ABSTRACT

Title of Dissertation: **ATTENTION PERFORMANCE IN CHILDREN AFFECTED WITH ABSENCE EPILEPSY AND THEIR FIRST DEGREE RELATIVES**

Maria L. Levav, Doctor of Philosophy, 1991

Dissertation directed by: Elizabeth A. Robertson-Tchabo, Associate Professor, Department of Human Development and Allan F. Mirsky, Professor, Laboratory of Psychology and Psychopathology at the National Institute of Mental Health [NIMH]

This study attempted to identify possible familial markers of absence epilepsy (petit mal epilepsy) as evidenced in the performance on tests of attention. The objective of this study examined attention as measured by neuropsychological test performance among the first degree relatives (parents and siblings) of children affected by absence epilepsy. Twelve families, with a total of 45 members including 14 children affected with absence epilepsy, were selected and assessed with the NIMH-Neuropsychological Attention Battery (based on four factor model, ENCODE, FOCUS-EXECUTE, SHIFT and SUSTAIN) at the Pediatric Neurology Unit at the Shaarei Tzedek Hospital in Jerusalem, Israel. Partial support was found for a pattern of familial association in one of the four factors (SUSTAIN, assessed with the computerized version of the Continuous Performance Test, CPT) in attention performance for children affected with absence epilepsy and their first degree

relatives. Statistically significant correlations were obtained between male probands and both parents (independently for mother and father) and between probands and their siblings in the sustained attention factor (SUSTAIN). Probands scored consistently lower than parents and siblings on the tasks in the same factor. The SUSTAIN factor is a sensitive measure of sustained attention, and in this study it detected the familial behavioral pattern of reaction time, percentage of errors and correct responses in some of the CPT tasks. Gender comparison revealed differences in performance. The results in the current study indicate that SUSTAIN is the only factor included in the model of attention that discriminates between probands, parents and siblings, and is sensitive to very subtle impairments. Analyses of the psychometric properties of the NIMH-Neuropsychological Attention Battery are presented. The significance of the study and the implications for education are examined. Recommendations for further research are elaborated and the need to replicate the study with additional subjects is suggested.

Attention performance in children affected with absence epilepsy and their first degree relatives

by

Maria L. Levav

Dissertation submitted to the Faculty of the Graduate School
of The University of Maryland in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
1991

Advisory Committee:

Associate Professor Elizabeth A. Robertson-Tchabo
Professor Allan F. Mirsky
Professor John Eliot
Professor Robert C. Hardy
Professor Grace Yeni-Komshian

DEDICATION

To my children, Jonathan and Shlomit, who helped me in every stage and "survived" this period without homemade cakes and cookies.
To my husband Itzhak, who supported my work and "survived" the life with a student.

In memory of my father who taught me that knowledge is the best resource.
In memory of my mother who taught me about resilience and determination.

ACKNOWLEDGMENT

This dissertation project is the product of many hours of work and a lot of help from a number of people. First, the participating families, who invested long hours of their time and overcame their fears of computerized tests. I am grateful to them and to neurologists Dr. Naomi Amir (my mentor during the years I worked in the Pediatric Neurology Clinic in Jerusalem) who so skillfully selected the cases for this study; and Dr. P. Lerman from the EEG Department at Beilinson Medical Center who ascertained some of the cases. Next, I am thankful to Dr. Elizabeth A. Robertson-Tchabo for the endless hours of help in organizing, correcting and expressing my ideas. I am grateful to the other members of my committee, Dr. Robert Hardy, Dr. John Eliot and Dr. Grace Yeni-Komshian who patiently read the manuscript and offered their suggestions. I am especially thankful to Dr. Jerri Benson from whom I learned all that I know about statistics and measurement, and all that I was afraid to ask.

I am especially grateful to Dr. Allan F. Mirsky, Chief of the Laboratory of Psychology and Psychopathology at NIMH, who transformed an almost "mission impossible" into reality. Dr. Mirsky offered me an outstanding opportunity to work in a project of my interest and to use data sets from his research. He taught me about the intricacies of clinical research, was always available to answer even my lengthiest questions, and supported the project all along. And finally, I am grateful to Dr. John Ingeholm Jr. of the Laboratory staff who diligently solved all my computer problems, to Mrs. Marie Elliott who taught me test administration, and to Mrs. Mary LaPadula who took down my long and frequent phone messages at the office.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER I

INTRODUCTION

This study attempted to identify possible familial markers of absence epilepsy (petit mal epilepsy) as evidenced in the performance on tests of attention. The objective of this study was to examine attention as measured by neuropsychological test performance in the parents and siblings of children affected by absence epilepsy (petit mal epilepsy).

Absence epilepsy, Absence, petit mal epilepsy or centrencephalic epilepsy are terms that have been used in the literature to refer to the same clinical phenomenon. In this dissertation, the term absence epilepsy will be adopted. Absence epilepsy is a type of seizure disorder characterized by a change in behavior, an observable phenomenon which consists of a brief (usually 5 to 10 seconds length) decrement in awareness, and in the responsiveness to the environment. This brief alteration in behavior is accompanied by a unique electroencephalographic pattern, the generalized bilateral 3-cycles per second (cps) spike-wave rhythm. "Aside from sleep itself, it represents the only safe round-trip excursion into unconsciousness " (Myslobodsky, 1988, pp.vii). The 'loss of consciousness', or as more explicitly stated by Mirsky (1988) a "decreased responsiveness to the environment", is the main behavioral feature of absence epilepsy. The prevalence rate of this kind of epilepsy is highest during childhood, mainly during the school years. It is important to note that even brief decrements in attention or awareness could interfere with a child's school performance.

The only descriptive behavioral study of absence seizures that has been reported was conducted by Penry, Porter and Dreifuss (1975) on 48 patients (28 females and 20 males) ranging in age from 4 to 24 years. The authors examined simultaneous video tape and EEG recordings under several conditions: during seizures, during resting state, hyperventilation, photic stimulation, and sleep. Each subject was observed individually in an isolated room. Most subjects had multiple recordings and some were followed for a period ranging from 22 to 27 months. As a result of this study, the authors collected 374 records of seizures and developed a classification of absence epilepsy based on clinical criteria. The behavioral components identified were as follows: sudden onset, no warning, and the cessation of the activity in which the subject was engaged (e.g., walking, talking, eating) The subject appears to be in a trance; he/she would occasionally respond with a grunt if asked any question, the eyelids may drop slightly and the eyes may rotate upwards. The face will typically have a 'blank stare'. Finally, the attack will "evaporate as rapidly as it commenced" (Penry, Porter & Dreifuss, 1975). When an attack is over, the person will carry on with his/her activity as if nothing had happened, although he/she could be partially aware of the attack. This phenomenon, which occurs very frequently (10 to 100 attacks per day), has been shown to interfere with the subject's ability to learn and to perform during tasks measuring attention (Mirsky & Van Buren, 1965; Fedio & Mirsky, 1969).

Genetic vulnerability seems to play a role in some types of seizures, including absence epilepsy. Studies have shown a positive family history as evidenced by a higher incidence rate of the disorder among the relatives than in the general population (Annegers, Hauser & Anderson, 1982). The early age of onset, the positive response to drug treatment, and the lack of evidence of acquired brain

lesions or diseases, have encouraged the belief of a genetic etiology of absence epilepsy (Shovron, 1988).

Different research strategies have been used to explore the role of genetics in the transmission of epilepsy and absence epilepsy in particular. These include: family EEG studies, research on the offspring of epileptic parents, and twin studies. Family studies have shown that the risk of developing a seizure disorder among the relatives of patients with epilepsy (parents of the probands, siblings, nieces and nephews, grandnieces and grandnephews) is three times higher than in the general population, 11% in the siblings and 14.3% in the offspring of the probands. The risk of other relatives (nieces and nephews) is not different from that of the general population (Annegers, Hauser & Anderson, 1982). While it is generally known that the EEG features related to epilepsy are transmitted genetically, the point has been made that absence epilepsy has an even greater genetic component (Benninger, Matthis & Scheffner, 1982). For example, in one of the largest twin studies on probands with idiopathic epilepsy (including absence) a concordance rate of 84% (Lennox and Lennox, 1960) was found among 58 monozygotic pairs. This was in contrast to a rate of 15.9% concordance among 63 dizygotic pairs. In the same study, the subsample affected with absence epilepsy showed a concordance rate of 75% for monozygotic pairs (N=20) in contrast to 0% for dizygotic pairs (N=14). Another twin study reported similar findings although the sample size investigated was smaller (Annegers, Hauser & Anderson, 1982).

The classic family studies by Metrakos and Metrakos (1960,1961,1969), that reported centrencephalic EEG abnormalities (including absence epilepsy) in 37% of the siblings of the probands, have served as a stimulus for generating

hypotheses on the genetics of absence seizures. In order to test the genetic hypothesis, Andermann (1982) compared familial incidence of epilepsy among a group of controls with normal EEG, 60 patients with focal seizures who were treated surgically, and 336 probands with generalized epilepsy (including absence) from the Metrakos and Metrakos studies (1960, 1961). He found a significant increase in positive family history for epilepsy among the generalized group (17.9%) than among those with a focal disorder (3.5%) and the normal controls (2.9%).

Cognitive aspects of absence epilepsy: a model of attention

Epilepsy does not express itself solely in seizure activity, but it also may be manifest in more subtle cognitive dysfunctions that have the potential of interfering with the development of basic academic competencies during school years. These are of considerable importance, since they form the basis of future educational, social, and occupational adjustment and functioning. Indeed, studies have shown that children with epilepsy have significant impairments in academic abilities (Seidenberg, Beck, Geisser, Giordani, Sackellaras, Berent, Dreifuss & Boll, 1986). However, the elements underlying this academic vulnerability have not yet been identified. A strong suspicion of the existence of vulnerability arises from Giordani, Berent, Sackellares, Rourke, Seidenberg, O'Leary, Dreifuss and Boll study (1985) that dealt with the differential impairment of patients with partial and generalized seizures. They stated:

> ..."the patients with different types of seizures did not differ significantly in terms of overall intellectual level. However, differences in the pattern of subtest on the Wechsler Scales were observed. Those with generalized seizures or partial seizures secondarily generalized performed more poorly.than did patients with simple or complex seizures.

> The subtests on which these differences were noted included Digit Span, Arithmetic, Block Design, Object Assembly, Digit Coding. Poor performance on these specific subtests holds functional consequences for the affected individuals. These subtests challenge abilities hat are important to successful performance in school and vocational settings"...(pp. 39).

Neuropsychological tests have been developed to provide information regarding the more subtle nature of these problems. Subjects affected with absence epilepsy have been shown to perform poorly on tests measuring sustained attention (Mirsky, Primac, Ajmone-Marsan, Rosvold & Stevens, 1960; Mirsky & Van Buren, 1965; Fedio & Mirsky, 1969). This selective impairment in sustained attention has been reported to occur not only during but also between seizures (interictal phase), presumably because of a persistent disturbance in central subcortical structures of the brain (Mirsky & Van Buren, 1965; Stores, 1981). Recently, Aarts, Binnie, Smit and Wilkins (1984) argued that processing is impaired during generalized larval seizures/subclinical seizures. This impairment can be observed only with sensitive tests, such as the Continuous Performance Test (CPT) or signal detection tests. Tests requiring simple motor performances, such as rhythmic tapping, tracking, or simple reaction time may not be sensitive enough to be affected or disrupted by larval/subclinical seizures. Aarts and his colleagues (1984) stated that these brief alterations of information processing, which they termed "transient congnitive impairment" (TCI), may have serious consequences for learning and for the safety of the individual.

Mirsky (1988) approached the issue of the impairment of attention by expanding on the model of attention formulated by Zubin (1975). The construst of attention was subdivided into four elements or factors: (1) capacity to focus and execute; (2) ability to sustain attention; (3) ability to encode; and (4) ability to

shift attention. Mirsky (1988) applied this neuropsychological model to data generated from studies conducted on several different populations at the Laboratory of Psychology and Psychopathology of the National Institute of Mental Health [NIMH] with a standardized battery of instruments including the Continuous Performance Test (CPT). These data had been collected from large sample studies conducted in different populations in the United States and in Israel. Among those tests were some commonly used to assess different aspects of attention. One of the assumptions of the construction of the Battery was that the four scales/elements/factors of attention are considered to be uncorrelated. Factor analysis principal components techniques yielded four factors base on ten test scores. The four factors were suggested by Mirsky as the primary elements of attention as displayed in Table 1. (From Mirsky, 1988, pp. 332). Data from a recent study by Mirsky and colleagues (1991, In press) using this neuropsychological battery currently are being analyzed. An epidemiologically based sample of 435 elementary school age children in Baltimore County was selected for the project. The attention battery tests for children used in this study (see description in chapter III) were similar, or equivalent, to the adult battery used in other studies at NIMH and in a heterogeneous group of neuropsychiatric patients (N=223) and a group of healthy adults. The preliminary results suggest that the factors obtained from the analysis of the children's data are similar to those of the adults, although the amount of the variance explained by each factor differs for children and adults. However, when the comparisons were restricted to parallel measures of attention for the two samples, the rank of the variances and the factors were almost identical. The authors stated "that the same elements underlie attentive behavior in the two samples (adults and children): focus-

execute, sustain, encode, and shift". Mirsky expanded his model by attempting to map the attention factors or elements in different areas in the brain, suggesting that performance on these tests may be impaired by certain lesions in specific brain areas.

Table 1: Factor Analysis of Attention Measures (Principal Components)

Factor	Major loadings	Variance explained	Identity of factor
1= **Focus-Execute**	Trail Making Test Talland Letter Cancelation Digit Symbol Sub-Test Stroop Test	24%	Perceptual-Motor Speed
2= **Sustain**	CPT-Omission Errors CPT-Commission Errors CPT-Response Time	21%	Vigilance
3= **Encode**	Digit Span Arithmetic	14%	Numerical Mnemonic
4= **Shift**	Wisconsin Card Sorting	12%	Flexibility

This model as well as the NIMH-Neuropsychological Attention Battery were used in the current study. Prior to considering the central research questions in this study on families with children with absence epilepsy, reliability for the NIMH-Attention Battery on an independent American sample of subjects was estimated.

The purpose of this study

The purpose of this study was to examine familial aggregation at the level of the performance in attention tasks in the first relatives of children affected by this type of epilepsy. Consequently, it was decided to approach this question adopting the same design strategy of familial aggregation used in studies of cognitive functions and psychopathology (e. g., schizophrenia).

Originally, the goal of this project was to compare familial aggregation of attention performance in two diagnostic groups: absence epilepsy and complex-partial epilepsy. Complex partial epilepsy/temporal lobe epilepsy is a focal type of epilepsy. It was found at the end of the study that the group of families with children affected with complex partial epilepsy was not available. This dissertation, therefore, limits its report to the data collected on the familial aggregation of attention test performance for the absence epilepsy group.

Research questions

Absence epilepsy is considered to be a familial-transmitted-dysfunction of the brain. Absence epilepsy has been shown to impair a child's attention as measured by the performance on tests of sustained attention. Studies of the attention performance of family members of affected children, however, have not yet been performed. This project adopted the strategy of familial aggregation to study the performance on attention tasks of the parents and siblings of children with absence epilepsy.

The research question may be formulated as follows: Does the deficit in sustained attention (as measured by the NIMH-Attention Battery) found in the probands also exist in the siblings and/or parents who do not have absence

epilepsy? Or stated differently, is it possible to identify markers of attentional dysfunction among family members of probands affected with absence epilepsy that would support the notion of a familial transmission of the disorder?

Significance of the study

The prevalence rate of epilepsy is highest during childhood. The latest study reporting the prevalence of epilepsy in children and adolescents from birth to age 19 years based on the "active" cases registry in two central Oklahoma counties (Cowan, Bodensteiner, Leviton & Doherty, 1989) is one of the few that calculated the rates for specific epileptic diagnoses. In this study 1,159 cases (0-19 years only) were collected. The overall prevalence rate was 4.71 per 1,000, slightly higher in males than in females in each age group up to 14 years. Thereafter, the rates were equal. The total rate for simple absence epilepsy (which is the type of epilepsy considered in the current study) was 0.10 per 1,000 and the age group with the highest prevalence was 10-14 years. Absence epilepsy as well as other generalized epilepsies, was more common in girls (0.12 per 1,000) than in boys (0.08 per 1,000). The most recent study of the prevalence of childhood epilepsy in Israel was published in 1968, (Leibowitz & Alter). The reported rate for childhood epilepsy (of any type) in the study was 4.1 per 1,000.

The identification of familial markers may permit further guidance for the families when one of the members is affected with absence epilepsy. Ziegler (1979, 1981, 1982), based on his studies of observations conducted on the psychological impairment in children affected by epilepsy, concluded that this disorder disrupts a patient's sense of control and competence. This, in turn, affects

those family processes that are related to the establishment of the child's growing sense of autonomy and competence . The impact of the medical status of the child may become a long term complication for the whole family. Mental health professionals are familiar with these concerns and the general feelings of guilt experienced by parents of the affected children. ("What did we do wrong?" is a guilt-laden question that parents frequently raise with the neurologist or the mental health counselor).

Studies of all types of epilepsies in children indicated that, in general, this population has lower IQ scores than healthy children and has higher rates of neuropsychological impairment on measures of brain function. Many of these children are placed in special schools or repeat grades almost twice as often as children without epilepsy (Farwell, Dodrill & Batzel, 1985).

The knowledge of the existence of a familial trait which is uncontrollable by external actions may ameliorate parental feelings of incompetence regarding the difficulties observed in their affected child. On the other hand, the knowledge that a sibling may have a higher probability of being affected by the same attentional difficulties, even in the absence of seizures, may contribute to the secondary prevention of scholastic failures of additional children in the same family. An informed and alerted teacher may be in a better position to avoid the common misconceptions surrounding the child affected with epilepsy as a 'daydreamer and inattentive' who, in many instances, is an underachiever (Ricks & Mirsky, 1974). Familial aggregation data might also be used as a basis for programs of educational enhancement for children affected with absence epilepsy.

Definitions

A number of terms were used in this study which are defined as follows:

Absence epilepsy: absence, petit mal epilepsy or centrencephalic epilepsy are terms that have been used in the literature to refer to the same phenomenon. In this chapter, the term absence epilepsy has been adopted. Absence epilepsy is an observable phenomenon indicated by two main components: (1) a unique electroencephalographic pattern, the generalized bilateral 3-cycles per second (cps) spike-wave rhythm, and (2) a brief (5 to 10 seconds length) decrement in awareness, responsiveness to the environment and memory.

Epilepsy: This is a relatively common neurological disorder that was identified early in medical history (Temkin, 1971). It was defined by Gastaut (1973) as a chronic brain disorder of various etiologies characterized by recurrent seizures due to excessive discharge of cerebral neurons associated with a variety of clinical and laboratory manifestations. Penry (1986) further specified the definition as a symptom of brain dysfunction that involves the recurrent paroxysmal and disorderly depolarization of neurons and the spread of the neuronal discharge through the brain tissue. A seizure is a brief temporary malfunction of the electrical systems of the brain. These malfunctions produce an excessive discharge of electrical energy between the cells and are manifested by certain clinical signs (e.g., convulsions, stereotyped alterations of behavior, loss of consciousness). The abnormal discharges may involve a small part of the brain, as in the partial or focal seizure, or a more extensive area in both hemispheres, as in the generalized seizures. The International Classification of Epileptic Seizures (The International League Against Epilepsy) divides seizure disorders in two main categories: (1) Partial seizures, are those with a focal area of electrical malfunction which may or

may not be associated with impairment of consciousness, depending on the location or involvement of other brain structures. Partial seizures include those called focal motor seizures, temporal lobe seizures/complex partial seizures; and (2) Generalized seizures, characterized by simultaneous malfunction of both hemispheres and without local onset. These include the grand mal, absence/petit mal, which are described earlier in this chapter and minor motor seizures (Penry, 1986).

Seizure: This is an attack of cerebral origin affecting a person in apparent good health resulting from a transient dysfunction of part or all of the brain.

Ictal phase: This is the segment of time when the seizure is occurring.

Interictal phase: This is the interval between seizures.

Postictal phase: This is the segment of time after the seizure.

Burst, paroxysm: This is a wave or group of waves, constituting the EEG representation of an epileptic discharge.

Tonic-clonic: Tonic refers to the state of rigidity of muscles in continuous contraction, clonic refers to the jerky nature of certain convulsion (Gastaut, 1973).

Centrencephalic epilepsy: Penfield and Jasper, in 1954, proposed the word centrencephalic to "identify that system within the diencephalon which has bilateral functional connections with the cerebral hemispheres". They formulated a classification of epilepsies: localized, unlocalized and centrencephalic, depending upon the site of origin of the discharge within the brain. The Penfield-Jasper classification has the advantage that if the individual suffers from repeated episodes of clinical seizures that correlate with the type of EEG specific forms of epilepsy could be singled out on the basis of their closeness in the EEG pattern.

Patients with centrencephalic epilepsy may have petit mal and/or grand mal seizures.

Generalized epilepsy: This is the form of epilepsy characterized exclusively by epileptic seizures generalized (to both hemispheres) from the outset of any symptomatology or etiology (Gastaut, 1973).

Focal epilepsy: This is the form of epilepsy characterized by partial seizures related to a locus in the brain (e. g., complex partial epilepsy). The onset is at any age and the etiology is linked to brain disease.

Idiopathic epilepsy: designates the type of epilepsy that could not be linked to an obvious organic cerebral cause.

Symptomatic epilepsy: This is the type of epilepsy in which the seizures result from a well defined pathological condition of which they are a symptom (Gastaut, 1973).

Probands/index cases: This is the term used to identify the subjects in the sample or the population that is affected by the particular disorder under study, e. g., an individual affected by epilepsy. The patients that are the focus of a genetic study are known as the probands while the manifestations of the trait being analyzed are known as the phenotype. When there is no apparent etiology, the data about possible genetic factors, the genotype, come from the history of epilepsy and from the identification of near relatives of the proband.

Ascertainment: This is the term that refers to the way the data and the index cases/probands have been collected. If we wish to know the risk for a sibling of a child with a specific type of epilepsy to become similarly affected, the probands must be ascertained on a single criterion of the specific form of epilepsy under study.

Family member: is a first degree relative, biological mother, father and siblings.

Age at onset: This refers to the earliest identified date of the appearence of the disorder, usually a determination made by a neurologist or other professional health-care worker. In seizures it is critical to carefully define the age at onset in the proband and in the affected relatives. Many of the abnormal EEG patterns in humans have an onset peak at a certain age and decline in frequency later; this situation is particularly true for the generalized S-W (spike-wave) pattern associated with absence. With respect to age of onset it is usually assumed that: (1) The earlier the age of onset of the seizure disorder, the higher the influence of the genetic factor (assuming a multifactorial etiology). (2) If the assumption is of a single etiologic factor, the probands with early onset of seizures may have a higher genetic liability. It has been postulated that the convulsion-threshold in each individual is under genetic control; the affected gene, however, is yet to be identified.

Familial aggregation: This is a strategy developed to study the tendency of certain disorders to occur in the members of the same family, (i. e., first, second or third degree relatives).

Marker/familial marker: In this context, it designates a specific type of performance or behavior that characterizes individuals who are having or have had epilepsy.

Attention: Following the approach put forth by Zubin (1975) "it is an activity of mediating processes which supports (facilitates) the central effects of a sensory event, usually with the implication that other sensory events are shut out (inhibited)", pp. 144. Zubin limited the concept to the specific type of behavior

in which the stimulus and response can be specified. He presented a model which, by definition, is an attempt at a reconstruction and simplification of observed behavior for the purpose of a scientific study. The model includes the following elements:

a - The act of selecting among different parts of the environment (an object or a thought) upon which to **focus;**

b - The maintenance/**sustaining** of the focus for a required period of time.

Parasuraman (1985) states that the sustained attention or vigilance starts to decrease and performance starts to fail after a period of time. He distinguishes between successive and simultaneous vigilance tasks. In successive discrimination/vigilance tasks, target and non-target stimuli are presented in succession and the subject is required to distinguish between them. In the simultaneous discrimination tasks, target and non-target features are provided within the same stimulus-event. Parasuraman (1985) indicates that the decrements in sustained attention occur only for the successive discrimination vigilance tasks. He adds that the vigilance decrement and the overall level of vigilance performance vary, depending on the task to be performed and mainly on the tasks that show changes in the criterion.

c - **Shift** of the focus to another part of the environment. "Shifting attention refers to the switching mechanism that directs attention from one sector to another" in the environment (Zubin 1975, pp. 141). Zubin observed that what we call 'lack of attention' is caused by a shift of attention. He assumed that those shifts are a result of innate mechanisms or prior experience of the organism which an individual regards as relevant and the observer thinks is irrelevant.

d - **Encoding** refers to the mnemonic operation of storing the information by the subject in order to perform the task required by the instruction.

CHAPTER II

REVIEW OF THE LITERATURE

This literature review covers an extensive number of studies, following in such a pursuit a chronological order. The first section deals with the definitions of the different types of epilepsies, on issues of diagnoses and differential diagnoses, particularly between absence and complex-partial epilepsy. The second section summarizes selected prevalence studies, and reviews the etiology of the disorder, based on studies on the genetics of epilepsies, including twin and family strategies that were used to answer the question of heritability. The third section concludes with a detailed description of the studies on the impairment in performance in subjects affected with absence epilepsy compared with other kinds of epilepsies.

Epilepsy: historical review

The words "epilepsy" and "epileptic" are originally from the Greek and have the same root as the word "epilambanein" which means "to seize" or to "attack" (Temkin,1971). This word implied in the past, as in modern times, that epilepsy is a symptom due to the existence of a chronic dysfunction in the brain. An epileptic seizure is caused by an excessive, transient, and abnormal discharge of nerve cells much like a "small electrical storm". The electrical discharge of the cells may involve just a part of the brain (partial or focal seizure) or a more extensive area in both hemispheres (generalized seizure). The abnormal discharges may thus vary in site, and both on extent and severity. The clinical classification is based both on the behavior reported or observed in the patient and in the EEG measures. Any seizure may be divided in three phases: (1) The pre-ictal phase, usually

referred to as "aura", which is an autonomic reaction, a feeling of fear, a sudden change of mood, or pain. In brief, it is a different type of state that an individual recognizes and describes as marking the onset of a seizure (except for absence seizures which do not have auras as a pre-ictal characteristic); (2) The ictal phase, which is the burst itself accompanied by behavioral indicators; and (3) The post-ictal phase, which is indicated by different behavioral characteristics according to the type of seizure. The burst-free phase between seizures is referred as the interictal phase and is considered to be of normal brain activity.

Absence epilepsy: The clinical picture

Absence seizure/petit mal seizure was described for the first time by Poupart in 1705 (see Temkin, 1971). He observed the state of unconsciousness in a female patient, and gave the following description: "at the approach of an attack, the patient would sit down in a chair, her eyes open, and would remain there immobile and would not afterward remember having fallen into this state"..."If she has begun to talk, and the attack interrupts her, she takes it up again at precisely the point at which she stopped and she believes she has talked continuously". The terms grand mal and petit mal are from that same period. Temkin cited Tissot, a French physician, who was consulted about a 14 years old girl known as healthy until she become terrified by a storm. Tissot wrote: "A few days after the storm, one noticed a movement of the eyelids which at first seemed to be a tic, but which was soon recognized as convulsive". The attacks went on for a long period, "during part of this time the patient, in the intervals between the "great attacks" (grand acces), frequently had very short little (petit) attacks, which were merely marked by an instantaneous loss of consciousness interrupting her speech together

with a very slight movement of the eyes. Often, when recovering, she finished the sentence in the middle of which she had been interrupted; other times she had forgotten it". The loss of consciousness and the unawareness were ever since accepted as the distinguishing signs between absence epilepsy and other kind of seizures. Absence attacks are very brief, usually lasting 5 to 10 seconds. The essential behavioral feature consists of a very short period of cessation of any ongoing activity and loss of responsiveness or "decrement of awareness" (Myslobodsky, 1988).

The only descriptive behavioral study on absence seizures was conducted by Penry, Porter & Dreifuss, 1975) on 48 patients, 28 females and 20 males, aged 4-24 years. The authors observed with videotape, each of the patients while seated in an isolated room and recorded concurrently the EEG's. The observations were performed during resting state, hyperventilation, photic stimulation and sleep. Most subjects had multiple recordings, some of them were followed during a period ranging from 22 to 27 months. There were 374 observed and recorded seizures to classify at the end of the data collection. As a result of this study, the authors developed a classification of absence epilepsy based on clinical criteria. In the simple absence, one of the five types identified, the behavioral components are as follows: sudden onset, no warning, cessation of ongoing activities, eyes become vacant, occasionally the lids drop slightly, and the eyes may rotate upwards. The face will typically have a "blank stare". As noted, the onset is sudden, there is no warning. The person stops the activity he was engaged in, (e.g.,walking, talking, eating) and appears to be in a trance. The person will occasionally respond with a grunt if asked any question; and the attack will "evaporate as rapidly as it commenced" (Penry, Porter & Dreifuss, 1975). When the attack is over, the

person will carry on with his/her activity as if nothing had happened but, he/she remain partially aware of the attack. In the study reported above, only 9% of the absences were classified as typical simple absence whereas the reminder had some additional behavioral components, such as mild clonic movements, some automatisms and some increased or decreased postural tone. The clinical description and the EEG records (spike-wave bilateral 3 cycles per second tracings) are the two parameters used to classify the absence epilepsy.

Absence epilepsy: the terminology

In the 1981 revision of the International Classification of Epileptic Seizures two types of absence are categorized: (1) Typical absences, characterized by an EEG discharge of symmetrical, synchronous spike-wave complexes recurring regularly at a rhythm of about 3 and 2 cycles per second, and (2) Atypical absences associated with varied EEG patterns. Typical or atypical absences are considered simple as long as there is impairment in consciousness and limited motor activity. Petit mal epilepsy is used as a synonymous for typical absence or simple typical absence. Since the term petit mal was used in different countries with some different meanings it is generally suggested to used the term Absence (Aicardi, 1986).

In the literature from the fifties and the sixties, petit mal/absence epilepsy is called centrencephalic epilepsy following the denomination given by Penfield and Jasper (1954). These authors postulated the origin of the generalized seizures at the centrencephalic system, involving the upper brain stem. The latter has the function of maintaining the state of consciousness connecting that area to the two cerebral hemispheres. (In the section on the etiology of absence epilepsy this, and

other hypotheses, will be presented in greater detail). Lately, in work done by Holmes, McKeever and Adamson (1986), the bimodal classification as atypical and typical absence seizures has been challenged. These authors, who collected 800 pediatric patients ages 0 to 18 during 5 years, evaluated the absence seizures using EEG, radiotelemetry and videotape monitoring. They classified 926 seizures into 426 typical and 500 atypical in 54 patients. The study concluded that, clinically, the two types of seizures constitute a continuum. In fact, they are not discrete entities given the considerable overlap between the two. Etiological hypotheses suggesting a disturbance of the normal interaction between the cortex and subcortical mechanisms, may indeed explain the similarities between the two types of absence.

Absence epilepsy: the EEG pattern

The EEG features are the same both for the simple and the complex absence. The absence discharge during the ictal phase consists of generalized, symmetrical, and synchronous negative slow waves preceded by one, occasionally two or more, negative spikes or sharp waves that recur at a rhythm of about 3 cycles/second that usually last for 5-15 seconds. There is a progressive slowing of the discharge from about 3.5 to 2.5 c/sec. The interictal phase EEG recordings are usually normal, with occasional slower background rhythm. Aicardi (1986) pointed out that even though there is a strong correlation between changes in the level of consciousness and the occurrence of 3/cps discharges, the depth of the loss of awareness does not always seem to be related to the EEG characteristics as amplitude or diffusion of the discharge (see also Lennox and Lennox, 1960). Loiseau (1970) indicated that, occasionally, it has been noted complete normal

behavioral responsiveness during absences that were concurrently recorded in EEG. Several authors have reported that changes in the level of awareness are not the only behavioral accompaniments of the spike-wave discharges typical for absence epilepsy, (Mirsky & Van Buren, 1965; Guey, Bureau, Dravet & Roger, 1969; Penry & Dreifuss 1970; Browne & Mirsky, 1982). A review on these studies will be presented later in this chapter.

Current diagnostic definitions

In general, since the first clinical descriptions in the 18th century and the first electrophysiological document by Berger in 1933, the absence seizure is clearly described. The terminology, however, changed along the years as a consequence of the still unconfirmed hypothesized etiologies. The current accepted components for the clinical diagnosis of the typical simple absence seizure are the following:

1. The episode is usually short, often lasting less than 10 seconds and rarely more than 1 minute;
2. The onset is abrupt, without warning or aura;
3. The end is abrupt. without post-ictal abnormalities or post-ictal malaise;
4. Accompanying features of postural tone changes (retroflexion of the head), automatisms clonic motion (eye lid flutter), and autonomic alterations (pallor, change of respiratory and pulse rate) are common;
5. The seizure type may be accompanied by occasional generalized tonic-clonic attacks or other seizure types but accompaniment by partial seizures is unusual; and

6. The attacks begin in childhood or adolescence , (Niedermeyer, 1974; Porter, 1988).

In most of the patients the diagnosis can be established by history. The diagnostic confirmation is made by the EEG (showing the characteristic 3/sec spike-waves bilaterally) recorded with some hyperventilation and photic stimulation techniques, if needed.

Aicardi (1986) indicated that the diagnosis of absence is often wrongly made. A common error is the confusion between daydreaming at school or in front of the TV, or tics, for an absence. In fact, very careful clinical questioning could dispel the confusion. Another common error is the confusion between absence epilepsy and complex-partial seizures with impairment of consciousness or psychomotor/temporal lobe seizures. The performance and cognitive characteristics of the individuals affected with complex partial seizures/temporal lobe seizures are clearly different from the absence seizures (see Table 2). Regarding the general cognitive level of functioning, subjects affected with absence epilepsy are of normal intelligence. However, some studies indicate that some mental defects appears in about 42% of the cases (Sato, 1976; Loiseau, 1985).

Complex-partial epilepsy

Complex partial seizures/psychomotor/temporal lobe are also characterized by altered consciousness, short duration and minor behavioral manifestations. Table 2 shows a comparative list of the clinical and EEG characteristics of the two types of epilepsy. (From Mirsky, 1983).

Table 2: Differential Diagnosis of Absence vs. Complex Partial Seizures

Features	**Absence**	**Complex - partial**
Age of onset	Childhood	Any age, although rare in childhood
Aura	None	Common
Seizure		
Duration	Seconds	Minutes
Alertness	Out of contact	Out of contact
Automatisms	Simple or complex	Simple or complex
Staring	Yes	Yes
Speech	Never formed, patient sometimes hums	Incoherent , dysphasic, or none
Postictal confusion	Never	Often
Amnesia for attack	Yes	Yes, some islands of memory
Precipitation by hyperventilation	Often	Rarely
Precipitation by photic stimulation	Sometimes	Very rarely
EEG	3 cps spike-wave	Temporal slowing or sharp activity

The complex-partial and the absence seizures are considered non convulsive seizures.

Studies on the prevalence of epilepsies

The prevalence rateof a disorder refers to the total number of patients with the disorder from a defined population at any given time (point, period, life-time).

For epilepsy it is usually estimated by the number of cases per 1000 individuals in a specified population.

Table 3: Prevalence Rates of Epilepsy in Developed Countries per 1000 Adults

Countries	Prevalence rate/1000 adults	Author
Japan	1.5	Sato (1964)
United States	0.5-37	Davenport (1923)
	7-13.57	Haerer et al. (1984)
	3.76	Kurland (1959)
	3.7-6.2	Hauser and Kurland (1975)
Great Britain	4.19	Crombie et al. (1960)
	5.5	Brewis et al. (1960)
	3.45	Toone and Eden (1985)
	3-1.9	Pond et al. (1985)
	5.3	Pond et al. (1985)
Island	3.4	Gudmumsson (1966)
Israel	2.32	Wajsbort et al. (1967)
Jerusalem	4.1	Leibowitz and Alter (1965)
Norway	2.3	Krohn (1961)
	3.5-5	De Graaf (1974)
Italy	6.2	Granieri et al. (1983)
Denmark	2.4	Juul-Jensen and Foldspang (1983)
	4.3	Wagner (1983)
Poland	4.2-9.2	Zielinski (1974)
Australia	7.5	Beran et al. (1982)
France	8.0	Beaussart et al.(1980)

The United States National Health Survey on the population groups that seek medical treatment found a prevalence rate for epilepsy of 3 to 4/1000.

A rather exhaustive review of epidemiological studies on epilepsy in children and adults, reveals that the figures on the prevalence rates of epilepsy disorders are conflicting (Jallon & Dartigues, 1987). Tables 3 and 4 (Extracted from Jallon & Dartigues, 1987) show the wide range in prevalence rates in the different countries. Part of the problem lies on the use of different diagnostic criteria, and on the population-base used for the study. Probably, the best documented prevalence and incidence study was conducted in the United States in Rochester, Minnesota, by Hauser and Kurland (1975). They found a prevalence rate of 6/1000 for all kind of epilepsies. The criteria for inclusion of cases in this study were: the person had received medical care for seizures or have had a seizure in the last 5 years.

As noted above, the definition of what is a 'case', the inclusion and exclusion criteria used, generate some of the difficulties underlying the varied figures on the vital statistics on epilepsy. As an illustration, rates may vary if febrile seizures are included (the prevalence is then much higher). In contrast, data bases relying on the number of cases that seek treatment for epilepsy fail to include, by definition, people that are not aware of their epilepsy or people that have single seizures. In one of the most extensive studies on pregnant women, the United States National Institute of Health Collaborative Perinatal Study (based on a sample of 54,500 subjects), it was found that 2.% of these women reported having had a seizure, while 0.7% reported at least one seizure in the past 5 years. However, only 50% of the respondents were receiving medication.

Some of the most reliable comparisons between studies are those that have used similar research protocols. One of those investigated a population of school children in Maryland (Rose, Penry, Markush, Radloff & Putnam, 1973), the prevalence rate of epilepsy found was 19/1000. A second one was conducted by Meighan, Queener and Weitman (1976) in Oregon. In this study, the prevalence rate was 10/1000. The third study was conducted by Chiofalo, Kirschbaun, Fuentes, Corder and Madsen (1979) in Chile, the prevalence rate found was 28/1000. In the three studies, the diagnosis of complicated febrile seizures was included. In contrast, in most of the other epilepsy studies febrile seizures were excluded, thus turning difficult the comparison between those three and all others. Baumann, Marx and Leonidakis (1978) carried out an epidemiologic study of epilepsy in two school populations in two counties in Kentucky, grouping all febrile seizures separately from the rest of the epilepsies. In this study the prevalence rate for one county was 6/1000 and for the second, 9/1000.

The representation of absence seizures among all epilepsies varies from study to study. In 1985, Janz summarized the data for 6500 cases. He found 7.7% affected by absence epilepsy among all cases. In the Rochester, Minnesota, study by Hauser and Kurland (1975), there are estimates for the years 1935-1944 that may have included some cases with partial epilepsy, particularly temporal lobe epilepsy. The estimates for years 1945-1964 are considered more accurate. The percentage of cases of absence with or without tonic clonic seizures was 15.5%, and the rate for all types of generalized epilepsy was 6.3%. Data from a report by Juul-Jensen and Foldspang in 1983 in Aarhus, Denmark, indicates that out of a total of 1,505 individuals with seizures there were 437 with provoked seizures; and 58 (5.4%) of the remaining 1,068 suffered from petit mal epilepsy.

Table 4: Prevalence Rates of Epilepsy in Children by Countries. Per 1000

Countries	Prevalence rate/1000 children	Author
United States		
Oakland	6	Van der Berg & Yerushalmy (1969)
Maryland	2 - 5	Balwin et al. (1953)
	14- 20	Rose et al. (1973)
Oregon	7.8 - 12.8	Spencer (1976)
Clay	27 - 5	Baumann et al. (1977)
	9.3	
Hardin	5.7	Baumann et al. (1978)
Clarke	4.0	Wishik (1956)
Rochester	3.5 - 6.6	Hauser and Kurland (1975)
Italy	4.3	Pisani et al. (1985)
	3.0	Pazzaglia and Franck (1976)
	8.7	Violante (1978)
Germany	4.5	Dosse and Stein (1983)
England	4.1	Ross et al. (1980)
	4- 22.7	Cooper (1965)
	6.2	Pirrie (1952)
Sweden	14.7	Hagberg and Hanson (1976)
Yugoslavia	4.58	Ravnik et al. (1965)
Japan	8.2	Ishida (1979)

Incidence of epilepsies

Cumulative incidence and cumulative risk of epilepsy

The incidence rate refers to the number of new cases, per year, per 100,000 population. As in prevalence studies, the incidence rates of epilepsy vary in a range from 11 to 49 per 100,000. In Hauser and Kurland's study (1975) the incidence over a 33-year period in the same community was 48.7/100,000. The incidence is at its highest point during the first year of life, 103/100,00; lower and constant during middle age; and higher at the age of 55 and above. Life-time incidence is about 4/1000, according to Hauser (communication at the Consensus Conference on Surgery in Epilepsy, NIH, March 1990)

Table 5: Comparison Between Age-Specific Prevalence of All Types of Epilepsy with Cumulative Incidence, Rate/100,000

Age group	Prevalence	Cumulative Incidence
0 - 9	2.8	8.3
10 - 19	4.1	11.4
20 - 39	5.6	15.7
40 - 59	7.0	20.3
60 +	10.2	32.2

A recent study by Annegers (1989), of 375 cases of epilepsy under age 25 included 58 cases (15.5%) with absence. The cumulative incidence of absence epilepsy was 1,9/1000 up to age 20. Among all forms of epilepsy up to age 20, the cumulative incidence was 11/1000. Thus 15 to 20% of the cumulative risk/incidence of epilepsy by age 20 was composed of epilepsy characterized by

absence seizures with or without other convulsive manifestations. For the comparative prevalence and cumulative incidence see Table 5, extracted from Annegers (1989).

Incidence of absence epilepsy and complex partial seizures in children

Table 6: Incidence of Seizure Type in Five Selected Studies. Rate /1000 population

Author	Hauser & Kurland	Juul-Jensen & Foldspang	Cavazzuti	Sofijanov	Todt
Year	(1975)	(1983)	(1980)	(1982)	(1984)
Ages	All ages	All ages	5-14	2 mos-14	3-16
Complex-partial	19.2	25.4	18.1	13.5	1.9
Absence	6.3	5.4	8.0	7.4	**26.8**

(Extracted in part from Holmes, 1987, pp.4)

Gerken and Doose (1973) reported, on the basis of their studies on normal population of children, that the incidence of generalized spike-wave pattern in the EEG (which is the characteristic pattern in absence epilepsy) during rest and hyperventilation is 1.8%. The highest incidence of this pattern is at age 7-8 years (2.9%). The incidence rate in the absence and complex-partial seizures in later studies varies. Table 6 shows two studies from patients of all ages (Hauser & Kurland, 1975; Juul-Jensen & Foldspang, 1983) and another three of childhood epilepsy only (Cavazzuti, 1980; Sofijanov,1982; Todt, 1984). As shown in Table 6, complex partial/temporal lobe type of seizures are more common in the

populations of all ages. When age brackets are taken into account trend differences are noted.

In conclusion, this summary on the prevalence and incidence studies indicates that the rates found for the two types of epilepsy are different according to the type of sample, the age group considered and, the inclusion- exclusion criteria used.

Genetic etiology of epilepsies

Epilepsy is a dysfunction of the brain, and a convulsion is the clinical manifestation of abnormal electrical activity of groups of neurons. From this perspective, all humans are potentially able to convulse. However, there are individual differences in the convulsive threshold; it is this variability which, in part, is considered of genetic origin. The causes of this vulnerability in the absence epilepsy are not certain yet. It is known, however, that seizures occur with higher frequency in family members of patients affected with epilepsy.

There are data that support the notion of a genetic vulnerability or predisposition to epilepsy since the beginnings of medical history. Hippocrates wrote as early as the year 400 B.C., in his book "On the holy disease" about the hereditary aspect of epilepsy. Furthermore, in opposition to the prevailing beliefs, he stated that epilepsy was not "holier" than other diseases and that it is caused by some sickness of the brain, (Temkin,1971). This concept of disease was central during centuries to come, thus, in the 19th century it was included in the laws that prohibited marriage to an epileptic. In the period of the Third Reich in Germany, sterilization was mandated in cases of genuine (familial) epilepsy (Janz 1989).

After almost 2,500 years of history, the stigma has begun to disappear; the discriminating laws to change, but the causes of epilepsy remain still shrouded in some misconception. The understanding of the epileptic phenomenon has been approached along several paths, among them via three main strategies: family studies, twin studies and research on the offspring of epileptic parents.

Family studies

Most of the recent investigations which have attempted to elucidate the hereditary factors in epilepsy agree that the prevalence of convulsive disorders and EEG abnormalities among the near relatives of some classes of epileptics may be much higher than among the relatives of non-epileptics. There is less agreement, however, regarding the relative importance of heredity as an etiologic factor in epilepsy.

One of the issues that appears in the literature is the familiar controversy heredity vs. environment. With the advance of genetics studies it became apparent that human traits, for the most part, are the result of an interplay between environmental and genetic factors. Such an assessment has been done also on the relative roles of heredity and environment as etiologic factors in the production of epilepsy. Every genetically-controlled character is dependent on two environmental factors, space and time, for its phenotypic manifestation (Metrakos & Metrakos, 1961). Most human characters are the result of the interplay between heredity and environment and have, therefore, a wide range of phenotypic variability. When hereditary factors are studied, it is fundamental that the exact number of the affected and unaffected individuals within each sibship is known. A prerequisite of that knowledge is the most exact identification, description, and

classification of the trait so that there is a clear cut dichotomy between the affected and unaffected subjects. The present knowledge in neurophysiology accepts the view that all clinical forms of epileptic attacks, irrespective of etiology, have the same physiologic mechanisms.

The epileptic seizure is a manifestation of excessive neuronal discharges originating within the brain and affecting a part or all the body. Metrakos and Metrakos (1960) argued that a convulsive episode is not a disease entity but rather a symptom of a disease while the etiologic factors are varied, as in fever or pain. But, is heredity one of those etiologic factors? If it is, in which of the epilepsies is heredity a primary factor? Are there specific genes that may contribute to an individual's resistance or susceptibility to convulsions? Those are questions that intrigue researchers, the answers still remain elusive. There are clues to pursue some of them, however, and those will be succinctly reviewed in the next sections.

Metrakos and Metrakos (1961) suggest to consider genes for specific cerebral diseases in which a convulsion may be an associated sign although individual cases suffering from these cerebral diseases may not necessarily exhibit convulsions. In such cases, the role of the threshold genes must be considered. Threshold genes are defined as the level at which any individual can be made to convulse if subjected to sufficient convulsant stimulation such as electroshock, metraxol, hyperventilation or others. Since individuals differ considerably in the amount of stimulation needed to provoke a convulsion it can be conceived that the convulsion-threshold is under genetic determination. Are there specific genes for epilepsy? If there are such genes how do they differ from the threshold genes responsive for the individual's innate capacity to convulse? No gene acts alone;

indeed, its effect is dependent upon the whole genotype of the individual. This interaction remains unclear. There are other additional factors operating in the production of the epilepsies, such as the expressivity and penetrance of the gene and its chronicity which, combined, make the identification of the affected and unaffected more difficult.

Expressivity, refers to the severity of the convulsive condition. If a gene responsible for convulsions has variable expressivity, it is necessary to state what minimum signs and symptoms will be accepted as identifying an affected individual. The variability in the clinical expression of the gene may be due to the expressivity of the gene and/or to the action of separate and distinct modifying genes. The same gene responsible for a specific type of epilepsy may affect the individual in different ways, and not only by setting off excessive neuronal discharges. The expression of the genetic trait is the level of penetrance of the gene. There are individuals that have the potential genetic constitution for exhibiting epilepsy, but the expressivity of the gene is zero. Those individuals are carriers from the genetic point of view but there are clinically unaffected. As a consequence of this phenomenon, there can be found a negative family history for epilepsy among those individuals. This fact, however, does not necessarily mean that the condition under investigation is not hereditary. If the frequency of the major gene for a particular type of epilepsy in a population is high but its penetrance low, the prevalence of this particular type of epilepsy will tend to be nearly the same in the relatives of epileptics as in the relatives of non-epileptics.

Chronicity is a special aspect of the expressivity of a gene. It accounts for the variability in the age of onset of epilepsy and for the periodicity of the convulsive episodes may appear, disappear, and reappear. Most of the first

convulsive episodes occur within the first four years of life, but there is no age group that is completely immune.

Familial aggregation of absence epilepsy

Metrakos and Metrakos (1961) delineated the general methods used to investigate the risk of a near relative of an individual with a history of one or more convulsive episodes with of without an abnormal EEG to have epilepsy. These are: (1) The probands are usually ascertained from the clinical records; (2) The controls must be as comparable as possible; similar in age, size of sibship, ethnic origin, birth order, socioeconomic status, among other variables; (3) The controls are drawn at random from the same population to which the epileptics belong; (4) When a suitable subject is found, control or proband, the investigator obtains the pedigree data and records the EEG on them to confirm his/hers abnormality or normality.

The tendency to develop seizures and particularly absence seizures has been considered familial (Anderson, Elving, & Hauser, 1988). In research done until 1960 this question was addressed but it presented some problems due to methodological difficulties: (1) Differences in the definition of the syndromes to be included; (2) The tendency to equate any generalized spike-wave EEG discharges with absence seizures; (3) Difficulties in defining the nature of the seizure disorder in relatives; and (4) The failure to report separately the data for parents, siblings, children and other relatives.

The first empirical study on the familial aggregation in epilepsies in general and of centrencephalic/generalized epilepsies in particular was conducted by Metrakos and Metrakos (1961). This study constituted a landmark on the

investigation of the heritability of generalized epilepsies such as the absence. The above mentioned authors asked the following questions: (1) What is the prevalence of the spike-wave EEG in siblings of different groups of epileptic probands and (2) Which of the genes may be common to more than one type of epilepsy. The variables included in their study were spike-wave EEG trait, at any time when:

a - The EEG shows bursts of paroxysmal, bilaterally synchronous spike-wave complexes, occurring rhythmically at a frequency of 2.5-3.5 cycles/second;

b - The record shows a relatively good background pattern and no localizing features;

c - The trait is spontaneously obtained in the resting record and/or during hyperventilation and /or during photic stimulation.

The procedures used were: Intermittent photic stimulation carried on with eyes closed at frequencies of 3, 15, 18 alpha, 20 and 25 flickers per second for 6 to 8 seconds. An individual with the trait may or may not have a history of clinical seizures. The individual may show the trait with activation only in one record and spontaneously, in the resting record at another time. Approximately 85% of the probands, who usually have several EEG records, show the trait in the resting record, 10% with hyperventilation, and 5 % with photic stimulation. In the sample of siblings which usually have one EEG, only 60% show the trait in the resting record and the remainder in the other two conditions (hyperventilation, 30% and photic stimulation, 10%). The results of this study showed that, approximately, 37% of the siblings of probands with spike-wave epilepsy have the same EEG trait compared to 5% in the controls. For other types of dysrhythmia there was no difference between the control and the proband's siblings. The trait is not fully developed at birth but its prevalence rises very rapidly. In the age group

of 5-15 years more than 40% of the siblings show the trait. The trait tends to disappear in older ages and by 40 years of age it is seldom present, as evidenced by the low prevalence in the parents. Similar results were obtained with another three groups of probands. Regarding the probands with focal EEG, the study reveals a familial convulsive tendency in the focal epilepsy group. The prevalence of abnormal EEG among the siblings of the focal group was significantly higher as compared to the siblings of a control group. There is also a higher prevalence of EEG abnormality among siblings of probands treated surgically for focal epilepsy. However, it is noteworthy that in all the groups, the elevated prevalence of the abnormal EEG in the siblings is mainly due to the higher prevalence of the spike-wave EEG trait. The authors suggested that, perhaps, several of the epilepsies, including febrile convulsions, have at least one genetic factor in common which may be the autosomal dominant gene responsible for the spike-wave EEG traitwith a frequency of about 4% of a randomly mating population. The presence of this gene can be demonstrated in the resting record or solicited with hyperventilation or photic stimulation but it depends on the age of the individual at the time the EEG is taken. In the population as a whole, when all age groups are included, the spike-wave EEG trait may not be demonstrable in more than 1% of the cases tested (Metrakos and Metrakos, 1961).

Andermann (1982) studied 60 families of patients with focal cerebral seizures who were treated surgically at the Montreal Neurological Institute; EEG tracings were obtained from the 315 relatives (average 5 EEG per family). Their control group were parents and siblings of patients admitted to the hospital with no history of seizures and normal EEG. For comparison purposes, data from 998 first degree relatives of 336 probands with centrencephalic epilepsy were ascertained

from the Metrakos and Metrakos records at the same hospital. There was no significant increase in positive seizure history in first degree relatives of focal probands when compared to control first degree relatives but, in contrast, there was a highly significant increase of positive seizure history in the relatives of the probands diagnosed with generalized seizures. (Table 7, extracted from Andermann, 1982).

Table 7: History of One or More Seizures in First Degree Relatives of Focal, Generalized and Control Probands

	Focal			**Generalized**			**Control**		
	History of Seizures			History of Seizures			History of Seizures		
Relationship	N	No.	%	N	No.	%	N	No.	%
Parents	120	1	0.8	400	67	16.8*	322	41	2
Siblings	229	11	4.8	519	104	20.0*	458	18	3.9
Offspring	28	1	3.6	80	8	10.0	37	2	5.4
Total Relatives	377	13	3.5	999	179	17.9*	817	24	2.9

(First degree)*p <0.001 compared with control relatives

Genetic analysis requires family and population data and cumulative incidence or cumulative risk (the chance that persons of a given age will have been affected by that age), and not only prevalence and incidence data. In a study by Andersen and Hauser (1987) on probands having onset of idiopathic epilepsy or recurrent seizures without acute precipitating CNS insult before age 15, 3.6% of the siblings developed epilepsy by age 40 as compared to a cumulative incidence

rate of 1.7% in the general population. The cumulative risk by age 40, for offspring of probands with onset of idiopathic epilepsy before age 15 in the Rochester Minnesota study (Annegers et al., 1982), was 10.6% for epilepsy.

In a study by Tsuboi (1980) among the relatives of probands with absence epilepsy there were 62 of them with some form of epilepsy 22 (35%), of them had absences. Among the affected relatives of other probands, the proportion with absence varied from 12% to 26%. Among the affected relatives of absence probands only one third had absence epilepsy and a number of cases of absence were found among affected relatives of probands with other type of seizure. There is a similar phenomenon within individuals, some patients having absence seizures show generalized tonic clonic seizures at some time during their lives and some cases start with absences and later develop generalized tonic-clonic seizures. This suggests that those two temporal patterns may be indicating an etiological heterogeneity.

A recent figure from a study by Annegers (1989) shows for all ages under 25 that among the 375 cases of epilepsy 58 (15.5%) were affected with absence. The family studies briefly reviewed above indicate that in the case of epilepsies there is a need to consider the existence of genetic heterogeneity. Any given individual may show distinct seizure syndromes at different ages. The age related changes in seizure type appear to reflect the interaction of the nature of antecedent factors, the developmental maturation of the nervous system and the genetic variation influencing the structure and biochemistry of the developing brain.

Studies in the offspring of probands

Research in the offspring of any sample affected by a disease is a difficult strategy since it requires longitudinal techniques and follow up of samples and populations.

Tsuboi (1982) found 1.7% of epilepsy among offspring of epileptic parents, but when the age was corrected the proportion climbed to 4.8% of the offspring. This risk was several times higher than in the general population (0.4 to 0.6%). The risk was higher in daughters than in sons. The incidence rate among offspring of probands with generalized epilepsy was higher than among those with focal or partial epilepsy (9.4% versus 8.7%). In a later study by Tsuboi (1985), the data were confirmed anew in a different population (see Table 8, partially extracted from Tsuboi, 1985).

Table 8: Frequency of Seizures and Spike-Wave EEG Abnormality in Offspring of Probands with Epilepsy

Type of epilepsy in probands	Total No. offspring	% with epilepsy	% with febrile convulsion	%with S-W EEG
Absence	**30**	**6.7**	**10.0**	**63.6**
Focal	28	0	3.6	16.7

Lately, in an epidemiological study by Ottman, Annegers, Hauser and Kurland (1989), the data from the Rochester, Minnesota, study was revised. In this study, epilepsy was defined as 'recurrent unprovoked seizures'. The offspring of these probands were identified and considered 'affected' if they had either single

or recurrent unprovoked seizures. Overall, the results show no difference between offspring of parents with generalized and of partial epilepsy. The number of affected offspring was about three times higher than the expected number in the general population, regardless of the type of seizure the parents had. The morbidity ratios for offspring of parents with absence seizures were much higher than that for offspring of parents with other generalized seizures. The cumulative incidence up to age 20 was much higher for offspring of parents with absence epilepsy compared to parents with other kinds of generalized seizures. All the generalized cases had younger ages at onset both in the parents and in the offspring. The authors concluded that their findings support Metrakos and Metrakos' (1961) earlier studies.

Twin studies

The overall concordance rate for epilepsy in six major twin studies was 60% for monozygotic (MZ) pairs and 13% for dizygotic (DZ) pairs (Tsuboi, 1985). In a study by Harvald and Hauge (1965), in Denmark among MZ pairs in which one or both reported a history of epilepsy, 10 out of 27 (37%) were concordant, among the DZ only 10% were concordant. Data on absence epilepsy exist in very small samples, 3 out of 6 in MZ pairs and none out of 2 DZ pairs from the same study. In a study by Lennox and Lennox (1960), among a group of probands without any evidence of structural brain lesions, the concordance was 33 out of 47 (70.2%) in MZ pairs in contrast to 3 out of 54 (5.6%) in the DZ pairs. In the cases of absence/petit mal, the concordance was 15 out of 20 (75%) for the MZ pairs and none out of 14 for the DZ pairs. These findings suggest a clear genetic influence in absence/petit mal epilepsy. The twin studies are undoubtedly an

experiment in nature to clarify the role of genetics and environment in the development of epilepsy, however, in order to obtain definite data on absence seizures larger samples are needed.

Behavioral effects of absence epilepsy: The impairment of consciousness

In early descriptions of the behavioral effects of absences, the "loss of consciousness" was one of the important indications for the diagnosis. One of the most common questions the neurologist asks the patients or their relatives is whether consciousness was lost in the course of a seizure. It is thus not surprising that for many researchers the central questions are: is it really 'lost'? and, what is lost? Myslobodsky (1988) suggested, following Chatrian, Lettich, Green and Kupfer (1970), that in absence/petit mal epilepsy some neural circuits "continue to perform their functions, although with varying degree of alterations in the face of unrelenting spike-wave activity" (pp. 161). The third question asked by researchers is how do we measure whatever is 'lost'?

I shall follow Myslobodsky (1988) and Trevarthen (1979) to answer these research issues. Consciousness has eight components: attention (in the sense of alertness, wakefulness); intentionality or purpose; awareness; skill; understanding or full knowledge; sincerity; and moral sense. Those are the different content definitions of the concept in twelve different languages and represent a cognitive, discriminating, intentional, communicative and shared process between individuals. In order to operationally define the concept I shall adopt, following the same author, the term awareness in the sense of processing of input information. The lowering of the degree of awareness is to be considered the behavioral component of the absence epilepsy. Since the processing of input

information is measured via the individual's performance, the terms 'decreased responsiveness' or 'impairment of responsiveness', coined by Mirsky (1988), are most appropriate in order to observe naturally or experimentally what is it that is lost during an absence seizure and, probably, what it is retained.

Empirical studies on the impairment of responsiveness or awareness

Gibbs, Davis and Lennox (1935) described for the first time the petit mal seizure electroencephalographic pattern and indicated that the recordings of these patients made in the interictal phases are normal except for scattered groups of waves of similar patterns seen at the onset of a seizure. Those patterns were termed by them as 'larval seizures' because they begin as a spike-wave, they do not fully develop, they fade out, and are "not associated with loss of consciousness". Moreover, patients may continue certain activities (e.g., counting numbers or singing) concurrently with the 'larval attack'.

The phenomenon of decreased responsiveness during petit mal seizures was assessed for the first time by Schwab (1939, 1941). Schwab raised the question as to what happens to the individual during that 'larval seizure' that may influence other cerebral functions. He showed, in a experimental design, that there is a behavioral response decrement to visual stimuli. The experiment was as follows: 14 subjects that showed larval attacks of absence epilepsy were tested on a reaction time device connected to the the EEG apparatus. Each subject seated in a dark room was instructed to squeeze a rubber bulb placed in his hand the moment he saw a light coming from a 150-watt bulb located 3 feet over his head which was bright enough to be perceived even if the eyes were closed. The subject, who was in the dark until the light went on, was observed as long as necessary in order to

obtain a normal reaction pattern. Then, he was hyperventilated to provoke a seizure, or observed reacting to the light stimuli during a spontaneous seizure. The results showed that brief seizures have less, or no effect, on the reaction time, whereas long seizures have stronger effects on performance. He also indicated that light and sound tend to terminate moderate petit mal attacks, sound being more effective. In another study Schwab (1947) reported that response time to an auditory stimulus was delayed in seizures lasting 5 seconds or less, but in those lasting more than 8 seconds there was no response at all suggesting a state of unconsciousness.

Following this early study other investigators addressed the issue of the decrement of responsiveness with different techniques. Shimazono, Hirai, Okuma, Fukuda and Yamamasu (1953), observed 6 patients during the application of 4 stimuli: (1) Name of patient was called; (2) The patient pulled a string rhythmically; (3) Patient counted on his fingers in sequence following the examiners calling of numbers from one to ten, repeated; and (4) Patient was told to answer simple requests and calculation problems. EEG was concurrently recorded during the experiment. When the patient was called by his name, the seizure sometimes stopped. During a larval or subclinical seizure the patient continued to pull on the string as requested. But when the other two stimuli that require higher cognitive processing were introduced the patients could perform the actions only when the burst was over. The authors noted that the pattern of response did not serve as a clear strategy to differentiate between a full blown seizure and a 'larval seizure'/subclinical seizure because there is not always correspondence between the duration of the seizure and the degree of disturbance in the level of awareness as suggested by Schwab. Bates (1953) showed that a female

patient was able to resume reading activity, carried out before the onset of the seizure without affecting performance at the time that posterior seizure activity stopped, whereas anterior seizure activity still continued to be observed on the EEG records. Interestingly, the person will start reading the last sentence she read at the time when the seizure began. This observation suggested that there is an impairment of retrograde memory. Jus and Jus (1962) studied the question of retrograde amnesia during petit mal seizures. Their results indicated that there is a retrograde amnesia that lasts a few seconds before seizure onset. During this period the brain activity, the reactivity of the individual, the reception, the storage memory, are all normal. In turn, the length of the amnestic period depends on the degree of concentration, it is shorter if the 'attention is highly concentrated'. To be noted, the recall of the events from the period of the retrograde amnesia is the most difficult aspect of the absence periods.

Tizard and Margerison (1963) established that patients with petit mal work more slowly and make more errors during spike-wave brain activity, even when the bursts were of one to one and a half seconds. In a extension of the first study, Tizard and Margerison selected 6 patients under strict inclusion criteria: (1) They suffered from very frequent seizures of presumed subcortical origin; (2) Their EEGs showed bursts of bilaterally synchronous discharges; (3) Each burst could be clearly demarcated; and (4) They agreed to participate in the study. Three of the subjects had very brief seizure periods while the other three had long bursts periods. Their age ranged from 15 to 62 years and their IQ ranged from 64-105. The procedures used were various psychological tests that included: a tape test; the 5-lights test; the visual reaction test; the auditory reaction test; the tactile reaction test; and verbal commands and questions. All the procedures were

performed with concurrent electroencephalographic recordings. At least ten records, each containing spontaneous spike-wave discharges, were obtained from every subject. The results showed that there was no direct function of the duration of the spike-wave and the level of responses, as it was indicated by Schwab, but by some other mechanism that is not clear yet. The response failures occurred more often in the tape test and less often in all the other tests. Spontaneous speech always stopped during the seizure, but some verbal responses were made. A possible explanation of the results was suggested by the authors in the light of the concept of 'capacity' from information theory, that during the bursts there is a temporary reduction in the capacity of the brain to handle information. If the reduction in capacity is small, only the rate of response may be affected; if the reduction is big, only messages of low information value can be transmitted. For this reason, more errors are made in reaction tests in which a choice is made among the stimuli.

Guey, Bureau, Dravet, and Roger (1969) performed an interesting study with school children in France, ages 6-20 years (mean 11 years and 5 months), all affected with absence epilepsy who had large number of seizures in short periods of time. The EEG was recorded by telemetry and the children were observed in: (1) Periods of inactivity; (2) Drawing; (3) Testing procedures (the WISC or the Brunet-Lezime intelligence scales); (4) Projective tests (Rorschach, Duss fables and non-directive interviews); and (5) School exercises. The minimum length of seizure discharge considered for analysis was above 1 second. The results indicated that the frequency of seizures varied according to the activity performed. In the group that started with a lower baseline frequency of absences, seizures were observed during the experiment in 90% in the inactivity or drawing

condition, only 10% during intelligence tests and not at all during projective tests. The second group, which included the children who had a high baseline frequency of absence seizures during the day, showed the highest proportion of absence seizures during inactivity condition, 2.81%. (For drawing, 2.69% and for intelligence test, 0.74%). However, there were some differences within each of the conditions of the experiment. In a subsample of eight of the children the school exercises were added to the experiment and the results indicated that absences were present in 2.41% of the inactivity condition, 2.28%, for drawing; 0.83% for intelligence test and 3.36%, for the school exercises condition. This study seems to suggest that when an epileptic child focuses his attention, the number of seizures tend to diminish. However, attention is not a single factor, and when the effort of focusing exceeds a certain limit, the number of seizures start to increase. The authors argued in their discussion that attention does not seem to be the only factor of importance in the outcome of the experiments. The determinant factors are "the subject's motivations", "the interplay of emotions which a given situation involves". They indicate that they have observed children who, during intelligence tests, started a series of absences as soon as they found themselves in a situation of failure. The authors observations are backed by their clinical experiences, however, there is no systematic attempt to demonstrate those heuristic observations. Psychosomatic research maintains that seizure disorders of many kinds are 'psychosomatic entities' and some experiments have shown that, indeed, this is the case. The immediate onset of petit mal episodes show affective expressions of rage, depression, unfocused attention, passivity, lack of control, anxiety and helplessness (Allen, 1956; Barker, 1948; Freedman & Adatto,1968; Gottschalk, 1953; Zegans, Kooi, Waggoner & Kemph, 1964) however, these

studies were not well controlled. Parents of children affected by epilepsies in general do comment on the psychological and affective aspects during the pre-seizure onset, but there is no definite systematic study that clarifies the question.

Duborsky, Docherty, Todd, Knapp and Mirsky (1975) dealt with the question as to which are the context symptoms prior to a petit mal seizure, and if there are any pre-paroxysmal signs. They intensively observed three patients by the method of context analysis which consists of recording a patient's behavior just before, during, and just after a symptom appears. This technique of analysis requires that: (1) The symptom should be independently observable; (2) Its duration should be clearly demarcated; and, (3) Its frequency of occurrence should be sufficient to allow for statistical treatment of the data. A seizure disorder meets the above criteria. The attacks have a clear onset and can be monitored via the EEG (the attack starts usually without the awareness of the patient or the observer). The authors used the interview protocols of the three patients, for each patient the paroxysmal contexts in four sessions were analyzed and segments of patients words before the EEG paroxysms were selected. The content of the patient's speech before the paroxysm was analyzed in contrast to the contents during non-paroxysmal periods. The results based on the content of four sessions showed strong psychological antecedents to a seizure. However, there were neither clear nor consistent psychological indicators of a pre-petit mal paroxysm/seizure. In general, the paroxysms occurred more often during silence than during speech. The study is an interesting attempt to deal with a controversial issue, however, the sample was too small, the measures were not tested for their reliability, and the objectivity of the judges was questionable because the criteria for observation were not well defined.

Measures of the elements of attention: The Continuous Performance Test

Rosvold, Mirsky, Sarason, Bransome and Beck, published in 1956 a paper presenting the results of an investigation using a new test, the Continuous Performance Test (CPT) which attempted to serve as a clinical instrument for the diagnosis of brain damage. The four groups of subjects were: 72 institutionalized adult patients with either "organic etiology" or "familial idiophatic etiology"; 45 children treated for different brain disorders; 26 adults epileptic patients or brain surgery patients; and 24 adult control subjects. No attempt was made to select patients on the basis of locus, extent, or type of brain damage in the study. The new instrument (CPT) used in this study was based on the evidences from EEG records that brain damaged individuals score lower than the non-brain damaged on tasks that require sustained attention or alertness. This test appears in the same period when some of the questions on the relationship between the decrement in awareness or 'loss of consciousness' and cognitive processes were considered central for the understanding of the behavioral components of the absence epilepsy. There was almost no discussion in this literature on the definition of attention as a concept. As a consequence, the studies I shall present hereunder will equate attention with alertness. Until the appearance of the CPT the common measures of attention or alertness were the Digit Span and the Digit Symbol substitution subtests of the Wechsler Intelligence Test (1974) which were assessing at the same time several memory functions. However, those tests did not detect the case of an individual that shows generalized hypersynchronic electrical activity in the brain. A test that will require a sustained state of attention or alertness will tend to reflect the attentional deficit in this kind of brain damage. The results of Rosvold et al.'s (1956) study showed that the brain damaged subgroup test scores

were significantly lower than the non-brain damaged controls, the differences among the two groups increased according to the difficulty of the tasks.

Mirsky, Primac, Ajmone-Marsan, Rosvold and Stevens (1960) implemented the new technique to assess sustained attention/vigilance by asking the question if patients with non-focal centrencephalic epilepsy perform more poorly than the focal patients? Can a group of patients be discriminated with psychological tests as having focal or non-focal (generalized) epilepsy? They used two samples, one of 5 epileptic (outpatients without history of brain surgery and focal spike abnormality in the temporal lobe) and 5 matched pairs that had one or more EEG's indicating some type of diffuse unlocalized abnormality. There were no differences in age, onset of seizures but no match by frequency of seizures. They selected a second sample of three diagnostic categories in epilepsy patients, temporal, frontal and generalized, to test them with the same procedures as the post-operative group. All the patients were administered the Wechsler Adult Intelligence Scale, the memory scale, the Goldstein Scheerer Weigl Color Form Sorting Test, the Rorschach Test, the Thematic Aperception Test and the Continuous Performance Test (CPT). The results from the CPT scores indicated that there was a difference between the temporal (complex partial epilepsy) and the centrencephalic (absence/petit mal) groups. The latter performed more poorly than the temporal and more poorly than either the frontal or the control group. The centrencephalic group had lower IQ scores, much higher frequency of seizures and a more abnormal EEG. Finally, the authors suggested that tests of memory and of sustained attention used in conjunction may provide a behavioral method in the differential diagnosis of temporal lobe/focal/complex-partial, and non-focal/generalized epilepsies. The authors concluded that the CPT is a measure of

sustained attentiveness or vigilance and an index of integrity of the functioning of subcortical mechanisms within the thalamic and or brain stem reticular activation system. The deficit in these patients is interpreted as an impairment in the functioning of the brain structures within the reticular system. The last statement is based on the hypothesis of Penfield and Jasper (1954), that the initial site of the pathological discharge in the centrencephalic/absence epilepsy is subcortical and possibly in the area of the nonspecific reticular system. This study was the landmark for later studies on the same subject. It was the first attempt of a neuropsychological approach to the understanding of the behavioral phenomena concurrent with brain dysfunctions.

A second study, comprising a sample of 84 (mean-age range 31.4 to 22.8 years) patients, dealt with the effects on the test scores of patients' attention after surgical removal of epileptogenic foci (Landsell & Mirsky, 1964). The classification criteria applied was based on Ajmone Marsan and Ralston's; illness onset was set at the beginning date for the recurrent seizures. Thirty three of the patients had the CPT before and after unilateral temporal lobe neurosurgery for relief of epilepsy. The original version of the CPT and two subtests of the Wechsler Adult Intelligence Scale (WAIS) were administered. The IQ level of the two groups was similar and the length of time they had suffered from seizures was similar. The centrencephalic group was younger. The difference in the scores between the two types of epilepsy on the CPT tasks was almost entirely the result of differences among the female cases, the differences among the males were not statistically significant. The 33 patients that had temporal lobe operation were retested 3 weeks after the surgery and showed a non significant improvement over the preoperative scores. There was a decline in the verbal score (WAIS) in the

patients that had the left temporal lobe removal. No change in the performance score was seen neither in the right hemisphere nor in the left hemisphere resection cases. A significant association was found between the performance scores on the CPT, level of intelligence and duration of illness. This study replicated the former one from 1960 in which a group of patients with centrencephalic epilepsy was found not to perform as well on the CPT as compared with a group with focal epilepsy. Note should be made that the group in the 1964 study was atypical because of the severity of their epilepsy. It was observed that there was a marked variability in CPT scores within the centrencephalic group thus raising the issue on the relationship between test performance and the frequency of attacks at the time of testing. Poor performance has been observed in the absence of simultaneous EEG abnormality suggesting that the CPT may also be measuring some more or less persistent deficit or deterioration that is associated with centrencephalic epilepsy specifically and, perhaps, to epilepsy in general. The authors concluded, as in the former studies, that the maintenance of attention depends on normal functioning of central subcortical structures.

The Continuous Performance Test (CPT) was designed as a measure of sustained attention. In this test, the subject is required to watch a visual display on which the stimuli appear for 0.2 seconds at fixed intervals of 1 second and to press a response key whenever a certain critical letter appears. The cognitive or associative effort required by the CPT is of a relatively low order.

Mirsky and Kornetsky (1964), argued, that the Continuous Performance Test (Rosvold, Mirsky, Sarason, Bransome Jr. & Beck, 1956) and the Digit Symbol Substitution Test/ DSST (Wechsler, 1944) are each one of them dependent upon a distinctive neural organization. They were able to show indirectly through

the effects of different drugs that there is a difference in performance in the two tests. The authors suggested that the CPT has greater sensitivity to the effects of treatments that act on the structures that mediate or regulate attention whereas the DSST has greater sensitivity to the effects of treatments that affect the brain areas that are critical for associative power. The CPT is more sensitive to the effects of chlorpromazine and sleep deprivation. The DSST, that requires an intense cognitive or associative effort for a short period of time and it is regarded as a relatively good estimate of the intelligence level is more sensitive to the effects of barbiturates, meprobamate and LSD.

One of the most important studies on the relationships between the Continuous Performance Test, the EEG measures and other autonomic measures in patients affected with centrencephalic epilepsy/absence was carried out by Mirsky and Van Buren in 1965. The sample consisted of 38 subjects. All subjects in the sample showed the typical clinical and EEG patterns of absence epilepsy. The sample consisted of 8 females and 10 males, aged 13 to 42 years with a duration of illness ranged from 1 to 37 years. The subjects IQ ranged from 64 to 117; and all the subjects were on some maintenance dose of medication. The CPT, the Delayed Identification Test (a memory task) and the Simple Motor Response Test were administered. Concurrently, EEG was recorded on six channels from bipolar scalp electrodes. The other physiological variables taken were: blood pressure, EKG, skin resistance, esophageal and gastric motility and, during periods of burst activity, photographs of the face taken at irregular intervals. The EEG was measured by: (1) Voltage of discharge; (2) Burst length; (3) Frequency of the discharge; (4) Burst stimulus interval (interval from the onset of the burst to the point at which the stimulus occurred); (5) Background, a normal background in

terms of frequency (8-13 cycles/sec) was distinguished from an abnormal of continuous 6-7 c/sec. Autonomic variables were measured on a 3-point ratio scale, a (+) for an increase of the variable, a (-) for a decrease or (0) for absence of changes. The correct response mean score among the centrencephalic patients, in the X-task of the CPT from the first test session, was 76.5%; 13 out of 18 patients did not have any seizures during the task performances. The focal epileptic patients had a correct responses mean score of 94.4%. The comparison between this group with the centrencephalic patients indicated the latter were significantly inferior on the X -task, whether the seizure periods were included or not. The AX- task did not show differences. There was a strong tendency for errors to occur during bursts, the average percentage of correct responses during bursts was 24.1%, whereas in the burst-free periods the average was 84.8 %. The data were divided in two groups: "A", with 11 patients, in which the correct responses during bursts were 20% or less, and "B", with 7 patients, in which more than 20% correct responses were made during bursts. There were significant differences in the two groups in character, organization, maximum discharge, background and voltage. There was a statistically significant lowering in performance in the pre-burst period. Once the EEG burst became evident, the decrement in performance was more marked and a steady improvement was observed during its last 5 seconds, in a U-shaped format. There was a sharp improvement in performance after the end of the burst. Behavioral accompaniments become manifest before the burst itself was seen in the EEG and they dissipated somewhat earlier than the EEG effects. On the memory test, there was a significant impairment in recall of stimuli when they appeared during a burst as compared to occasions when they appeared before the burst. For the

authors this impairment was an indication that the burst interferes with the reception of the stimuli and that it may, to some extent, interfere with the memory or consolidation process involved in retaining the stimulus until called upon to verbalize it. There were also seen autonomic changes in respiration, vasoconstriction, skin resistance and esophageal motility.

In this study the division of the results into two groups, A and B, resembles Gibbs and Gibbs' distinction between petit mal and petit mal variant epilepsy. Petit mal variant epilepsy is found more often in a group of persons with abnormally slow background EEG activity, seizures without clinical concomitants, and lower intelligence, than in pure petit mal cases. Gibbs and Gibbs (1952) suggested that petit mal variant is more likely to be associated with brain damage than with pure petit mal. This last group was more impaired in the CPT scores even in the absence of seizures recorded by the EEG. Mirsky and Van Buren suggested that: (1) Impaired attentiveness can be due to the abnormal function of some subcortical structure which does not manifest itself in scalp leads, and (2) That the neural systems regulating the cortical EEG and attention are independent. Bursts which are symmetrical, regular and bilaterally synchronous, tend to produce more behavioral deficit than other bursts. Tests requiring the complete "attentive act, reception, discrimination, and motor response are more impaired during bursts than those which require only a part of this sequence. "The motor tasks tend to be affected least and there is a retrograde amnestic effect." The spike and wave pattern and the attention impairment are separable signs. Indeed, the patients were impaired on the sustained attention test in the absence of observable bursts, while the behavior change tended to lead the electrographic symptom in time and, in some cases, lack of behavioral changes were observed in the presence

of well organized symmetric bursts. The authors concluded that the results reflect a decreased capacity to process information during spike-wave activity and not a process of loss of consciousness.

Some studies attempted to measure the general cognitive function of children affected by absence/petit mal and compare them with children affected by temporal lobe epilepsy/complex partial epilepsy. Fedio and Mirsky (1969) tested right temporal lobe affected children with left temporal lobe affected children and compared the two of them with children with centrencephalic epilepsy/absence. The CPT test, which was used to measure sustained attention, showed similar results as in former studies; the centrencephalic group performed poorly as compared to the complex-partial and to the controls.

Sustained attention, measured by the CPT, was tested in a group of school children (second graders) selected by their teachers as underachievers and inattentive and matched controls defined as attentive and good achievers. The results on the CPT were much lower for the underachievers than for the control group. The authors of the above study (Ricks & Mirsky, 1974) tested the children with a variety of measures and included a distraction procedure to observe its effect on attention. The authors offered some interesting suggestions for classroom management and teaching strategies stating that, contrary to accepted views, children with lower sustained attention scores are to be screened much earlier for their difficulties. Finally, the underachievers are perhaps those children that have difficulty in sustaining attention on the task, reach the limit much earlier than the rest of the class, and develop to function as a "slow learners".

Recently, Aarts, Binnie, Smit and Wilkins (1984) argued that there are impairments in processing during generalized larval seizures/subclinical seizures

which can be observed with sensitive tests only, such as the CPT or the signal detection tests. Tests requiring simple motor tasks, such as rhythmic tapping, tracking, or simple reaction time are not sensitive enough to be affected or disrupted by generalized seizures. Aarts and his colleagues (1984) stated that whatever the situation may be, detected or undetected by a test, the cognitive attentional or processing functions are impaired and a state they termed "transitory cognitive impairment" (TCI) is to be considered of practical importance. If those TCI moments appear when a person is driving a car, or learning, the consequences can be very serious. The authors developed two short-term memory tasks, one verbal and the other nonverbal, and tested 46 subjects that had confirmed subclinical seizures. Their EEG was recorded during 30 to 60 minutes. During the testing session the subjects' behavior was monitored with closed circuit TV, subjects who exhibited overt seizures during the experiment were excluded. The results indicated that TCI was demonstrable in 50 % of the cases with generalized seizure discharges. Regarding the results from the TCI in subjects with focal seizures, the impairment was specific to the task lateralized in the appropriate hemisphere.

Fifty four years after Gibbs and Lennox (1936) described the 'larval seizures' in generalized epilepsy, a group of researchers in Japan (Sengoku, Kanzawa, Kawai & Yamguchi, 1990), asked the very same question. They tested , with simultaneous video-EEG monitoring, a single subject diagnosed with generalized seizure disorder of The Lennox-Gastaut type. They used three different tests: tapping a button according to a rhythm, a reaction time test to a visual stimuli and a signal detection task. Their results replicated Schwab's (1939) original study, a significant correlation between the length of the spike-waves and

the length of the reaction time, and a sudden interruption (motor inhibition) of the tapping performance with the onset of the seizure. The authors stated that those subclinical seizures were not to be considered simple absence but "transitory cognitive impairment", as had been suggested by Aarts and colleagues (1984).

Comments

After this relatively extensive review of the studies on the behavioral components of the absence seizures it can be concluded that there is agreement regarding the fact that generalized seizures, overt or subclinical, cause a transitory decrement of some cognitive functions, among them a lowering effect on the subject's ability to sustain attention on a task. Over time, different authors using different techniques assessed the dysfunction, or decrement, concurring that only sensitive tests are able to detect the problem. Obviously, this dysfunction affects the ability to learn and its early detection is crucial for the prevention of later problems. However, this behavioral and medical detection is not that simple. Often, children affected with undiagnosed absence seizures are mistakenly labeled as non attentive or daydreaming. (Conversely, daydreaming or lack of attention are confounded with seizures). This common confusion may lead to the attempt to relate the child's behavior to motivational factors or environmental stress.

Some attention to 'attention'

The studies reviewed above did not attempt to define the construct of attention. (This construct is analogous to intelligence, which fails to be defined under the assumption that everybody knows what it is). The review which follows

addresses this issue with the sole purpose of providing the basis for the operationalization of the term to be used in the current project.

Zubin (1975) opened his analysis of the concept of attention with a quote from William James (1890, pp. 403-404):

> " Every one knows what attention is. It is the taking possession by the mind, in clear vivid form, of one out of what seems several simultaneously possible objects or trains of thought. Focalization, concentration of consciousness are of its essence. It implies withdrawal from some things in order to deal effectively with others".

The definition by James included several aspects of attention that were later studied separately by most of the cognitive psychologists and the information processing theorists:

(1) Attention takes place without the need to be aware of it, constituting **a state of tonic arousal;**

(2) Attention includes **focusing** on one object or thought. For cognitive psychologists (e. g., Posner, 1980), it is orienting, that is, the aligning of attention with a source of sensory input or an internal structure stored in the memory;

(3) Attention includes **selecting or detecting** from competing aspects in the environment. For Posner (1980), detecting means to be aware or conscious of the stimulus. The stimulus, in the detecting process, has reached a level of the nervous system at which it is possible for the individual to report its presence by a reaction or performance, e. g. pressing a key or replying to a question; and

(4) Attention means also to maintain the selected focus for a required period of time. The **maintenance or sustaining of attention** is analyzed by Parasuraman (1985) as that aspect of the construct which is simultaneously efficient and inefficient. The former refers to the adaptive innate ability of the

human being to focus, which enables him/her to single out one source among other competing targets in the environment. The inefficient aspect comprises both, the divided and the sustained attention. Parasuraman (1985) states that the sustained attention or vigilance starts to decrease and performance starts to fail after a period of time. Parasuraman considers that it is necessary to distinguish between successive and simultaneous vigilance tasks. In successive discrimination tasks target and non-target stimuli are presented in succession and the subject is required to distinguish between them. In the simultaneous discrimination tasks, target and non-target features are provided within the same stimulus event. Parasuraman (1985) indicates that the decrements in sustained attention occur only for the successive discrimination vigilance tasks. He adds that the vigilance decrement and the overall level of vigilance performance vary, depending on the task to be performed and mainly on the tasks that show changes in the criterion. Posner (1980) included the attention shifts.in his model of attention behavior He stated that attention shifts are connected with the movements of the eyes to different positions in the spatial field. It is important to add that Posner's assumptions regarding attention argue that "attention movements (eyes in space) have properties that are analogous to the skilled movements of the hand and eye" and, consequently, it can be studied as we study any other movements.

As it may be concluded from the complexity of the attempts made to define the concept of attention, when planning to use this concept in any research project, it is always necessary to reduce the definition to the level at which it can be measured, or to the level of the behavior that is being observed.

In the current project it is intended to measure the specific impairment in attention in the first degree relatives of children affected with absence epilepsy.

With this objective, I will follow the approach put forth by Zubin (1975) in studies on schizophrenic patients. He defines attention as: "an activity of mediating processes which supports (facilitates) the central effects of a sensory event, usually with an implication that other sensory events are shut out (inhibited)", (pp. 144). Zubin and others (e.g., Posner, 1980; Parasuraman, 1985) limited the concepts to the specific type of behavior in which the stimulus and response can be specified. Zubin (1975) presented a model which, by definition, is an attempt at a reconstruction and simplification of observed behavior for the purpose of the scientific study. The model includes the following elements:

(1) Selection of the part of the environment to focus;

(2) Maintenance of the focus; and

(3) Shift of the focus to another part of the environment.

The selective aspect is dependent on the individual tendencies, on prior experience, and on expectancy (in information processing terms). The maintenance aspect of attention is to be separated for the analysis in: (a) preparatory attention behavior (orienting in Posner's terms), usually measured by reaction time experiments, and (b) vigilance behavior, measured by tasks in which the subject is required to attend continuously to the appearance of a signal and react in a specific manner as an indication of its detection. Stimuli in the environment are spatially distributed. Selective attention refers to the process of selection among those simultaneously competing stimuli from the environment. "Shifting attention refers to the switching mechanism that directs attention from one sector to another" in the environment (Zubin, 1975; pp. 141). Zubin observed that what we call 'lack of attention' is caused by a shift of attention. He assumed that those shifts are a result

of innate mechanisms or prior experience of the organism which an individual regards as relevant and the observer thinks is irrelevant.

Mirsky (1988) adopted and extended Zubin's model which suits very well the data obtained at the Laboratory of Psychology and Psychopathology of the National Institute of Mental Health [NIMH]. The data are an outcome of large studies in different normal and clinical populations with neuropsychological test batteries. Among those tests there are some commonly used to assess different aspects of attention. Factor analytic principal component techniques yielded four factors using ten tests scores. Those four factors are suggested by Mirsky as the four main elements of attention. A study by Mirsky and colleagues (1991, In press) using the shortened version of an extended neuropsychological battery is currently in the stage of analysis. A population sample of 435 school age children in Baltimore County was selected for the project. The tests of the Attention Battery used for this sample of children are similar, or equivalent, to the adult battery used in another research study in normal adults and an heterogeneous group of neuropsychiatric patients (N=223). The preliminary results suggested that the factors obtained from the analysis of the children data are similar to those of the adults, but their rank, regarding the amount of the variance explained by each one of them, is different in the two sets of data. However, when the comparisons were made on parallel measures of attention for the two samples, the rank of the variances and the factors were almost identical. The authors conclude that these results suggest that it is possible to hold to the notion "that the same elements underlie attentive behavior in the two samples: focus-execute, sustain, encode, and shift". Mirsky expanded the model of attention by attempting to map the

factors or elements in different areas in the brain, suggesting that performance on these tests may be impaired by certain lesions in specific areas in the brain.

As it has been indicated in Chapter I, in order to test the hypotheses of the current study, it was decided to adopt the strategy of familial aggregation This strategy was used in studies of offspring of parents that were affected with schizophrenia. Some of these studies will be reviewed in the following section.

Studies on attention in offspring of schizophrenic and psychotic mothers

A review of the literature on the measures of attention in schizophrenic patients shows that reaction time in this population is slower than among healthy control subjects when there is a shift in the stimulus or in the sensory modality. According to Zubin (1975) schizophrenic patients suffer from 'deviant attention' rather than from lack of attention.

Studies on children at risk for schizophrenia (offspring of schizophrenic and of other psychotic mothers were compared with normal controls) have been performed following Zubin's hypothesis. Thus, Grunebaum, Weiss, Gallant and Cohler (1974) studied the attention patterns of 50 psychotic mothers and their children and 50 control mothers and their respective children and predicted a positive relationship between maternal and child attention in probands and controls. Different tests were used to assess sustained attention, the CPT among them. The results showed that errors of omission of mothers and sons were statistically significantly correlated but not those of mothers and daughters. Rutschman, Cornblatt and Erlenmeyer-Kimling (1977) gave the CPT to a group of 58 children at risk for schizophrenia and a group of 92 control children, adding a distraction effect to compete with the information processing task. The results

indicated a significant difference in performance between the two groups. The authors emphasized that such a difference exists prior to the manifestation of the pathology. On the basis of a former study by Erlenmeyer-Kimling in 1975, the above authors (Rutschman, Cornblatt & Erlenmeyer-Kimling, 1977) expected 10% to 16% of the high risk children to be 'pre-schizophrenic'. If it is assumed that findings in the CPT may reflect early developmental disturbances in information processing, the results of Rutschman et al's. study support the hypothesis of the familial aggregation in schizophrenia. A similar study was carried out by Herman, Mirsky, Ricks and Gallant (1977) on a very small sample (N=6) of children of schizophrenic mothers. In this study, the CPT was administered with concurrent EEG recordings of evoked potentials in different conditions. No differences between the normals (N=6) and the probands were found on the sustained attention measure. The differences, however, appear in the evoked potentials which were of longer latencies among the probands than among the controls in response to the "non-X" task of the test.

Asarnow and MacCrimmon (1982) used a different strategy to assess the issue of the relationship between information processing dysfunction as a marker of vulnerability to schizophrenia. Ten patients and six controls were assessed with the same neuropsychological tests at two stages, when acutely disturbed and when partially recovered. The comparison with the six control subjects indicated that, even when the patients were partially recovered, they continued to show the impairment in the processing as measured by those specific tests. The authors argued that this set of results, and others obtained with a group of foster children at risk for schizophrenia, suggest that the impairment of the information

processing may be a marker of vulnerability to schizophrenia; this process might antedate the development of the thought disorder.

The last study to be reviewed here is by Nuechterlein (1983) who examined the possibility that a group of children of schizophrenic mothers would show an impairment on a signal detection task measuring sustained attention as an indication of vulnerability to schizophrenia. The sample comprised 24 children of schizophrenic mothers, 20 children of mothers with non-psychotic disorders, 14 children diagnosed as hyperactive, and 67 matched control children. The procedures focused on stimulus and response manipulations within the vigilance tasks that measure sustained attention in the CPT, The Porteus Maze Test, and behavioral changes observed during the testing session. The group of children of non-psychotic mothers were included (a) to ascertain the specificity of the testing procedures and (b) to examine any generalized effects of maternal psychiatric disturbance on the children's vigilance. The results indicated that a disproportionate number of offspring of schizophrenic mothers had a very low perceptual sensitivity during the vigilance tasks, as compared to the matched controls, the non psychotic group and the hyperactive group. The data supported the conclusions of the above-mentioned studies that there is a significant deficit in signal detection ability and sustained attention in the offspring of schizophrenic mothers. These differences are considered by the authors as markers of vulnerability and early manifestations of the schizophrenic disorder.

This Study: the hypothesis

The familial aggregation strategy used in the studies on children of schizophrenic mothers is currently used in other psychiatric disorders too. The

current study adopted a similar strategy to test the families of the children affected with absence epilepsy. It searched, in both parents and siblings, for those impairments that have been detected in the probands. As mentioned earlier, the literature shows definite evidences of a genetic etiology in absence epilepsy. Family members of probands affected by absence seizures are at a much higher risk to develop a seizure disorder than family members of probands affected with complex-partial epilepsy. A similar pattern was expected for offspring of parents affected with absence epilepsy.

For over 60 years studies have shown that there is a definite impairment in cognitive processing in the probands with absence seizures (clinical and subclinical), measured with attention tasks, vigilance tasks, reaction time experiments, video observations, using concurrent EEG and evoked potentials. No studies have been performed as yet aiming at the detection of markers of cognitive impairment in the members of the families of children affected with absence as measured by some components of attention. To pursue this objective I followed the model of attention presented by Mirsky (1988), who in turn, capitalized and further developed Zubin's (1975) model.

CHAPTER III

METHODOLOGY

Sampling

The data for this study had been collected in the Pediatric Neurology Department at the Shaarei Tzedek Hospital in the city of Jerusalem, Israel. This Department (affiliated with the Hebrew University of Jerusalem) runs the only clinic in the city serving children from birth up to 20 years of age. Families to be tested were identified from the medical files at the clinic by the neurologist Director of the Department who had agreed to collaborate with NIMH and to ascertain the probands. Originally, the design included two groups of probands, children with absence epilepsy and children with complex partial epilepsy and their respective first degree relatives. Probands affected with complex partial epilepsy were to serve as a comparison group for the absence epilepsy probands and their families. Unfortunately, the group of complex partial epilepsy families were not available. Only after all the data had been collected did it become known that no subjects in the proposed comparison group had been identified since this researcher was kept blind regarding the porband's diagnoses diagnoses until the testing was finished. (This strategy avoided any bias during the testing or interview of the families). Families were invited to participate in the project as part of the clinical routine and the probands had an EEG during the week of the testing session.

A sample of fifteen children aged 5 to 15 years with a diagnosis of absence epilepsy, their parents and siblings were ascertained. The criteria for inclusion were:

(1) A diagnosis by a neurologist (based on the clinical picture and supported with a recent EEG) of absence epilepsy, or a previous diagnosis of epilepsy although currently free of seizures; and

(2) A normal IQ and attendance at a regular school;

No children were excluded if their parents or siblings also had a diagnosed seizure disorder.

The criteria for exclusion from the sample were:

(1) Children who were aphasic, blind, deaf, or who had a neurodegenerative disease; and

(2) Children with cerebral palsy.

Twelve of the 25 families, initially approached by the neurologist, consented to participate in the study. The final analysis refers to 12 families, 9 from the Jerusalem Pediatric Neurology Clinic and 3 from a similar setting in a Tel Aviv Clinic (Beilinson Medical Center). Children diagnosed with complex partial epilepsy were not available from these clinics, probably for two reasons: The complex partial epilepsies are less prevalent among younger children, and their diagnosis is more difficult to ascertain. Regretfully, the few cases identified declined to participate in the study.

Subjects

Twelve families, among them two families with two probands each, were included in the final analyses. A total of 45 subjects, 14 probands (6 boys and 8 girls) assessed in this study were current patients, former patients or patients see in consultation who had had a complete neurological evaluation in the clinic. The parents (N=16, 9 mothers and 7 fathers), 15 siblings (N=15, 9 boys and 6 girls)

and the probands were tested by one of two trained researchers who, as noted, were blind to the of the children's diagnoses The parents were advised by the neurologist not to inform the researchers about either the treatment or the diagnosis of their children.

The demographic data of the study sample are presented in Table 9.

Table 9: The Sample by Selected Socio- Demographic Characteristics

	PARENTS N=16	SIBLINGS N=15	PROBANDS N=14*
		AGE (years)	
MEAN	39	12.13	10.6
SD	6.07	3.3	1.98
RANGE	29-48	6-18	8-13
		GENDER	
FEMALE	9	6	8
MALE	7	9	6
	NUMBER OF YEARS OF EDUCATION		
MEAN	14.31	6.67	4.70
SD	4.25	3.70	2.10
RANGE	8-17 females 9-24 males	1-12	2-8

*Two families had two probands (girls) each belonging to the same family.

All the probands and their siblings were attending regular schools needing no special help. None of the parents were taking medication at the time

of testing. In the study sample, 36% of the families had a history of seizures in the same family unit or among close relatives. One family with two female probands reported epilepsy via the grandparents' sister; one family had the proband's (boy) younger sibling (boy, aged 2.5 years) affected too; one family of a female proband had an affected twin brother who could not be included because of his low level of functioning and one family of a female proband reported two affected paternalaunts.

The Instruments

The Neuropsychological Attention Test Battery developed at the NIMH Laboratory of Psychology and Psychopathology was used in this study. Adults and children were tested with equivalent procedures. This Battery has been used with several samples in Israel, including a longitudinal study of children of schizophrenic parents.

The Battery for Adults

ENCODE FACTOR: was assessed by three tests, Digit Span, Arithmetic and Wechsler Memory Scale Form I, (3 scores).

Digit Span: is a sub-test of the Wechsler Adult Intelligence Scale (WAIS-R, Wechsler, 1974, 1981). This test has two sections:(1) Digit forward and (2) Digit backwards. The score is the sum of the correct answers to the two sections. (single score). This test is a measure of mental tracking and digit recall and it is assumed to measure attention span based on the number of items to which a person is able to attend at on time (Lezak, 1983). This test inits original version (WAIS)

is standardized in Israel for the Jewish, Arab and Druze population (Reliability of the Israeli WAIS Digit Span Test is r=. 83).

Arithmetic: is a sub-test of the Wechsler Adult Intelligence Scale (WAIS-R). This test measures short term memory for mathematical facts and the ability to encode information in a mathematical problem (Reliability for the test in the Israeli WAIS r=.84). The score is the total number of correct responses given by the subject (single score).

Wechsler Memory Scale Form I: There are three tasks in this test. In the first one the subject is asked to tell backwards a list of digits beginning with the number 20 and ending in 1 (in a 30 seconds period); the score is higher depending on how fast th esubject performs. The second task is the recitation of the letters of the alphabet as fast as possible (in a 30 seconds period). The third task is to count from 1 to 40 by threes (e.g., 1,4,7,...), in a 45 seconds period. The final score is based on the sum of scores received in each of the three tasks, (single score). There are no norms for the Israeli population and for that reason it was considered experimental. The test was given in Hebrew.

FOCUS - EXECUTE FACTOR: was assessed with four tests, Digit Symbol Substitution, Stroop Color, Trail Making Test and Letter Cancellation Test.

Digit Symbol Substitution Test: is part of the Wechsler Adult Intelligence Scale (WAIS-R). In this test, subjects are asked to use a code to write the corresponding geometric symbols beneath a series of digits. It is considered a measure of the ability to focus attention. The subject is asked to perform as accurately and as quickly as possible. The score is the number of correct symbols completed. (single score).

Stroop Color-Test: this is a classic test used since 1935 when Stroop developed the procedure. Golden (1978) reviewed these tests and the norms for adults extending them downward to the age of 7 years. However, those norms are still based on small samples. The subject is required to read, as fast as possible, a list of color names ("red", "blue" and "green") printed in black ink, and then to name the colors in which "XXX" are printed. The third step is to read a list of colors that are printed in non-matching colored inks, e. g., the word "red", is printed in "green" ink, the word "green" is printed in "blue" ink. The total number of correct responses during 45 seconds in each of the three lists is recorded. Typically, subjects read the words printed in the first list and the symbols in the second list very quickly. However, when subjects are required to read the third list with the non matching ink the speed of performance decreases almost 50% below that of the first two lists. This decrease in speed was termed the "color-word interference effect". Stroop suggested that, while colors are associated with different behavioral responses, words had only one association: reading (Golden, 1978). This test is considered to be a sensitive measure of the ability to focus attention and of visual perceptual speed (Mirsky, 1987). It has been shown to differentiate brain damaged patients from psychiatric and normal populations (Golden, 1976). It has been used for 30 years in clinical research, in psychopharmacology and in cognitive psychology assessing brain damaged individuals. The reliability estimates reported for this test ranged from 89, .84, and .73 in different studies (Golden, 1975, 1978). The scores are the total number of correct words, colors and color words read, (3 scores). The test has been standardized in Hebrew by Ingraham, Chard, Wood and Mirsky (1988). In this project the test was administered in the Hebrew version.

Trail Making Test: This test is a measure of visual conceptual and visuomotor tracking speed (Lezak, 1983). Test performance is drastically affected by brain injury. It is administered in two parts. In Part A, the subject must draw lines to connect consecutively numbered circles, and in Part B, a subject must connect numbers and letters. The test is timed, and a subject has to focus attention and execute the task without lifting the pencil from the paper. Lezak (1983) indicated that the test-retest reliability as measured by coefficient of concordance for Part A was .78 and for Part B was .67. Lewinsohn (1973) found that Part A of the test shows the examiner how a subject responds to a visual stimuli, whereas Part B how well he performs if he needs to shift from one strategy to another (Lezak, 1983). This test was a part of the Army Individual Test Battery (1944) and adapted by Reitan and Davidson (1974) for the Halstead-Reitan Neuropsychological Test Battery. For the purposes of administering the test in a Hebrew-speaking sample the letters in Part B were changed to the Hebrew alphabet. The test is scored separately for each part. The number of seconds used to perform each task are the final scores, (2 scores).

Letter Cancellation Test: This a test that requires visual detection of stimuli at a fast speed. It assesses visual scanning, the capacity to sustain attention and visual-motor speed. Low scores in this test can reflect the general response slowing and inattentiveness of diffuse brain damage (Lezak, 1983). This test was originally designed by Bourdon (1901) and adopted by Talland (1965). It has been used with Korsakoff patients and Parkinson disease patients, (Lezak, 1983) who were shown to have difficulties with alternative response possibilities. This test is timed, the subject has to follow a pattern of response by checking off the target letters as fast as possible. Three forms of the test, of increasing difficulty, are

presented to the subject. Each page of the test contains 16 rows of 26 lower case letters interspersed with 10 capital letters. In Form A the subject must cross out capital letters. In Form B the subject crosses out capital letters and letters that follow double spaces. In Form C the subject crosses out all capitals letters preceding the double spaces. The scoring is based on speed (number of correct cancellations in 60 seconds), errors and omissions. The final score is the sum of the number of correct answers, (single score). No reliability estimates were reported in the literature. In the current study a Hebrew adaptation of the test was administered.

SHIFT FACTOR: was assessed by the Wisconsin Card Sorting Test.

Wisconsin Card Sorting Test: This test was originally designed by Berg (1948) to assess abstract reasoning among normal adults. Later research found that it is sensitive for the evaluation of the cognitive effects of cerebral dysfunction, particularly of the frontal lobes. The test has been standardized more recently by Heaton (1981), and it is widely used in clinical and research settings for testing of brain damaged population. Chelune (1987, 1988) has developed norms for children. The subjects are presented with a set of stimulus cards which differ in color, form and number. The subject has to arrange the set of response cards he receives according to the samples in front of him. The tester answers with 'wrong' or 'right' after each trial. After ten trials, the examiner changes from one category of arranging to another and the subject has to shift the criteria for grouping according to the feedback given by the examiner without any warning before the change of criteria. The ability to shift from one set of criteria to another is measured in the test. There are 4 scores obtained in the test: number of

errors, number of perseverations, number of correct answers and number of categories completed. Subjects that suffer from brain damage to the frontal lobes cannot perform the shifts and perseverate in the task, (Milner, 1963; Drewe, 1974; Robinson, Heaton, Lehman & Stilson, 1980).

SUSTAIN FACTOR: was assessed by the Continuous Performance Test.

Continuous Performance Test, CPT (Computerized version): This test, originally developed by Rosvold (1956) and coworkers (Rosvold, Mirsky, Sarason, Bransome & Beck, 1956) was designed to differentiate and test the existence of brain damage via the performance in a discrete test. It measures the ability to sustain attention/vigilance in a task that is repetitive. The visual and the auditory sub-tests of the computerized version of the test were used in this project as elaborated by Mirsky and colleagues. During the visual tasks the subjects are required for periods of 10 minutes to press a response-button every time a target letter appears on a small screen. In the first task the letter 'X' is the target. The letter X following the letter A is the target in the second 'AX' task. In the third task, a degraded 'X' is the stimuli to which the subject presses the response button. The letters appear at a rate of 1 per second and the stimulus duration is of 0.2 seconds. The auditory sub-test is as follows: auditory stimuli low, medium and high pitch tones equated for loudness are presented binaurally via stereo headphones. The subject presses the button when he detects the high tone. All the tasks in the CPT, visual and auditory, begin with training trials and practice trials before the actual test starts. The scores on each of the tasks are recorded concurrently by the computer unit. The scores obtained are: total reaction time for each task, reaction time for each stimuli, number of correct responses, number of

errors of omission, number of errors of commission, and mean total reaction time for each of the tasks, (16 scores). The test is used in many clinical settings and research protocols. Studies of the sensitivity of the test were presented in the chapter on the review of the literature.

For parts of the analyses three factor-sum-variables were computed for the factor SUSTAIN: (1) Mean reaction time composite of four scores from the variable "Mean reaction time" in the four tasks (X, AX, degraded X and auditory X); (2) The percentage of correct responses, a composite of the scores from the four tasks on the variable "Correct"; and (3) Percentage error, a composite of the scores from the four tasks on the variable "Errors".

The Battery for Children

The tests in the Battery for Children are similar to the adults version with the exception of the Cancellation test. A short description of each test is presented in the section that follows.

ENCODE FACTOR

Digit Span: is a subtest, from the Wechsler Intelligence Scale for Children, Revised version (WISC-R), and is designed to assess the same functions as in the adult test.

Arithmetic: is a sub-test, from the Wechsler Intelligence Scale for Children, Revised version (WISC-R), and is designed to assess the same functions as in the test for adults.

Wechsler Memory Scale Form I: the test is given and scored the same as for the adults. There are no normative data for children in Israel.

FOCUS-EXECUTE FACTOR

Coding sub-test: is the version for children of the Digit Symbol Substitution Test used for adults and is a sub-test of the Wechsler Intelligence Scale for Children, Revised Hebrew version (WISC-R).

Stroop Color - Test: this test was administered as in the adult subjects.

Digit Cancellation Task: this test has a similar function as the Talland Letter Cancellation Test described above. It was developed at the NIMH laboratories for an epidemiological sample of school children in Baltimore, Maryland, and it was used in that project for the first time. The test requires from the subjects to cancel numbers (digits) aligned vertically on a page. The test has two parts: in Part 1 the child has to search for the numbers "3" and "7" and circle them from a list of digits ; in Part 2, the child looks for the numbers "2" and "4" and at the same time listens to a voice (via a tape recorder) that calling numbers randomly which have an interference function. The score for this test is the total time in seconds used in Part 1 and Part 2, the number of errors and the number of intrusion errors . This test is in the process of defining norms for different ages. The test was used in the current project experimentally.

SHIFT FACTOR

Wisconsin Card Sorting Test; was administered and scored in the same form as with the adults using the scoring tables developed by Chelune (1987, 1988) for children.

SUSTAIN FACTOR

Continuous Performance Test (CPT): has been described above. The same version for adults is used for the children.

Procedures

The probands and their families ascertained from the medical files were contacted by phone by the neurologist during the month of May 1990. The families were invited to participate in the study that was conducted during the last week of June until the last week in July, 1990. The scheduling for the testing was done during the last week in June immediately after an update of the EEG on the probands was made. With the help of a trained research assistant, the testing sessions began on the first week in July. The testing was performed simultaneously by two trained researchers.at the clinic in two independent offices. The administration of each Battery lasted about two and a half hours, including practice trials.

At the conclusion of the testing sessions, mothers and fathers answered a short questionnaire requesting sociodemoographic information (age, years of schooling, occupation, history of seizures in their extended family, ethnicity and chronic illness in the family. The data for the siblings were collected from the parents regarding age, school placement, disabilities, history of seizures.and medications.

Additional data on the probands were extracted from the medical records (onset of seizures, medications, other illness and disabilities, school placement, and history of seizures of the proband since birth). Following the testing sessions of each complete family the EEG diagnoses were blindly and independently verified by two different neurologists in the Clinic for reliability purposes.

Data analysis

The analyses were performed in three phases. The first two phases dealt with the estimation of the reliability of the scales in the Neuropsychological Attention Battery while the third phase related to the hypothesis testing.

Reliability

Reliability estimates were obtained: (1) From an independent, large sample of 223 adult American subjects (146 patients and 77 controls, of those 178 females and 45 males) collected at the NIMH laboratories, and (2) From the current sample of 14 children with absence epilepsy and their first degree relatives (12 families, total N=45). Subsequently, data for adult Israeli healthy subjects tested with the same NIMH Battery became available and was included for control comparisons on the performance in the CPT (N=23).

Internal consistency was estimated for each of the four scales/elements/factors (encode, focus-execute, shift and sustain) in the Battery. A validity estimation was performed using the independent NIMH sample (N=223). Discriminant analysis techniques were used in order to observe the discriminant power of the Battery. The analyses on the larger sample were performed using the SPSS statistical package from the University of Maryland UNISYS main-frame. The analyses on the sample of families were performed on SYSTAT 5.1 1990/91 statistical and graphics package for Macintosh computers.

Scoring: The factor-sum scores

All the test scores were standardized in order to combine them into four factors: ENCODE, FOCUS-EXECUTE, SHIFT and SUSTAIN. The score for each subject

for each factor was the sum of the standardized test scores included in that scale. This data reduction procedure was used to facilitate further analysis and to adhere to the theoretical framework. The item-total correlation of each test score with a factor obtained from the reliability estimates, was the criterion adopted to determine which scores were included in the final factor-sum. Test scores which had an item-total correlation below .30 (Ebel's cut-off criterion) were generally not included in the total factor-sum-score.

Hypothesis testing statistical analysis of the data

A correlational approach was implemented to assess the familial aggregation in attention test performance. Pearson product-moment correlations were obtained among the three familial groups: parents, siblings and probands. Three pairs of correlations were obtained for each attention factor in each step: correlation between parents and probands scores, correlation between parents and siblings scores and correlation between siblings and probands scores for each of the four scales measured. Since the correlation coefficients indicate the degree of association between the scores of the subjects, t-tests to assess the statistical significance of the correlations were computed. This procedure was repeated including gender as a variable.

The correlations were computed on the combined fathers and mothers mean scores and on the two parents separately in each one of the comparisons. The same procedure was used for the brothers and sisters scores. In addition, a separate analysis was done pairing the proband and siblings by their respective gender. A separate t-test was computed for the data obtained from the parents in this current study and data from a group of adult control subjects of similar mean age.

Table 10 provides an itemized dscription of the probands, (N=14) in the current study.

Table 10: Probands by Selected Characteristics (N=14)

FAMILY #	DIAGNOSIS	GENDER	AGE	ONSET	TREATMENT
1	PM	BOY	8	1989 (AGE 7)	Valporal
2	PM	BOY	13	1988 (AGE 11)	Valporal
3	PM	GIRL	11	?	Valporal
3	PM	GIRL	8		
4	PM2	GIRL	13	1983 (AGE 6)	None
4	PM2	GIRL	10	1982 (AGE 2)	None
6	PM	GIRL	11	1988 (AGE 9)	Depalept
7	PM	BOY	8	1988?	Depalept
8	PM2	GIRL	8	–	–
9	PM2	BOY	12	1981 (AGE 3)	None
10	PM2	BOY	11	1988 (AGE 9)	None
11	PM	GIRL	9	1990 (AGE 9)	Valporal
13	PM	BOY	13	1989 (AGE 12)	Zarontin
14	PM	GIRL	13	1989 (AGE 11)	Depalept

All testing was performed in June -July 1990
Total families= 12

PM=9 petit mal currently treated 5 girls and 4 boys
PM2=5, petit mal not treated , early onset, 3 girls and 2 boys

The probands were split into two groups: absence epilepsy (PM) currently in treatment and receiving medication; absence epilepsy of early onset (PM2) with no symptoms and not medicated; and controls. The U-test on the PM and the PM2 groups were not statistically significant indicating that the two groups seem to be similar. However, given the size of the groups it was decided to pull the two petit mal diagnoses together and exclude the attention deficit disorder (N=1) and complex partial cases (N=1).

Differences in the level of attention test performance by group and by gender among the probands, parents, siblings and adult control subjects also were obtained, using ANOVA procedures.

Adult normal healthy Israeli control sample

A sample of adult subjects (N= 23, 15 females and 8 males) was used as a control group for the parents of the current study. This sample of adult controls was collected in Israel for another NIMH study and sections of the same attention Battery of tests were used to assess their performance. Only comparisons for the CPT tests results will be presented.

CHAPTER IV

RESULTS

This chapter presents the analyses and results of the study. First, the reliability estimation of the internal consistency of the four subscales in the NIMH-Neuropsychological Attention Battery will be presented for the American sample and for the sample of Israeli families included in the current study. Second, the research questions and the results of the correlational analyses of the probands, parents and siblings will be presented. Third, the results of the group comparisons (probands, parents and siblings) will be reported.

Reliability estimates: the American sample

The NIMH Neuropsychological Attention Battery previously had not had a complete estimation of its psychometric properties. Consequently, the first step in the current research process was to obtain reliability estimates from samples of subjects that were collected at NIMH. The next step was to obtain reliability estimates for the sample of Israeli families of children affected with absence epilepsy. An estimation of the validity of the Battery was attempted only for the larger sample. Cronbach *alpha* coefficient was used as an index of internal consistency. Alpha coefficient is a function of item/test score covariances.

Reliability estimates were obtained from the independent large sample of 223 adult American subjects (146 patients and 77 controls, of those 178 females and 45 males) collected at the NIMH laboratories (See Table 11).

Table 11: Reliability-Internal Consistency of Subscales for the American Sample [NIMH]

RELIABILITY Scales/elements of attention	TOTAL N=223 **Alpha**	PATIENTS N=146 **Alpha**	CONTROLS N=77 **Alpha**
ENCODE 2 sub-tests scores	0.57	0.60	0.29
WAIS Arithmetic (single score)	0.84*		
WAIS Digit Span (single score)	0.83*		
FOCUS-EXECUTE 4 sub-tests scores	0.69	0.66	0.72
Trail Making Test (two scores)	0.75	0.75	0.69
Stroop Test (three scores)	0.84	0.86	0.70
Letter Cancellation Test (12 scores)	0.77	0.78	0.74
WAIS Digit Symbol Test (single score)	0.82*		
SUSTAIN 2 sub-tests scores together CPT "X" (4 scores) CPT "AX" (4 scores)	0.58	0.62	0.41
SHIFT sub-test scores			
Wisconsin Card Sorting Test (3 scores)	0.65	0.64	0.64

*The reliabilities are from the WAIS-R

The reliability estimates for the sample of patients were, in general, better than among controls. Discriminant analysis was performed on the sample of patients, the discriminatory power of the Battery was 70%, which is a further indication of the higher reliability of the scales especially smong the

patients. (See Table 11).

Reliability estimates: the sample of Israeli families

The reliability estimates for the sample of families studied at the Neurology Clinic both in Jerusalem and in Tel Aviv are shown in Table 12 comparing the parents, probands and siblings in the families that were tested. This table shows the *alpha* coefficients for the four subscales. The reliability estimates for the parents (r=.64) and the siblings (r=.60) groups are better than for the probands (r=.36) in the ENCODE scale. The reliability estimates for the parents (r=.88) and probands (r=.70) are better than the siblings group (r=.34) in the FOCUS-EXECUTE scale. The estimates for the SHIFT scale are low in the three groups. The estimates for the SUSTAIN scale are similar in the three groups (.68 for parents, .67 for probands and .67 for siblings), as observed in Table 12.

Table 12: Reliability-Internal Consistency of Subscales for the Sample of Israeli Families

RELIABILITY Scales /elements of attention			
ENCODE (3 scores) WAIS Arithmetic WAIS Digit span Wechsler Memory test*	PARENTS N=16 Alpha=.64	PROBANDS N=14 Alpha= .36	SIBLINGS N=15 Alpha=.60
FOCUS-EXECUTE (7 scores) Stroop word, color and C-W Digit Symbol Trails "A" and Trails "B" Hebrew Letter Cancellation**	PARENTS N=16 Alpha=.88	PROBANDS N=14 Alpha=.70	SIBLINGS N=15 Alpha=.34
SHIFT (6 scores) Wisconsin Card Sorting Test # of errors, perseverations, corrects, categories completed.	PARENTS N=16 Alpha=.37	PROBANDS N=14 Alpha=.39	SIBLINGS N=15 Alpha=.39
SUSTAIN (16 scores) CPT test "X": corrects, omissions, errors, mean reaction time "AX": corrects, omissions, errors, mean reaction time "degraded X": corrects, errors omissions, mean reaction time "auditory X": corrects, omissions, errors, mean reaction time.	PARENTS N=16 Alpha=.68	PROBANDS N=14 Alpha= .67	SIBLINGS=15 Alpha=.67

**In the probands and siblings groups the scale includes the "Digit number cancellation test for children instead of the Hebrew letter cancellation" test.

Research question

The research question had been stated as follows: Does the deficit in sustained attention encountered in the probands also exist in the siblings and/or parents who do not have absence epilepsy? Or stated differently, is it possible to identify a marker of attentional dysfunction among family members of probands affected with absence epilepsy that would suggest a familial transmission of the disorder? In statistical terms, this question could be formulated as follows: is the magnitude of the correlations sufficiently high to support an association in the level of performance among the family members. In other words, are the correlations of the scores of the parents with siblings, parents with probands and siblings with probands different from zero?

Correlational analysis:

The final analysis was limited to 12 families with 14 probands since two families contained two affected siblings. Significant correlations were observed with the SUSTAIN factor only. In the SUSTAIN factor, parents' (mother and father together) scores correlated significantly with the male probands scores ($r=.87$, $p< .05$). Male probands correlated significantly with the scores of their siblings, male and female ($r=.96$, $p<.01$, $r=.98$, $p<.02$). When the parents were individually correlated with the probands, the results showed that the scores of the fathers and probands (male and female) were strongly correlated, ($r= .95$, df 3, $p<.02$). The correlation of the male proband with father was strong but not statistically significant ($r= .94$, df 3).

Table 13: Pearson Correlations among the Family Members on Attention Measures

	Proband & Brothers	Proband & Sisters	Proband & Mothers	Proband & Fathers	Siblings & Mothers	Siblings & Fathers
ENCODE	.25	.13	.58	.02	.78	.01
FOCUS-EXECUTE	.05	.06	.79	.28	.95*	.53
SHIFT	-.76	.30	.59	.18	.53	.47
SUSTAIN	.25	.80	.11	.95**	.25	.76
REACTION TIME	-.22	.82*	.20	-.59	-.08	.79
% CORRECTS	.25	.42	.40	.06	.09	.43
% ERRORS	.06	.21	.35	-.06	.23	-.02

* p<.05
**p<.02

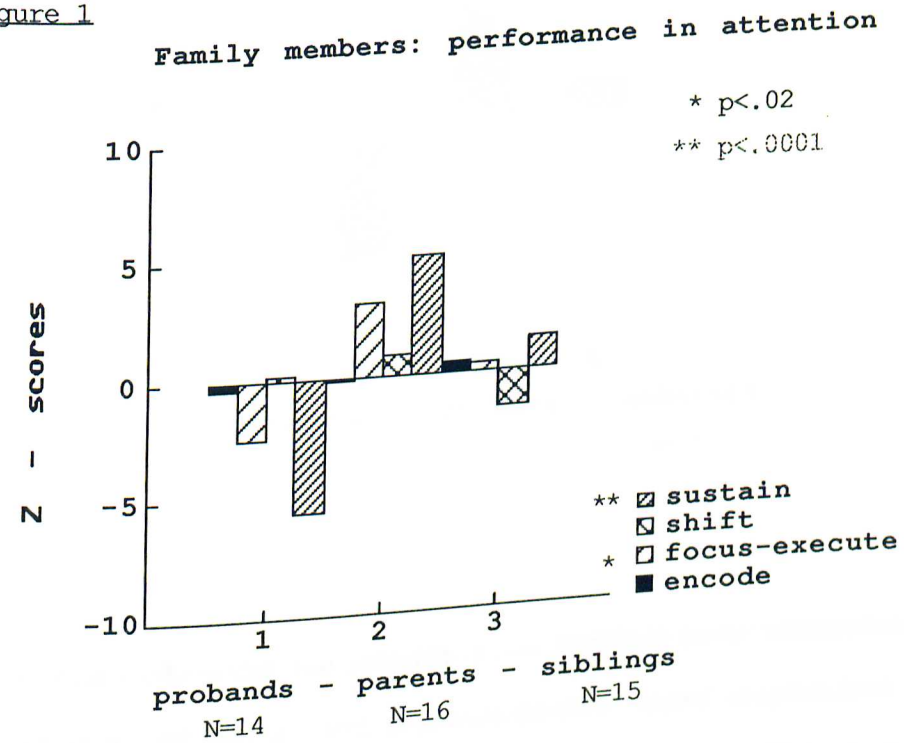
The correlation between siblings and probands was statistically significant (r= 63, df:10, p<.02). The correlation on total reaction time (TRT) measures for the four CPT tasks (visual "X", visual "AX", degraded "X" and auditory "X") among the scores of the sisters and of the probands were statistically significant (r= .82, df:4, p<.05). Other correlations were high too but did not reach statistical significance (See Table 13).

Comparisons among family members

The performance scores of the three groups, parents, probands and siblings were compared with an Anova test on the four factors: encode, focus-execute, shift and sustain and the three groups. Significant differences among the probands and relatives were observed on two of the factors SUSTAIN

(F=11.317, p<.0001), see Figure 1 and FOCUS-EXECUTE (F=7.152, p<.002), see Figure 4.

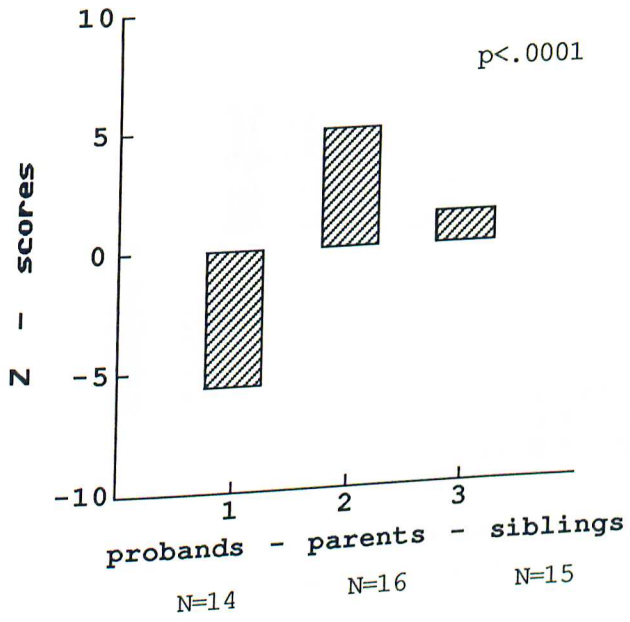
Figure 1



Mean comparisons by group (parents, probands and siblings) are presented for the SUSTAIN factor (see Figure 2).

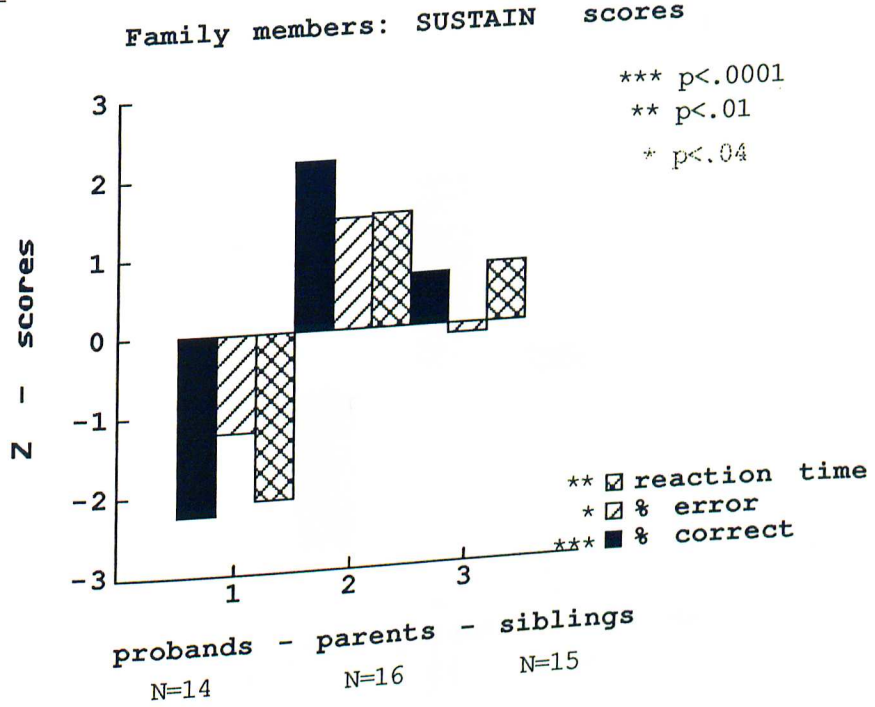
Figure 2

Family members: performance in SUSTAIN factor



Significant differences are observed in the SUSTAIN factor composites among the probands-siblings and probands-parents: mean reaction-time, percentage corrects and percentage errors. Probands are consistently lower in the three composites (See Figure 3).

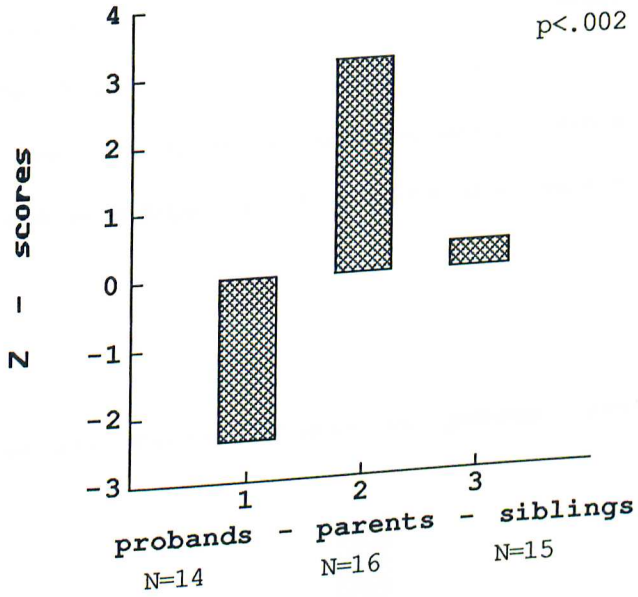
Figure 3



Statistically significant differences by group pairs were observed in the FOCUS-EXECUTE factor when probands and parents and, parents and siblings were compared; Probands were consistently lower (See Figure 4).

Figure 4

Family members: performance in FOCUS-EXECUTE factor



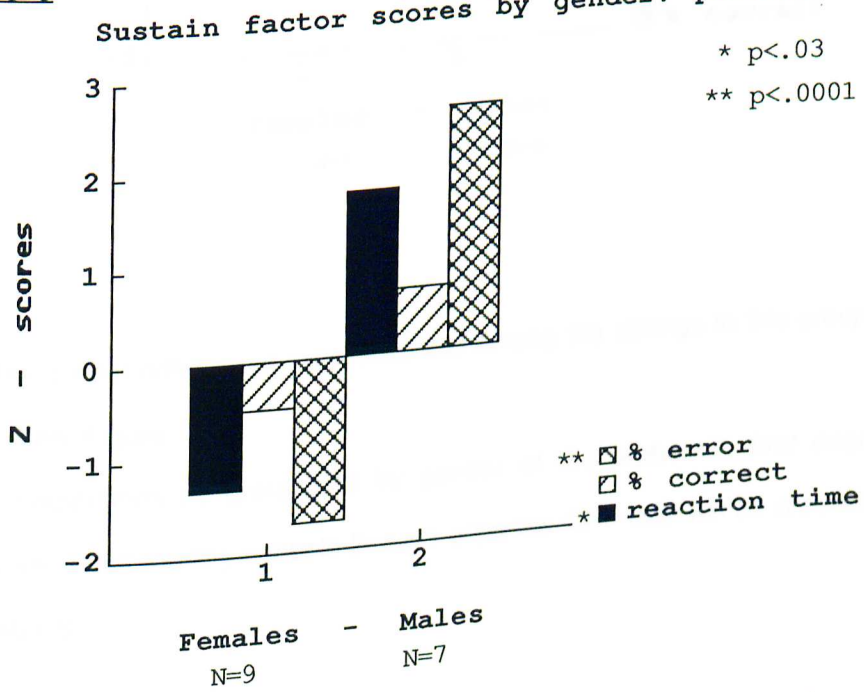
Covariate effects

The variables of gender, age, years of schooling and group were tested for their effects as covariates on the four factors. The results indicated that age did not have statistically significant effects on the scores in any of the four factors. Years of schooling had a statistically significant effect on the FOCUS factor ($F=18.3$, $p<.0001$). Group (parent-proband-sibling) has a significant effect on the scores in the SUSTAIN factor ($F=3.57$, $p<.04$) and the SHIFT factor ($F=5.74$, $p<.008$). Gender had a statistically significant effect on the SUSTAIN factor ($F=5.376$, $p<.028$).

Gender comparisons: parents, probands and siblings

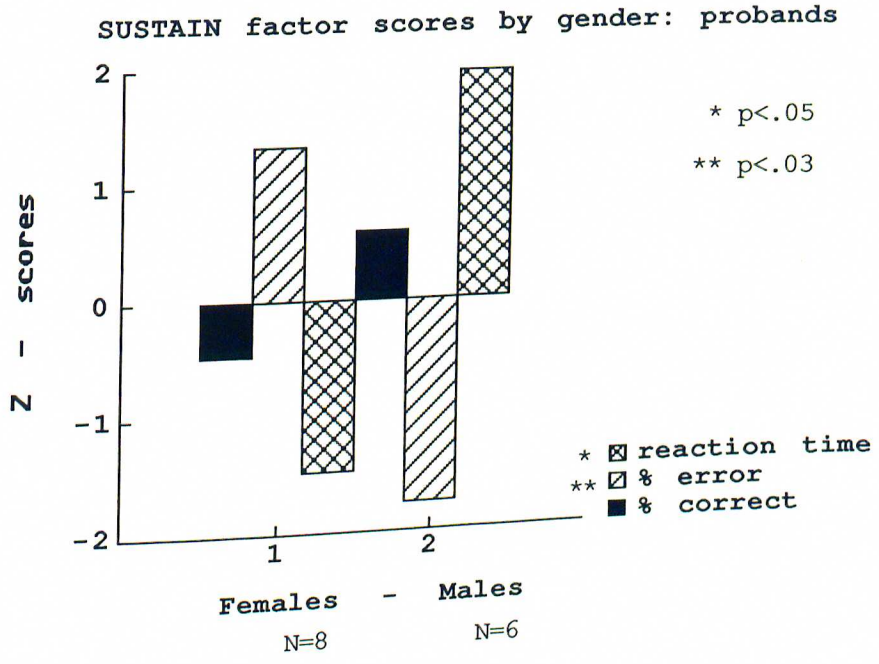
When gender was included as a variable and group comparisons of parents, probands, siblings were made, the results indicated statistically significant gender differences for the SUSTAIN factor only. The gender differences were found among the parents of the epileptic children, specifically in reaction time and percentage of errors, as indicated in Figure 5.

Figure 5



Gender differences were also observed in the SUSTAIN factor among the probands in reaction time and percentage of error in the CPT tasks as shown in Figure 6.

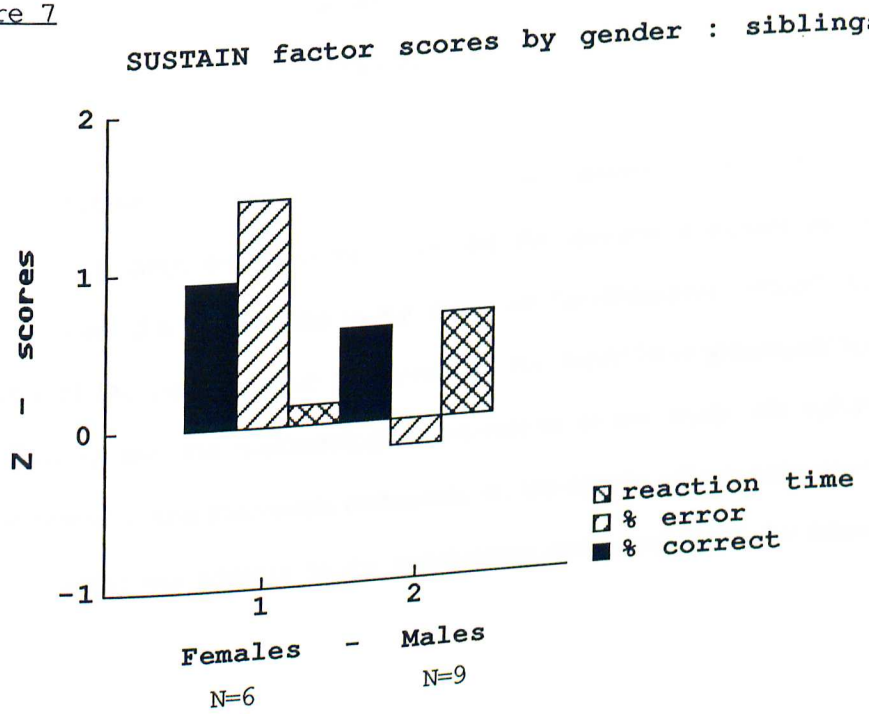
Figure 6



No gender differences were observed among the siblings in this group of families.(See Figure 7).

Comparisons by group and by gender of the probands, first degree relatives and adult healthy controls in each separate CPT task will be presented in Appendix B.

Figure 7


SUSTAIN factor scores by gender : siblings
2
1
0
-1
Z - scores
reaction time
% error
% correct
1
2
Females - Males
N=6
N=9

CHAPTER V

DISCUSSION

This chapter discusses the results in the following order: First, the summary of the findings are presented. Second, the research questions will be addressed. Third, the significance of the study will be discussed. Fourth, the investigation of the psychometric properties of the NIMH-Neuropsychological Attention Battery and the methodological limitations of the study will follow. Fifth, some practical and theoretical comments on the results will be suggested. Finally this chapter will address to the conclusions and suggestions for future research.

Summary of findings

Partial support was found for a pattern of familial association in SUSTAIN, one of the four factors in attention performance for children affected with absence epilepsy and their first degree relatives. There were statistically significant correlations between the scores of male probands and those of both parents (analyzed separately) and between the scores of the probands and their siblings in the SUSTAIN factor. Therefore, the answer to the question raised by the hypothesis is positive. The tendency of the results seem to support the familial aggregation of attention disorders. Additional subjects, however, are needed to further explore the question and test the power of the results obtained since our sample of families is small Furthermore, no comparison group was available.

Most of the statistically significant results obtained after testing for the

differences in performance were found in the comparison of parents with probands and between parents with siblings, in the SUSTAIN factor and in the FOCUS-EXECUTE factor.

Discussion of the research questions

The research question was stated as follows: Does the deficit in sustained attention encountered in the probands also exist in the siblings and/or parents who do not have absence epilepsy? Or stated differently, is it possible to identify a marker of the attentional dysfunction among family members of probands affected with absence epilepsy that would suggest a familial transmission of the disorder?

Statistically ignificant correlations were observed between father and siblings (r=.96, p<.01), and between male probands and parents (r=.87, p<.05). Probands and sisters were highly (r=.80, 64% of variance explained), but not significantly correlated on the total factor score in SUSTAIN. The SUSTAIN factor in the model of attention in the Battery used for this study is the standardized sum of 12 scores from four tasks, three visual and one auditory. Each task assesses four variables: reaction time, number and percentage of correct hits to the stimuli, number of omissions and number and percentage of errors. Three of them, reaction time, percentage of correct hits and percentage of errors are combined for the sum score.

In order to specify in which of those measures the differences were found, a separate composite-reaction time was computed: the sum of the reaction time scores in the four tasks. A second composite was the sum of the percentage of correct hits in the four tasks and a third composite, the sum of

the percentage of errors in the four tasks. Number of omissions was not included in the factor-sum-score because it was observed to have a low item-total correlation in the reliability analysis and as a consequence was dropped from the rest of the analyses. All the analyses were performed on the total SUSTAIN factor and on the three composites in order to observe the differences within each of them in the families.

When probands and sisters were correlated on their scores on the reaction time composite, the correlations reached statistical significance (r=.82, df: 4, p<.05). Other correlations between probands-mothers only, probands-fathers only, and siblings-fathers only in FOCUS-EXECUTE factor were high (r=.92, r=.96 respectively) but did not reach statistical significance. The sample sizes in the cells were small and therefore many correlations although high, failed to achieve statistical significance. Probands scored lower than the parents and the siblings on the tasks comprising the SUSTAIN factor.

As indicated earlier in this chapter no other studies have been reported on the familial aggregation of attention performance in first degree relatives of children affected with absence epilepsy. There are studies reported from other areas of research that hypothesized familial aggregation of certain impairment as markers of a disorder, for example in schizophrenia.

Similarities among first degree relatives in measures of attention were reported in studies of schizophrenia. A preliminary report (Mirsky, Lochhead, Jones, Walsh & Kendler, 1991) on a sample from a county in western Ireland indicated that schizophrenics and their first degree relatives perform more poorly on the attention tests (NIMH Attention Battery) when

compared to a group of control subjects. In this Irish sample, two of the attention factors FOCUS-EXECUTE and SUSTAIN discriminated strongly between the groups. In addition, a study by Kendler, Ochs, Gorman, Hewitt, Ross & Mirsky (1991), found evidence of similarity in the performance on attention tests (NIMH Attention Battery) in pairs of twins tested in order to assess the existence of Schizotypal Trait and Personality Disorder. Correlations in monozygotic twins were significantly higher than among dizygotic twins on the measures of attention. The findings in the studies in schizophrenia support the assumptions on the existence a familial pattern expressed at a behavioral level, specifically on the attentional dimension.

In a recent study in Germany (Degen, Degen & Roth, 1990), waking and sleep EEG abnormalities were found in the siblings of children affected with idiopathic absence epilepsy in a higher proportion than among siblings of children affected with symptomatic absence seizures. Idiopathic epilepsy designates the type of epilepsy that could not be linked to an obvious cerebral cause. Symptomatic is the term used for the type of epilepsy in which the seizures result from a well defined pathological condition of which they are a symptom. A sample of 22 patients with idiopathic absence and their respective 50 siblings was tested with waking and sleep EEG. The percentage for males was significantly higher than for females and some had a history of one or more family members affected with epilepsy. The EEG findings indicated that epileptic activity was observed in 72% of the siblings of idiopathic absence patients (ages 7-14 years) and a higher proportion of males than of females. The results of this study support the hypothesis of genetic transmission of EEG abnormalities. No cognitive functions were assessed in this sample. The

findings in this EEG study support the assumptions underlying the hypothesis in the current study concerning the familial aspect of this disorder. The findings in the studies in schizophrenia support the assumptions of the existence of a familial pattern expressed at a behavioral level, specifically on the attentional dimension.

Comparisons by group and by gender

Some interesting questions and findings emerged when the variable gender was included in the analyses. Each group, i. e., parents, siblings and probands were compared on the SUSTAIN factor by gender. These comparisons were performed on each one of the four tasks in the CPT. The test is a combination of three visual tasks: "X", "AX" and "degraded X" and one auditory task. Three scores were obtained from each task: reaction time, percentage of correct responses and percentage of errors. Each one of the groups was compared on each of those scores. A total of twelve comparisons by gender were performed. The parents were compared, in addition, to a sample of adult-control subjects from a longitudinal study on schizophrenia that has been recently completed in Israel using, among other measures, the NIMH Neuropsychological Attention Battery. (See Appendix B).

The comparison between the parents of the children with absence and the Israeli adult-control subjects yielded no differences in the SUSTAIN measures. However, those same variables when compared by gender within the two groups yielded statistically significant differences. Females in the 'parents' group had slower reaction times and had a lower percentage of correct hits than males. This finding led to the next question: will the same gender

differences be found in these areas of performance among the probands and the siblings in the affected families? The comparison by gender suggests that the same pattern of longer reaction time in females exists in the CPT "degraded X" task, among the parents and among the probands, regardless of age. These results are only suggestive of the existence of a familial pattern; however, it is still not clear if it is specific to absence epilepsy and to the families with the affected child.

Some genetic studies on familial patterns in epilepsy may potentially clarify the findings. For example, studies of the risk of seizure disorders in the offspring and siblings of affected subjects are helpful in this regard. These data butress the underlying assumption regarding the possible familial aggregation of the cognitive or attentional performance in families of children affected with absence epilepsy. The risk of seizure disorder of any kind, among the siblings and offspring of probands, is three times higher than in the general population (11.0% in siblings and 14.3 % in offspring of the probands). Annegers, Hauser and Anderson, 1982; Doose and Baier, 1987; Doose and Baier, 1989, reported that from the 10% of the sibling's risk for any seizure type, 25% of them manifested absence epilepsy. Doose and Baier (1989) stated that considering all epilepsies with absences the risk of the probands' siblings is largely due to the "maternal effect". The same authors indicated that a propensity in the maternal generation (mothers or mothers' siblings) with early onset seizures results in a distinctly higher risk in the probands' siblings than in an affected paternal generation. If the mothers showed an abnormal EEG (spikes and waves, photosensitivity, dysrhythmia) the risk in the probands' siblings was higher. "The maternal EEG is, (of all the

parameters tested in Doose and Baier's study), the best predictor of siblings' risk", (pp.38). This suggestion by Doose and Baier (1989) is further explained as follows: only 26% of the mothers with an abnormal EEG recording manifested seizures. So, the EEG (i. e. more sensitive) is an appropriate measure for detecting "seizure liabilities" (pp. 38).

In the current study no EEG recordings were available from the parents in order to replicate Doose and Baier's findings. However, the results of the comparison by gender in the attention performance in the Battery indicated a similar pattern, (see Appendix B). In the SUSTAIN factor tasks the similarities emerged among the mothers and the female probands. The "maternal effect or female effect" concept may be applied in order to explain these results. Thirty six percent in the sample of twelve families in this study had a history of seizures in the same family unit or among close relatives. One family with two female probands had reported epilepsy via the grandparents' sister; one family had the probands' (boy) younger sibling (boy) affected too; one family of two female probands had an affected twin brother that could not be included because of his low functioning level and one family of a female proband reported on two affected paternal aunts. The numbers are too small to obtain statistically significant results; yet, the data on the incidence of epilepsy cases among the families tested and the results from the assessments are suggestive of possible intriguing relationships among the variables and provide some support to the hypothesis about familial aggregation of the attentional disorder.

Significance of the study

To date, no other study has examined the cognitive attentional

performance of all family members of a child affected with absence epilepsy or with any other type of epilepsy.

Studies of cognitive functioning have consistently indicated that children affected with absence epilepsy show specific sustained attention and cognitive performance impairments (Mirsky, Primac, Ajmone Marsan, Rosvold & Stevens, 1960; Mirsky & Van Buren, 1965; Fedio & Mirsky, 1969; Stores, 1981; Giordani, 1985). None of these studies addressed the question of the familial aggregation of the disorder as a means of detecting early markers or of assessing the risk of the same disorder in other members of the same family. Patterns of familial association have been studied for other disorders and specific methodological strategies have been developed in order to assess them. The strategy employed in most of the family studies in the psychological and psychopathological literature (Grunebaum, Weiss, Gallant & Cohler, 1974; Rutschmann, Cornblatt & Erlenmeyer-Kimling, 1977; Asarnow & MacCrimmon, 1982; Nuechterlein, 1983; Mirsky, Lochhead, Jones, Walsh & Kendler, 1991) uses the affected parent as the proband and tests the offspring in order to detect any early dysfunction as a marker of the disorder.

In the case of absence epilepsy, the prevalence rate is highest during childhood. The latest study reporting the prevalence of epilepsy in children and adolescents from birth to age 19 years based on the "active" cases registry in two central Oklahoma counties (Cowan, Bodensteiner, Leviton & Doherty, 1989) is one of the few that calculated the rates for specific epileptic diagnoses. In the Oklahoma study 1,159 cases (0-19 years only) were collected. The overall prevalence rate was 4.71/1,000, slightly higher in males than in females in each age group until after 14 years of age, when the

rates were equal. The total rate for simple absence epilepsy (which is the type of epilepsy considered in the current study) was 0.10 per 1,000 and the age group with the highest prevalence was 10-14 years. Absence epilepsy, as well as other generalized epilepsies, was more common in girls (0.12 per 1,000) than in boys (0.08 per 1,000 boys). The results of a follow-up study on 100 patients affected with different types of generalized seizures (37 males, 46 females, age range from 5.3 to 24.3 years) indicated that 64% of the patients with absence were free of seizures at follow-up after 9.5 years, the age range at follow-up was 14.8 to 35.8 years (Sato, Dreifuss, Penry, Kirby & Palesch, 1983). A second follow up study by Dieterich, Baier, Doose and Tuxhorn (1985) of patients with absence epilepsy up to the age of 45 years indicated that, with modern therapy, 78% of the cases were free of seizures 10-20 years later. The prevalencerates reported and the results of follow-up studies are an indication that the chance of finding an affected adult is much lower, since absence epilepsy generally is considered to disappear after the age of 40 years.

Since the current study was concerned with absence epilepsy, a condition that occurs primarily in childhood, it was decided to ascertain the proband-children first and then to request the family participation after the selection of the case. This approach may be more difficult, because the expected degree of refusal is higher. Often parents are not very interested in testing their healthy children or in being tested themselves because, as some of them said, "we do not want to go through this anxiety".

Methodological limitations

On the one hand the sample size in this study was small and in some cases it was not possible to study all family members. On the other, there are no data on a group of control children. This is a limitation which is common to clinical samples and which reduces the power of the results. Nevertheless, the fact that the results obtained were statistically significant even with this small number of families is an indication of the power of the effect. One of the hypotheses in the study of families of children with absence epilepsy concerned correlations between the scores of the relatives and the scores of the probands. The fact that few statistically significant correlations were observed may be due to the small sample size. The same limitations affect the reliability estimation of the scales used.

From a strictly measurement and statistics point of view any reliability estimate in a scale should aim to an r=.80 level of precision, however "there are no hard fast rules for what constitutes a minimally acceptable value" (Crocker & Algina, 1986, pp. 132); some authors accept an estimate of r=.50. When a scale is undergoing testing and revisions, or used in research settings, the level of the estimations may vary and frequently changes may be made in the specific items included.in analyses. Consequently, the reliability estimations for the larger NIMH sample and for the sample of families are not identical. However, regardless of the sample size, reliability for the SUSTAIN factor was higher in the sample of families, (r= 58, NIMH sample, and r=.68 for parents, r=.67 for probands and for siblings as well). The FOCUS-EXECUTE factor estimates for the NIMH sample was r=.69; for the parents, r=.88, probands r=.70, and siblings, r=.34. Those two factors are

particularly important and appear to be more sensitive to group differences. Those factors seem to detect the correlations among parents and probands, thus constituting one of the main preliminary findings in the current study. Moreover, in the current sample of Israeli families, testing was performed in Hebrew, and some cultural and language differences might be expected. All the WAIS subtests had local norms, this was true for the Stroop test as well. All of the tests were used in another Israeli sample but only for adults. Some of the tests are expected to be more "culture free", as the CPT. However, no comparison data were available. To be noted too is that the sample size affects the reliability estimates; more subjects add variability to the data. Also the number of scores included in each scale affects the level of estimation. Thus,more scores in a scale may elevate the reliability estimate. The reliability estimation of the sample in the current study was performed while taking into consideration the above limitations.

Practical and educational implications

One of the suggestions derived from this study of attention is that in a sample of children affected with absence epilepsy the number of tests administered may be reduced almost exclusively to the tasks of the Continuous Performance Test; these appear to be the most sensitive of all for the detection of the disorder. Thompson (1987) indicated that learning problems occur in an estimated 5-50% of children with epilepsy, specially among the therapy-resistant epilepsies. Absence epilepsy is the most simple of the epilepsies and can be successfully controlled with a single drug (mono-therapy). It should be stressed however, that cognitive impairment in children with absence epilepsy

is not necessarily confined to spike-wave bursts but may occur between them (Mirsky, 1989). Stores (1990) suggests that when there is no convincing evidence of significant daytime EEG events, attention should be focused on the sleep periods to investigate if there is poor sleep quality or seizures that affect the daytime functioning. Studies reported earlier in the review of the literature indicated that the attentional impairment, even if considered a "transitory cognitive impairment", affects the child's learning capacities. Sub-clinical seizures have been shown to disturb cognitive and psychological functions and increase the number of errors during tests (Kastelijn-Nolst Trenite, Bakker, Binnie, Buerman & Van Raaij, 1990; Binnie, Channon & Marston, 1990).

Preliminary results from an ongoing study by Dekker, Aldenkamp and Alpherts (1989) on a sample of 145 learning disabled children with epilepsy (of all types) indicated that three types of learning disability were observed in this group compared with children without neurological disorders, with learning disabilities and with normal controls. The types are: (1) "Memory deficit type, with impairment in short-term memory and memory span that led to disorders in language consolidation; (2) "Attention deficit type" that generates underachievement in academic skills; (3) "Speed factor type" that shows slowness in information processing especially in complex tasks. The two most common underachievement areas in all the types are reading and arithmetic. From all the affected cognitive domains in the varieties of learning disability, speed of information processing, memory, vigilance, alertness, sustained and focused attention and motor fluency are particularly vulnerable to the epileptic condition. There are few studies that are concerned with the

specificity of learning disabilities in epilepsy. In the last years, with the inclusion of neuropsychological assessment, the observations are more specific.

The study of children affected with absence epilepsy serves as a unique opportunity to assess a specific impairment which is probably common to all epilepsies. The information about the existence of a subtle familial pattern of attention impairment may guide the prevention of more difficulties. By nature, sustained attention difficulties tend to accumulate and children seem to be chronically "under-aroused" (Stores, 1978). The transient short inattentive periods, if they occur during class, during instructions or in social verbal interactions, accumulate and led to general slowness, underachievement, or to a large number of errors during the performance of tasks in the classroom. Teachers informed about those difficulties may be better able to assist the children without misinterpreting their behavior as due to lack of motivation or laziness. Parents informed about the possibility that the siblings of their affected child may be at risk for the same impairment will have the opportunity to intervene earlier in order to detect a possible difficulty. There is some limited experience with remedial teaching for the child with epilepsy; instructional guides for teachers were published in Holland and Australia (Besag, Mills, Wardale, Andrew, & Craggs, 1989). The most novel technology is a miniature spike-wave detection system that produces a visual or auditory signal to the patient and the teacher whenever a discharge occurs, specially to detect interictal discharges (Besag et. al.,1989). Simultaneous auditory and visual instruction inputs are suggested in order to enhance the teaching material.

Conclusions and suggestions for future research

Some positive indications of familial markers of performance in attention tasks were observed. The SUSTAIN factor (assessed with the CPT) was a sensitive measure of sustained attention and in this study it detected the familial behavioral pattern of reaction time, percentage of errors, and correct responses in some of the CPT tasks. The same pattern was observed in the mothers and their affected children in the visual modality. The significant correlations between the male-proband and the fathers was an indication of some support for the hypothesis of the familial aspect of the attentional performance level. The results obtained in the current study indicate that SUSTAIN is the only one of the four factors included in the model of attention that discriminates between groups and is sensitive to very subtle impairments. Sustain attention is difficult to measure, it is a basic function for most of the human actions. Attention is needed continuously in daily activity. Sustained attention is needed when a repetitive action is to be performed, when listening to a lecture, when listening to a conversation, when performing such skilled tasks driving and operating machinery. It is vigilance or sustained attention that underlies the learning processes. The inattention or shifting of attention during an activity leads to slower performance and more errors. All the capacities needed in any activity are related to the attentional level of the individual. If this aspect of human behavior is impaired, difficulties may arise in many other cognitive activities.

The CPT is basically a repetitive test, presenting simple and identical stimuli in every trial. The motor action involved is pressing a small device that remains in the subjects' hand; the motor activity is effortless. As some of

the children expressed: "this thing is boring, when does it finish? Is it all that easy?" Most of the other tests in the Battery require more complex cognitive activity and the tests are more interesting. It takes a "boring activity" to test sustained attention, because in only those kind of situations are we able to "test the limits" in an individual. The accumulation of many seconds of inattention is what creates the phenomenon called "attention disorder".

There is almost no doubt, at this stage in our knowledge, that generalized seizures (as in absences) cause a "transitory cognitive impairment" (Aarts, Binnie & Smit, 1984) of some functions, among them an impairment of sustained attention. There is also extensive support for the hypothesis of the genetic origin of absence epilepsy and of the increased risk of the offspring of affected probands.

New and larger sample studies have to be performed on children with absence epilepsy and their relatives in order to test the familial aggregation hypotheses. If outcomes similar to the one obtained in this study are observed it will be possible to state definitely that the impaired performance in sustained attention is a familial indication of the expression of the genetic load. The same gene responsible for a specific type of epilepsy may affect the individual in different ways and not only by the excessive neuronal discharge seen in spike-wave bursts.

The distribution of the impairment of attention in the general population is not known. No comparison to the frequency of this condition among the relatives of the probands affected with absence epilepsy and the rest of the population can be made. The question about the similarities and differences among the children with absence and children or adults with

Attention Deficit Disorder also may be assessed in future research. In the meantime, it is possible to suggest that they might be the same phenomenon but expressed at different levels.

APPENDIX A

NEUROPSYCHOLOGICAL SUMMARY SHEET

NIMH ATTENTION BATTERY

NIMH NEUROPSYCHOLOGICAL SUMMARY SHEET

ATTENTION BATTERY

Name_____

Date of birth_____ Gender_____

Age_____ Test date_____

Tester_____

****

ENCODE

DIGIT SPAN RAW SCORE____ SCALED SCORE___

ARITHMETIC RAW SCORE____ SCALED SCORE___

WECHSLER MEMORY SCALE MENTAL CONTROL

BACKWARD___ ALPHABET___ COUNT/3 TOTAL SCORE____

****

FOCUS-EXECUTE

DIGIT SYMBOL RAW SCORE_____ SCALED SCORE_____

STROOP NUMBER CORRECT

WORDS _____

COLORS _____

COLOR/WORD _____

LETTER CANCELLATION

HEBREW VERSION NUMBER CORRECT_____

TRAIL MAKING TEST

TMT PART A_____SECONDS TMT PART B_____SECONDS

****

SHIFT

WISCONSIN CARD SORTING TEST

CORRECTS_____# ERRORS_____# CATEGORIES COMPLETED_____

PERSEVERATIVE ERRORS_____

****

SUSTAIN

CONTINUOUS PERFORMANCE TEST (STANDARD PARAMETERS)

	CRITICAL	CORRECTS	INCORRECT	OMISSIONS	MEAN RT
CPT X					
CPT AX					
CPT DEG					
CPT AUD					

ADDITION FOR CHILDREN

DIGIT CANCELLATION TEST

Part 1

(3 - 7) Time (in seconds)_____

Omission errors_____

Comission errors_____

Part 2

(2 - 4) Time (in seconds)_____

Omission errors_____

Comission errors_____

Intrusions_____

****

WISC-R CODING

	Time	Score
A (for children under 8)	120"	(0-50)
B (for children 8 and older)	120"	(0-93)

Coding A: score including time bonus for perfect performance

Time in seconds	Score
111-120	45
101-110	46
91-100	47
81-90	48
71-80	49
1-70	50

LIST OF TESTS TO ADMINISTER

BATTERY FOR ADULTS

ID Number: _____

___ Digit Span

___ Digit Symbol

___ Arithmetic

___ Memory Wechsler

___ Letter Cancellation Test (Hebrew)

___ Trail Making Test A, B

___ Wisconsin Card Sorting

___ Stroop Test

___ CPT X

___ CPT AX

___ CPT DEG

___ CPT AUD

___ Questionnaire

BATTERY FOR CHILDREN

ID Number: _____

___ Coding, A and B

___ Arithmetic

___ Digit Span

___ Digit Cancellation.1,2

___ Memory Wechsler

___ Trail Making Test A, B

___ Wisconsin Card Sorting

___ Stroop Test

___ CPT X

___ CPT AX

___ CPT DEG

___ CPT AUD

___ Questionnaire

DIGIT CANCELLATION TEST: FORM I (3-7)

1 8 3 0 0 4 9 4 2 2
6 3 5 8 7 4 0 9 1 2
1 9 8 9 0 0 6 7 8 0
9 9 1 3 1 9 3 6 7 2
1 1 2 0 7 5 6 6 2 3
5 7 3 2 3 6 9 8 2 6
6 8 8 4 8 8 3 7 9 7
3 2 0 9 2 8 6 2 1 6
7 4 6 6 8 4 7 9 2 0
4 9 7 8 2 5 5 4 4 3
8 6 7 6 3 4 3 0 5 3
4 7 6 7 3 9 8 4 2 1
5 5 1 3 2 8 2 0 2 1
1 8 7 5 6 4 0 8 0 9
3 6 7 9 2 8 9 7 2 0

DIGIT CANCELLATION TEST: FORM II (2-4)

9 8 6 8 4 2 5 4 2 4
9 4 8 2 8 0 3 3 2 4
8 3 2 6 1 6 8 3 8 0
1 0 0 5 8 6 9 9 0 4
4 3 9 1 9 8 2 3 8 2
4 8 3 7 9 9 3 7 3 2
0 7 8 8 6 6 8 9 2 1
3 7 2 3 1 7 2 4 1 9
4 3 9 4 3 5 1 9 5 4
6 0 2 8 6 0 4 0 7 0
0 6 3 8 4 0 7 1 3 6
0 0 9 3 8 4 3 8 1 5
7 0 6 2 8 1 0 1 2 0
5 6 2 9 6 8 3 6 7 9
7 8 4 7 9 0 2 9 1 6

APPENDIX B

GENDER ANALYSES

(EXTENDED RESULTS)

Comparisons by group and by gender of the probands, relatives and Israeli control sample

In this Appendix, results of the comparisons of the parents in the current sample and the Israeli adult controls are reported. The comparisons by gender of the parents on each of the variables in the SUSTAIN factor (CPT scores) are shown in Figures B1 and B2. The comparison by gender of the probands and siblings in each one of the separate variables in the CPT are displayed in Figures B3 and B4).

When examining the data set of Israeli adult control subjects (from a longitudinal project in schizophrenia), as compared with the parents of the children affected with absence epilepsy, a new question arose. Do parents of children in the sample in this study perform differently from those adult control subjects, and are there any gender differences between the two groups? Consequently, the same question about the gender differences was tested on the probands and the siblings. T-tests comparisons were used as well as Mann-Whitney -U non- parametric test in the cases when the distributions were not normal. Comparisons were performed by group and by gender.

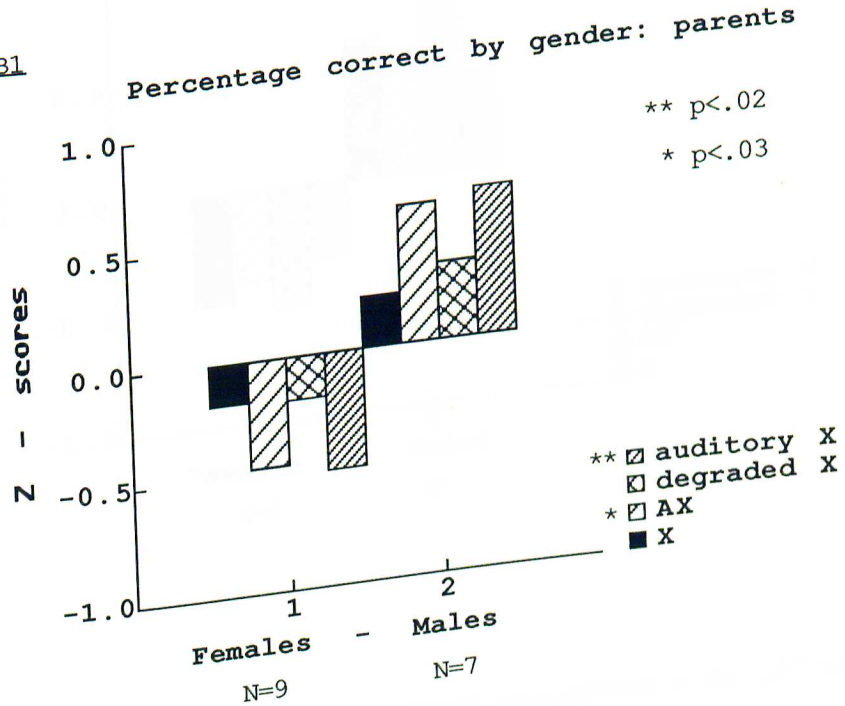
Comparisons by group and by gender between parents and adult-controls

A sample of Israeli healthy adults subjects (N=23, 15 females and 8 males) was included during this analysis as a control group for the parents in the current study. This sample of adult controls was collected in Israel for another NIMH study and most of the tests of the same attention Battery were used to assess their performance. The mean age in this control sample was (32 years). Only comparisons for SUSTAIN (CPT) factor in the the 4 tasks

separately will be presented.

The parents of the children affected with epilepsy in the sample gathered for this study do not perform significantly different on SUSTAIN factor (CPT tasks) when compared with a sample of adult controls of similar demographic background. However, some statistically significant differences were observed when comparisons among the parents were made by gender as indicated in Figures B1 and B2.

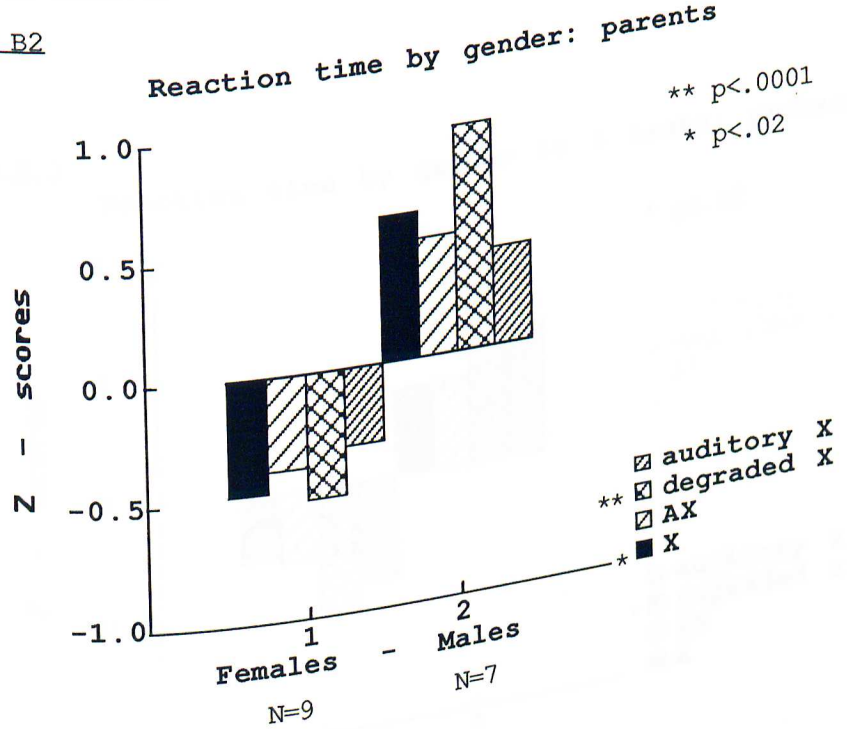
Figure B1



Parents of children affected with absence epilepsy perform differently from other adults when compared by gender. Females reach a lower percentage

of correct hits in two of the four tasks, "AX" and "auditory X" (auditory modality), see Figure B1. Females (mothers) have a longer reaction time than males (fathers) in two of the four tasks, "degraded X" (visual) and 'X' (visual), see Figure B2.

Figure B2

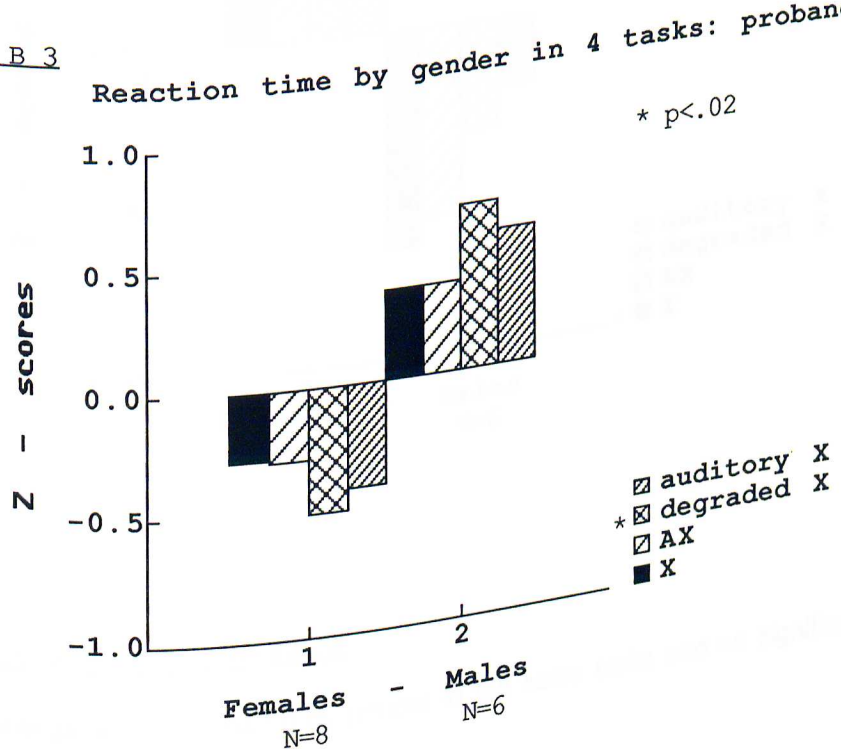


The comparison by gender of the Israeli adult-controls in the CPT tasks showed one statistically significant difference. Females had a longer reaction time than males in the 'auditory X' task(t=2.42, p<.03).and no other significant differences were observed in the other tasks.

Gender comparisons among probands

Probands were compared in the 4 tasks separately in order to test for any differences by gender. Significant differences in reaction time scores in the "degraded X", visual modality task was observed (t=2.30, df 10, p<.02) Females (proband children), have a longer reaction time than males (proband children), as observed in Figure B 3.

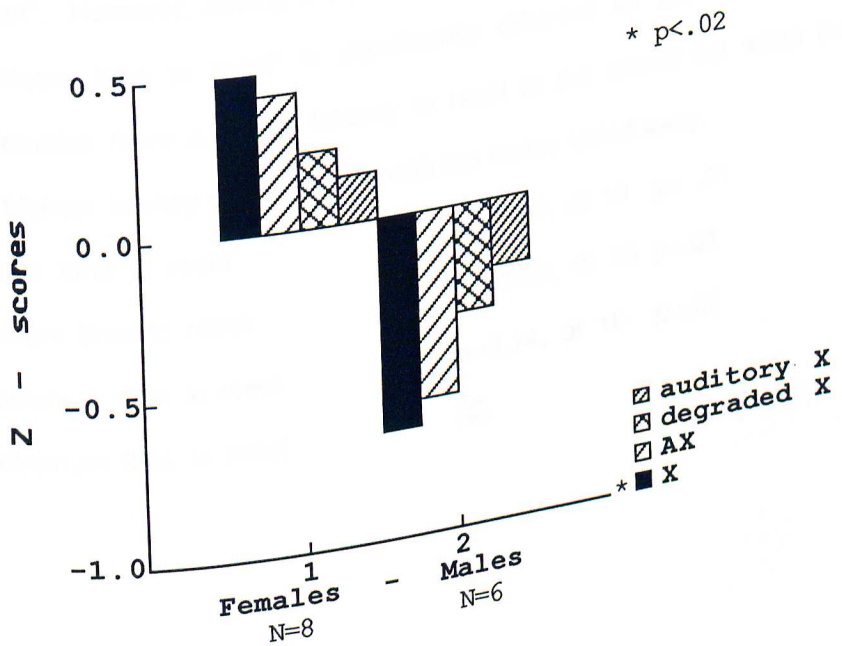
Figure B 3



A significant difference by gender among the proband children in the percentage of error in the CPT'X' task was observed, indicating that female probands tend to make less errors in that task, (see Figure B4). No other

differences by gender were observed.

Figure B4



Gender comparisons among siblings

Siblings were compared by gender in the same tasks and no significant differences were observed.

Range of reaction time by gender

In the CPT tasks, each subject had a "mean score of minimum time to react" assessing the latency to react when a stimuli is presented and a "mean score of maximum time to react" assessing the longest latency to react to each

stimuli in each task. Those scores were collected but not included in the SUSTAIN factor-sum . When comparing those two scores by gender, however, some differences were observed following the same pattern as above. Probands, parents and siblings in the sample do not differ on the "mean-score maximum time to react". However, among the probands and only among them, the mean-score minimum time to react" is significantly different for females than for males. Females have a longer latency to react to the stimuli but when they reach the highest latency the difference with the males faded away.

"X" minimum time to react	t= -3.03, df 10 p< .01
"AX" minimum time to react	t= -3.39, df 10 p<.01
"deg X" minimum time to react	t=-3.14, df 10 p<.01
"aud X" minimum time to react	NS

APPENDIX C

DESCRIPTIVE STATISTICS

(TABLES)

Table C 1: Descriptive Statistics, Probands
Standardized scores included in the four Attention factors

N=14
12 families

ENCODE	Females Mean	Females SD	Males Mean	Males SD	Total group Mean	Total group SD
Digit span	0.57	0.74	-0.23	0.65	0.17	0.79
Arithmetic	-0.19	0.84	0.2	0.37	0.01	0.66
Memory	0.38	0.52	-0.51	1.2	-0.07	1

FOCUS-EXECUTE	Females Mean	Females SD	Males Mean	Males SD	Total group Mean	Total group SD
Digit symbol	0.6	1.26	-0.34	0.87	0.13	1.15
Stroop word	-0.6	0.86	-0.52	0.63	-0.56	0.73
Stroop color	-0.6	0.76	-0.5	0.94	-0.56	0.73
Stroop C-W	-0.74	0.55	-0.7	0.5	-0.72	0.5
Trails A	0.02	0.55	-0.66	1.48	-0.32	1.12
Trails B	0.06	0.75	-0.72	1.04	-0.33	0.95

SHIFT	Females Mean	Females SD	Males Mean	Males SD	Total group Mean	Total group SD
WCST corrects	0.22	0.77	0.52	1.39	0.37	1.08
WCST categories	0.18	0.74	-0.23	1.02	-0.03	0.87

SUSTAIN	Females Mean	Females SD	Males Mean	Males SD	Total group Mean	Total group SD
CPT "X"	-0.66	1.38	-0.51	1.04	-0.59	1.17
% correct	0.32	0.48	-1.25	1.67	-0.46	1.43
% error	-0.94	1.07	-0.23	1.19	-0.59	1.14
Reaction time						
CPT "AX"	-0.73	1.16	-0.38	1.26	-0.56	1.17
% correct	0.06	0.35	-1.45	2.12	-0.69	1.65
% error	-0.6	0.92	-0.06	1.1	-0.33	1.01
Reaction time						
CPT "degraded X"	-0.55	1.08	-0.57	1.15	-0.56	1.06
%correct	-0.1	1.16	-0.58	1.14	-0.34	1.12
% error	-1.21	0.57	0.11	1.29	-0.55	1.18
Reaction time						
CPT "auditory X"	-1.37	1.44	-0.29	0.93	-0.83	1.29
% correct	-0.14	0.73	-0.27	0.58	-0.21	0.63
% error	-1.17	1.11	-0.03	1.13	-0.6	1.22
Reaction time						

Table C 2: Descriptive Statistics, Parents
Standardized scores included in the four Attention factors

N=16
12 families

ENCODE	Females Mean	SD	Males Mean	SD	Total group Mean	SD
Digit span	-0.06	1.02	-0.3	0.92	-0.17	0.94
Arithmetic	0.29	1.19	0.02	1.2	-0.01	1.31
Memory	-0.19	0.82	0.16	1.68	0.16	1.15

FOCUS-EXECUTE	Females Mean	SD	Males Mean	SD	Total group Mean	SD
Digit symbol	-0.37	1.25	-0.48	0.93	-0.42	1.07
Stroop word	0.78	0.57	0.41	1	0.56	0.84
Stroop color	0.79	1.01	0.65	0.61	0.73	0.83
Stroop C-W	1.15	0.69	0.27	0.61	0.78	0.77
Trails A	0.36	0.63	0.21	0.7	0.29	0.36
Trails B	0.73	0.17	-0.01	0.8	0.64	0.68

SHIFT	Females Mean	SD	Males Mean	SD	Total group Mean	SD
WCST corrects	-0.53	0.26	0.79	1.46	-0.64	0.91
WCST categories	0.47	0.89	-0.23	1.55	0.18	1.2

SUSTAIN	Females Mean	SD	Males Mean	SD	Total group Mean	SD
CPT "X"						
% correct	0.49	0.17	0.54	0.1	0.51	0.14
% error	0.5	0.45	0.32	0.61	0.42	0.51
Reaction time	0.24	0.5	0.95	0.78	0.54	0.71
CPT "AX"						
% correct	0.38	0.27	0.62	0.09	0.48	0.24
% error	0.4	0.12	0.36	0.25	0.38	0.18
Reaction time	-0.43	1.09	0.45	0.71	-0.05	1.02
CPT "degraded X"						
%correct	0.63	0.35	0.5	0.45	0.55	0.4
% error	0.5	0.33	0.3	0.43	0.38	0.4
Reaction time	1.04	0.61	0	0.49	0.4	0.74
CPT "auditory X"						
% correct	0.69	0.05	0.53	0.16	0.6	0.14
% error	0.36	0.2	0.34	0.16	0.35	0.17
Reaction time	0.8	0.84	0.25	0.87	0.49	0.87

Table C 3: Descriptive Statistics, Siblings
Standardized scores included in the four Attention factors

N=15
12 families

ENCODE	Females		Males		Total group	
	Mean	SD	Mean	SD	Mean	SD
Digit span	0	1.59	-0.06	0.82	-0.03	1.21
Arithmetic	0.16	0.77	0.45	1.27	0.3	1.02
Memory	-0.25	1.27	0.29	0.62	0.02	1

FOCUS-EXECUTE	Females		Males		Total group	
	Mean	SD	Mean	SD	Mean	SD
Digit symbol	0.47	1.16	-0.6	0.36	-0.11	0.97
Stroop word	-0.09	1.26	-0.3	1.07	-0.2	1.13
Stroop color	0.01	1.2	-0.24	0.78	-0.11	0.98
Stroop C-W	0.03	1.32	-0.3	0.62	-0.14	1.01
Trails A	0.34	0.53	0.23	0.38	0.28	0.44
Trails B	0.21	0.88	-0.15	1.02	0.02	0.94

SHIFT	Females		Males		Total group	
	Mean	SD	Mean	SD	Mean	SD
WCST corrects	0.16	0.72	0.01	0.74	0.7	0.91
WCST categories	-0.58	0.59	-0.4	1.2	0.09	-0.49

SUSTAIN	Females		Males		Total group	
	Mean	SD	Mean	SD	Mean	SD
CPT "X"						
% correct	-0.44	1.63	0.4	0.28	0.01	1.15
% error	0.01	0.64	0.06	0.51	0.04	0.58
Reaction time	-0.39	0.99	0.34	0.71	0	0.9
CPT "AX"						
% correct	-0.2	1.29	0.43	0.22	0.12	0.95
% error	0.28	0.17	0.14	0.32	0.21	0.26
Reaction time	0	1.22	0.31	0.57	0.16	0.93
CPT "degraded X"						
% correct	-0.05	1.05	0.09	1.32	0.02	1.15
% error	0.39	0.62	-0.3	1.67	0.02	1.3
Reaction time	-0.04	1.03	0.21	1.2	0.09	1.09
CPT "auditory X"						
% correct	-0.1	0.7	-0.08	1.26	-0.09	1
% error	0.11	0.15	-0.82	2.45	-0.39	0.01
Reaction time	-0.29	0.96	0.27	0.85	1.8	0.91

REFERENCES

Aarts, J. H. P., Binnie, C. D., Smit, A. M. & Wilkins, A. J. (1984). Selective cognitive impairment during focal and generalized epileptiform EEG activity. Brain, 107, 293-308.

Aicardi, J. (1986). Epilepsy in children. International Review of Child Neurology Series, (pp. 79-99).

Aldenkamp, A. P., Alpherts, W. C. J., Dekker, M. J. A. & Overweg, J. (1990). Neuropsychological Aspects of Learning Disabilities in Epilepsy. Epilepsia, 31 (Suppl.4), S9-S20.

Aldenkamp, A. P., Alpherts, W.C.J., De Bruine-Seeder, D. and Dekker, M.J.A. (1990). Test- Retest Variability in Children with Epilepsy: a Comparison of WISC-R Profiles. Epilepsy Research, 7, 165-172.

Allen, I. M. (1956). The emotional factor and the epileptic attack. New Zealand Journal, 55, 297-308.

Annegers, J. F. , Hauser, A. W. & Anderson, E. V. (1982) Risk of seizures among relatives of patients with epilepsy: families in a defined population, In V. E. Anderson , W A. Hauser , J. K. Penry & C. F. Sing (Eds.), Genetic Basis of the Epilepsies, New York: Raven Press.

Asarnow R. F. & MacCrimmon D. J. (1982). Attention/information processing neuropsychological functioning and thought disorder during the acute and partial recovery phases of schizophrenia: a longitudinal study. Psychiatry Research, Vol 7, 309-319.

Barker, W. (1948). The petit mal attack as a response within the CNS to distress organism environment situations. Psychosomatic Medicine, 10, 73-94.

Bates, J. A. V. (1953). A technique for identifying changes in consciousness. Electroencephalography and Clinical Neurophysiology, 5, 445-446.

Baumann, R. J., Marx, M. B. & Leonidakis, M. G. (1978). Epilepsy in rural Kentucky: Prevalence in a population of school age children. Epilepsia, 19, 75-80.

Benninger, C. K. , Matthis P. & Scheffer, D. (1982). EEG findings in children of epileptic parents In V. E. Anderson , W A. Hauser, J. K. Penry & C. F. Sing (Eds.), Genetic Basis of the Epilepsies. New York: Raven Press.

Berg, E. A. (1948). A simple objective technique for measuring flexibility in thinking. The Journal of General Psychology, 39, 15-22.

Besag, F., Mills, M., Wardale, F., Andrew, CM.& Craggs, MD. (1989). The validation of a new ambulatory spike and wave monitor. Electroencephalography and Clinical Neurophysiology, 73, 157-161.

Binnie, C. D., Channon, S. & Marston, D. (1990). Learning disabilities in epilepsy: neurophysiological aspects. Epilepsia, 31, (Suppl.4), S2-S8.

Bourdon, B. (1901). La perception et designation des nombres. Entre camarades. Paris : Felix Alcan.

Browe, T. R. & Mirsky, A. F. (1983). Absence (petit mal) seizures. In : T. R. Browne and R. G.. Feldman (Eds.), Epilepsy : Diagnosis and management. (pp. 61-74) Boston: Little, Brown.

Cavazzuti, G. B. (1980). Epidemiology of different types of epilepsy in school age children of Modena , Italy. Epilepsia, 21, 57-62.

Chatrian, G. E., Lettich, E., Miller, L. H., Green, J. R., & Kupfer, C. (1970). Pattern sensitive epilepsy. Part 2. Clinical changes, test of responsiveness

and motor output, alterations of evoked potentials and therapeutic measures. Epilepsia, 11, 151-162.

Chelune, G. J. & Baer, R. A. (1987). Developmental norms for the Wisconsin Card Sorting Test. Journal of Clinical and Experimental Neuropsychology, 8, (3), 219-228.

Chelune, G. J., & Thompson, L. L. (1987). Evaluation of the general sensitivity of the Wisconsin Card sorting Test. among younger and older Developmental Neuropsychology, 3, (1), 81-89.

Chiofalo, N., Kirschbaum,A., Fuentes, A., Corder, M. L., & Madsen,J. (1979). Prevalence of epilepsy in children in Melipilla, Chile. Epilepsia, 20, 261-266.

Cohen, R. M., Semple, W., Gross, M., Holcomb, H. H. Dowling, M. S. &Nordall T. E. (1988). Functional localization of sustained attention: comparison to sensory stimulation in the absence of instruction. Neuropsychiatry, Neuropychology, and Behavioral Neurology, 1, (1) 3-20.

Cowan, L. D., Bodensteiner, J. B., Leviton, A. & Doherty L. (1989). Prevalence of epilepsies in children and adolescents. Epilepsia, 30 (1), 94-106.

Crocker, L. & Algina., J. (1986). Introduction to Classical and Modern Test Theory Holt, Rinehart and Winston.

Degen, R., Degen, H.E. & Roth Ch. (1990). Some genetic aspects of idiopathic and symptomatic absence seizures: waking and sleep EEGs on siblings. Epilepsia, 31(6), 784-794.

Dodrill, B. C. (1991). Behavioral effects of antiepileptic drugs. In D. Smith, D. Treiman & M. Trimble (Eds.) Advances in Neurology, Vol 55 New York: Raven Press, (pp.213-224).

Doose, H. & Baier, W. K. (1989). Absences. In G. Beck-Mannagetta & V. E. Anderson (Eds.), Genetics of the Epilepsies (pp.35-42). Springer-Verlag.

Drewe, E. A. (1974). The effect of type and area of brain lesion on Wisconsin Card Sorting Test performance. Cortex, 10, 159-170.

Duborsky, L., Docherty, J. P., Todd, T. C., Knapp, P. H., Mirsky, A. F. & Gottschalk L. A. (1975). A context analysis of psychological states prior to petit mal EEG paroxysms. The Journal of Nervous and Mental Disease., Vol. 160, 282- 298.

Duncan, C. C. (1988). Application of event - related brain potentials to the analysis of interictal attention in absence epilepsy. In M. S. Myslobodsky & A. F. Mirsky, (Eds.). Elements of petit mal epilepsy. New York: Peter Lang.

Faraone, S. V., Biederman, J., Keenan, K. & Tsuang, M. T. (1991). Separation of DSM-III attention deficit disorder and conduct disorder: Evidence from a family -genetic study on American child psychiatric patients. Psychological Medicine, 21, 109-121.

Farwell, J. R., Dodrill, C. B. & Batzel, L. W. (1985). Neuropsychological abilities of children with epilepsy. Epilepsia, 26, (5), 395-400.

Fedio, P. & Mirsky, A. F. (1969). Selective intellectual deficits in children with temporal lobe or centrencephalic epilepsy. Neuropsychologia, 7, 287-300.

Freedman, D. A. & Adatto, C. P. (1968). On the precipitation of seizures in an adolescent boy. Psychosomatic Medicine, 30, 437-447.

Gastaut, H. (1973). Dictionary of epilepsy, Part I: definitions. World Health Organization, Geneva, Switzerland.

Gerken, H., Doose, H. (1973). On the genetics of EEG anomalies III. Spikes and waves in the resting record and/or during hyperventilation. Neuropaediatrie, 4, 88-97.

Gibbs, F. A., Davis, H. & Lennox, W. (1935, December). The electroencephalogram in epilepsy and the conditions of impaired consciousness. Archives of Neurology and Psychiatry, Vol 34, 1133-1148.

Giordani, B., Berent, S., Sackellares, J. Ch., Rourke, D., Seidenberg, M., O'Leary, D. S., Dreifuss, F. E., & Boll, T. J. (1985). Intelligence test performance of patients with partial and generalized seizures. Epilepsia, 26, (1), 37-42.

Golden, Ch. J. (1978). Stroop Color and Word Test, Manual for Clinical and Experimental Uses. Chicago: Soelting

Goode, D. J , Penry, J. K. & Dreifuss, F. E. (1970). Effects of paroxysmal spike - wave on continuous visual motor performance. Epilepsia , 11, 421-254.

Gottschalk, L. A. (1953). Effects of intensive psychotherapy on epileptic children. Archives of Neurology and Psychiatry, 70, 361-384.

Gowers, W. R. (1964). Epilepsy and other chronic convulsive diseases: their causes symptoms and treatment. (pp. 241-242). (Reprinted). New York: Dover.

Grunebaum, H., Weiss, J. L., Gallant, D. & Cohler, B. J. (1974, August). Attention in young children of psychotic mothers. American Journal of Psychiatry, 131, (8) 887-891.

Guey, J. , Bureau, M., Dravet, C., & Roger, J. (1969). A study of the rhythm of petit mal absences in children in relation to prevailing situations. The use

of EEG telemetry during psychological examinations school exercises and periods of inactivity. Epilepsia, (Amsterdam), 10, 441-451.

Harvald, B. & Hauge, M. (1965). Hereditary factors elucidated by twin studies. In J. V. Neel, M. W. Shaw, & W. J. Schull (Eds.). Genetics and the epidemiology of chronic diseases. (pp. 61-76). Public Health Service publication, No.1163.

Hauser, W. A. and Kurland, L. T. (1975). Epidemiology of epilepsy in Rochester Minnesota 1935 through 1967. Epilepsia, 16, 1-6.

Hauser, W. A. (1982). Genetics and the clinical characteristics of seizures. In V. E. Anderson, W. A. Hauser, J. K. Penry, & C. F. Sing. (Eds.). Genetic basis of the epilepsies. New York: Raven Press.

Heaton, R. K. (1981). A Manual for the Card Sorting Test. Psychological Assessment Resources. Florida: Odessa,

Herman, J., Mirsky, A. F., Ricks, N. L. & Gallant, D. (1977). Behavioral and electrographic measures of attention in children at risk for schizophrenia. Journal of Abnormal Psychology, 86, (1), 27-33.

Hoffman, M. (1991). Research News: How Parents Make their Mark on Genes. Science, 252 (31 May), 1250-1251.

Holmes, G. L., McKeever, M. & Adamson, M. (1986). Absence seizures in children: clinical and electroencephalographic features. Annals of Neurology, 21, 268 -273.

Holmes, G. L. (1987). Psychosocial factors in childhood epilepsy. In G. L. Holmes, Diagnosis and management of seizures in children. Series: Major Problems in Clinical Pediatrics, Vol 30, pp.112-124. Philadelphia: W. B. Saunders.

Ingraham, L. J., Chard, F., Wood, M. & Mirsky, A. F. (1988). An Hebrew language version of the Stroop Test. Perceptual and Motor Skills, 67, 187-192.

Jallon, P. & Dartigues, J. F. (1987). Epidemiologie descriptive des epilepsies. Rev. Neurol. (Paris), 143, 341-350.

James, W. (1890). The principles of Psychology. (Vol. 1). New York: Holt.

Jus, A. & Jus, K. (1962). Retrograde amnesia in petit mal. Archives of General Psychiatry, 6, 163-167.

Juul-Jensen, P. & Foldspang, A. (1983). Natural history of epileptic seizures. Epilepsia , 24, 297-312.

Kastekeijn-Nolst Trenite, D. G. A., Siebelink, B. M., Berends, S.G.C., van Strien, J.W. & Meinardi, H. (1990). Lateralized effects of subclinical epileptiform EEG discharges on scholastic performance in children. Epilepsia, 31(6), 740-746.

Kendler, K. S., Ochs, A. L., Gorman, A. M., Hewitt, J. K., Ross, D. E. & Mirsky, A. F. (1991). The structure of schizotypy: A pilot multitrait twin Study. Psychiatry Research, 36, 19-36.

Landsell, H & Mirsky, Allan, F. (1964). Attention in focal and centrencephalic epilepsy. Experimental Neurology , 9, 463- 469.

Leibowitz, U. & Alter, M. (1968). Epilepsy in Jerusalem. Epilepsia, 9: 87-105.

Lennox, W.G. & Lennox, M. A. (1960). Epilepsy and related disorders. Boston:

Lezak, D. M. (1983). Orientation and attention. In M. D. Lezak, Neuropsychological assessment. (pp. 533-559), (2nd ed.) New York: Oxford University Press.Little , Brown.

Loiseau, P. & Cohadon, F. (1970). Les petit mal et ses frontieres. Paris: Masson.

Loiseau, P. (1985). Childhood absence epilepsy. In J. Roger, C. Dravet, M. Bureau, F. E. Dreifuss, & P. Wolf. (Eds.) Epileptic Syndromes in Infancy, Childhood and Adolescence. (pp. 106-120). London: John Libbey.

Meighan, S., Queener, L. & Weitman, M. (1976). Prevalence of epilepsy in children of Multnomah County Oregon. Epilepsia, 17, 245-256.

Milner, B. (1963). Effects of different brain lesions on card sorting. Archives of Neurology, 9, 90-100.

Mirsky, A. F. , Primac D.W., Ajmone Marsan, Cosimo , Rosvold , H. E. & Stevens,J. (1960). A comparison of the psychological test performance of patients with focal and nonfocal epilepsy. Experimental Neurology, 2, (1), 75-89.

Mirsky, A. F., & Kornetsky Conan. (1964). On the dissimilar effects of drugs on the digit symbol substitution and the CPT. Psychopharmacologia, 5, 161-177.

Mirsky, A. F. & Van Buren, J. M. (1965). On the nature of the "absence" in centrencephalic epilepsy: A study of some behavioral, EEG and autonomic factors. Electroencephalography and Clinical Neurophysiology, 18, 334-348.

Mirsky, A. F., Bloch-Rojas, S. & McNary, W.F.(1966). Experimental petit mal epilepsy produced with chlorambucil. Acta Biol. Exper. (Warsaw) Vol 26, (1), 55-61.

Mirsky, A. F. (1989). Information processing in petit mal epilepsy. In B. P. Herman & M. Seidenberg (Eds.), Childhood epilepsies: neuropsychological, psychosocial and intervention aspects .(pp. 51-70). New York: John Wiley

Mirsky, A. F., Anthony, B. J., Duncan, C. C., Brouwers, P., Ahearn, M. & Kellam, S. G. (1991). Analysis of the elements of attention: A neuropsychological

approach. (In press). Laboratory of Psychology and Psychopathology, NIMH.

Mirsky, A. F., Lochhead, S. J., Jones, B. P., Dermot Walsh, M.B. & Kendler, K. S. (1991). On familial factors in the attentional deficit in schizophrenia: A preliminary report. (In Press), Laboratory of Psychology and Psychopathology, NIMH.

Myslobodsky, M. (1988). Petit mal status as a paradigm of the functional anatomy of awareness. In M. S. Myslobodsky & A. F. Mirsky, (Eds.). Elements of petit mal epilepsy. New York: Peter Lang.

Neuechterlein, K. (1983). Signal detection in vigilance tasks and behavioral attributes among offspring to schizophrenic mothers and among hyperactive children. Journal of Abnormal Psychology, 92, (1), 4-28.

Niedermeyer, E. (1974). Compendium of the epilepsies. (pp. 26-29), Springfield, Illinois: Ch. Thomas.

Ottman, R., Annegers, J. F., Hauser, W. A. & Kurland, L. T. (1989). Seizure risk in offspring of parents with generalized versus partial epilepsy. Epilepsia, 30, (2), 157-161.

Parasuraman, R. (1985). Sustained attention: multifactorial approach. In M. I. Posner & Marin, O. (Eds.), Attention and Performance. Lawrence & Erlbaum Association.

Penfield, W., & Jasper, H. (1954) Epilepsy and the Functional Anatomy of the Human Brain. Boston: Little, Brown.

Penry, K. J., Porter, R. J. & Dreifuss, F. E. (1975). Simultaneous recording of absence seizures with video tape and electroencephalography. Brain, 98, 427-440.

Porter, R. J. & Penry, K. J. (1973). Responsiveness at the onset of spike-wave bursts. Electroencephalography and Clinical Neurophysiology, 34, 239-245.

Posner , M. I. (1980). Orienting of attention. Quarterly Journal of Experimental Psychology, 32, 3-25.

Posner , M. I., Snyder, C. R. R.,& Davidson, B. J. (1980). Attention and the detection of signals. Journal of Experimental Psychology: General, 109,

Porter R. J. (1986). Diagnosis of partial seizures. In J. K. Penry (Ed.) Epilepsy: Diagnosis Management , Quality of Life. New York : Raven Press.

Posner, M. I., Petersen, S. E., Fox, P. T., & Raichle, M. E. (1988, June). Localization of cognitive operations in the human brain. Science, 240, 1627-1631.

Reitan, R. M. & Davidson, L. A. (Eds.) (1974). Clinical Neuropsychology: Current status and applications. Washington, D.C.: V.H. Winston & Sons.

Ricks, N. L.& Mirsky, A. F. (1974). Sustained attention and effects of distraction in underachieving second grade children. Journal of education, 156, 4-17. Boston University.

Robinson, A. L., Heaton, R. K., Lehman, R. A. W. & Stilson, D. W. (1980). The utility of the Wisconsin Card Sorting test in detecting and localizing frontal lobe lesions. Journal of Consulting and Clinical Psychology, 48, 605-614.

Rose, S. W., Penry, J. K., Markush,R. F., Radloff, L. A. & Putnam, P. L. (1973). Prevalence of epilepsy in children. Epilepsia, 14, 133-152.

Rosvold, H. E., Mirsky, A. F., Sarason, I., Bransome, Jr.,E. D. & Beck, L. H. (1956). A continuous performance test of brain damage. Journal of Consulting Psychology, 20, (5), 343 - 350.

Rutschman, J., Cornblatt, B. & Erlenmeyer-Kimling, L. (1977, May). Sustained attention in children at risk for schizophrenia. Report on a Continuous Performance Test. Archives of General Psychiatry, 34, 571-575.

Sato, S., Dreifuss, F. E., & Penry, J. K. (1976). Prognostic factors in absence seizures Neurology, 26, 788-796.

Sato, S., Dreifuss, F. E., Penry, J. K., Kirby, D. D., & Palesh, Y. (1983). Long term follow up of absence seizures. Neurology, 33, 1590-1595.

Schwab, R. S. (1939). A method of measuring consciousness in petit mal epilepsy. Journal of Nervous and Mental Disease, 89, 690-691.

Schwab, R. S. (1941). The influence of visual and auditory stimuli on the electroencephalographic tracing of petit mal. American Journal of Psychiatry, 97, 1301-1316.

Schwab, R. S. (1947). Reaction time in petit mal epilepsy. Association of Research in Nervous and Mental Diseases, 26, 339-341.

Seidenberg, M., Beck, N., Geisser, M., Giordani, B., Sackellaras, J. C., Berent, S., Dreifuss, F. E., & Boll, T. J. (1986). Academic achievement in children with epilepsy. Epilepsia, 27, 753-759.

Seidenberg, M. (1989). Academic achievement and school performance of children with epilepsy. In B. Herman & M. Seidenberg, (Eds.) Childhood epilepsies: neuropsychological and intervention aspects. (pp. 105-118) New York: John Wiley Sons.

Sengoku, A., Kanazawa, O. Kawai, I. & Yamaguchi, T. (1990). Visual disturbance during spike-wave discharges. Epilepsia, 31 (1), 47-50.

Shavelson, R. J. (1988). Statistical reasoning for the behavioral sciences. (2nd ed.) Boston: Allyn & Bacon.

Shimazono, Y., Hirai, T., Okuma, T., Fukuda, T., & Yamamasu, E. (1953). Disturbance of consciousness in petit mal epilepsy. Epilepsia, 2, 49-55.

Shovron,S.D., (1988). Epilepsy a general practice perspective. Basel: CIBA, GEIGY,

Sofijanov, N. G. (1982). Clinical evolution and prognosis of childhood epilepsies. Epilepsia, 23, 61-69.

Stores, G. (1971). Cognitive function in children with epilepsy. Developmental Medicine and Child Neurology, 13, 390-393.

Stores, G. (1973). Studies of attention and seizure disorders. Developmental Medicine and Child Neurology, 15, 376-382.

Stores, G. (1990). Electroencephalographic parameters in assessing the cognitive function of children with epilepsy. Epilepsia, 31 (Suppl.4), S45-S49.

Stroop, J. R. (1935). Studies in interference in serial verbal reactions. Journal of Experimental Psychology, 18, (6), 643-662.

Talland , G. A. (1965). Deranged memory. New York: Academic Press.

Temkin Owsei. (1971). The falling sickness, a history of epilepsy from the Greeks to the beginning of modern neurology. (2nd edition rev.) Baltimore: Hopkins Press.

Thompson, P. J. (1987). Educational Attainment in Children an Young People with Epilepsy. In J. Oxley & G.Stores (Eds.), Epilepsy and Education, (pp.15-24). London: The Medical Tribune Group.

Tizard, B. & Margerison , J. H. (1963). Psychological functions during wave-spike discharge. British Journal of Social and Clinical Psychology, 3, 6-15.

Todt, H. (1984). The late prognosis of childhood epilepsies. Epilepsia, 23, 61-69.

Trial Making Test , (1944). From the: Army Individual Test Battery, Manual for Directions and Scoring. Adjutant General's Office . Washington, D C, War Department.

Tsuboi, T. (1982). Seizures in children of epileptic parents. In H. Akimoto, H. Kazamatsuri, M. Seino & A. Ward. (Eds.). Advances in epileptology: XIII th Epilepsy International Symposium. New York: Raven Press.

Wechsler, D. (1974). Wechsler Intelligence Scale for Children-Revised. New York: Psychological Corporation.

Wechsler, D. (1981). Wechsler Adult Intelligence Scale-Revised. New York: Psychological Corporation.

Zegans, L., Kooi, K., Waggoner, R., & Kemph, J. (1964). Effects of psychiatric interview upon paroxysmal cerebral activity and autonomic measures in a disturbed child with petit mal epilepsy. Psychosomatic Medicine, 26, 151-161.

Ziegler, R. G. (1979). Psychologic vulnerability in epileptic patients. Psychosomatics, 20, (3).

Ziegler, R. G. (1981, June). Impairment of control and competence in epileptic children and their families. Epilepsia, 22, 339-346.

Ziegler, R. G. (1982, July). Epilepsy: individual illness, human predicament and family dilemma. Family relations, 435-444.

Zubin, J. (1975). Problem of attention in schizophrenia. In M. L. Kietzman, S. Sutton, & J. Zubin. (Eds.) Experimental approaches to psychopathology. New York: Academic Press.