertation research. The first sample (Sample One) was employed to investigate the amount of variance accounted for by primary (age of onset, duration of illness, and TLE focus) and secondary (level of education achieved) factors in the prediction of intellectual outcome. The second sample (Sample Two) was employed to investigate the amount of variance accounted for by primary (age of onset, duration of illness, TLE focus, and gender) and secondary (level of education achieved) factors in the prediction of verbal retrieval, verbal learning and verbal memory.

Criteria for Subject Inclusion in Sample One Analyses Consisted of:

1a) Neurophysiological evidence of uni-lateral hemispheric dysfunction localized to the temporal lobe. Individuals with mirror foci were excluded from data analysis in this study. Ictal and inter-ictal scalp EEG activity was used to determine unilateral seizure focus from the temporal lobe. The diagnosis of temporal lobe epilepsy and localization of the seizure focus was confirmed by data obtained from surface EEG with concurrent intensive video monitoring (see APPENDIX A for procedure) and in some cases the use of stereotaxically-implanted depth electrodes (Spencer, 1981). The presence of other neurological disorders such as brain tumor, stroke, or vascular malformations were ruled out by evidence obtained from neuroradiographic procedures (e.g., computed tomography, cerebral angiography, magnetic resonance imaging). The diagnostic work-up also included neuropsychological examination to assess cognitive functioning.

1b) For inclusion each subject had to have complete data available regarding all of the following:

- age at time of testing
- level of education
- age of first seizure
- age of onset of chronic seizures
- duration of disorder
- etiology of disorder (symptomatic, idiopathic)
- gender
- handedness

1c) Each subject had to have been assessed on the Wechsler Adult Intelligence Scale-Revised (WAIS-R) administered according to the standardized procedure for administration provided in the instruction manual.

Criteria for Subject Inclusion in Sample Two Consisted of:

2a) Meeting criteria 1a-1c required for inclusion into Sample One.

2b) Assessment on the following tasks was an additional inclusion criterion for Sample Two. The analysis performed on the Sample Two data were designed to test specific predictions related to verbal retrieval and verbal learning. Sample Two was much smaller[24] than Sample One, because inclusion criteria required for Sample Two required completion of the following tasks:

The Boston Naming Test ($BNT_{60\ item}$)
The Controlled Oral Word Association Test (CWAT)
The California Verbal Learning Test (CVLT)

B. Testing Materials and Procedures

All subjects (from Sample One (n=795) and Sample Two (n=77)) were administered the WAIS-R. The smaller sample (Sample Two) was also administered the Boston Naming $Test_{(60\ item)}$, the Controlled Oral Word Association Test, and the California Verbal Learning Test. Testing was administered and scored according to the standardized instructions and guidelines provided in the manuals.

The Wechsler Adult Intelligence Test-Revised is a standardized intelligence test that provides results that were used for the purpose of selection criteria and group comparison. The other tests listed

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[24] Subjects could only be selected from the Epi-Care Center and Hospital for Joint Disease as these centers administered both the $BNT_{60\ item}$ and the CVLT.

below have been selected because they have been shown to be sensitive to the language and verbal learning deficits experienced by unoperated TLE patients. These tests will be described in the following paragraphs.

The Wechsler Adult Intelligence Test-Revised (WAIS-R) is an extensively used standardized test for assessing intellectual functions. It consists of 11 subtests; 6 Verbal scale subtests and 5 Performance scale subtests.

The WAIS-R manual (Wechsler,1981) provides detailed administration and scoring procedures. Individual subtests provide raw, scaled, and age-corrected scaled scores. Norms are presented in the WAIS-R manual and are based on large groups representative of the U.S. population. The WAIS-R takes account of age differences when the IQ scores are computed. Intelligence quotients (IQs) are obtained for the Verbal scale, Performance scale, and the Full scale, the average reliability coefficients across age groups for the above mentioned scales are .97, .93, and .97 respectively (Wechsler,1981).

The WAIS-R provides accurate characterization of the sample for both descriptive purposes and comparison to other samples as it is routinely administered pre- and postoperatively in most epilepsy centers.

The Boston Naming Test (BNT) (Kaplan, Goodglass & Weintraub,1983) is the most widely used instrument for assessing naming disorders and anomic aphasia. The BNT provides a method to assess lexical retrieval in patients with mild language disturbances. The test consists of 60 line drawings[25] presented in order of graded difficulty. Subjects are asked to name each item. Stimulus cues are provided if the subject misperceives the stimulus. If the subject is unable to correctly name the item, a phonemic cue is provided after 20 seconds. The scoring of this test focuses on the number of items responded to without cuing, and with cues.

The norms provided with this test are based on small groups of adults ranging in age from 18-59 years. Age-related changes or differences between adults with 12 years of education or less are not provided. Normal control adult subjects obtain an average of 55-56

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[25] In the Bozeman Consortium both the 60 item and 85 item versions of the Boston Naming Test (BNT) were used. It has been reported that these two versions of the BNT are not equivalent and that significant differences exist between the percentage correct when comparing the two forms (Thompson & Heaton,1989). Due to its more common use in the literature and among epilepsy centers it was decided that the data from the 60 item form would be used in this thesis.

correct responses. Norms for school children ranging in age from 6-12 have been published (Halperin et al., 1989). Construct validity of the test in children was also investigated by Halperin et al. (1989) the BNT loaded highly on a word knowledge or vocabulary factor, but showed low loadings on a verbal fluency or a memory factor. Test-retest reliability data are not available.

The Controlled Oral Word Association Test (CWAT) (Benton,1968; Benton & Hamsher,1989) is a widely used task that allows for the systematic study of oral production of words that begin with a designated letter. This test consists of three word naming trials. The letters selected for this task were chosen based on the frequency of English words that begin with these letters. Subjects are instructed to say as many words as they can that begin with the specified letter, excluding proper nouns, numbers, and the same word with different suffixes. Production on phonemic fluency tasks are guided by phonemic and/or lexical cues, employment of efficient search strategies vary between subjects. It is accepted that children's ability to organize and retrieve words phonemically develops more slowly than the ability to organize and retrieve words from different categories (McCarthy, 1970).

Yeudall et al. (1996) have collected norms for males and females stratified by age (the age range from 15-40 years). Normal control subjects ranging in age from 15-40 years produce an average 44 or 45 word over three trials (Yeudall et al., 1986). Test-retest reliability in adults has been reported as .88 (desRosiers and Kavanagh, 1987). Yeudall et al. (1986) report this test's correlation with age to be -.19, with education .32, and with VIQ .14.

The California Verbal Learning Test (CVLT) (Delis, Kramer, Kaplan and Ober,1987) assesses the processes and strategies involved in learning and retaining verbal material. This instrument measures the rate of learning a 16 word categorized list (List A) that is orally presented over 5 trials. The list is comprised of 4 items from each of 4 categories (fruits, spices, clothing, tools), but the subjects are not informed of this. Adjacent words on the list are from different categories in order to assess the degree to which a subject uses the active learning strategy of recalling the words in semantic clusters. Following the 5 list learning trials, a second, interference list (List B) is presented for 1 trial. List B is also composed of 4 items from each of 4 categories: two categories are the same as those in List A (fruits and spices) and two are new categories (fish and utensils). Following recall of List B, free and category cued recall of List A is tested. After a 30 minute interval, long delay free recall, category cued recall, and recognition memory for List A are assessed.

This instrument extends the verbal list-learning paradigm that has been used in clinical and experimental assessment of memory disorders. The manual (Delis, Kramer, Kaplan and Ober,1987) provides extensive test construction information and normative data. Norms for males and females stratified by age (the age range from 17-80 years) were collected on 273 neurologically intact individuals. Normal control subjects usually reach a level of 13 or 14 words recalled by $Trial_5$ and retain an average of 12 to 13 words after the long delay. This test has been employed to demonstrate retention deficits and inappropriate use of verbal strategies (e.g., serial vs semantic) in a variety of clinical populations.

Factor analytic studies of the California Verbal Learning Test (CVLT) have yielded six factors: a general learning factor, learning strategy, acquisition rate, serial position effect, discriminability, and learning interference (Delis et al., 1988). Reliability studies are supplied in the test manual, they report split-half (odd-even), odd-even learning trials, 2 X 2 categories reliability coefficients ranging from .77 to .86.

C. Statistical Analysis

Description and Comparison of Sample One and Sample Two:

Sample One (n=795): First, the distribution parameters of the demographic characteristics of Sample One (n=795) were examined. Chi square was used to test for significance of categorical frequency data (gender, laterality of TLE focus, and handedness). A set of analyses were performed to examine the characteristics of the sample by gender, laterality of TLE focus, and handedness on age of onset and IQ indices. Another set of analyses examined the characteristics of the sample by the epilepsy center where they had been treated. Attention was concentrated on characteristics of epilepsy center samples and seizure-related variables. Demographic, seizure-related variables and IQ scores were subjected to univariate analyses of variance [26]. Chi square was used to test for significance of categorical frequency data (gender, handedness, and laterality of TLE focus). Each epilepsy center sample was then compared to determine if the samples from the different epilepsy centers could be combined. Comparisons of epilepsy center means were carried out using

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26 Variables that did not meet the assumption of the normal distribution were treated with non-parametric measures.

Newman-Keuls' statistic (with an alpha level set a priori = .05) when ANOVA yielded a significant ($p < .05$) effect for epilepsy center. Newman-Keuls' multiple range method of comparing groups' means corrects for the increase in probability of Type I errors associated with making multiple comparisons. When necessary, ANCOVA procedures were employed to explore differences between epilepsy center samples.

Sample Two (n = 77): The examination of Sample Two included descriptive statistics of the sample and exploration for differences between the lateralized TLE groups within Sample Two. First, the distribution parameters of the demographic characteristics of Sample Two (n = 77) were examined. Chi square was used to test for significance of categorical frequency data (gender, handedness, and laterality of TLE focus). A set of analyses were performed that examined the characteristics of the samples by the laterality of TLE focus. Attention was concentrated on characteristics of each lateralized TLE group. Demographic, seizure-related variables and IQ scores were subjected to univariate analyses of variance [27]. Chi square was used to test for significance of categorical frequency data

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[27] Variables that did not meet the assumption of the normal distribution were treated with non-parametric measures.

(gender, handedness, and laterality of TLE focus). The characteristics of Sample One and Sample Two were then compared.

Statistical Analyses Employed to Test Predictions:

Analyses were conducted to evaluate the unique and combined contribution of primary and secondary variables in the prediction of intellectual functioning (FSIQ, VIQ, and PIQ), performance on tasks of confrontation naming, phonemic fluency, and verbal learning and delayed verbal recall.

To explore the relationships between primary and secondary factors and measures of IQ a series of semipartial correlations[28] were performed. The semipartial correlation technique was employed because it allowed for the removal (or partialling out) of the relationship between the relevant variables being examined (age of onset, laterality of TLE focus, duration of illness, and level of education) and measures of IQ.

Hierarchical regression techniques were employed to assess the

[28] A semipartial correlation refers to the unique independent relationship of a variable to an outcome, after removing the relationship between relevant variables and other non-relevant variables (Cohen and Cohen, 1983, pp. 88-90).

effects of primary factors on education, and primary and secondary factors on task performance measures. Recognizing that the order of predictor variables may have an effect on the outcome of a regression analysis, a hierarchical model was constructed, so that a later variable could not be the cause of an earlier variable or that variables temporally preceding later ones would be entered into the equation first (Cohen and Cohen, 1983). The order of the variables was as follows: The first block of entry consisted of age of onset, laterality of focus, and duration of illness. The second block consisted of educational level achieved. Regression analysis assumes that the variables are measured quantitatively, therefore the variable of TLE focus was re-coded as a "dummy variable" to avoid the imposition of a quantitative assumption on laterality of TLE focus.

To begin to explore the verbal retrieval and verbal learning, and delayed verbal recall outcome in Sample Two, the inter-correlations between VIQ, BNT, and phonemic fluency with CVLT indices of learning and delayed free recall were assessed. Since these analyses were performed within-group, the conservative method, Spearman Rank Correlations, were used. To explore the relation between age of onset and laterality of focus in confrontation naming performance a 2 X 2 ANOVA was performed. To explore a possible gender effect a series of t-tests were performed to assess group differences on performance measures.

Hierarchical regression techniques were employed to assess the effects of primary and secondary factors on task performance measures. The variable of TLE focus was excluded from the set of primary factors in the regression model based on the results of the ANOVA. In light of the relatively small sample size of Sample Two (n=77), the number of variables included in analysis was conservatively restricted. It has been recommended that the number of subjects be at least 5-10 times the number of variables under study (Kleinbaum et al., 1988). The order of the variables was as follows: The first block of entry consisted of gender, age of onset, focus, and duration of illness. The second block consisted of educational level achieved. Since, regression analysis assumes that the variables are measured quantitatively, the variable of gender was re-coded as a "dummy variable" to avoid the imposition of a quantitative assumption on gender.

The final set of analyses were exploratory in nature. The purpose of these analyses was to assess if it were possible to observe the impact of age of onset on educational outcome. To this end subjects were divided into two groups (seizure onset by age 3 years, seizure onset after age 3 years. Age of Onset groups were compared on the variable of education with the Mann-Whitney U-Wilcoxon Rank Sum W Test to explore significant differences between groups.

Chapter 3

Results

This section begins with the examination of the distribution parameters of the demographic characteristics of Sample One (n=795). The examination of Sample One included descriptive statistics of the sample, examination of distribution parameters of the demographic variables within each epilepsy center that was included in Sample One, and exploration for significant differences between the epilepsy centers included in Sample One to determine if the epilepsy center samples could be merged together for data analysis. The examination of Sample Two included descriptive statistics of the sample and exploration for differences between the lateralized TLE groups within Sample Two. This section of the Results Section ends with comparison between Sample One and Sample Two.

The next set of analyses were conducted to evaluate the unique and combined contribution of primary and secondary variables in the prediction of intellectual functioning (FSIQ, VIQ, and PIQ), performance on tasks of confrontation naming, phonemic fluency, and verbal learning and delayed verbal recall.

The final section of the Results Section was exploratory in nature. It consisted of integrating the results obtained in this dissertation research.

A. Subject Variables of Sample One and Sample Two

Sample One (n=795) Characteristics: As shown in Table 5, Sample One consisted of 795 people: 406 males and 389 females (x^2 =.36, NS). The resulting sample consisted of patients from five of the participating epilepsy centers.[29] The majority of subjects (n=680 or 85.5%) were right-handed[30] (x^2 =997.28, $p<.0000$), 112 (14%) were left-handed, and 3 (.4%) were ambidextrous. In 369 or 46.4% of the cases temporal lobe seizures were lateralized to the right-hemisphere and in 426 cases or 53.6% seizures lateralized to the left-temporal lobe (x^2 =4.09, $p<.05$). The mean age at which seizures began was 13.2 (10.6), the median was 12, the mode was 1. Age of onset ranged from 1-56 years of age. The mean age at time of testing

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29 The data from Center 4 was excluded from analysis because the WAIS-R was not administered as part of the pre-surgical work-up. The data from Center 3 was excluded due in part to incomplete demographic information (e.g., levels of education). The resulting data set was compiled from the following epilepsy centers: Cleveland Clinic, Epi-Care, Mayo Clinic, Hospital for Joint Disease, and L.I.J.M.C..

30 The elevated incidence of 17-20% sinistrality in epilepsy is well established (Bolin,1953; Satz, Baymur & Van der Vlugt, 1979; Satz, Yanowitz & Willmore, 1983; Silva & Satz, 1979).

was 32.0 (9.4), the median and mode were both 31. The mean duration of illness was 18.8 (10.8), the median was 18, and the mode was 21. The distribution of FSIQ scores ranged from 48-132, with the mean FSIQ falling in the Low Average range (FSIQ=88.9), the median 88, and the mode 91.

Table 5

Demographics and IQ Scores for Sample One
Subject Characteristics
Total Sample

Variable	Sample (N=795)
	Mean(S.D.) (Range)
Chronological Age(yrs)	32.0(9.4) (16-65 yrs)
Years of Education	12.8(2.4) (3-22 yrs)
Age of Onset (yrs)	13.2(10.6) (1-56 yrs)
Gender (M:F)	406M,389F
Focus (L:R)*	426L,369R
Handedness (L:R)**	112L,680R[31]
Duration (yrs)	18.8(10.8) (1-62 yrs)
FSIQ	88.9(12.2) (48-132)
VIQ	89.6(12.6) (54-132)
PIQ	89.9(13.2) (48-139)

Note: FSIQ=Full Scale IQ; VIQ=Verbal IQ; PIQ=Performance IQ.
$*p<.05$. $**p<.0000$

31 Three of the 795 subjects (.4%) were assessed to be ambidextrous.

The pattern of performance between males and females revealed that males obtained significantly higher VIQ scores than females ($t(787)=2.53$, $p<.01$) (Mean VIQ: males = 90.7 (13.3); females = 88.4 (11.7). It should be noted that males and females did not differ significantly in mean age of seizure onset.

Comparison of performance between subjects with right- and left-TLE groups revealed that they did not differ significantly in mean age of onset ($t(793)= .13$, NS). Individuals with right-TLE foci obtained significantly higher scores on all three IQ measures: Mean VIQ: R-TLE = 92 (13); L-TLE = 88 (12), ($t(734)=4.04$, $p<.000$); Mean PIQ: R-TLE = 91 (14); L-TLE = 89 (13), ($t(788)=2.08$, $p<.05$); Mean FSIQ: R-TLE = 91 (13); L-TLE = 87 (12), ($t(746)=3.66$, $p<.000$).

Right-handed individuals obtained significantly higher VIQ scores ($t(170)=2.26$, $p<.05$) than left-handed subjects (Mean VIQ of: right-handed = 90 (13); left-handed = 87 (11). Individuals classified as left-handed began experiencing chronic seizures earlier in life ($t(790)=2.58$, $p<.01$) than those who were identified as right-handed (Mean age of onset of: right-handed = 14 (11); left-handed = 13 (11).

To further explore the relation left-handedness and age of onset the data was examined to see if left-handed individuals were equally represented in the sample when the sample was divided into age of onset groups (either chronic seizure onset prior to age five or chronic seizure onset after the age of five). This was performed to explore if there was a link between left-handedness, gender and neuro-developmental vulnerability, as has been discussed by Geschwind and Galaburda (1987). More detailed inspection of the handedness data revealed an association between left-handedness and left-TLE foci; 64.3% of the 112 cases who were left-handed had been diagnosed with left-TLE. It is important to note that in Sample One nearly 54% of the subjects were diagnosed with left-TLE. Examination of the age of onset data revealed that in 238 or 30% of the cases chronic seizures began by the age of five, 17% of these subjects were left-handed (a similar percentage (13%) of left-handedness was seen in individuals with seizure onset after age 5). Of the cases with chronic seizures by the age of five, 144 (61%) were diagnosed with left-TLE. In comparison, 557 subjects (70%) acquired chronic seizure disorders after the age of 5, of these 557 cases 282 or 51% of the cases were diagnosed with left-TLE. Examination of the 144 subjects with early onset left-TLE revealed that 64 (44.4%) were males; 13 (20.3%) of those 64 males were left-handed. A comparable ratio of left-handedness (18.8%) was seen in the females of this sub-group. Thus, the composition of this sample was not suggestive that the left-handers or left-handed males were more vulnerable to early onset idiopathic seizures.

Characteristics of Sample One by Epilepsy Center: The Cleveland Clinic sample consisted of 201 people (25% of Sample One): 110 males and 91 females ($x^2 = 1.80$, NS). The majority of subjects (n = 170 or 84.6%) were right-handed ($x^2 = 96.12$, $p < 0000$). In 99 or 49.3% of the cases temporal lobe seizures were lateralized to the right-hemisphere and in 102 cases or 50.7% seizures lateralized to the left-temporal lobe ($x^2 = 0.04$, NS). The mean age at which seizures began was 12.9 (10.0), the median was 10, and the mode was 7. The subjects ranged in age of onset from 1-44 years of age. The mean age at time of testing was 31.2 (8.2), and the median and mode were both 31. The mean duration of illness was 18.3 (9.6), the median was 18, and the mode was 26. The distribution of IQ scores ranged from 66-132, with the mean FSIQ falling in the Average range (FSIQ = 90.3), the median was 89, and the mode was 92 (see APPENDIX B, Table A).

The Epi-Care Center sample consisted of 248 people (31.1% of

Sample One): 117 males and 131 females (x^2 =0.79, NS). The majority of subjects (n=219 or 88.3%) were right-handed (x^2 =145.56, p<.0000). In 121 or 48.8% of the cases temporal lobe seizures were lateralized to the right-hemisphere and in 127 cases or 51.2% seizures lateralized to the left-temporal lobe (x^2 =0.15, NS). The mean age at which seizures began was 12.0 (10.7), the median was 10, and the mode was 1. The subjects ranged in age of onset from 1-56 years of age. The age at time of testing was averaged at 31.6 (9.7), the median was 31, and the mode was 22. The mean duration of illness was 19.6 (11.3), the median 19, and the mode 5. The distribution of IQ scores ranged from 67-128, with the mean FSIQ falling in the Low Average range (FSIQ=87.7), the median was 86, and the mode was 82 (see APPENDIX B, Table B).

The Mayo Clinic sample consisted of 146 people (18.4% of Sample One): 86 males and 60 females (x^2 =4.63, p<.05). The majority of subjects (n=125 or 85.6%) were right-handed (x^2 =183.30, p<.0000). In 68 or 46.6% of the cases temporal lobe seizures were lateralized to the right-hemisphere and in 78 cases or 53.4% seizures lateralized to the left-temporal lobe (x^2 =0.68, NS). The mean age at which seizures began was 12.7 (9.9), the median 12, and the mode was 2. The subjects ranged in age of onset from 1-

52 years of age. The mean age at time of testing was 31.9 (9.3), the median was 31, and the mode was 22. The mean duration of illness was 19.2 (11.4), the median 19, and the mode was 21. The distribution of IQ scores ranged from 48-120, with the mean FSIQ falling in the Low Average range (FSIQ=87.6), the median was 87, and the mode was 89 (see APPENDIX B, Table C).

The Hospital for Joint Disease sample consisted of 127 people (16% of Sample One): 56 males and 71 females ($\chi^2 = 1.77$, NS). The majority of subjects (n=107 or 84.3%) were right-handed ($\chi^2 = 151.20$, $p<.0000$). In 52 or 40.9% of the cases temporal lobe seizures were lateralized to the right-hemisphere and in 75 cases or 59.1% seizures lateralized to the left-temporal lobe ($\chi^2 = 4.17$, $p<.05$). The mean age at which seizures began was 16.5 (12.1), the median was 14, and the mode was 12. The subjects ranged in age of onset from 1-56 years of age. The mean age at time of testing was 33.9 (10.8), the median and mode were both 32. The mean duration of illness was 17.4 (11.3), the median was 15, and the mode was 6. The distribution of IQ scores ranged from 69-130, with the mean FSIQ falling in the Average range (FSIQ=91.2), the median was 89, and the mode was 91 (see APPENDIX B, Table D).

The Long Island Jewish Medical Center sample consisted of 73 people (9.2% of Sample One): 37 males and 36 females (x^2 =0.01, NS). The majority of subjects (n=59 or 80.8%) were right-handed (x^2 =27.74, p<.0000). In 29 or 39.7% of the cases temporal lobe seizures were lateralized to the right-hemisphere and in 44 cases or 60.3% seizures lateralized to the left-temporal lobe (x^2 =3.08, NS). The mean age at which seizures began was 13.85 (9.6), the median was 13, the mode was 2. The subjects ranged in age of onset from 1-50 years of age. The mean age at time of testing was 33.1 (8.9), the median was 33, the mode was 35. The mean duration of illness was 19.2 (9.9), the median and mode were both 20. The distribution of IQ scores ranged from 67-131, with the mean FSIQ falling in the Low Average range (FSIQ=87.8), the median was 87, and the mode was 73 (see APPENDIX B, Table E).

Comparison of the patient composition within each epilepsy center revealed that they were essentially more alike than different in terms of the population of TLE, medication-refractory, pre-surgical candidates which they attract. The composition of subjects in each center was similar to the others, but there was a great deal of variability between subjects within each center. The variability found in demographic factors related to age at time of testing, age of onset, duration of illness, laterality of TLE focus, and level of education achieved are summarized in the following paragraphs.

The mean chronological age at the time of testing ranged between 31-34 years of age. Examination of the minimum and maximum age ranges within each center varied from as young as 16 up through 65 years of age.

The variable of age of onset was quite fascinating in its diversity within each center. Seizures began as early as within the first year of life to as late as 56 years of age. Such a range is important to be aware of, because epilepsy center means for this variable ranged from 12-16.5 years of age; which is certainly deceiving if one were only to examine the group mean. This underscores the necessity of examining the median and mode in samples of seizure patients.

As can be deduced from knowledge of the variability within samples on the variables of age at time of testing and age of onset the variable of duration of illness revealed differences between subjects within epilepsy center samples. The proportion of males to females and laterality of seizure focus was similar within each center. Another similarity between centers was that approximately 20% of each sample was composed of left-handed individuals, a finding often reported in the epilepsy literature (Hermann, Wyler, Steenman and Richey,1988; Satz, Yanowitz & Willmore, 1983). It is important to note that the incidence of left-handedness in the general population has been reported to be considerably lower, about 5-10% of the normal population have been reported to be consistently left-handed (Obrzut et al., 1992; Spreen and Strauss, 1991).

Diversity within each center sample was also evident in the level of education achieved by subjects. The mean level of education achieved by participants ranged from 12-13 years. Formal education ranged in one center (the Mayo Clinic sample) from as low as three up through twenty-two years. The range in other centers generally varied from 6-20 years.

Between Center Characteristics: To determine if the samples from the different epilepsy centers could be combined, the epilepsy center samples were compared to assess if they were significantly different. In Table 6 the means and standard deviations for the demographic characteristics and IQ Scores of the 795 subjects included in this study sample are presented by epilepsy center to allow for summarization and comparison between epilepsy centers. Each center was compared on the demographic variables.

Analysis of variance revealed significant differences between epilepsy centers on the variable of Age of Seizure Onset ($F(4,790)=4.07$, $p<.005$) and Level of Education ($F(4,790)=3.55$, $p<.01$). Significant differences between epilepsy centers were also observed on IQ indices (FSIQ: ($F(4,790)=2.97$, $p<.05$), VIQ: ($F(4,790)=3.19$, $p<.01$), PIQ: ($F(4,790)=2.48$, $p<.05$)). The results of each ANOVA are provided in Tables 7-11.

Table 6

Demographic and IQ Scores for Five Epilepsy Centers

Subject Characteristics of Total Sample by Epilepsy Center (N=795)

Variable	Center 1 (N=201) Cleveland Clinic	Center 2 (N=248) Epi-Care Center	Center 5 (N=146) Mayo Clinic	Center 6 (N=127) Hospital for Joint Disease	Center 7 (N=73) L.I.J.M.C.
	Mean(S.D.)	Mean(S.D.)	Mean(S.D.)	Mean(S.D.)	Mean(S.D.)
Chronological Age	31.2(8.2)	31.6(9.7)	31.9(9.3)	33.9(10.8)	33.1(8.9)
Years of Education**	13.0(2.3)	12.4(2.4)	12.5(2.6)	13.2(2.5)	13.1(1.9)
Age of Onset (yrs)***	12.9(10.0)	12.0(10.7)	12.7(9.9)	16.5(12.1)	13.9(9.6)
Gender (M:F)	110M,91F	117M,131F	86M,60F	56M,71F	37M,36F
Focus (L:R)	102L,99R	127L,121R	78L,68R	75L,52R	44L,29R
Handedness (L:R)	31L,170R	29L,219R	20L,125R[32]	18L,107R[33]	14L,59R
Duration (yrs)	18.3(9.6)	19.6(11.3)	19.2(11.4)	17.4(11.3)	19.2(9.9)
FSIQ*	90.3(12.4)	87.7(11.4)	87.6(12.2)	91.2(12.9)	87.8(12.7)
VIQ**	90.7(12.2)	88.4(11.8)	88.3 (12.6)	91.5(13.3)	88.2(13.7)
PIQ*	91.7(13.7)	88.7(12.9)	88.4(12.8)	92.5(13.6)	89.7(12.5)

Note: FSIQ=Full Scale IQ; VIQ=Verbal IQ; PIQ=Performance IQ.
*p<.05, two-tailed. **p<.01, two-tailed. ***p<.005, two-tailed.

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[32] 1 of the 146 (.7%) subjects from this center was assessed to be ambidextrous.

[33] 2 of the 127 (1.6%) subjects from this center were assessed to be ambidextrous.

Table 7
Tests of Significance for Age of Seizure Onset Between Epilepsy Centers Using Unique Sums of Squares

Source of Variation	SS	DF	MS	F	Sig. of F
Between Groups	1805.44	4	451.36	4.07	.0028
Within Groups	87612.62	790	110.90		
Total	89418.05	794			

Table 8
Tests of Significance for Level of Education Achieved Between Epilepsy Centers Using Unique Sums of Squares

Source of Variation	SS	DF	MS	F	Sig. of F
Between Groups	83.16	4	20.79	3.55	.0071
Within Groups	4631.33	790	5.86		
Total	4714.50	794			

Table 9
Tests of Significance for FSIQ Between Epilepsy Centers Using Unique Sums of Squares

Source of Variation	SS	DF	MS	F	Sig. of F
Between Groups	1761.38	4	440.34	2.97	.0189
Within Groups	117177.77	790	148.33		
Total	118939.15	794			

Table 10
Tests of Significance for VIQ Between Epilepsy Centers Using Unique Sums of Squares

Source of Variation	SS	DF	MS	F	Sig. of F
Between Groups	1997.32	4	499.33	3.19	.0130
Within Groups	123744.63	790	156.64		
Total	125741.95	794			

Table 11
Tests of Significance for PIQ Between Epilepsy Centers Using Unique Sums of Squares

Source of Variation	SS	DF	MS	F	Sig. of F
Between Groups	1706.62	4	426.65	2.48	.0426
Within Groups	134957.97	790	171.92		
Total	136664.59	794			

Newman-Keuls' multiple range test (alpha=.05) indicated that the sample in Center 6 (Hospital for Joint Disease sample) presented with a later mean age of onset, acquired more education, and obtained higher FSIQ and VIQ scores relative to the other epilepsy centers' samples with the exception of the sample from the Cleveland Clinic (Center 1) who were also identified as having acquired more education.

The difference between epilepsy centers appeared to be related to the later mean age of onset of the Center 6 (Hospital for Joint Disease sample) sample relative to the other center samples and the impact that this primary factor exerts on level of education achieved and ultimately IQ. To explore this suspicion two sets of ANCOVAs were performed, in the first set age of seizure onset was co-factored into the analysis of FSIQ and VIQ, in the second set of ANCOVAs education was co-factored into the analysis of FSIQ and VIQ. When either variable was co-factored into the analyses significant differences between epilepsy centers were no longer obtained. Tables 12a and 12b presents the analyses when age of onset was co-factored into the ANCOVA examining FSIQ and VIQ.

Table 12a

Tests of Significance for FSIQ using Unique Sums of Squares: Age of Onset Co-factored into Analysis:

Source of Variation	SS	DF	MS	F	Sig.of F
Within+Residual	111710.19	789	141.58		
Regression	5467.58	1	5467.58	38.62	.000
Center	1225.92	4	306.48	2.16	.071
(Model)	7228.96	5	1445.79	10.21	.000
(Total)	118939.15	794	149.80		

Table 12b

Tests of Significance for VIQ using Unique Sums of Squares: Age of Onset Co-factored into Analysis:

Source of Variation	SS	DF	MS	F	Sig. of F
Within + Residual	118027.00	789	149.59		
Regression	5717.63	1	5717.63	38.22	.000
Center	1340.92	4	335.23	2.24	.063
(Model)	7714.95	5	1442.99	10.31	.000
(Total)	125741.95	794	158.37		

Tables 13a and 13b present the analyses when education was co-factored into the ANCOVA examining FSIQ and VIQ.

Table 13a

Tests of Significance for FSIQ using Unique Sums of Squares: Education Co-factored into Analysis:

Source of Variation	SS	DF	MS	F	Sig. of F
Within + Residual	81870.47	789	103.76		
Regression	35307.30	1	35307.30	340.26	.000
Center	660.05	4	165.01	1.59	.175
(Model)	37068.68	5	7413.74	71.45	.000
(Total)	118939.15	794	149.80		

Table 13b

Tests of Significance for VIQ using Unique Sums of Squares: Education Co-factored into Analysis:

Source of Variation	SS	DF	MS	F	Sig. of F
Within + Residual	82693.86	789	104.81		
Regression	41050.77	1	41050.77	391.67	.000
Center	845.33	4	211.33	2.02	.090
(Model)	43048.10	5	8609.62	82.15	.000
(Total)	125741.95	794	158.37		

These results support the notion that both primary and secondary factors must be considered when attempting to predict intellectual outcome. In addition they support the earlier work of Berent et al. (1984) on the importance of taking into account level of education when exploring the relation between age of onset and intellectual outcome.

Sample Two (n=77) Characteristics: As shown in Table 14, Sample Two consisted of 77 people from the combined data sets of the Epi-Care Center and Hospital for Joint Disease (only these centers administered both the $BNT_{60\ item}$ and the CVLT) that met inclusion criteria. The sample consisted of 28 males and 49 females (x^2 =5.73, p<.05). The majority of subjects (n=70 or 90.1%) were right-handed (x^2 =51.55, p<.0000). In 31 or 40.3% of the cases temporal lobe seizures were lateralized to the right-hemisphere and in

46 cases or 59.7% seizures lateralized to the left-temporal lobe (χ^2 =2.92, NS). The mean age at which seizures began was 12.9 (11.1), the median was 10, and the mode was 1. Age of onset ranged from 1- 43 years of age. The mean age at time of testing was averaged at 32.9 (9.3), the median and mode were both 32. The subjects ranged in age from 16 - 55 years of age. The mean duration of illness was 20.0 (11.5), the median was 19, and the mode was 12. The distribution of FSIQ scores ranged from 69-128, with the mean FSIQ falling in the Low Average range (FSIQ=88.4), the median 87, and the mode 91.

Table 14

Demographics and IQ Scores for the Sample Two
Subject Characteristics

Variable	Sample (n=77)
	Mean(S.D.) (Range)
Chronological Age (yrs)	32.9(9.3) (16-55 yrs)
Years of Education	12.9(2.5) (7-18 yrs)
Age of Onset (yrs)	12.9(11.1) (1-43 yrs)
Focus (L:R)	46L:31R
Gender (M:F)*	28M,49F
Handedness (L:R)**	7L,70R
Duration (yrs)	20.0(11.5) (1-49 yrs)
FSIQ	88.4(11.6) (69-128)
VIQ	89.7(12.0) (65-126)
PIQ	88.9(12.2) (67-127)

Note: FSIQ=Full Scale IQ; VIQ=Verbal IQ; PIQ=Performance IQ.*p<.05.
**p<.0000.

Table 15 provides summarized characterization of Sample Two by lateralized TLE groups in demographic (age, education, gender, FSIQ, PIQ, VIQ) and seizure-related variables (age of onset of chronic seizures, duration of disorder). As was shown in Table 8 there were no statistically significant differences between the two lateralized TLE groups in demographic, IQ measures, or seizure-related variables. The Left-TLE group of Sample Two consisted of 46 people: 16 males and 30 females ($x^2 = 4.26$, $p < .05$). The majority of subjects (n=41 or 89.1%) were right-handed ($x^2 = 28.17$, $p < .0000$). The Right-TLE group of Sample Two consisted of 31 people: 12 males and 19 females ($x^2 = 1.58$, NS). The majority of subjects (n=29 or 93.5%) were right-handed ($x^2 = 23.52$, $p < .0000$).

Table 15
Demographics and IQ Scores of Sample Two Presented by Laterality of Temporal Lobe Seizure Focus
Subject Characteristics

Variable	L- TLE (N=46)	R-TLE (N=31)
	Mean(S.D.) (Range)	Mean(S.D.) (Range)
Chronological Age (yrs)	33.1(10.1) (17-55 yrs)	32.6(8.1) (16-47 yrs)
Years of Education	13.0(2.5) (8-18 yrs)	12.8(2.6) (7-18 yrs)
Age of Onset (yrs)	12.5(11.3) (1-43 yrs)	13.6(11.0) (1-41 yrs)
Gender (M:F)	16M,30F*	12M,19F
Handedness (L:R)	5L,41R**	2L,29R**
Duration (yrs)	20.6(11.2) (1-49 yrs)	19.1(12.0) (1-46 yrs)
FSIQ	88.6(12.3) (69-128)	88.2(10.8) (74-119)
VIQ	89.3(12.2) (65-120)	90.3(11.8) (75-126)
PIQ	89.6(12.6) (67-127)	87.9(11.8) (67-112)

Note: FSIQ=Full Scale IQ; VIQ=Verbal IQ; PIQ=Performance IQ.
*p<.05. **p<.0000.

Comparison of Sample One (n=795) and Sample Two (n=77) revealed that although the gender ratio was nearly equal in Sample One (51% male;49% female) it was not in Sample Two (36% male;64% female). In both samples the majority of subjects were right-handed (85.5% in the Sample One; 90.1% in the Sample Two). The samples were similar in the percentage of subjects diagnosed with Right-TLE (Sample One=46.4%; Sample Two= 40.3%). The mean, median and mode for age of onset in the two samples were also similar (Sample One=13.2 (10.6),12,1; Sample Two=12.9 (11.1),10,1). The mean age at time of testing was alike in both samples (Sample One=32.0 (9.4); Sample Two=32.9 (9.3)). The mean duration of illness was 18.8 (10.8) in Sample One and 20.0 (11.5) in Sample Two. Mean IQ scores in both samples were in the Low Average range.

B. Exploration of the Predictions

The first step involved in the exploration of the predictions consisted of examining the impact of IQ and age of onset on level of education achieved. To this end, a hierarchical multiple regression analysis were performed in which educational attainment was the dependent variable. The predictor variables entered in block 1 included age of seizure onset, laterality of TLE focus, and duration of illness. In block 2, FSIQ was entered into the equation. An overall multiple correlation coefficient of .56 was obtained between the total set of primary and secondary predictor variables and years of education achieved, $F(4,790)=89.26$, $p<.0000$. All variables together accounted for 31% (adjusted R^2) of the variance in years educated. Statistically significant contributions were noted for age of seizure onset and FSIQ which accounted for 1%, and 29% of the variance respectively when the variance accounted for by the other predictors was held constant (see Table 16).

Table 16
Prediction of Educational Attainment: Results of Multiple Regression Analysis

Variable	Beta	Significance
Age of Onset	.082035	.0319
Duration of Illness	.017940	.6320
TLE Focus	.015321	.6074
FSIQ	.538826	.0000

Multiple $R=.56$, $R^2=.31$, Adjusted $R^2=.31$

To investigate the relationships between the primary and secondary factors and measures of IQ, the relationships between age of seizure onset and duration of illness with IQ indices were explored by a series of semipartial correlations[34]. The semipartial correlation technique was employed because it allowed for the removal (or partialling out) of the relationship between the relevant variables being examined. This is important because the variables of age of onset and duration of illness are interdependent (duration of illness is defined as the period of time that has accumulated since the time seizures became chronic to the time of testing). The need to control for education has been demonstrated by the work of Berent et al. (1984), and in the analysis of differences between epilepsy centers discussed in this dissertation.

Table 17 shows the relationships between age of onset and duration of illness with IQ Scores. Partial correlations controlling for level of education revealed that there were weak significant positive correlations between the variable of age of seizure onset and all indices of intellectual functioning as assessed by FSIQ ($r = .15$, $p < .001$), VIQ ($r = .14$, $p < .001$), and PIQ ($r = .11$, $p < .005$), although the effect was quite small.

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[34] A semipartial correlation refers to the unique independent relationship of a variable to an outcome, after removing the relationship between relevant variables and other non-relevant variables (Cohen and Cohen, 1983, pp. 88-90).

Table 17
Education Controlled Partial Correlations between Age of Onset and Duration of Illness with IQ Scores

Variable	FSIQ	VIQ	PIQ
Age of Onset	.15***	.14***	.11**
Duration of Illness	-.07**	-.06	-.08*

Note: FSIQ=Full Scale IQ; VIQ=Verbal IQ; PIQ=Performance IQ.
*p<.05, two-tailed. **p<.005, two-tailed. ***p<.001, two-tailed.

In the case of the variable of duration of illness the relationships with IQ scores were negative. A significant, but weak negative relationship was observed between duration of illness and FSIQ (r=-.07, p<.05) and PIQ (r=-.08, p<.05), a negative but non-significant relation was observed between duration of illness and VIQ (r=-.05, NS). Although several correlations reached statistical significance in this set of analyses it is important to note that generally they accounted for only 1-2% of the variance on IQ measures.

To further explore the relations between age of onset, duration of illness and education two more partial correlations were performed to examine the relation with measures of intelligence (see Tables 18 and 19). Table 18 shows the relationships between duration of illness and education with IQ Scores, while age of onset was controlled.

Table 18
Age of Onset Controlled Partial Correlations between Education and Duration of Illness with IQ Scores

Variable	FSIQ	VIQ	PIQ
Education	.53***	.56***	.38***
Duration of Illness	.04	.05	.00

Note: FSIQ=Full Scale IQ; VIQ=Verbal IQ; PIQ=Performance IQ.
*p<.05, two-tailed. **p<.005, two-tailed. ***p<.001, two-tailed.

The partial correlations controlling for age of onset revealed that there were significant positive correlations between the variable of education and all indices of intellectual functioning as assessed by FSIQ ($r=.53$, $p<.001$), VIQ ($r=.56$, $p<.001$), and PIQ ($r= .38$, $p<.005$).

In the case of the variable of duration of illness no significant relations were observed with IQ measures. Several correlations reached statistical significance in this set of analyses. It is important to note that partial correlations with education controlling for age of onset accounted for up to 31% of the variance in IQ measures.

Table 19 reveals the relationships between age of onset and education with IQ measures while duration of illness was controlled. The partial correlations controlling for duration of illness revealed that there were significant positive correlations between the variables of age of onset and education with IQ measures. In the case of the variable of age of onset the highest correlation accounted for only 4% of the variance whereas partial correlations with education accounted for up to 35% of the variance in FSIQ.

Table 19
Duration of Illness Controlled Partial Correlations between Age of Onset and Education with IQ Scores

Variable	FSIQ	VIQ	PIQ
Age of Onset	.20***	.21***	.14***
Education	.59***	.58***	.39***

Note: FSIQ = Full Scale IQ; VIQ = Verbal IQ; PIQ = Performance IQ.
*$p < .05$, two-tailed. **$p < .005$, two-tailed. ***$p < .001$, two-tailed.

Three Hierarchical regression analyses were conducted to evaluate whether FSIQ, VIQ, and PIQ were related to the predictor variables combined (age of seizure onset, duration of disorder, laterality of TLE focus, and education), and if so to specific variables within the set under investigation. For these analyses the three seizure-related predictor variables were entered into the equation on block 1 followed by the entering of education on block 2. Each measure of IQ was evaluated separately. It was predicted that a greater amount of variance in performance on intelligence measures would be accounted for when the primary and secondary variables were considered in combination than when assessed in isolation.

FSIQ: An overall multiple correlation coefficient of .57 was obtained between the total set of primary and secondary predictor variables and FSIQ, $F(4,790)=97.16$, $p<.0000$. All variables together accounted for 33% (adjusted R^2) of the variance in FSIQ. Statistically significant contributions were noted for laterality of seizure focus, age of seizure onset, and education which accounted for 1%, 2%, and 27% of the variance respectively when the variance accounted for by the other predictors was held constant (see table 20).

Table 20
Prediction of FSIQ: Results of Multiple Regression Analysis

Variable	Beta	Significance
Age of Onset	.134438	.0004
Duration of Illness	.024646	.5048
TLE Focus	-.093507	.0014
Education	.524386	.0000

Multiple $R=.57$, $R^2=.33$, Adjusted $R^2=.33$

VIQ: When VIQ was examined a statistically significant multiple regression correlation coefficient was also generated. An overall multiple correlation coefficient of .60 was obtained between the total set of predictor variables and VIQ, $F(4,790)=111.61$, $p<.0000$. All variables together accounted for 36% (adjusted R^2) of the variance in

VIQ. Statistically significant contributions were noted for laterality of seizure focus, age of seizure onset, and education which accounted for 1%, 2%, and 30% of the variance respectively when the variance accounted for by the other predictors was held constant (see Table 21).

Table 21
Prediction of VIQ: Results of Multiple Regression Analysis

Variable	Beta	Significance
Age of Onset	.137389	.0002
Duration of Illness	.037853	.2942
TLE Focus	-.106016	.0001
Education	.550366	.0000

Multiple R=.60, R^2 =.36 Adjusted R^2 = .36

PIQ: When PIQ was examined a statistically significant multiple regression correlation coefficient was also yielded. An overall multiple correlation coefficient of .41 was obtained between the total set of predictor variables and PIQ, $F(4,785)=40.75$, $p<.0000$. All variables together accounted for only 17% (adjusted R^2) of the variance in PIQ. Statistically significant contributions were noted for age of seizure onset and education which accounted for 1% and 14% of the variance respectively when the variance accounted for by the other predictors was held constant (see Table 22).

Table 22
Prediction of PIQ: Results of Multiple Regression Analysis

Variable	Beta	Significance
Age of Onset	.093438	.0259
Duration of Illness	-.014994	.7162
TLE Focus	-.046178	.1569
Education	.376327	.0000

Multiple R=.19, R^2 =.04, Adjusted R^2 = .03

The results of this series of analyses clearly support prediction 2. Recall that it was anticipated that the combination of the primary and secondary factors would account for a greater amount of the variance in performance on IQ measures than when any of the independent variables were considered in isolation. Of the primary seizure-related variables under investigation, age of onset was consistently found to be the best predictor of intellectual functioning. The secondary factor of education was clearly able to account for the largest amount of variance. These findings support and extend previous research indicating that seizure onset in early childhood is associated with a higher risk of decrement to intellectual functioning (Dodrill,1992; Levine et al., 1987; O'Leary et al., 1981; Woods, 1980); it extends previous findings by demonstrating that the secondary consequences on educational success are intimately involved in this increased risk. In this research the findings were observed in a sample of chronic, medication-refractory, TLE presurgical candidates, with seizure disorders of unknown etiology.

The variable of duration of illness appeared to be unrelated to the prediction of intellectual outcome. Laterality of seizure onset appeared to aid in the prediction of intellectual outcome in relation to FSIQ and VIQ.

The inclusion of subjects in this study that were 16 years of age presented a potential problem related to including subjects who might not have finished their schooling, yet were being considered as if their years of education had been completed. It was expected that since the secondary factor of education was found to be the best predictor of intellectual functioning, a larger amount of the variance in IQ performance would be accounted for when subjects who had not yet completed their education (as in the case of individuals who are still in High School) were excluded from analysis. To explore this issue the series of regression analyses mentioned above were re-run excluding subjects that ranged in age from 16-24 years (n=605). (See APPENDIX C for demographics and IQ scores of Sample One excluding subjects ranging in age from 16-24 years).

FSIQ: An overall multiple correlation coefficient of .65 was obtained between the total set of predictor variables and FSIQ, $F(4,600) = 108.90$, $p < .0000$. All variables together accounted for 42% (adjusted R^2) of the variance in FSIQ.

VIQ: When VIQ was examined a statistically significant multiple regression correlation coefficient was also generated. An overall multiple correlation coefficient of .68 was obtained between the total set of predictor variables and VIQ, $F(4,600) = 130.80$, $p < .0000$. All variables together accounted for 46% (adjusted R^2) of the variance in VIQ.

PIQ: When PIQ was examined a statistically significant multiple regression correlation coefficient was also yielded. An overall multiple correlation coefficient of .47 was obtained between the total set of predictor variables and PIQ, $F(4,595) = 42.25$, $p < .0000$. All variables together accounted for only 22% (adjusted R^2) of the variance in PIQ.

The findings of the Sample One analyses indicate that a portion of the variance in intellectual functioning in this sample was accounted for by the primary factors of age of onset and laterality of TLE focus. The combined influence of age of onset and laterality of seizure focus in the prediction of intellectual outcome was modest, relative to the secondary factor of education. The magnitude of the relations varied depending on the IQ index examined and accounted for 1-2% of the variance. The secondary factor of education was a more robust predictor of intellectual functioning than the primary factors, the magnitude of the relations varied depending on the IQ index examined and accounted for up to 30% of the variance. In combination the primary and secondary factors accounted for 33% of the variance in FSIQ performance and up to 36% of the variance in VIQ performance. This finding indicates that the variance in intellectual functioning in this sample is best understood by combining the primary and secondary factors. The magnitude of these results were even greater when subjects ranging in age from 16-24 years were excluded from analysis, in which case 42% and 46% of the variances in FSIQ and VIQ respectively were accounted for.

The Prediction of Naming, Phonemic Fluency, and Verbal Learning Performance: Sample Two (n=77): In order to begin to resolve some of the issues in the literature related to select aspects of verbal retrieval and verbal learning, it was necessary to evaluate several of the measures commonly reported in the literature in the same sample of subjects. This step, of employing the tasks commonly reported on in the literature allowed for the exploration of whether discrepancies in the literature were the result of different samples. Furthermore, having all measures on the same sample permitted the exploration of interrelationships between measures, and whether the tasks measure similar or different abilities in this population (see APPENDIX D for factor analysis of tasks). The only subjects included in this portion of the study (Sample Two) were those who had complete data on VIQ, the BNT, the phonemic fluency task, and the CVLT. Table 23 provides summarized descriptions of the task variables used in these analyses.

Table 23
Descriptions of the Task Variables Included in Analyses

Variable	Description
VIQ	Verbal IQ from WAIS-R
BNT # Correct	# correct spontaneous responses on the Boston Naming Test
Phonemic Fluency	Total number of words over three 60 second trials
CVLT: List A total recall	Total number of List A words recalled across Trial 1-5
CVLT: Short delay free recall	Number of List A words recalled immediately after the List B trial without re-presentation of List A words
CVLT: Long delay free recall	Number of List A words recalled after a 20-minute delay

Note: VIQ=Verbal IQ; BNT=Boston Naming Test; CVLT=California Verbal Learning Test.

The next set of analyses were conducted to determine the interrelationships between the tasks used in this study. It was predicted that proficiency in confrontation naming would be positively correlated with VIQ, phonemic fluency, and verbal list-learning performance. Significant positive correlations were found between confrontation naming and VIQ (r_s = .62, p< .000) and confrontation naming and phonemic fluency (r_s = .37 p< .001), a significant positive correlation was also evident between VIQ and Phonemic fluency (r_s = .38 p< .001). Table 24 shows the inter-relationships between test measures. Although several of these correlations reached statistical significance none accounted for more than 19% of the variance. Table 25 provides summarized data on scores from VIQ, confrontation naming, phonemic fluency, and verbal list-learning tasks.

Table 24 Correlations Between Test Measures (n=77)

Variable	CVLT List A $Trials_{1-5}$	CVLT Short Delay Recall	CVLT Long Delay Recall
VIQ	.40***	.27*	.26*
BNT # Correct	.43***	.36***	.40***
Phonemic Fluency	.25*	.19	.20

Note: VIQ=Verbal IQ; BNT=Boston Naming Test; CVLT=California Verbal Learning Test. *p<.05, two-tailed. **p<.01, two-tailed. ***p<.001, two-tailed.

Table 25
Mean Test Scores of TLE Groups in Sample Two Analyses (N=77)

Variable	L-TLE (n=46)	R-TLE (n=31)
	Mean(S.D.) (Range)	Mean(S.D.) (Range)
VIQ	89.3(12.2) (65-120)	90.3(11.8) (75-126)
BNT # Correct	42.0(11.0) (22-57)	44.8(9.5) (24-60)
Phonemic Fluency	28.6(9.8)[35] (14-57)	31.2(11.5) (12-56)
CVLT: List A total recall	46.6(11.2) (20-74)	44.5(12.1) (18-66)
CVLT: Short delay free recall	7.6(3.3) (3-16)	6.6(3.0) (2-15)
CVLT: Long delay free recall	7.5(3.7)[36] (2-16)	6.7(3.2) (3-15)

Note: VIQ=Verbal IQ; BNT=Boston Naming Test; CVLT=California Verbal Learning Test.

As shown in Table 25 there were no statistically significant differences between TLE groups in mean scores obtained on these measures. The performance of the left- and right-TLE groups on the language measures of confrontation naming and verbal fluency were compared. Based on the work of Hermann et al. 1992, Mayeux et al., 1980 and Vargha-Khadem et al. (1985) it was anticipated that as a group individuals with right-TLE would perform with higher accuracy

35 The reader should note that the sample size for this mean was 45.

36 The reader should note that the sample size for this mean was 45.

than those with left-TLE. This finding was not replicated. There were no statistically significant differences between TLE groups in level of performance on these tasks (BNT: $F(1,75)=1.31$, NS; Fluency: $F(1,74)=1.13$, NS), although the pattern of performance was in the expected direction. In addition, lateralized TLE groups did not differ on the CVLT indices ($CVLT_{1-5}$: $F(1,75)=.60$, NS; Short Delayed Recall: $F(1,75=2.0$, NS; Long Delayed Recall: $F(1,74)=1.04$, NS). Reference to the norms provided in the Methods Section reveal that the mean test scores for the L-TLE and R-TLE groups were lower than those expected from the results of normal control studies provided for these tests.

To explore the relation between age of onset and laterality of TLE focus in confrontation naming a 2 x 2 ANOVA was performed. In this analysis early onset was defined as seizure onset prior to age five and late onset was defined as after age five (as was the case in the work of Vargha-Kahdem et al., 1985). This division of subjects into age groups with lateralized TLE foci resulted into four groups (Early R-TLE (n=10); Late R-TLE (n=21);Early L-TLE (n=18); Late L-TLE (n=27). As seen in Table 26 a significant main effect for age of onset was obtained ($F(1,73)=6.31$, $p<.01$, not for laterality ($F(1,73)=1.00$, NS). A significant interaction between age of onset and laterality of TLE focus was not observed (F(1,73)=.25, NS).

Table 26
2 X 2 Analysis of Variance Examining Confrontation Naming in Lateralized Early and Later Age of Onset Groups

Source of Variation	SS	DF	MS	F	Sig. of F
Onset Group	646.92	1	646.92	6.31	.014
Laterality of TLE	102.68	1	102.68	1.00	.320
Interaction of Onset Group X Laterality of TLE	25.78	1	25.78	0.25	.618
Explained	775.38	3	258.46	2.52	.065
Residual	7484.75	73	102.53		
Total	8260.13	76	108.69		

Based on the reports of Seidenberg et al. (1986) and Strauss, Hunter and Wada (1995) which suggests that men and boys may be at greater risk for impairment in verbal abilities relative to girls and women it was anticipated that there would be a gender effect evident in tasks of verbal retrieval and delayed verbal recall, with females performing better than males. There were no statistically significant differences between males and females in level of performance on the verbal retrieval tasks (BNT: t (75) =1.13, NS; Fluency: t (74) =-.52, NS). There were significant differences noted between males and females on the verbal learning task ($CVLT_{trial1-5}$: $t(75) = -2.11$, $p < .05$; CVLT Short Delay Recall: $t(75) = -2.59$, $p < .01$; CVLT Long Delay Recall: $t(74) = -1.99$, $p < .05$). The means and standard deviations for the CVLT indices are provided in Tables 27-29.

Table 27
Means and Standard Deviations of Males and Females on CVLT Trials 1-5

Variable	Number of Cases	Mean	Standard Deviation	S.E. of Mean
Males	28	42.14	9.27	1.75
Females	49	47.78	12.27	1.75

Table 28
Means and Standard Deviations of Males and Females on CVLT Short Delay Free Recall

Variable	Number of Cases	Mean	Standard Deviation	S.E. of Mean
Males	28	6.00	2.71	0.51
Females	49	7.88	3.24	0.46

Table 29
Means and Standard Deviations of Males and Females on CVLT Long Delay Free Recall

Variable	Number of Cases	Mean	Standard Deviation	S.E. of Mean
Males	28	6.18	2.97	0.56
Females	49	7.80	3.63	0.52

To investigate the combined and unique contributions of the predictor variables in the estimation of performance on the BNT and phonemic fluency tasks a series of Hierarchical regression analyses were performed. It was predicted that a greater amount of variance in performance on measures of confrontation naming and phonemic fluency would be accounted for when the primary and secondary variables were considered in combination than when assessed in isolation. Based on the results of the 2X2 ANOVA the variable of laterality of TLE focus was not included in the prediction of verbal retrieval, verbal learning and delayed verbal recall. For these analyses gender and the seizure-related predictor variables were entered into the equation on block 1 followed by the entering of education.

BNT: An overall multiple correlation coefficient of .48 was obtained between the total set of predictor variables and BNT, $F(4,72)=5.29$, $p<.0009$. All variables together accounted for 18% (adjusted R^2) of the variance in BNT. Statistically significant contributions were noted for age of seizure onset and education accounting for 15% and 7% of the variance respectively when the variance accounted for by the other predictors was held constant (see Table 30).

Table 30
Prediction of BNT: Results of Multiple Regression Analysis

Variable	Beta	Significance
Age of Onset	.393203	.0089
Duration of Illness	.188052	.1788
Gender	.133703	.2140
Education	.260015	.0248

Multiple R=.48, R^2 =.23, Adjusted R^2 =.18

Phonemic Fluency: An overall multiple correlation coefficient of .37 was obtained between the total set of predictor variables and phonemic fluency, $F(4,71)=2.78$, $p<.05$. All variables together accounted for 9% (adjusted R^2) of the variance in performance on the fluency task. No statistically significant contributions were noted for any of the predictor variables in isolation (see Table 31).

Table 31
Prediction of Phonemic Fluency: Results of Multiple Regression Analysis

Variable	Beta	Significance
Age of Onset	.247764	.1138
Duration of Illness	-.098899	.5073
Gender	-.036722	.7473
Education	.093448	.4374

Multiple R=.37, R^2 =.14, Adjusted R^2 =.09

It was predicted that a greater amount of the variance in delayed recall performance on the CVLT would be accounted for when the primary and secondary variables were considered in combination than when assessed in isolation. An overall multiple correlation coefficient of .35 was obtained between the total set of predictor variables and List A total recall over trials $_{1-5}$, $F(4,72)=2.54$, $p<.05$. All variables together accounted for 7% (adjusted R^2) of the variance in learning performance. A statistically significant contribution was noted only for gender, which accounted for 7% of the variance when the variance accounted for by the other predictor variables was held constant (see Table 32).

Table 32
Prediction of CVLT Trails $_{1-5}$: Results of Multiple Regression Analysis

Variable	Beta	Significance
Age of Onset	-.124904	.4251
Duration of Illness	-.244469	.1017
Gender	-.255775	.0274
Education	.169206	.1655

Multiple $R=.35$, $R^2=.12$, Adjusted $R^2=.07$

An overall multiple correlation coefficient of .46 was obtained between the total set of predictor variables and short delay free recall on the CVLT, $F(4,72)=4.73$, $p<.002$. All variables together accounted for 16% (adjusted R^2) of the variance in performance.

Statistically significant contributions were noted for duration of illness, gender, and education which accounted for 11%, 10%, and 7% of the variance respectively when the variance accounted for by the other predictor variables was held constant (see Table 33).

Table 33
Prediction of CVLT Short Delay Free Recall: Results of Multiple Regression Analysis

Variable	Beta	Significance
Age of Onset	-.210521	.1592
Duration of Illness	-.326098	.0228
Gender	-.322742	.0038
Education	.258376	.0274

Multiple R=.46, R^2=.21, Adjusted R^2 = .16

An overall multiple correlation coefficient of .37 was obtained between the total set of predictor variables and long delay free recall on the CVLT, $F(4,71)=2.77$, $p<.05$. All variables together accounted for only 9% (adjusted R^2) of the variance in learning performance. Statistically significant contributions were noted for gender and education which accounted for 7% and 7% of the variance respectively when the variance accounted for by the other predictor variables was held constant (see Table 34).

Table 34
Prediction of CVLT Long Delay Free Recall: Results of Multiple Regression Analysis

Variable	Beta	Significance
Age of Onset	-.156188	.3261
Duration of Illness	-.195091	.1923
Gender	-.271238	.0203
Education	.265876	.0327

Multiple R=.37, R^2 =.13, Adjusted R^2 = .09

To explore the amount of variance accounted for by VIQ in the prediction of performance on $CVLT_{1\text{-}5}$ learning and delayed recall these multiple regression analyses were re-run including VIQ as a secondary factor. An overall multiple correlation coefficient of .52 was obtained between the total set of predictor variables and List A total recall over trials $_{1\text{-}5}$, $F(5,71)=5.18$, $p<.0004$. All variables together accounted for 22% (adjusted R^2) of the variance in learning performance. Statistically significant contributions were noted for gender, which accounted for 8% of the variance and VIQ which accounted for 22% of the variance when the variance accounted for by the other predictor variables was held constant. The association of VIQ with learning Trials1-5 on the CVLT is consistent with the correlation reported by Hermann et al. (1988).

An overall multiple correlation coefficient of .49 was obtained between the total set of predictor variables and short delay free recall on the CVLT, $F(5,71)=4.50$, $p<.001$. All variables together accounted for 19% (adjusted R^2) of the variance in performance. Statistically significant contributions were noted for duration of illness and gender which each accounted for 11% of the variance when the variance accounted for by the other predictor variables was held constant.

An overall multiple correlation coefficient of .40 was obtained between the total set of predictor variables and long delay free recall on the CVLT, $F(5,70)=2.66$, $p<.03$. All variables together accounted for only 10% (adjusted R^2) of the variance in performance. A statistically significant contribution was noted for gender which accounted for 8% of the variance when the variance accounted for by the other predictor variables was held constant.

The results of the inclusion of VIQ into the regression of CVLT performance are likely related to the factor structure of this test. VIQ aided most in the prediction of learning over five trials, but was not a significant predictor of delayed recall performance.

The findings of the Sample Two analyses indicate that variance in verbal retrieval and delayed verbal recall, but not list learning in this sample is accounted for by the primary and secondary factors under investigation in combination, better than when factors are considered in isolation. Thus, it can be concluded that this set of factors does supply sufficient information in making predictions of verbal retrieval or verbal learning.

The results in this section demonstrate that the combined contribution of the predictor variables accounted for 18% of the variance in BNT performance. The combined contribution of the predictor variables accounted for 9% of the variance in phonemic fluency performance. The final result to take note of was related to the prediction of Short Delay Recall on the CVLT. In combination the predictor variables accounted for 16% of the variance. Duration of illness in isolation accounted for 11% of the variance in CVLT Short Delay Recall when all other predictors were held constant.

The results of this dissertation support previous reports of the relation between age of onset and level of education achieved and how these variables interact with intellectual functioning (Berent et al., 1984). In the case of education and IQ, a reciprocal relationship was observed. The primary and secondary factors provided a modest account of the variance in performance in tasks of verbal retrieval and verbal learning.

C. Exploratory Analysis of the Impact of Age of Onset on Educational Outcome

The results of the Sample One analyses support the inclusion of education into analyses of intellectual measures in this sample of TLE patients. In an attempt to further our understanding of the relationship between age of onset on education an exploratory analysis was performed. The purpose of this analysis was to assess if it was possible to observe the impact of age of onset on educational outcome (defined as the number of years of schooling that individuals ultimately achieve). It was suspected that if a chronic seizure disorder began prior to schooling it would limit the educational level achieved that an individual would acquire. Specifically, it was predicted that a seizure disorder acquired prior to age three would be associated with a lower educational outcome than if it was acquired after this age. To this end, the data of Sample One was re-examined (excluding subjects ranging in age from 16-24 to avoid possible inclusion of subjects who have not completed their schooling). This sample was divided into two age of onset groups: Group 1 (n=123) age of onset up through 3 years of age; Group 2 (n=482) age of onset from 4 years and above. The two groups obtained significantly different mean FSIQ scores: (Group 1=mean FSIQ = 85 (10.6); range = 62-128; Group 2 = Mean FSIQ = 90.2 (12.5); range = 59-132) (see APPENDIX E). Table 35 provides the Means and Standard Deviations for the variable of years educated by age of onset groups.

Mann-Whitney U-Wilcoxon Rank Sum W Test indicated that Group 1 (age of onset ranging from 0-3 years) and Group 2 (age of onset after age 3 years) were significantly different in terms of level of education achieved. This finding suggests that individuals who acquire chronic (and ultimately medication-refractory) seizure disorders up through age 3 are at greater risk to obtain lower FSIQ scores and leave the educational system earlier than those who acquire a chronic seizure disorder after this age. Thus indicating that age of onset impacts intellectual outcome and educational outcome; furthermore that intellectual outcome and educational outcome are reciprocally related.

Table 35
Means and Standard Deviations of Years of Education Achieved for Age of Onset Groups

Group	# of Subjects	Mean	S.D.	Range
1	123	12.02	2.42	6-19
2	482	13.18	2.56	3-22

Chapter 4

Discussion

In this concluding section of the dissertation the major findings presented in the Results Section are discussed with respect to the literature and the ways they add to and support, or refute previous reports. The Discussion Section begins with a review of the findings. The limitations and qualifiers of this study are discussed. Finally, the research that must follow this work to address the questions raised by this endeavor and how we might pragmatically use the information attained from this dissertation research in research and clinical settings are discussed.

The purpose of this dissertation research was to explore the primary seizure-related variables and some of the secondary consequences of these variables in relation to intellectual outcome and verbal retrieval, verbal learning, and delayed verbal recall outcomes. As discussed previously the concentration on verbal as opposed to non-verbal material was chosen due to the results of factor analytical studies on commonly used tasks to assess memory which have failed to demonstrate the existence of an independent non-verbal memory factor (Larrabee & Curtiss, 1995; Larrabee, Kane, Schuck & Francis, 1985; Roid, Prifitera & Ledbetter, 1988; Smith, Malec & Ivnik, 1992).

The present study was designed to remove many of the methodological and statistical problems/issues which have made it difficult to predict intellectual and cognitive outcome in chronic, unilateral, medication refractory TLE of unknown etiology. This research explored the secondary consequences of age of onset in TLE in relation to intellectual and cognitive outcome. This dissertation research investigated the unique and combined effect of seizure-related variables and level of education achieved on intellectual functioning, components of verbal retrieval, verbal learning, and verbal memory. The primary aim of this project was to investigate the interactions that occur between seizure-related factors, as well as the secondary consequence of these primary variables on subsequent level of education achieved. The prediction of intellectual and cognitive outcome was attempted within a hierarchy of factors. Specifically, seizure-related factors and the factor of education were employed in the construction of regression models in the prediction of intellectual outcome, verbal retrieval, verbal learning, and delayed verbal recall. The amount of variance accounted for by knowledge of these factors was assessed and will be briefly reviewed following comment on merging the data from various epilepsy centers.

A. Review of the Findings

Access to the database of the Bozeman Epilepsy Consortium provided an opportunity to examine a very large sample of chronic, medication-refractory, uni-focal TLE pre-surgical candidates from a number of different epilepsy centers. This exploration provided a chance to look at the similarities and differences between and within epilepsy centers. Comparison of the patient composition within each center revealed that they are essentially more alike than different in terms of the population of TLE, medication-refractory, pre-surgical candidates which they attract. This observation suggests that the data sets of epilepsy centers may be combined in future research, but with caution. Care should be taken to examine within and between center differences, because as was seen in the Results Section some centers may attract samples that are different in demographic characteristics and these differences may be associated with differences in the dependent variables of interest. For example, it would not be surprising that the results yielded from the sample of subjects from the Hospital for Joint Disease would differ than those from the other epilepsy centers due to the patients that it attracts (later mean age of onset, higher mean level of education).

A. 1. The Prediction of IQ:

To explore the relationships between the primary and secondary factors and measures of IQ, the relationships between age of seizure onset and duration of illness with IQ indices were explored by a series of semipartial correlations. Partial correlations controlling for level of education revealed that there were weak significant positive correlations between the variable of age of seizure onset and all indices of intellectual functioning, although the effect was quite small. In regard to the variable of duration of illness, significant but weak negative correlations were observed with FSIQ and PIQ.

The partial correlations controlling for age of onset revealed that there were significant positive correlations between the variable of education and all indices of intellectual functioning. In the case of the variable of duration of illness no significant relations were observed with IQ measures. Partial correlations controlling for duration of illness revealed that there were significant positive correlations between the variables of age of onset and education with IQ measures.

The sequence of Hierarchical regression analyses were conducted to evaluate whether age of onset and IQ were related to level of education achieved. They were also employed to evaluate whether FSIQ, VIQ, and PIQ were related to the predictor variables combined (age of seizure onset, duration of disorder, laterality of TLE focus, and education), and if so to specific variables within the set under investigation. The results of this series of analyses clearly supported the predictions related to intellectual outcome. Recall that it was anticipated that the combination of the primary and secondary factors would account for a greater amount of the variance in performance on IQ measures than when any of the independent variables were considered in isolation. Of the primary seizure-related variables under investigation, age of onset was consistently found to be the best predictor of intellectual functioning. The secondary factor of education was clearly able to account for the largest amount of variance. These findings support and extend previous research indicating that seizure onset in early childhood is associated with a higher risk of decrement to intellectual functioning (Dodrill,1992; Levine et al., 1987; O'Leary et al., 1981; Woods, 1980). They extend previous findings by demonstrating that the secondary consequences on educational success are intimately involved in this increased risk. The relationship between age of onset and education with IQ indicated that both of the factors of age of onset and education impact IQ; and that both the factors of age of onset and IQ impact level of education achieved. The variable of duration of illness appeared to be unrelated to the prediction of intellectual outcome. Laterality of seizure onset appeared to aid in the prediction of intellectual outcome in relation to FSIQ and VIQ. In this research the findings were observed in a sample of chronic, medication-refractory, TLE presurgical candidates, with seizure disorders of unknown etiology.

The findings of the Sample One analyses indicated that a small portion of the variance in intellectual functioning in this sample was accounted for by the primary factors of age of onset and laterality of TLE focus. The combined influence of age of onset and laterality of seizure focus in the prediction of intellectual outcome was modest, relative to the secondary factor of education. The magnitude of the relations varied depending on the IQ index examined and accounted for 1-2% of the variance. The secondary factor of education was a more robust predictor of intellectual functioning than the primary factors, the magnitude of the relations varied depending on the IQ index examined and accounted for up to 30% of the variance. In combination the primary and secondary factors accounted for 33% of the variance in FSIQ performance and up to 36% of the variance in VIQ performance. This finding indicates that the variance in intellectual functioning in this sample was best understood by combining the primary and secondary factors. The magnitude of these results was even greater when subjects ranging in age from 16-24 years were excluded from analysis, in which case 42% and 46% of the variances in FSIQ and VIQ respectively were accounted for.

Age of Onset: The results of this dissertation indicated that individuals with earlier ages of onset were at relatively greater risk for intellectual deficiencies than those with later onset, but that this risk was best understood within the context of the secondary factor of education. The findings did confirm that age of onset was the strongest correlate of intellectual functioning relative to the other seizure-related variables investigated as has been previously reported (Dodrill, 1991; Dodrill and Mathews, 1992), but the partial correlations controlling for level of education were modest for all IQ indices. It is likely that the consistent finding of the importance of age of onset is the product of a multifactorial interaction which might be related to neuronal development, medication effects on cognition and behavior, seizure frequency throughout life, and education (just to name a few) and the potential influence (secondary consequences) this variable could exert on so many other variables.

The literature related to the impact of age of onset of seizures on intellectual functioning has been somewhat inconsistent. Generally, studies have reported that seizure onset in early childhood has been associated with a higher risk of decrement to intellectual functioning than onset during late childhood or adolescence (Dodrill,1992; Ellenberg et al., 1984; O'Leary et al., 1981), but not all studies have reported this profile (Bourgeois et al., 1983) and most studies have not considered the secondary consequence of age of onset on education. In this dissertation research the impact of IQ and age of onset on level of education achieved were explored. Statistically significant contributions were noted for age of seizure onset and FSIQ which accounted for 1%, and 29% of the variance respectively in the prediction of level of education achieved. It appears that the association between age of onset and IQ was related to level of education achieved, and that level of education achieved was best understood within the context of age of onset and IQ.

The findings of this dissertation research support previous reports which have suggested that age at seizure onset (Huttenlocher & Hapke,1990; Loiseau, Strube, Broustet, Battellochi, Gomeni &

Morselli,1983; O'Leary, Seidenberg, Berent and Boll,1981; Saykin, Gur, Sussman, O'Connor & Gur,1989) is a key factor related to the intellectual functioning in this sample. The findings did confirm that age of onset was the strongest correlate of intellectual functioning relative to the other seizure-related variables investigated as has been previously reported (Dodrill, 1991; Dodrill and Mathews, 1992).

Age of seizure onset appears to be one of those factors in life that is not only a crucial determining variable at the time of its occurrence, but one that could be viewed as a factor that continues to influence and impact other factors throughout life which may in turn also impact other aspects of life. It appears that the influence of age of onset may be likened to the repercussions of a "dominoe effect" or a "cascading influence", such that it impacts knowledge acquisition at functional (in some cases the interaction between component parts of functional systems required for a given task are also impacted) and psycho-social levels, particularly in relation to education.

Duration of Illness: The impact of duration of illness showed a weak yet significant negative correlation with IQ measures which is a generally consistent finding in published work (Dodrill and Matthews, 1992). The variable of duration of disorder is complex. It is well known in the literature and in the clinical setting that many patients may experience long spans of time when they have few or no seizures (at times off medication) whereas others may have frequent non-remitting seizure activity (Dodrill and Matthews, 1992). In the sample of adult patients studied in this dissertation the duration of disorder could have been characterized in one of a number of ways, in some cases it was: 1) early onset of illness with a long duration of illness, or 2) late onset of illness with a short duration of illness, or even 3) late onset of illness with a long duration of illness. Even with this type of estimation of duration of illness there were subtle details related to fluctuations in seizure frequency and the characteristics of the illness that were simply left unknown. In future studies it would be wise to include variables that characterize the profile of the illness. For example, inclusion of data regarding periods of remission on or off medication, whether or not seizures cluster temporally, number of seizure types, and number of medications that the subject is treated with at the time of testing. This information should be combined in the construction of a severity index for use in future research studies. A severity index might be employed to further explore the secondary consequences of seizure-related variables on education. An index could also be used to extend this research by looking at other secondary consequences (e.g., psycho-social functioning, depression, adjustment to illness). It could also be employed to investigate specific aspects of educational attainment (e.g., GED, special education services, reading proficiency, repeating of grades).

Laterality of TLE Focus: The impact of laterality of seizure focus was helpful in characterizing group performance; that is when comparing relative performance between the Right- and Left-TLE groups, but offered little in terms of accounting for variance in performance. It should be noted that the two lateralized TLE groups did not differ significantly in mean age of onset nor mean level of education, yet individuals with Right-TLE foci obtained significantly higher mean scores on all three IQ measures.

Education: The finding that level of education achieved was a much more robust predictor of intellectual outcome, relative to the seizure-related variables raises an interesting application of this research. Specifically, the regression analyses were initially constructed to improve the prediction of intellectual outcome in chronic, medication refractory TLE, but the results related to educational attainment are much more general and might be applicable to any chronic disorder that effects classroom attendance and alterations in attention, not just TLE, as the seizure-related variables only accounted for a small portion of the variance in performance on measures of intelligence.

The results of this dissertation research supported and extended the work of Berent et al. (1984) which had argued that the effect of age of onset, often referred to in the literature, is intimately tied to the level of education achieved. It was level of education that was found to account for the most variance in measures of intellectual performance. This was observed in the Partial Correlations and Hierarchical Regression analyses performed on the Sample One data. The impact of age of onset on level of education achieved was seen in the last set of exploratory analyses presented in the Results Section. Recall that it was observed that individuals who had acquired chronic medication-refractory seizure disorders up through the age of 3 years were at greater risk to leave the educational system earlier than those who had acquired chronic medication-refractory seizure disorders after the age of 3. A related issue regarding the variable of education relates to the observation that age of onset did have an effect of educational attainment. In light of that finding, it may not be wise, in a logistical sense, to use level of education as a variable to match study samples with control samples in future research studies on TLE; as the independent variable of age of onset had an effect on level of educational attainment. It was demonstrated in this research that earlier onset seizure disorders were associated with lower levels of educational attainment, by matching samples on the variable of education one risks "weeding out" those subjects with early ages of seizure onset. In future studies it may be wise to consider alternative methods of matching study and control samples (e.g., parental SES).

In future studies other "secondary" variables should be assessed in the prediction of intellectual and cognitive outcome as well. Assessment of these secondary or even tertiary factors might begin with construction of a seizure severity index. A seizure severity index might be designed to include data related to the length of time treated with medication and the number of medications an individual is treated with at the time of testing. More detailed examination of the profile of the seizure disorder might include details related to epochs of remission of seizures either on or off medication, whether or not seizures cluster temporally, and number of types of seizures that an individual experienced.

A. 2. The Prediction of Verbal Retrieval:

To begin to resolve some of the issues in the literature related to select aspects of verbal retrieval and verbal learning, it was necessary to evaluate several of the measures commonly reported in the literature in the same sample of subjects. Analyses were conducted to determine the interrelationships between the tasks used in this study. Significant positive correlations were found between confrontation naming and VIQ and confrontation naming and phonemic fluency, a significant positive correlation was also evident between VIQ and phonemic fluency.

Laterality of TLE Focus and Age of Onset: Based on the work of Hermann et al. (1992), Mayeux et al. (1980) and Vargha-Khadem et al. (1985) it was anticipated that as a group individuals with right-TLE would perform with higher accuracy than those with left-TLE. This finding was not replicated. There were no statistically significant differences between TLE groups in level of performance on BNT or phonemic fluency. Lateralized TLE groups did not differ on the CVLT indices either.

To explore the relation between age of onset and laterality of TLE focus in confrontation naming a 2 x 2 ANOVA was performed. In this analysis early onset was defined as seizure onset prior to age five and late onset was defined as seizure onset after age five (as was the case in the work of Vargha-Kahdem et al., 1985). A significant main effect for age of onset was obtained, but there was not a significant interaction with laterality.

Gender: Based on the reports of Seidenberg et al. (1986) and Strauss, Hunter and Wada (1995) which have suggested that men and boys may be at greater risk for impairment in verbal abilities relative to girls and women it was anticipated that there would be a gender effect evident in tasks of verbal retrieval and delayed verbal recall, with females performing better than males. There were no statistically significant differences between males and females in level of performance on BNT or phonemic fluency. There were significant differences noted between males and females on the verbal learning task ($CVLT_{trial\ 1\text{-}5}$), CVLT Short Delay Recall and CVLT Long Delay Recall.

The combined influence of the primary and secondary variables was able to account for much of the variance in intellectual performance, but was relatively modest in accounting for variance on tasks of verbal retrieval, verbal learning, and verbal memory. One possible explanation for the restriction of the range of variance accounted for might be related to the higher error variance associated with the measures used to examine confrontation naming, phonemic fluency, and verbal memory relative to the more stable measure of the WAIS-R. This relative weakness in accounting for the variability in performance on these measures may stem from the unreliability of each one of these criterion measures. Predictor variables cannot be expected to predict the part of the criterion measure that is error variance. It should also be acknowledged that this sample was relatively homogeneous (e.g., all subjects were evaluated as presurgical candidates for temporal lobectomy to relieve chronic, medication-refractory TLE of unknown etiology), which also restricted the range of variance that could be explained.

<u>The Combination of Factors</u>: The combined influence of age of onset, duration of disorder, gender and education in the prediction of confrontation naming accounted for 18% of the variance. The combined influence of age of onset, duration of disorder, gender, and education in the prediction of phonemic fluency was even more modest, it accounted for 9% of the variance, no statistically significant contributions were noted for any of the predictor variables in isolation.

Age of onset was observed to be a significant predictor of confrontation naming ability which accounted for 15% of the variance when the variance accounted for by the other predictors was held constant; education only accounted for 7% of the variance in BNT performance when the variance accounted for by the other factors was held constant. It was somewhat surprising that education was only able to account for half the variance that age of onset did, since the BNT has been reported to load highly on vocabulary factors (Hawkins et al., 1993). One possible explanation for this might stem from the way education was coded and defined in the database. In this database, education was defined as the equivalent number of years a subject attended school. This is a gross measure, because it does not address issues related to GEDs, special education services, reading abilities, or even whether a subject was left back in some classes.

Another way to interpret the association between age of onset and confrontation naming might be related to issues of development. There are differences apparent in naming ability observed in normal older and younger children. It has been discussed that the skill of naming becomes more fluent gradually during childhood (Denckla and Rudel, 1974). The errors of younger children (age 6) have been characterized by the tendency to produce associates to target words which may be a manifestation of the incomplete development of their lexical access systems. As the organization within these systems progresses into hierarchical dimensions performance on this task improves. Younger children appear to have a horizontal aspect to their word-finding that is generally not observed later in development (Buckingham, 1981). This has been demonstrated in word association tasks. In these tasks younger children tend to give associates that could occur after the stimulus word in a sentence (e.g., noun-verb); whereas older children tend to give associates that could occupy the same position or substitute the stimulus word in a sentence (e.g., noun-noun).

To better understand the influence of age of onset on BNT, but not CVLT delayed free recall it might be helpful to discuss the way naming and verbal learning tasks dissociate in children. Halperin et al. (1989) demonstrated that in normal children, confrontation naming seems to relate more to word knowledge than to retrieval which might help explain the influence of age of onset on BNT performance. The factor analytic studies presented by these investigators indicated that verbal memory functions appear to be relatively independent of naming tasks in children. One could speculate that the dissociation between naming and CVLT delayed free recall is suggestive of a developmental process that should be investigated in future studies. One way to improve our understanding in this area is to incorporate measures of reading proficiency which are highly associated with word knowledge (vocabulary) (Wilkinson, 1993). This type of investigation might refine our understanding of the relation between age of onset, education, and word knowledge by examining the unique and combined impact of the variables of age of onset and education on literary proficiency.

A. 3. The Prediction of CVLT Performance:

The interpretation of the results related to CVLT performance is complicated, the lack of effects of age of onset and laterality require further exploration into understanding what the CVLT actually measures. Correlations with other memory tests (e.g.,WMS) have been reported to be "modest" (Schear and Craft,1989). The CVLT seems to involve the interaction between the components of verbal conceptual skills with learning and memory. To better understand the task of list-learning of familiar material presented in a unique way we must regard the nature of on-line processing, change/learning as well as stability over time, and the dynamic interaction between internal processing systems and the universe that is external to them.

If learning is thought of as an adaptive process through which behavior is modified with experience as some have discussed (Nelson,1991,1986,1985; Vygotsky, 1960), then the manner in which knowledge is acquired and the ways that information can be organized may shed some light on the interpretation of the findings of this dissertation research, particularly with CVLT performance. If we presume that material encoded from list learning tasks with repetitive trials is influenced by top-down processes like expectation and familiarity (Grossberg and Stone, 1986), then whatever is encoded into a knowledge base is likely influenced by the contents of what has already been acquired, attention, and the extent to which the stimulus has been processed. The issue arises as to whether this process of learning can be adversely affected by epilepsy, which is characterized by episodic disruption of neural activity. This episodic disruption could potentially compromise the acquisition of knowledge via fluctuations in attention and/or the extent of stimulus processing. It was mentioned in the Results section that both left- and right- TLE groups performed poorly relative to published norms, but at this point in time the issues related to fluctuations in attention can not be addressed as measures of attention were not analyzed in this research.

The literature on semantic development is somewhat suggestive that the verbal learning of lists of categorically related items would improve as age of onset increases, but age of onset was not found to be a significant predictor of CVLT performance. It appears that the index for CVLT "learning" over trials 1-5 measures some sort of organizational conceptual strategy and level of attention more than it measures recall. When VIQ was enter into the regression model it was found to be a significant predictor only when the criterion measure was learning across Trials 1-5, not in the delayed recall indices. Factor analytic studies of the California Verbal Learning Test (CVLT) have yielded six factors: a general learning factor, learning strategy, acquisition rate, serial position effect, discriminability, and learning interference (Delis et al., 1988). The factor structure demonstrates that this task measures some level of interaction between verbal memory and conceptual ability, rather than rote verbal memory. The combined influence of age of onset, duration of disorder, gender and education in the prediction of CVLT learning on Trials 1-5 only accounted for 7% of the variance. Gender was observed to be the only significant predictor of learning on Trials 1-5 which accounted for 7% of the variance when the variance accounted for by the other predictors was held constant. In other words, knowledge of gender provided as much predictive ability as the combination of the primary and secondary variables. This finding related to gender is consistent with the normative literature which has reported that women tend to outperform men on learning and recall indices of this test (Kramer, Delis, and Daniel, 1988). This finding differs from those reported by Hermann et al. (1992) who did not report a gender effect on CVLT performance in TLE samples. As was discussed in detail earlier in the literature review, this difference between the dissertation results and those reported by Hermann et al. (1992) is likely related to the method of regression employed in this study versus the method of regression used by Hermann et al. (1992).

The Combination of Factors: The combined influence of age of onset, duration of disorder, gender and education in the prediction of short delay free recall accounted for 16% of the variance. Duration of illness was observed to be a significant predictor of short delay recall ability which accounted for 11% of the variance when the variance accounted for by the other predictors was held constant, other significant predictors were gender and education which accounted for 10% and 7% of the variance respectively. For unknown reasons, only gender and education (which each, in isolation, accounted for 7% of the variance) were found to be significant predictors of CVLT long delay free recall. It could be speculated that this result was related to the learning strategies employed during the learning trials of the CVLT. Individuals with higher educational attainment might have organized list items categorically (semantically) as opposed to serially. A semantic organizational strategy would improve recall performance. This is an empirical question that merits future investigation

The relation between duration of illness and short delay recall may be related to the nature of the sample composition. All subjects in this dissertation research presented with seizure foci of the temporal lobe and were evaluated as pre-surgical candidates for relief of medication refractory seizure disorders. The role of the temporal lobes and associated subcortical structures in memory functions has been well documented (Squire, 1987, for review). A variable that should be considered in future studies is length of time treated with anticonvulsant medications; it is likely that the longer the duration of illness the longer the span of time on anticonvulsant medication. It might be wise to also consider the number of medications that a subject is treated with, as this variable might be related to the severity of the illness and the number of types of seizures a subject experiences. One way to explore this area in future studies would be to examine the relation between duration of illness and retrieval difficulty in individuals evaluated for surgical resection and those who have seizure disorders that are controlled by medication.

A. 4. Integration of the Findings:

The results of this dissertation indicate that some of the variance in intellectual functioning is accounted for by seizure-related variables so they should be considered when predicting outcome, but the secondary consequences of these factors on the level of education achieved accounted for a much larger portion of the variance in performance. The combination of seizure-related variables and level of education only accounted for a modest amount of the variance in performance on tasks of verbal retrieval and verbal learning. Individuals with ages of onset up through the age of 3 years were found to be at significantly greater risk to achieve lower levels of education and obtained significantly lower mean FSIQ scores (see APPENDIX E) than those with age of onset after age 3. In an attempt to further explore the issue of age of onset and intellectual outcome the mean age-corrected scaled scores for the WAIS-R subtests of Information and Vocabulary (referred to as Hold scores as they remain relatively stable in the presence of brain damage) were examined by age of onset groups (see APPENDIX F). The mean age-corrected scaled scores were slightly lower in the early onset group.

The results of this dissertation suggest that individuals with chronic, medication-refractory TLE of unknown etiology with earlier ages of onset are at relatively greater risk for intellectual deficiencies, decreased naming proficiency, and curtailment of verbal fluency than those with later onset. Within this sub-group of seizure patients, individuals with longer durations of illness are at relatively greater risk for impaired verbal memory on list-learning tasks. The complex role played by medication was not explored in this dissertation research, but should be in future studies. Issues that need to be clarified revolve around the age at which medication was initiated, because this might affect brain development, length of time treated on medication, number and type of medication(s) currently used, and periods of remission from seizures either on or off medication.

There have been a number of issues raised related to this dissertation research. The major concerns for future research that evolved during this research endeavor can be summarized in the following ways:

- There is a need to construct a seizure disorder severity index in future research endeavors that explore primary factors related to severity of illness and the relation of severity of illness to secondary factors. Potentially important variables that are likely to impact the educational process include: number of years treated with anticonvulsant medication, type of medication treated with, types of seizures subject experiences, whether or not seizures cluster temporally.

- There is clearly a justification to begin to assess the factor of education in a more detailed manner than the number of years in the school system, or the equivalent thereof. Additionally, the finding that age of onset impacts educational attainment raises concern about using education as a means of matching patient samples with control subjects.

- A second, but related issue regarding education refers to the robust impact of level of education relative to the primary seizure-related variables, and the possible application of these findings to other chronic illnesses that might interfere with educational attainment.

- Further investigation is required regarding the factor structure of tasks often used in the TLE literature. As was stressed several times in this document, although the CVLT is described as a test of verbal learning, it is not clear that verbal learning is what is measured by this task.

- In a similar vein, the error variance associated with performance measures must be considered when attempting to predict outcome. The relationship between predictability and reliability is such that the ability to predict an outcome is constrained by the reliability of the outcome measure.

B. Concluding Comments: The Practical Conclusions to be Drawn From This Dissertation Research

The results of this dissertation research confirm and extend previous reports in the literature regarding predictors of intellectual and cognitive outcomes in individuals with TLE. The analyses focused on the examination of relationships between primary and secondary variables and intellectual functioning, verbal retrieval, and verbal list-learning.

One important consideration related to the findings of this work involves developing methods of intervention that would improve the quality of life for individuals like those who were studied in this research. It is evident from this dissertation, as well as previous reports in the literature, that early onset and long duration of illness are associated with intellectual and cognitive deficiencies. In light of the fact that these individuals are at greater risk, there are a number of possible modes of early intervention that might be employed to assist their cognitive development. Psychological and social supports are needed for these individuals as well as their families to deal with issues related to self-esteem, independence, and the acquisition of age-appropriate skills.

Alternative and additional methods for the presentation of scholastic material need to be developed as well as methods to keep individuals from dropping out of high school. This issue is clearly evident in this dissertation research as well as the work of Dickmen et al. (1975;1977) and Berent et al. (1984). It was observed in these studies that education levels were significantly lower in individuals with early onset seizure disorders. Examination of the data revealed that the level of education achieved was a major factor related to intelligence. In the Berent et al. (1984) study all subjects with onset after the age of 18 had completed high school, unlike the rest of the sample with earlier ages of onset. In addition, when the effect for level of education was controlled across groups, no significant differences for age of onset were obtained in IQ functioning. The reader is asked to recall that this was also the case in this dissertation research when the epilepsy centers were compared. These findings suggest that it may be the disruption in the learning process, probably related to early cognitive and environmental difficulties (e.g., limited expectations from parents and teachers) associated with epilepsy as well as the physical and attention-related difficulties related to seizures, which interfere with educational achievement which may in turn be associated with subsequent intellectual status.

The observation that age of onset had an effect of educational attainment has important implications regarding the use of the variable of education as a means of matching patient samples with control samples. In future studies it is advised that alternative methods of matching study and control samples be considered (e.g., parental SES).

C. Limitations of the Present Investigation

The purpose of the present study was to remove many of the methodological and statistical problems/issues which have made it difficult to predict intellectual and cognitive outcome in TLE. In this thesis the approach chosen was to employ Hierarchical Regression analyses on data that had been collected from several comprehensive epilepsy centers. This technique allowed for the investigation of a narrow window of cognitive functioning and the examination of select variables in a very large data set. Although there were many benefits gained by employing this approach to the data, a longitudinal apprcach would have allowed for a broader examination of questions related to development and the acquisition of knowledge in a developing knowledge base. If children with early seizure onset were followed at various intervals it would be possible to track the progression of development in each subject during the observation period. This type of follow-through would provide both developmental information and a log of commonalities and differences among the sample of children under study. It would further understanding in the ways the semantic system changes over time, and would provide a perspective from which alterations in development might be viewed as a function of age of onset of a chronic seizure disorder. Furthermore, this type of follow-through would provide a vehicle to begin to explore who is likely to become medication-refractory and who will be medication-controlled. This type of follow-through would be useful in assessing various methods of remediation.

Another limitation of this study is related to the narrow restriction to select aspects of cognitive and verbal functions. Not only was the scope of examination in this study limited, but it was restricted to only those verbal measures included in the original database. Future exploration should include additional variables such as the employment of semantic and serial learning strategies in the CVLT, comparison of phonemic versus semantic fluency performance, and further exploration of academic achievement (e.g., reading, spelling, comprehension, and arithmetic). In addition, further examination should include the study other verbal memory measures as well as the examination of non-verbal memory measures, and measures of sustained attention and executive functioning.

This dissertation research did not examine measures of psycho-social functioning, depression, occupational status, adjustment to illness, family histories or school records. It is likely that all of these factors influence performance in daily functioning. For instance, although a relation was found between duration of illness and learning performance, it might be that there is a relation between duration of illness and depression that was not explored. It is conceivable that the longer one experiences an uncontrolled seizure disorder the more likely they are to experience depression; perhaps the relation between duration of illness and CVLT short delay free recall performance observed was only a component of a larger relation between depression and memory functioning. Thus, the absence of this information raises yet more questions in this domain, and underscores the fact that there is more we do not know about the secondary and tertiary consequences of seizure-related variables than we do know.

Finally, although this dissertation research looked at the impact of chronic, medication-refractory, uni-focal TLE of unknown etiology on cognitive outcome there was not a control group of medication-controlled TLE patients to compare performance at time of testing. Thus, the results of this study are restricted to the generally homogeneous sample that was under study and the reader is cautioned that the findings should not be generalized to all subjects with seizure disorders, or even to all subjects with TLE.

D. Future Investigations

Although this research has addressed many questions, clearly it has raised more questions than it has answered. So many interesting explorations merit further investigation in the future:

1) The need for improved normative data on the tasks employed in this dissertation research is well recognized. This need is especially apparent for persons with epilepsy. It should be stated that the absence of appropriate norms for this select sample is a major problem encountered every time a patient is evaluated. Access to this large database has provided an opportunity to amass a great deal of information on confrontation naming performances on the BNT, phonemic fluency, and verbal list-learning as measured by the CVLT with knowledge of age, gender, and level of education. In the future, publication of these norms would greatly aid in future research and clinical evaluation of this select sample of individuals.

2) One issue that became increasing clear during this project was that many of the often explored variables need to be defined in a more precise fashion, or need to be coded via a number of variables into vectors. For instance, further clarification is required for what is

meant by level of education. Generally, in the literature this refers to the number of years in school, however it is not clear if subjects were receiving special education services or not.

The issue of medication needs to be clarified as well. Clarity in this context refers to length of time treated with medication and the number of medications an individual is treated with at the time of testing. More detailed examination of the profile of the seizure disorder is also needed. Details in this case may refer to epochs of remission of seizures either on or off medication, whether or not seizures cluster temporally, and number of types of seizures that an individual experiences.

3) The conclusions drawn from this dissertation research are based on the functioning of a unique group of patients tested at one point in time. Additional studies are required to address the generalizability of these findings to other patient samples with chronic illnesses. One of the future studies that is planned in the area of epilepsy will include not only subjects that meet criteria for this dissertation research, but a group of subjects who also experience chronic seizure disorders who are not surgical candidates, but are well controlled on anticonvulsant medication, and a group of age, SES, and

gender matched normal control subjects.

4) Another important investigation in the future consists of a longitudinal approach in which pediatric subjects are followed over time. This type of prospective approach is needed to provide a means for broader examination of some of the questions raised by this study. By following children with early seizure onset at various intervals and retesting them on comparable tasks, the process of development can be observed. This type of study would also provide a vehicle by which subjects could be divided into categorical groups by age of onset or by the progression in severity of their seizure disorder. In this type of study comparison with normal age-matched controls would be invaluable to further our understanding of normal development as well as development in the presence of a chronic seizure disorder. A longitudinal study would allow for further exploration and identification of those individuals who go on to develop a chronic medication-refractory seizure disorder and those who do not. This type of method would also provide a means of follow-back to study those with positive post-operative outcomes and those who do less well with surgical intervention. With the aid of case histories and school records it would be possible to track the progression of development in each subject during the observation period. This type of follow-

through would provide a log of commonalities and differences among the sample of children under study. It would also further understanding in the ways cognitive functioning changes over time, and would provide a perspective from which alterations in development might be viewed as a function of seizure-related variables.

5) Examination of psycho-social functioning, depression, and adjustment to illness by patients and their families would also help identify the needs of this patient population and further identify additional methods by which we could improve their quality of life. This type of investigation would allow for further investigation of the relationship between depression and memory impairments in epileptic patients.

APPENDIX A

Subjects were evaluated at Comprehensive Epilepsy Centers for surgical consideration because of medication resistant epilepsy. This evaluation consisted of a week long hospital admission which included 24 hour video-tape monitoring with concurrent EEG, neuropsychological examination, and MR imaging. Seizure focus was operationally defined by the converging evidence of interictal and ictal scalp and sphenoidal recordings, in addition to the clinical assessment of behavior during seizures. Ictal criteria was based on at least 3 seizures with onset and early evolution of EEG alterations. Interictal criteria were based on lateralized spike ratios. Behavioral assessment included ictal lateralizing signs such as versive head turning, speech alterations, and dystonic posturing.

All determinations as to the localization and lateralization of the ictal onset were made independently by the electroencephalographer who was blind to the results of neuropsychological testing. To be included in this investigation subjects must have all monitored seizures originating from one temporal lobe.

APPENDIX B

Tables of Demographic Data and IQ Scores by Epilepsy Center

Table A: Demographics and IQ Scores for the Center 1 Sample

Subject Characteristics of Center 1

Cleveland Clinic (25% of Total Sample)

Variable	Sample (N=201)
	Mean(S.D.) Range
Chronological Age	31.2(8.2) 16-55
Years of Education	13.0(2.3) 8-20
Age of Onset (yrs)	12.9(10.0) 1-44
Gender (M:F)	110M,91F
Focus (L:R)	102L,99R
Handedness (L:R)**	31L,170R
Duration (yrs)	18.3(9.6) 1-42
FSIQ	90.3(12.4) 66-132
VIQ	90.7(12.2) 71-129
PIQ	91.7(13.7) 60-139

Note: FSIQ=Full Scale IQ; VIQ=Verbal IQ; PIQ=Performance IQ.
**$p < .0000$.

Table B: Demographics and IQ Scores for the Center 2 Sample

Subject Characteristics of Center 2

Epi-Care Center (31.1% of Total Sample)

Variable	Sample (N=248)
	Mean(S.D.) Range
Chronological Age	31.6(9.7) 16-63
Years of Education	12.4(2.5) 6-19
Age of Onset (yrs)	12.0(10.7) 1-56
Gender (M:F)	117M,131F
Focus (L:R)	127L,121R
Handedness (L:R)**	29L,219R
Duration (yrs)	19.6(11.3) 1-56
FSIQ	87.7(11.4) 67-128
VIQ	88.4(11.8) 63-126
PIQ	88.7(12.9) 65-134

Note: FSIQ=Full Scale IQ; VIQ=Verbal IQ; PIQ=Performance IQ.
**$p < .0000$.

Table C: Demographics and IQ Scores for the Center 5 Sample
Subject Characteristics of Center 5
Mayo Clinic (18.4% of Total Sample)

Variable	Sample (N=146)
	Mean(S.D.) Range
Chronological Age	31.9(9.3) 17-59
Years of Education	12.5(2.6) 3-22
Age of Onset (yrs)	12.7(9.9) 1-52
Gender (M:F)*	86M,60F
Focus (L:R)	78L,68R
Handedness (L:R)**	20L,125R[37]
Duration (yrs)	19.2(11.4) 1-49
FSIQ	87.6(12.2) 48-120
VIQ	88.3(12.6) 54-124
PIQ	88.4(12.8) 48-116

Note: FSIQ=Full Scale IQ; VIQ=Verbal IQ; PIQ=Performance IQ.
*p<.05. **p<.0000, two-tailed.

[37] One of the 146 (.7%) subjects from this center was assessed to be ambidextrous.

Table D: Demographics and IQ Scores for the Center 6 Sample
Subject Characteristics of Center 6
Hospital for Joint Disease (16% of Total Sample)

Variable	Sample (N=127)
	Mean(S.D.) Range
Chronological Age	33.9(10.8) 16-65
Years of Education	13.2(2.5) 8-20
Age of Onset (yrs)	16.5(12.1) 1-56
Gender (M:F)	56M,71F
Focus (L:R)*	75L,52R
Handedness (L:R)**	18L,107R[38]
Duration (yrs)	17.4(11.3) 1-62
FSIQ	91.2(12.9) 69-130
VIQ	92.5(13.6) 67-131
PIQ	91.5(13.3)[39] 68-127

Note: FSIQ=Full Scale IQ; VIQ=Verbal IQ; PIQ=Performance IQ.
*$p<.05$. **$p<.0000$.

[38] Two of the 127 (1.6%) subjects from this center were assessed to be ambidextrous.

[39] In the calculation of PIQ for this center (n=122), all other calculations for this sample were performed with the entire sample (n=127).

Table E: Demographics and IQ Scores for the Center 7 Sample
Subject Characteristics of Center 7
Long Island Jewish Medical Center (9.2% of Total Sample)

Variable	Sample (N=73)
	Mean(S.D.) Range
Chronological Age	33.1(8.9) 16-55
Years of Education	13.1(2.0) 9-20
Age of Onset (yrs)	13.9(9.6) 1-50
Gender (M:F)	37M,36F
Focus (L:R)	44L,29R
Handedness (L:R)**	14L,59R
Duration (yrs)	19.2(9.9) 2-45
FSIQ	87.8(12.7) 67-131
VIQ	88.2(13.7) 66-132
PIQ	89.7(12.5) 65-121

Note: FSIQ=Full Scale IQ; VIQ=Verbal IQ; PIQ=Performance IQ.
**$p < .0000$.

APPENDIX C

Table F: Demographics and IQ Scores for Sample One Excluding Subjects Ranging in Age 16 - 24 years.

Variable	Sample (N=605)
	Mean(S.D.) Range
Chronological Age	35.6(7.8) 25-65
Years of Education	13.0(2.6) 3-22
Age of Onset (yrs)	14.8(11.3) 1-56
Gender (M:F)	312M,293F
Focus (L:R)	326L,279R
Handedness (L:R)**	85L,518R[40]
Duration (yrs)	20.8(11.2) 1-62
FSIQ	89.2(12.3) 59-132
VIQ	89.8(12.6) 62-132
PIQ	90.3(13.2) 59-139

Note: FSIQ=Full Scale IQ; VIQ=Verbal IQ; PIQ=Performance IQ.
**χ^2 = 761.38, p<.0000.

[40] Two subjects were ambidextrous.

APPENDIX D

A Principal Components Factor Analysis with Varimax Rotation was performed on the verbal retrieval and verbal learning measures. Six variables were utilized in the factor analyses: Three CVLT indices (Total recall of List A $_{(\text{trials } 1\text{-}5)}$, Short delay recall, Long delay recall), VIQ, BNT # correct (sum of spontaneous correct responses and names retrieved with semantic cues), and phonemic fluency total score (sum of three sixty second trials). Factor loadings of greater than 0.5 were considered significant for these analyses. Table 23 presents the Varimax-rotated factor structure. The factor analysis yielded two independent factors accounting for 74.0% of the variance. Factor 1, which accounted for 52.3% of the variance, consisted of loadings from CVLT recall indices. This factor seemed to be assessing recall of learned verbal material over a short period of time. Factor 2, which contained loadings from VIQ, BNT, and Phonemic Fluency and accounted for 21.6% of the variance, might be considered a factor of word knowledge or vocabulary.

The results of the correlations and factor analysis suggest that the tasks included in this dissertation research assess two related yet separable functions in this patient sample. The CVLT appears to measure attention, encoding and conceptual organization over a brief period of time. In comparison, the measures of VIQ, BNT, and Phonemic Fluency assess word knowledge and vocabulary acquired throughout life.

Table G:
Varimax-Rotated Principal Components Analysis (n=75)

Variable	Factor 1	Factor 2
VIQ	.13	.85
BNT # Correct	.25	.80
Phonemic Fluency	.11	.68
CVLT: List A Total Recall	.77	.36
CVLT: Short Delay Free Recall	.95	.12
CVLT: Long Delay Free Recall	.93	.13

Note: VIQ=Verbal IQ; BNT=Boston Naming Test; CVLT=California Verbal Learning Test.

APPENDIX E

Mann-Whitney U - Wilcoxon Sum W Test
FSIQ X Onset Groups

Mean Rank	Cases	
243.20	123	Group 1
318.26	482	Group 2

	605	Total

U	W	Corrected for ties Z	2-Tailed P
22287.0	29913.0	-4.2531	.0000

APPENDIX F

Mean and Standard Deviations of Age-Corrected Scaled Scores on the WAIS-R Subtests of Information and Vocabulary by Age of Onset Groups

Information Subtest

Group	Mean	S.D	Range
1	6.56	2.34	3 - 14
2	7.64	2.69	2 -16

Vocabulary Subtest

Group	Mean	S.D	Range
1	7.00	2.93	3 - 18
2	8.21	2.68	1 -17

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