MECHANISMS OF ACTION OF ANTIEPILEPTIC DRUGS

AND FINE MOTOR DEXTERITY

IN GENERALIZED AND LOCALIZATION-RELATED/FOCAL EPILEPSIES

by

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Abstract

MECHANISMS OF ACTION OF ANTIEPILEPTIC DRUGS AND FINE MOTOR DEXTERITY IN GENERALIZED AND LOCALIZATION-RELATED/FOCAL EPILEPSIES

by

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Antiepileptic drugs (AEDs) have been increasingly prescribed to manage seizures in patients with epilepsy and other neurologic and/or psychiatric disorders, which prompted many scientific inquiries of their associated cognitive effects. While research indicated AEDs' efficacy in up to 70% of the patients, they also implicated their role in worsening memory, attention, and other abilities such as fine motor dexterity. Questions remained as to what aspects of antiepileptic drug treatment influenced fine motor difficulty. This retrospective study attempted to examine the extent to which AEDs' mechanisms of action, duration of treatment, and the type of therapy (e.g., monotherapy vs. polytherapy) contributed to fine motor difficulty in adult patients with epilepsy. A review of medical records, as well as performance on measures of fine motor dexterity and speed, were performed in 164 patients with epilepsy. Results indicated the advantage of monotherapy with a sodium (Na^+)-channel blocker over polytherapy with a Na^+-channel blocker and a GABAergic enhancer. In addition, fine motor difficulty in patients treated with this combination regimen was associated with longer years of seizures and younger ages of seizure onset. Other variables such as gender, years of education, and FSIQ influenced a patient's susceptibility for fine motor difficulty, and indicated the

relevance of cognitive reserve in that higher education and intellectual functioning was associated with better outcome. The findings suggested the importance of considering mechanisms of action and the type of therapy when devising an AED regimen for patients with epilepsy and other neurologic and/or psychiatric disorders. This would maximize efficacy and minimize behavioral effects such as fine motor difficulty, the presence of which interferes with a patient's quality of life and functional independence.

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I. INTRODUCTION

A. RESEARCH QUESTION

Over the past 20 years, antiepileptic drugs have been increasingly prescribed by physicians to manage seizures in patients with epilepsy, prompting many scientific inquiries into the cognitive effects associated with these medications. While studies have shown antiepileptic drugs' efficacy in up to 70% of the patients, they have also implicated their role in worsening memory, attention, and other cognitive abilities such as fine motor dexterity. Questions remain as to what aspects of antiepileptic drug treatment influence fine motor dexterity. The current study attempts to examine the extent to which mechanisms of action, duration of treatment, and type of therapy (e.g., monotherapy vs. polytherapy) contribute to fine motor impairment in adult patients with epilepsy. Findings may have implications beyond the treatment of epilepsy given the broad use of antiepileptic drugs in the treatment of other diagnoses, such as brain tumor, migraine, as well as mood and psychiatric disorders.

B. EPILEPSY

Epilepsy is one of the most common neurologic disorders, and affects approximately 50 million people worldwide. It is nonspecific to geographical, racial, or social boundaries, and occurs in both men and women. Although it is frequently diagnosed in infancy, epilepsy can occur at any point in an individual's life [World Health Organization (WHO), 2005].

According to Temkin (1971), the first written account of epilepsy was by Hippocrates circa 400 B.C. Hippocrates stated that like all diseases, epilepsy was hereditary and caused by excessive phlegm in the brain. He speculated that seizures

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occurred when the excessive phlegm overflowed from the brain into the circulatory system. Although current findings support that only certain types of seizures are hereditary, Hippocrates was accurate in stating that the cause of seizures originated in the brain (Temkin, 1971).

1. Epidemiology of epilepsy

Despite epilepsy being a common neurologic condition, there are deficiencies in the understanding of its etiology. This is in part due to the methodological discrepancies in research studies, as well as the heterogeneous nature of epilepsy (Sander & Shorvon, 1996; Bell & Sander, 2001), since it may be hereditary or a result of a variety of sources, as will be discussed in this section under subheading B3 on the causes of epilepsy.

Nevertheless, the overall incidence[1] of epilepsy has been estimated to be 50 per 100,000/year (range 40–70 per 100, 000/year) in industrialized countries (Zarrelli, Beghi, Rocca, & Hauser, 1999; MacDonald, Cockerell, Sander, & Shorvon, 2000; Kotsopoulos, van Merode, Kessels, de Krom, & Knottneruss, 2002).

The prevalence[2] of epilepsy has been estimated to be between 4 and 10/1,000 people (Sander, 2003; Sander & Shorvon, 1996; Bell & Sander, 2001; Rwiza, Kilonzo, Haule, Matuja, Mteza, Mbena, Kilima, Mwaluko, Mwang'ombola, & Mwaijande, 1992; MacDonald et al., 2000; Placencia, Shorvon, Paredes, Bimos, Sander, Suarez, & Cascante, 1992; Olafsson & Hauser, 1999; Rocca, Savettieri, Anderson, Meneghini, Grigoletto, Morgante, Reggio, Salemi, Patti, & Di Perri, 2001; Al Rajeh, Awada,

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[1] Incidence here refers to the number of people who developed the condition of interest during a 1-year period divided by the total person-time at risk during that period, and is expressed as the number of cases per 100,000 people in the population (Sander, 2003).

[2] The number of deceased persons in a defined population at one point in time, divided by the number of persons in that population, and is expressed as the number of cases per 1,000 people in the population (Sander, 2003).

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Bademosi, & Ogunniyi, 2001; Gomes, Zeitoune, Kropf, & Beeck,, 2002s; Onal, Tumerdem, Ozturk, Gurses, Baykan, Gokyigit, & Ozel, 2002).

Approximately 2 million people in the United States have been diagnosed with epilepsy (Chang & Lowenstein, 2003), and approximately 50 million people worldwide are affected by the disorder (WHO, 2005).

2. Current classification and terminology of seizures and epilepsies

Seizures occur during the course of many diseases, such as tuberous sclerosis, lissencephaly, Menkes' syndrome, and Alpers' disease without translating to a formal diagnosis of epilepsy (Kolodny, 2001). What differentiates seizures in epilepsy from those occurring in other diseases is a specific set of criteria established by the International League against Epilepsy (ILAE) (Commission, 1981, 1989).

However, the classification system encountered resistance from the epileptology community due to its perceived rigidity in shaping how physicians and researchers characterize seizures in epilepsy. Over time the ILAE revised their guidelines to correspond to research findings and address clinical and research needs (Commission, 1981, 1989). Nevertheless, the continuous emergence of new research findings makes the classification of seizures and epilepsies a work in progress for the ILAE's Task Force on Classification and Terminology, who dedicate their efforts relentlessly to understand the complexity of this neurologic disorder.

In the current classification system, the ILAE recommends that epileptic seizures and epilepsy syndromes be categorized based on their clinical descriptions and the electroencephalographic (EEG) recordings of their onset, propagation, and termination (Commission, 1989); American Epilepsy Society, 2004). Epilepsy is a group of disorders

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characterized by:

> "an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure in the patient's history" (Fisher, van Emde Boas, Blume, Elger, Genton, Lee, & Engel, 2005, p. 471).

An epileptic seizure is defined as a transient occurrence of signs and/or symptoms due to abnormally excessive or synchronous neuronal activity in the brain" (Fisher et al., 2005, p. 471).

Currently, epileptic seizure type(s) are divided into generalized or localization-related/focal[3] seizures. In generalized epilepsies, the predominant type of seizures begins simultaneously in both cerebral hemispheres, as indicated by bilateral ictal EEG patterns. In localization-related epilepsies, the epileptogenic activity begins in one cerebral hemisphere only. There are many subtypes of generalized and localization-related/focal seizures, as shown in Table 1, which contains the current classification system of seizures and epilepsy. Table 2 is an annotated version.

3. Causes of epilepsy

Although localization-related seizures are among the most common seizure disorder in adults, less is know about their mechanisms than those of generalized seizures. This is to some extent due to the frequent occurrence of localization-related seizures following cerebral trauma or neurologic disorders such as traumatic brain injury,

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[3] The term "partial seizures" was replaced with "localization-related/focal seizures" in 1989 by the ILAE (Commission, 1989; Engel, 2001).

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infection of the central nervous system, brain tumors, prenatal and perinatal risk factors, and cerebrovascular disorders (WHO, 2005; White, 2002; Annegers, Rocca, & Hauser, 1996; Chang & Lowenstein, 2003).

On the other hand, the mechanisms of generalized epilepsies have been reported to involve multifaceted inheritance patterns, some Mendelian, and are associated with single-gene mutations. Almost all of these mutations are located in genes that encode ion-channel proteins (Berkovic & Scheffer, 2001; Stafstrom & Tempel, 2000; Prasad, Prasad, & Stafstrom, 1999). Mutations in genes encoding ion-channel proteins have been shown to result in hyperexcitability of cortical neurons through their alteration of channel functions. Since these genes are expressed throughout the brain, the effect of the mutations may be diffuse and thereby predisposes an organism to generalized seizures. These mutations, which are commonly referred to as channelopathies, occur in a variety of neurologic disorders. This raises the possibility that mutations in specific ion channels (e.g., calcium) may be among the causes of generalized epilepsies (Armijo, Shushtarian, Valdizan, Cuadrado, de las Cuevas, & Adin, 2005; Chang & Lowenstein, 2003; Kullmann, 2002; Lerche, Jurkat-Rott, & Lehmann-Horn, 2001; Graves & Hanna, 2005; Roll & Szepetowski, 2002).

4. The role of ion channels

"Virtually everything the brain does ultimately can be reduced to chemical processes" (Engel, 1991, p. 335). This statement is particularly true for epilepsy. In health, a network of excitatory and inhibitory circuits regulates the equilibrium in communication between neurons, and communication occurs through action potentials or synaptic transmission. In epilepsy, seizures occur when the electrical discharges in the

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central nervous system (CNS) become abnormal and excessively synchronized due to enhanced excitatory or impaired inhibitory mechanisms (Lerche et al., 2001). Since ion channels provide the fundamental foundation for these neuronal processes, they have become important targets for pharmacological treatment of epilepsy (Armijo et al., 2005; Yogeeswari, Ragavendran, Thirumurugan, Saxena, & Sriram, 2004).

Ion channels regulate the concentration gradient and excitability of the CNS, skeletal and heart muscles, and other tissues in the body. At rest, neurons exhibit a resting potential with the interior of the cell more negatively charged by the active export of sodium ions (Na^+) across the plasma membrane. During activation, ions move across the plasma membranes through channel openings created by membrane-bound proteins, which contain selective pores for Na^+, potassium (K^+), magnesium (Mg^{2+}), calcium (Ca^{2+}), or chloride (Cl^-) ions (Siegelbaum & Koester, 2000).

There are three types of gated ion channels, which are the voltage-, ligand-, and mechanically-gated ion channels. The two types most relevant to this paper are the voltage- and ligand-gated ion channels. At rest, the voltage-gated ion channels for Na^+, K^+, and Ca^{2+} ions are either open or closed, depending upon the resting membrane potential[4], and they are activated in response to neuronal depolarization. In contrast, the ligand-gated ion channels are closed at rest, and are activated in response to the binding of various neurotransmitters such as gamma-amino-butyric acid (GABA), glutamate, or acetylcholine (ACh) (Siegelbaum & Koester, 2000). A disturbance in the homeostatic mechanisms of these gated ion channels can cause the excessive excitation or impaired inhibition associated with epileptic seizures (Westbrook, 2000).

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[4] The resting membrane potential is always negative inside the cell, and ranges from –20 to –200 millivolts in different cells and species. In humans it is –70mV (Siegelbaum and Koester, 2000).

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5. Mechanisms underlying neuronal excitability

Each neuron within a seizure focus contains a synchronized electrical response called the paroxysmal depolarizing shift (PDS), which is recorded by the EEG as the seizure's onset and propagation. The PDS sequence begins with a rapid, large (20-40mV), and long-lasting (50-200ms) depolarization, which triggers hypersynchronization of a neuronal population and a series of high-frequency action potentials. The hypersynchronous discharges may begin and remain localized in a very discrete region of the cortex, or it may spread to other regions in either cerebral hemisphere resulting in a burst of action potentials. The next phase in the sequence is a plateau-like pattern indicating the completion of the action potentials, a rapid repolarization, and finally hyperpolarization. (American Epilepsy Society, 2004; Rogawski & Löscher, 2004).

The PDS sequence in a seizure focus and subsequent after-hyperpolarization are influenced by many properties of the neuron such as the voltage-gated ion channels, synaptic inputs from excitatory glutamatergic neurons, and inhibitory neurons involving GABA to form a surround inhibition, which encases the seizure focus (Engel, 1990; Kandel & Siegelbaum, 2000; Levy, Mattson, & Meldrum, 1995).

In healthy individuals, the propagation of excessive or synchronous discharges is prevented by intact GABAergic surround inhibition to prevent the spread of seizure activity, and intact after-hyperpolarization by GABA and Cl- influx, or K^+ efflux to limit the duration of the seizure. Disturbance of any of these neuronal properties results in seizure activity by enhancing excitation, decreasing inhibition, or promoting synchronization (Engel, 1990; Kandel & Siegelbaum, 2000; Levy et al., 1995).

In patients with epilepsy, the after-hyperpolarization disappears and the

surrounding inhibition is overcome, which allows the seizure to spread beyond the site of onset. The PDS sequence follows, allowing the influx of extracellular Ca2+ and Na^+, and repetitive action potentials. In addition, this sequence increases extracellular K^+ to depolarize neighboring neurons, causes Ca2+ to accumulate in the presynaptic terminals to increase neurotransmitter release, and activates the NMDA receptor to facilitate further Ca2+ influx and neuronal activation (Lothman, 1993; Kandel & Siegelbaum, 2000).

The mechanisms that increase neuronal excitability and the likelihood of recurrent seizures have been associated with disturbance of the homeostatic mechanisms of several neurotransmitter systems in the brain, as well as the neurophysiology of electrical activation. Neurotransmitters are substances released by the presynaptic nerve terminal at a synapse, and bind to specific postsynaptic receptors for that ligand. The binding of the ligands activates ion channels and allows passage of ions into or out of the cell. The neurotransmitter systems involving glutamate and GABA (Armijo et al., 2005; Engel, 1991; Dichter, 1994) are most relevant to the current investigation due to their mechanisms of action in the AEDs of interest.

Neuronal excitability has also been attributed to the disturbance of the physiological mechanisms that control electrical activation. These events may occur inside the neuron, in its interaction with other cells, or in the extracellular environment. The type, number, and distribution of voltage- and ligand-gated ion channels, as well as modulation of gene expression, such as editing a single base pair of mRNA encoding a specific glutamate receptor subunit, may determine whether or not an action potential will occur. A decrease in extracellular volume could cause an increase in extracellular

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K+ concentration, which inhibits the outflow of K+ ions necessary to repolarize the cell, therefore increasing neuronal excitability (Meldrum, 1995).

Other theories of neuronal excitability in epilepsy have been proposed based upon studies of the hippocampus, a common site of epileptogenesis in temporal lobe epilepsy. One theory proposes that selective loss of GABAergic interneurons decreases the normal feed-forward and feedback inhibition of the dentate granule cells (Mazarati & Wasterlain, 1997). Another theory suggests that synaptic reorganization following neuronal injury creates recurrent excitatory connections via axonal sprouting between neighboring dentate granule cells (Wuarin & Dudek, 1996).

In sum, the mechanisms underlying neuronal excitability in epilepsy vary widely as a function of epilepsy's heterogeneous nature. Since epilepsy is a diverse collection of disorders, the existing theories on the mechanisms of neuronal excitability are not mutually exclusive and may coexist in the brain.

6. Morphological changes associated with seizures

A wide variety of animal models of epilepsy have been developed, the majority of which utilized electrical stimulation, chemoconvulsants, physical conditions (e.g., hyperthermia, photic stimulations), genetic models, or spontaneous seizure models to elicit seizures in animals. The diversity of animal models offer enormous insight as well as challenges in interpretation. One challenge in interpreting findings from animal models of epilepsy is that many of the available models are of acute seizures or of status epilepticus[5], which are different from other types of seizures (e.g., localization-related), thus affecting the implications and generalization of the findings.

[5] A type of epileptic seizure with unclear termination of seizure activity (American Epilepsy Society, 2004).

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Another challenge pertains to the strain differences between animals. Some strains do not exhibit excitotoxic cell death as readily as others in response to similar epileptogenic stimuli (Schauwecker & Steward, 1997; Cole, Koh, & Zheng, 2002). Nonetheless, animal models are crucial in the study of epilepsy, and they have provided abundant knowledge of the morphological changes in the brain from seizures.

Seizures trigger a cascade of biochemical, metabolic, anatomic, and functional changes in the central nervous system (Cole et al., 2002; Meldrum, 1983). Based on a variety of electrical and chemoconvulsant animal models, the cascade of functional changes following a single seizure includes the influx of Ca^{2+} ions into neuron (msec-minutes post-seizure), immediate early gene activation (5 min-6 hours post-seizure), kinase activation (5 min-24 hours post-seizure), protein expression such as somatostatin[6] (2 hours-3 days post-seizure), glial activation (6 hours-5 days post-seizure), neuronal cell loss (6 hours-14 days post-seizure), and neurogenesis (days-weeks post-seizure) (Morgan, Cohen, Hempstead, & Curran, 1987; Saffen, Cole, Worley, Christy, Ryder, & Baraban, 1988; Cole, Saffen, Baraban, & Worley, 1989; Anderson, Adams, Varga, Selcher, Feng, Trzaskos, & Sweatt, 2000; Gall, Lauterborn, Isackson, & White, 1990; Baraban, Fiore, Sanghera, Paddon, & Pelech, 1993; Vezzani, Sperk, & Colmers, 1999; Madsen, Greisen, Nielsen, Bolwig, & Mikkelsen, 2000; Margerison & Corsellis, 1966; Corsellis & Meldrum, 1976; Sloviter, 1994).

It remains unclear whether any or all of the above consequences that follow a single seizure contribute to later recurrence, and whether they occur in parallel or in series. In a parallel model, the consequences of seizures such as axonal sprouting,

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[6] A neuropeptide that has been suggested to inhibit hyperexcitation by augmenting K+ currents and/or inhibiting glutamatergic excitatory postsynaptic currents, most likely by inhibiting its presynaptic release (Tallent & Siggins, 1999).

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neuronal injury, gliosis, neurogenesis, and/or functional change may occur independently of each other, as opposed to a series model, where each consequence of a seizure depends upon earlier events for its expression. These consequences are briefly discussed below.

a. Synaptic reorganization

In studies of the hippocampus, prolonged seizures can cause loss of neurons and synaptic reorganization, with aberrant growth/sprouting of granule cell axons in the supragranular zone of the fascia dentate and the infrapyramidal region of the CA-3 field. In addition, the loss of inhibitory neurons will also increase the excitability of the network (Babb & Brown, 1987). Sprouting of excitatory axons and the ensuing abnormal connections increase the overall excitability of the neuronal network, which strengthen the spread and duration of future seizure activity (Tauck & Nadler, 1985; Yang, Tandon, Liu, Sarkisian, Stafstrom, & Holmes, 1998; Binder, Routbort, & McNamara, 1999; Friedman, 1998; Schwob, Fuller, Price, & Olney, 1980; Sutula, He, Cavazos, & Scott, 1988; Cavazos, Golarai, & Sutula, 1991; Wuarin & Dudek, 1996; Patrylo, Schweitzer, & Dudek, 1999).

Sutula et al. (1988) discovered significantly altered patterns of Timm staining[7] in the dentate gyrus of rats after activation and kindling[8] of the perforant path when compared to unstimulated rats implanted with perforant path electrodes. After kindling, epileptiform activity propagated in the perforant path induced abnormal Timm granules in the supragranular layer of the dentate gyrus. Furthermore, the supragranular Timm granules were observed for as long as 5 months after the last stimulation, indicating long-

[7] A histochemical technique that stains neural elements containing heavy metals. It has been used to stain hippocampal mossy fiber axons and synaptic terminals due to their zinc content (Danscher, 1981; Frederickson et al., 1983).

[8] Repeated activation of neural pathways to induce seizures, and possibly a permanent epileptic state (Goddard, 1967).

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lasting effects of seizure, axonal growth, synaptic reorganization, and mossy fiber sprouting into the inner molecular layer of the dentate gyrus, which reportedly contributed to neuronal hyperexcitability.

b. Neuronal injury

Seizures result in neuronal injury due to the increased Ca^{2+} influx through the N-methyl-D-aspartate (NMDA) receptor, an ionotropic subtype of the excitatory amino acid glutamate. At rest, the NMDA receptor has a Ca^{2+} channel blocked by Mg^{2+} ions. During and after in vitro seizure activity, membrane depolarization displaces Mg^{2+} and allows the influx of Ca^{2+} to depolarize the cell and facilitate neurotransmitter release. In addition, a positive correlation has been reported between the duration of the seizure and the time it took for Ca^{2+} levels to return to baseline (Pal, Sombati, Limbrick, DeLorenzo, 1999; Raza, Pal, Rafiq, & DeLorenzo, 2001; Wasterlain & Shirasaka, 1994; Meldrum, 1981). Hence Ca^{2+}-mediated neuronal injury has been implicated during excessive neuronal activation (e.g., status epilepticus and cerebral ischemia), which potentially causes cell death or "excitotoxicity" (Meldrum, 1995) through necrosis or apoptosis. In necrosis, a cell becomes swollen and burst; in apoptosis, a cell utilizes energy to shrink itself, causing its DNA to break into fragments (Toescu, 1998).

Lesions of temporal lobe structures have been identified in lobectomy specimens from patients with epilepsy, with hippocampal sclerosis being a common pathology. Hippocampal sclerosis describes a shrunken and hardened hippocampus that results from neuronal loss and gliosis, most commonly of the CA1-CA3 pyramidal cells, neurons of the hilus of the dentate gyrus, and some dentate granule cells (Gloor, 1991; Meldrum & Bruton, 1992).

c. Cerebellar changes

In addition to lesions of the hippocampus, seizures associated with generalized or partial epilepsies have been associated with death of cerebellar neurons, which mediate motor functions such as fine motor dexterity (Shakkottai, Chou, Oddo, Sailer, Knaus, Gutman, Barish, LaFerla, Chandy, 2004; Botez et al., 1988, 1989; Ney, Lantos, Barr, & Schaul, 1994; Ohmori, Ogura, Yasuda, Nakamura, Hatta, Kawano, Michikawa, Yamashita, & Mikoshiba, 1999).

Cerebellar atrophy in epilepsy has been previously associated with pharmacological treatment with antiepileptic drugs, such as phenytoin (Botez et al., 1988, 1989; Ney et al., 1994; Ohmori et al., 1999; Tan, Chan, & Auchus, 2001; Theodore, 1995; Alioğlu, Sari, Velioğlu, & Ozmenoğlu, 2000). The mechanism of seizure-mediated damage has also been associated with cerebellar atrophy as a function of the cerebro-cerebellar diaschisis (Tien & Ashdown, 1992), hypoxia (Dam, 1970), or status epilepticus (Meldrum et al., 1973).

Recent structural imaging found that patients with epilepsy had reduced cerebellar volume at baseline compared to control subjects. Although the finding was not statistically significant, the study concluded the atrophy was consistent with existing research that suggested the occurrence of cerebellar damage after cerebral trauma, and of epilepsy-related cerebellar atrophy (Liu, Lemieux, Bell, Sisodiya, Bartlett, Shorvon, Sander, & Duncan, 2005; Crooks, Mitchell, & Thom, 2000), regardless of pharmacological treatment with phenytoin or other antiepileptic drugs.

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C. TREATMENT OF EPILEPSY

The main treatment options for epilepsy are medications, neurosurgery, vagus nerve stimulation, and a ketogenic diet for some children. Due to individual variation in the type and severity of epilepsy, some patients respond to pharmacological treatment while others are better served by undergoing neurosurgery or vagus nerve stimulation.

1. Non-pharmacological treatment of epilepsy

Non-pharmacological treatments for epilepsy such as neurosurgery, vagus nerve stimulation, ketogenic diet, and avoidance therapy[9] are available when pharmacological treatment is not efficacious or feasible[10]. Nevertheless, the number of patients whose seizures are managed by non-pharmacological treatments is smaller than those managed by pharmacological treatments (Stefan, Halasz, Gil-Nagel, Shorvon, Bauer, Ben-Menachem, Perucca, Wieser, & Steinlein, 2001; Loiseau, 2001; Sander, 2004). The current dissertation will focus on the pharmacological treatments of epilepsy.

2. Pharmacological treatment of epilepsy

The pharmacological treatment of epilepsy was initiated by Alfred Hauptmann, who discovered phenobarbital's antiepileptic properties in the early 20th century (Hauptmann, 1912; Sills & Brodie, 2001; Rho & Sankar, 1999). Antiepileptic drugs (AEDs) form the foundation in the treatment of epilepsy because they are commonly used as first-line treatment following seizures.

The goal of all AEDs is to prevent or inhibit excessive and pathological neuronal discharge (Perucca, 1993; Soderpalm 2002). Additionally, AEDs strive to achieve maximal prevention of seizures with relatively few or no adverse events, reduce

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[9] Of the precipitating stimuli, if identifiable (Loiseau, 2001).

[10] Due to co-morbid conditions or contraindications.

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morbidity and mortality, improve quality of life, minimize cognitive and behavioral side effects, and increase functional independence (Nadkarni, LaJoie, & Devinsky, 2005; Sander, 2003; Kwan & Brodie, 2002; Perucca, Beghi, Dulac, Shorvon, & Tomson, 2000). AEDs provide freedom from seizures in approximately 70% of patients, and the common side effects they may experience (i.e., sedation, nausea, skin rash) typically resolve as their bodies adjust to the medications. In contrast, the remaining 30% of patients achieve partial freedom from seizures while experiencing side effects that may not resolve over time (i.e., weight gain, skin rash, alopecia, tremor, gingival hyperplasia, decline in attention and/or memory, fine motor difficulty) (Nadkarni et al., 2005).

The criteria for selecting which AEDs to prescribe include its clinical efficacy, tolerability, drug interaction profile, and ease of use (Brodie & Kwan, 2001). The criteria for choosing a specific AED for first-line treatment vary due to individual differences such as seizure type and frequency, and pharmacological interaction with other medications in a patient's regimen. Although certain AEDs are recommended for specific epilepsies, it remains challenging to confirm which AED would result in maximal response and/or tolerability in specific epilepsy diagnosis (Nadkarni & Devinsky, 2005).

The history of the development of AEDs spanned three generations. The first generation of AEDs occurred from the early to mid 1900's, during which phenytoin (Dilantin®; PHT), phenobarbital (Luminal®), benzodiazepines, primidone (Mysoline®; PRM), and ethosuximide (Zarontin®) were discovered and prescribed for the treatment of epilepsy. The second generation of AEDs occurred in the 1960's to 1970's, during which carbamazepine (Tegretol®; CBZ) and valproate/valproic acid (Depakote®; VPA) were

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introduced. The third, and most prolific, generation of AEDs followed approximately twenty years later in the early 1990's, when vigabatrin (Sabril®), lamotrigine (Lamictal®; LMT), gabapentin (Neurontin®; GBP), tiagabine (Gabitril®; TGB), topiramate (Topamax®; TPM), felbamate (Felbatol®; FBM), oxcarbazepine (Trileptal®; OXC), and levetiracetam (Keppra®; LEV) were introduced and approved by the Food and Drug Administration (FDA) for the treatment of epilepsy (Schachter, 2004). See Tables 3 and 4.

The eight newer AEDs introduced in the past decade are commonly known as the "newer" AEDs by researchers and physicians, as opposed to the traditional or older AEDs that came before. A major difference between the traditional and newer AEDs is the newer AEDs are associated with fewer adverse effects and better tolerability than the traditional AEDs (Nadkarni & Devinsky, 2005).

Overall treatment success of the first and second generation AEDs was achieved most notably with carbamazepine, phenytoin, phenobarbital, and primidone (Mattson, Cramer, Collins, Smith, Delgado-Escueta, Browne, Williamson, Treiman, McNamara, & McCutchen, 1985). The large Veteran Administration studies (hereafter referred to as the VA studies) conducted in the 1980's provided valuable data on AEDs' efficacy and tolerability in hundreds of patients with primary generalized or focal/localization-related seizures. Among those treated initially with monotherapy ("one-drug"), approximately 70% achieved complete or excellent seizure control, while the remaining 30% had poor seizure control. Among those treated with two AEDs ("polytherapy"), approximately 40% experienced seizure control, but freedom from seizure occurred in only 9%. These findings, along with the work of others (Shorvon & Reynolds, 1977, 1979; Reynolds & Shorvon, 1981), supported the practice of monotherapy over polytherapy in the treatment

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of epilepsy (Mattson et al., 1985; Mattson, Cramer, & Collins, 1992; Prevey, Delaney, Cramer, Cattanach, Collins, & Mattson, 1996; Mattson & Cramer, 1997; Sander, 2004; Thompson & Trimble, 1982, 1983; Trimble & Thompson, 1984; Drane & Meador, 2002; Kelso & Cock, 2005).

Overall, the prognosis from AED treatment is generally positive in patients who experience seizures with the following characteristics: focal/localization-related; triggered by specific stimuli; childhood absence-type; and nonspecific with generalized tonic-clonic symptoms (Sander, 2004). Although all AEDs are effective in managing focal/localization-related epilepsies, with some newer AEDs (e.g., topiramate, levetiracetam, and lamotrigine) being very efficacious in managing primary generalized epilepsies, it remains unclear if specific combinations of AEDs are more effective than others in a polytherapy regimen (Kelso & Cock, 2005).

3. Mechanisms of action of AEDs

Given that a seizure is the clinical manifestation of a hyperexcitable neuronal network (Engel, 1989), the most effective AED essentially enhances inhibitory processes and/or reduces excitatory processes through their actions on specific ion channels. This is accomplished by either directly affecting the opening and/or closing of the channels, or indirectly by modulating the functions of neurotransmitters that control their activity.

The classification of AEDs based on mechanisms of action has been, and continues to be, a challenging task due to the diverse range of AEDs' pharmacological actions, and other unresolved issues. Some AEDs have more than one mechanism of action, while others (e.g., levetiracetam) remain divisive (Kwan, Sills, & Brodie, 2001; Upton, 1994; Schachter, 1995; Macdonald & Kelly, 1995; Meldrum, 1996; Coulter,

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1997; White, 1999; Armijo et al., 2005; Lukyanetz, Shkryl, & Kostyuk, 2002). A patient who does not respond to carbamazepine may respond to phenytoin, even though both mechanisms involve the blockade of Na^+ channels (Deckers, Czuczwar, Hekster, Keyser, Kubova, Meinardi, Patsalos, Renier, & Van Rijn, 2000).

Such diversity in classifying the mechanisms of action of AEDs is not surprising considering epilepsy is a group of disorders, rather than a single disease. It is important to establish possible relationships between specific mechanisms of action and their cognitive effect(s), as well as to promote and refine future development and use of AEDs in epilepsy and other neurologic or psychiatric disorders.

Known mechanisms of action of most AEDs include the modulation of voltage-dependent ion channels (e.g., Na^+, Ca^{2+}), enhancement of GABA-mediated inhibitory neurotransmission, and attenuation of excitatory transmission predominantly mediated by glutamate. See Table 5 for the classification of AEDs by their mechanisms of action as proposed by Meldrum (1996), Kwan et al. (2001), Armijo et al. (2005), and Coulter (1997).

New mechanisms of action of AEDs continue to be discovered. An example is levetiracetam (Keppra®), an AED often used in polytherapy to manage focal/localization-related epilepsies. While its exact mechanism of action remains to be discovered since its FDA approval in 1999, it does not appear to share the mechanisms common to other AEDs such as blockade of sodium channels or enhancement of GABA-mediated inhibition. Two papers published between June and July of 2004 reported conflicting mechanisms of action for levetiracetam. One paper proposed its antiepileptic properties derived from its binding to the synaptic vesicle protein 2A (SV2A) (Lynch, Lambeng,

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Nocka, Kensel-Hammes, Bajjalieh, Matagne, & Fuks, 2004), whereas the other paper proposed a selective blockade of N-type high-voltage-activated Ca^{2+} channels (Pisani, Bonsi, Martella, De Persis, Costa, Pisani, Bernardi, & Calabresi, 2004). Therefore, investigation in the mechanisms of AEDs remains a work in progress, particularly with the continuous emergence of new AEDs (e.g., pregabalin/ Lyrica®)[11] (Hamandi & Sander, 2006; FDA, http://www.accessdata.fda.gov/scripts/ cder/drugsatfda/).

a. Modulation of voltage-gated sodium channels

AEDs that block the voltage-gated Na^+ channels prolong the refractory period to stabilize the inactive state, and prevent repetitive firing and posttetanic potentiation of the seizure activity. This appears to be the primary mechanism of action of several AEDs, such as phenytoin, carbamazepine, and lamotrigine. Other AEDs proposed to exhibit similar mechanism of action include topiramate, oxcarbazepine, felbamate, and zonisamide (Kwan et al., 2001; Armijo et al., 2005).

b. Enhancement of GABA-mediated inhibition

The predominant and most prevalent inhibitory neurotransmitter of the central nervous system (Schwartz, 1988), GABA is localized primarily in short-axon interneurons that synapse on cell bodies and proximal axons. Its central purpose is to maintain neuronal inhibition to counterbalance excitation, thereby preventing seizure activity (Westbrook, 2000). The GABAergic system is the target of many AEDs, which suppress seizure activity through GABA's interaction with its receptor subtypes, $GABA_A$

[11] A new AED called Pregabalin (Lyrica) was approved by the FDA in June 2005 to treat localization-related epilepsies (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/).
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and $GABA_B$[12].

The activation of $GABA_A$ results in the influx of Cl- ions to hyperpolarize the membrane and inhibit action potentials, increase GABA synthesis, and inhibit GABA uptake and metabolism. The activation of the $GABA_B$ receptor, which is coupled to G-proteins pre- and post-synaptically, reduces the presynaptic Ca^{2+} current involved in neurotransmitter release, and increases the K^+ current to promote long-lasting inhibitory postsynaptic potentials (Olsen & Sapp, 1995; Julien, 2001; Armijo et al., 2005). AEDs reported to work on the GABAergic system include barbiturates, benzodiazepines, felbamate, valproic acid, primidone, tiagabine, and gabapentin[13] (Kwan et al., 2001; Armijo et al., 2005).

c. Attenuation of excitatory transmission (glutamate)

The most important excitatory neurotransmitter is glutamate, which interacts with several receptor subtypes. Glutamate receptor subtypes are categorized into either ionotropic or metabotropic, and both types are found post-synaptically on excitatory principal cells, inhibitory interneurons, and certain types of glial cells. Of relevance to the current investigation are the ionotropic subtypes, which consist of the alpha-amino-2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropanoic acid (AMPA), kainate, and NMDA receptors. They are distinguished from one another by their permeability to cations and their sensitivity to pharmacological agonists / antagonists (Kandel & Siegelbaum, 2000).

All ionotropic glutamate receptors are permeable to Na^+ and K^+. When activated

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[12] GABA also interacts with the newly-characterized $GABA_C$ receptor, although its role in suppressing seizures is unclear (Armijo et al., 2005).

[13] Gabapentin has been shown to suppress seizure activity by increasing synaptic GABA levels, but its exact mechanism of action is unclear. Nevertheless, its action appears to be different from those of the other AEDs, in that gabapentin does not directly interact with the $GABA_A$ and $GABA_B$ receptor subtypes to suppress seizures.

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by glutamate, they allow influx of Na^+ and outflow of K^+ through the channel openings, resulting in depolarization of the membrane and action potentials (Kandel & Siegelbaum, 2000; Meldrum, 1995). Experimental studies of epileptogenesis suggest that NMDA, AMPA and kainate agonists induce seizure activity, whereas their antagonists suppress seizure activity (Holmes, 1997). AEDs suggested to work as glutamatergic receptor antagonists include felbamate and topiramate (Kwan et al., 2001; Armijo et al., 2005).

d. Modulation of voltage-gated calcium (Ca^{2+}) channels

Voltage-gated Ca^{2+} channels regulate Ca^{2+} entry into neurons, therefore they play a significant role in Ca^{2+}-dependent functions such as neurotransmitter release and neuronal excitability. Calcium conductance is involved in the initiation and maintenance of ictal activity, which are prevented by specific AEDs with mechanisms at voltage-gated Ca^{2+} channels (Kandel & Siegelbaum, 2000; Lawthom & Smith, 2003)

Voltage-gated calcium Ca^{2+} channels are classified as high or low threshold depending on the membrane potential at which they are activated, and both groups affect neuronal excitability. The high-threshold activated Ca^{2+} channel (or high voltage-activated Ca^{2+} channel, HVACC) is further classified into L-, N-, P-, Q-, and R-types, and they control the release of neurotransmitters such as glutamate. They are prevalent throughout the central nervous system and are located on dendrites, cell bodies, and nerve terminals (Kandel & Siegelbaum, 2000). Felbamate and levetiracetam have been proposed to have antagonistic mechanisms on the high-voltage-activated Ca^{2+} channels (Cosford, Meinke, Stauderman, & Hess, 2002).

The low-threshold activated (or low-voltage-activated) T-type Ca^{2+} channel is located predominantly in the thalamocortical relay neurons, and is said to be directly

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involved in controlling the membrane potential and synchronized discharges in epilepsy. Ethosuximide and zonisamide have been proposed to have antagonistic mechanisms on the low voltage-activated T-type Ca^{2+} channel (Cosford et al., 2002; Armijo et al., 2005). See Figure 1 for the mechanisms of AEDs at excitatory and inhibitory synapses.

4. Cognitive effects of AEDs in epilepsy

The earliest systematic studies of the cognitive side effects of AEDs were conducted by Somerfeld-Ziskind and Ziskind (1940) and W. G. Lennox (1942), who were among the first to suggest the possible relationship between AEDs and cognitive changes. Many studies followed since their discoveries, most notably in the past 20-30 years, on the cognitive effects of both traditional and newer AEDs in adult patients with epilepsy. Unfortunately, the number of studies performed in adult patients outnumbers those performed in children and the elderly due to medical and ethical concerns, therefore the findings thus far are more applicable to adults between 18-59 years old than to other age groups.

Cognition varies remarkably as a function of factors associated with seizures such as etiology, frequency, duration and severity, age of onset, types of seizure, symptomatic etiologies such as brain lesions, and/or developmental anomalies (Meador, 2002; Dodrill, 2002). In addition to these variables, cognitive impairment also varies as a function of the AEDs.

However, a number of consistent risk factors associated with AED treatment has been reported. These factors include polytherapy, AED serum levels beyond the therapeutic range[14], and high seizure frequency and severity, all of which exacerbate

[14] "A small range of serum concentrations within which seizure prevention is achievable without significant toxicity or side effects" (Scheyer and Cramer, 1990).

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cognitive side effects (Ortinski & Meador, 2004). The importance of controlling for AED serum level in studies of cognitive effects of AEDs was illustrated by a double-blind cross-over[15] study conducted by Dodrill and Troupin (1977), who found that carbamazepine was associated with fewer cognitive effects than phenytoin in a monotherapy regimen. However, they refuted their findings 14 years later because they had included subjects with phenytoin serum levels greater than the therapeutic range, which possibly hindered their overall performance. A re-analysis to exclude data from those subjects demonstrated no statistical significance in all neuropsychological differences between carbamazepine and phenytoin, but the findings remain to be corroborated due to other flaws in the research design, such as small sample size for both groups of subjects (n = 46) (Dodrill & Troupin, 1977, 1991).

Some studies suggest that the newer AEDs are associated with fewer side effects and better seizure control than the older AEDs. The cognitive effects of older AEDs (i.e., barbiturates, benzodiazepines, phenytoin, and valproate) include sedation and cognitive deficits such as cognitive and motor speed, attention, and memory. Although carbamazepine, phenytoin, and valproic acid have been associated with similar cognitive effects, they appear to be less deleterious than those of phenobarbital. In addition, these effects occurred more frequently in polytherapy than monotherapy (Ortinski & Meador, 2004; Meador, 1998; Drane & Meador, 2002; Meador, Loring, Moore, Thompson, Nichols, Oberzan, Durkin, Gallagher, & King, 1995; Meador, 2002; Meador et al., 1993, 1995, 1991; Dodrill & Temkin, 1989; Dodrill & Troupin, 1991; Brunbech & Sabers, 2002).

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[15] A research design in which all subjects are given one drug for a specific period of time, followed by two double-blind periods during which subjects are randomly assigned into one of two groups to receive one drug, and complete crossover to the other drug for the second period. **AEDs** = antiepileptic drugs; **GPT** = Grooved Pegboard Test; **PEGDT** = Dominant T-scores on GPT; **PEGNDT** = non-dominant T-scores on GPT; **SDMT** = Symbol Digit Modalities Test, **SDMTLN** = natural logarithm for SDMT raw scores; **SD** (or ±) = standard deviation; **SEM** = standard error of the mean

The cognitive effects of newer AEDs (i.e., gabapentin, topiramate, lamotrigine, tiagabine, and levetiracetam) are considered to be less severe than those of the older AEDs, with the exception of tiagabine, which has been frequently associated with impaired attention, psychomotor speed, and verbal fluency (Cohen, Ashby, Crowley, Land, Peck, & Miller, 1985; Meador et al., 1999; Martin, Kuzniecky, Ho, Hetherington, Pan, Sinclair, Gilliam, & Faught, 1999; Ojemann, Ojemann, Dodrill, Crawford, Holmes, Dudley, 2001). Further study is necessary before conclusions can be drawn regarding the precise cognitive effects of the newer AEDs compared to the older AEDs.

D. FINE MOTOR DEXTERITY IN EPILEPSY

A review of research studies published between 1980 and 2005 suggest that patients with epilepsy undergoing mono- or poly-therapy with AEDs often experience problems in fine motor dexterity such as impaired psychomotor speed, deficits in visuomotor control, and motor incoordination, with patients on polytherapy demonstrating more problems than patients on monotherapy (Lendt, Gleissner, Helmstaedter, Sassen, Clusmann, & Elger, 2002; Weglage, Demsky, Pietsch, & Kurlemann, 1997; Thompson & Trimble, 1982, 1983; Trimble & Thompson, 1984; Reynolds & Trimble, 1985; Trimble, 1987; Smith, Mattson, Cramer, Collins, Novelly, & Craft, 1987; Dodrill & Temkin, 1989; Meador et al., 1990, 1991, 1995, 1998, 1999, 2003, 2005; Dodrill & Wilensky, 1992; Meador, 2002; Prevey et al., 1998; Brodie, McPhail, Macphee, Larkin, & Gray, 1987; Smith et al., 1986; Aldenkamp & Vermeulen, 1995; Beckung & Uvebrant, 1993; Braathen, von Bahr, & Theorell, 1997).

Such patterns of findings suggest a relationship of AEDs to the deficits in fine motor dexterity in patients with epilepsy. One limitation of these findings is the lack of

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specificity beyond concluding which AEDs produce the most (or least) amount of motor effects. In addition, there has been little exploration in the extent to which the mechanisms of action of AEDs contribute to fine motor functioning.

A third limitation is the use of imprecise measures of fine motor dexterity in the test batteries, such as the Finger Tapping Test (Dodrill & Troupin, 1977; Dodrill & Temkin, 1989; Thompson & Trimble, 1982, 1983; Trimble & Thompson, 1984; Reynolds & Trimble, 1985; Dodrill & Wilensky, 1992), which is more sensitive to tremor and motor slowing than to fine motor difficulty (Reitan & Wolfson, 1993). A fourth limitation is the use of total scores rather than task-specific scores, which made it difficult to separate fine motor functioning from other abilities (Smith et al., 1987).

Finally, other issues such as inadequate sample size in longitudinal designs (Meador et al., 1991; Thompson & Trimble, 1983; Meador et al., 2005; Germano, Gagliano, Magazu, Sferro, Calarese, Mannarino, & Calamoneri, 2005), lack of representation of AEDs in comparing effects on fine motor functioning (Meador et al., 1990, 1991, 1995, 2005; Dodrill & Temkins, 1989; Trimble & Thompson, 1984), and relatively short duration of AED treatment in the experimental conditions (e.g., months) made it difficult to generalize the findings to patients undergoing years of treatment (Meador et al., 1991).

1. Neuroanatomy of fine motor dexterity

Fine motor dexterity is mediated by the reciprocal connections between the motor cortex, the sensory cortex, and the cerebellum, which plays a crucial role in coordinating our movement, ensuring accuracy, and adjusting the speed at which we perform a

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response. These actions range from simple pointing and walking, to complex movements such as playing the piano fluidly (Horne & Butler, 1995; Ghez, 1991).

The cerebellum integrates afferents originating from the primary motor cortex, supplementary motor cortex, the basal ganglia, and the spinal cord through their projections via the corticopontine system. The primary motor cortex sends excitatory projections responsible for motor coordination to the spinal cord through the corticospinal tracts[16], which are the largest and most important descending fiber system in humans. These fiber tracts descend ipsilaterally to the internal capsules, the cerebral peduncles of the midbrain, and through the ventral pons to the ventral surface of the medulla to form the pyramids. Decussation of these fibers[17] occurs at the caudal region of the pyramids, where the corticospinal axons cross over the midline to continue their descent to the contralateral side, and enter the lateral funiculus of the spinal cord to become the lateral corticospinal tracts. Collateral fibers from the corticospinal tract synapse in the basis pontis, where they project to the opposite cerebellar hemisphere (Parent, 1996).

The efferents from the cerebellum to the cortex may be understood by studying the cerebello-thalamo-cortical (CTC) pathway, which has been implicated in monitoring skilled voluntary movement to ensure accuracy (Shinoda, Kano, & Futami, 1985; Horne & Butler, 1995). The CTC pathway arises from the neurons in the deep cerebellar nuclei, which send excitatory projections to the thalamo-cortical neurons in the ventrolateral (VL) and ventromedial nuclei of the thalamus, which in turn project excitatory outputs to the pyramidal tract neurons in the primary motor cortex. Electrolytic lesions applied to

[16] They arise from various cortical regions, including the premotor, supplementary motor, and primary motor areas of the frontal lobes (Parent, 1996).
[17] Also known as pyramidal decussation.
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the VL thalamus resulted in impaired motor coordination, balance, and equilibrium (Jeljeli, Strazielle, Caston, & Lalonde, 2003; Yoshida, Yajima, & Uno, 1966; Horne & Butler, 1995; Futami, Kano, Sento, & Shinoda, 1986; Aumann, 2002; Meldrum, 1981).

Through the CTC pathway, the cerebellum compares the intended actions with the actual performance through two features of its organization. The first feature consists of an internal feedback mechanism, whereby the cerebellum receives corticospinal projections responsible for planning particular movements through the corticopontocerebellar system. The second feature consists of an afferent sensory mechanism, whereby the cerebellum receives proprioceptive feedback about motor performance during the course of a movement. These two features of the cerebellum's organization work together to ensure movement accuracy (Futami et al., 1986; Horne & Butler, 1995; Aumann, 2002).

Patients with cerebellar lesions manifest impaired timing of their movement when compared to control subjects and patients with other neurologic disorders[18]. This impairment suggested the presence of an internal time-keeping mechanism involving the cerebellum, basal ganglia, thalamus, cerebral cortex, and spinal cord (Ivry & Keele, 1989). Disorders associated with cerebellar lesions were also well-described by Gordon Holmes' study of soldiers sustaining gunshot wounds during World War I. Holmes (1939) described three fundamental deficits in these patients. The first deficit was hypotonia in ipsilateral muscles, represented by reduced resistance to the displacements of limb(s) and loss of muscle tone. The second impairment was deficits in executing voluntary movements, commonly referred to as ataxia and characterized by several

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[18] Parkinson's disease, cortical lesions, peripheral neuropathy, sensory loss, epilepsy, (Ivry & Keele, 1989).

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symptoms such as delay in initiation, and errors in the range and force applied at the end of a directed movement[19] (Manto & Bosse, 2003; Holmes, 1939). The third deficit associated with cerebellar lesions is an action tremor, which was most apparent at the end of a movement when the patient attempted to achieve the greatest precision toward the target (Ghez, 1991; Holmes, 1939; Stolze, Klebe, Petersen, Raethjen, Wenzelburger, Witt, & Deuschl, 2002; Manto & Bosse, 2003).

Disorders of motor timing and coordination were also observed in some patients with epilepsy, who experienced ataxia (Alioğlu et al., 2000), dysmetria and/or hypermetria in the limbs (Holmes, 1939), abnormal gait (McLain et al., 1980; Stolze et al., 2002), dysdiadochokinesia (Alioğlu et al., 2000), reduced motor processing and response speed (Trimble, 1987; Braathen et al., 1997; Meador, 1998), and/or reduced fine motor dexterity (Lendt et al., 2002; Weglage et al., 1997). Research suggested the association of cerebellar lesions to these disorders in patients with epilepsy, given that anomalies in the vermis and flocculonodular lobe have been associated with impaired ability to control the muscles of the torso, while injury to the intermediate and lateral cerebellar hemispheres have been associated with impaired ability to control the action and motor planning of the extremities (Ghez, 1991; Parent, 1996).

Studies using positron emission tomography (PET) and MRI have shown that interictal cerebellar blood flow and cerebellar glucose metabolism are reduced in patients with generalized and focal seizures compared to healthy subjects (Schauble & Cascino, 2003; Engel et al., 1982; Meldrum, 1981; Theodore et al., 1987; Meldrum, 1983). Selective neuronal losses result from their low threshold for seizure activity, which are associated with an increased influx of Na^+ and Ca^{2+}. The increase in Ca^{2+} influx disrupts

[19] Also known as dysmetria.

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the neurons' ability to conduct synaptic transmission and maintain homeostasis, resulting in neuronal loss or ischemic cell damage. This may partially explain the selective loss of purkinje cells in the cerebellum in patients with epilepsy (Meldrum, 1981; 1983).

2. Neuropsychological measures of fine motor dexterity

Neuropsychological measures are typically utilized in assessing cognitive functions in patients with epilepsy and other neurologic disorders. The ideal test of any cognitive function in epilepsy should meet the following criteria: sensitivity and specificity for the deficit(s) produced by the disorder; reproducible by different researchers; ease of administration; and acceptance as the standard by researchers in epilepsy (Devinsky & Tarulli, 2002). For unknown reasons, established neuropsychological measures of fine motor dexterity are few in number compared to the measures for non-motor cognitive functions such as executive functions, memory, attention and concentration, perceptual organization, and language.

Fine motor dexterity is fundamental to any comprehensive neuropsychological evaluation, as its impairment may indicate the lateralization of lesions (Parent, 1996; Goldstein, 1974; Golden, 1978). Neuropsychological measures that are commonly used to assess fine motor dexterity and slowing, and are reportedly sensitive to difficulties associated with AEDs, include the Grooved Pegboard Test (Heaton, Grant, & Matthews, 1992) and Symbol Digit Modalities Test (Smith, 1993).

The Grooved Pegboard Test (GPT; Figure 2) is a component of several neuropsychological assessment batteries such as the Wisconsin Neuropsychological Test Battery (Harley, Leuthold, Matthews, & Bergs, 1980; Matthews & Klove, 1964), the Repeatable Cognitive-Perceptual-Motor Battery (Kelland, Lewis, & Gurevitch, 1992;

AEDs = antiepileptic drugs; **GPT** = Grooved Pegboard Test; **PEGDT** = Dominant T-scores on GPT; **PEGNDT** = non-dominant T-scores on GPT; **SDMT** = Symbol Digit Modalities Test, **SDMTLN** = natural logarithm for SDMT raw scores; **SD** (or ±) = standard deviation; **SEM** = standard error of the mean

Lewis & Kupke, 1992), and the expanded Halstead-Reitan Battery (Heaton et al., 1992). In this test, the pegs must be rotated into position as quickly as possible, which adds a dimension of complexity not found in other motor tasks such as the Purdue Pegboard Test (Tiffen, 1968), and therefore it has been found to be a sensitive instrument in detecting general slowing due to medication or disease progression. For example, researchers have used the Grooved Pegboard Test to evaluate cognitive and motor slowing in bipolar disorder (Wilder-Willis, Sax, Rosenberg, Fleck, Shear, & Strakowski, 2001), Asperger syndrome (Weimer, Schatz, Lincoln, Ballantyne, & Trauner, 2001), HIV infection (Honn, Para, Whitacre, & Bornstein, 1999), low birth-weight children (Miller, 1999), and diabetes (Deichmann, 1998). This test has also been used extensively for identifying lateralized impairment (Haaland, Cleeland, & Carr, 1977; Haaland & Delaney, 1981) in diseases such as Parkinson's disease (Demakis, Mercury, Sweet, Rezak, Eller, & Vergenz, 2002). See Methods section for further details.

The Symbol Digit Modalities Test (SDMT; Figure 3) was developed to identify individuals with neurological impairment, but its applications have broadened since its introduction. A written test that measured mental speed, motor speed, and mental flexibility, individuals had 90-seconds to identify and copy the symbols that corresponded to their numbers using a reference key (Smith, 1993; Lezak, 2004; Spreen & Strauss, 1998). It is an altered and inverse form of the Digit Symbol Test (Wechsler, 1955), which required the identification of the numbers to their symbols. See Methods section for further details.

AEDs = antiepileptic drugs; **GPT** = Grooved Pegboard Test; **PEGDT** = Dominant T-scores on GPT; **PEGNDT** = non-dominant T-scores on GPT; **SDMT** = Symbol Digit Modalities Test, **SDMTLN** = natural logarithm for SDMT raw scores; **SD** (or ±) = standard deviation; **SEM** = standard error of the mean

E. CURRENT STUDY

1. Purpose

Based on a review of the research on the cognitive effects of AEDs in patients with epilepsy, the paucity of findings on the extent to which mechanisms of action of AEDs contribute to fine motor difficulty justifies the current investigation. The findings from the current investigation may have implication beyond pharmacological treatment of epilepsy, given the diverse indication of AEDs in other neurologic or psychiatric disorders, which would improve treatment planning and quality of life in individuals treated with AEDs.

2. Hypotheses

a. Epilepsy

   i. Patients with epilepsy will show reduced fine motor dexterity when compared to normative means (Heaton et al., 1992; Smith, 1993).

   ii. Years of seizure will be negatively correlated with fine motor dexterity in patients with epilepsy.

b. Antiepileptic Drugs

   i. Years of AED treatment will be negatively correlated with fine motor dexterity in patients with epilepsy.

   ii. Mechanisms of action of AEDs will contribute to varying degrees of fine motor impairment in patients with epilepsy, with sodium channel blockers related to fewer motor problems compared to AEDs with other mechanisms of action.

iii. Number of ion channels targeted by AEDs regimen will contribute to varying degrees of fine motor impairment in patients with epilepsy.

iv. Patients with epilepsy on monotherapy AED regimen will show better fine motor dexterity than patients with epilepsy on polytherapy AED regimen.

AEDs = antiepileptic drugs; **GPT** = Grooved Pegboard Test; **PEGDT** = Dominant T-scores on GPT; **PEGNDT** = non-dominant T-scores on GPT; **SDMT** = Symbol Digit Modalities Test, **SDMTLN** = natural logarithm for SDMT raw scores; **SD** (or ±) = standard deviation; **SEM** = standard error of the mean

II. METHOD

This retrospective study was approved by the Institutional Review Boards at the NYU Comprehensive Epilepsy Center (NYUCEC), and Queens College of the City University of New York, prior to data collection.

A. DATA COLLECTION

All medical and neuropsychological data were previously collected between 2003 and 2005 from adult patients with epilepsy during their admission for Video-EEG monitoring at NYUCEC. The duration of their admission ranged from 5 – 7 days, during which all AED treatments were discontinued to elicit seizure activity, and neuropsychological evaluations were performed. Variability existed regarding to the onset of AED discontinuation[20] and of neuropsychological evaluation[21], which will be addressed in the "Discussion" section under subheading H2.

Neuropsychological evaluation was routinely requested by physicians and performed as part of a comprehensive neurologic examination. The purpose of the neuropsychological evaluation was to confirm or exclude the presence of cognitive impairment, and to construct a cognitive profile to assist in characterizing and/or lateralizing seizure activity. All neuropsychological evaluations were previously performed by trained graduate students or fellows in clinical neuropsychology at NYUCEC, under the supervision of a board-certified clinical neuropsychologist. Medical data for each patient were obtained through a clinical interview prior to the start of the neuropsychological evaluation, and confirmed by a review of medical records.

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[20] Discontinuation from AED regimens occurred at any time during admission due to individual variability (e.g., titration schedule for regimen, physician advice).

[21] Due to unpredictable variables such as patient fatigue, medical procedures (i.e., MRI) that delayed the evaluation or were incompatible with the examiner's availability, etc…

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Each patient was administered a neuropsychological test battery that included GPT, SDMT, or both. In some instances, both GPT and SDMT were administered to the same patient to provide additional support to confirm or exclude the presence of fine motor impairment. This discrepancy in test administration will be discussed in the section entitled "outcome variables."

1. Behavioral data

Data collected from the following noninvasive measures of fine motor dexterity, with established validity and reliability, will be selected for statistical analysis.

a. Grooved Pegboard Test (GPT; Heaton et al., 1992; Lezak, 2004) – a test of fine motor dexterity and speed. The pegboard consists of 25 equidistant holes in a 5 X 5 matrix with randomly-oriented slots. Each peg, which has a ridge along one side, must be rotated with only one hand to match the slot in the pegboard before it can be inserted. The goal is to insert a peg into each hole as quickly as possible, starting at the top row from left to right until all 25 holes are filled. A healthy individual would typically complete this task in approximately 50 seconds ($\mu = 50$, $\sigma = 10$), with slower performance in the non-dominant hand, which ranges from 70 seconds to the time limit of 300 seconds. This test generates two outcome variables: the time, in seconds, required to insert all pegs correctly with each hand. Each raw score is converted into standardized T-scores for clinical interpretation and/or statistical analysis.

b. Symbol Digit Modalities Test (SDMT; Smith, 1993; Lezak, 2004) - a written test of cognitive and motor speed, as well as attention. The goal is to identify nine different symbols corresponding to the numbers 1 through 9 using a reference

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key, and write as many correct matches as possible within a 90-second period. Using the dominant hand, an untimed practice trial is provided, followed by a timed test trial. The outcome variable generated from the timed test trial consists of the total number of correct matches within the time limit. Using normative data, raw scores will be standardized and used in statistical analysis.

c. Measures of intelligence – scores on tests of intelligence will be included in statistical analysis to ascertain its relationship to fine motor dexterity. All patients were previously administered standardized measures of intelligence [e.g., Wechsler Adult Intelligence Scale-Third Edition (WAIS-III), Wechsler Abbreviated Scale of Intelligence (WASI), (Wechsler, 1997; 1999)], which generated a Full Scale IQ (FSIQ) score for each patient.

B. DATA SELECTION: A THREE-STEP PROCESS

1. A review of neuropsychological records, which contain medical histories obtained through clinical interviews, will be performed to exclude patients with a documented or reported history of the following diagnosis or treatments:
    a. Nonepileptic seizures.
    b. Treatable cause of seizures.
    c. Status Epilepticus.
    d. Alcohol or other substance abuse.
    e. Co-morbid neurologic, psychiatric, or mood disorders requiring psychotropic treatment.
    f. Psychotic symptomatology or suicide attempt.

g. Treatment with any central nervous system depressants (e.g., barbiturates, benzodiazepines).

h. Poor compliance with AED regimen.

i. Current regimen contains more than three AEDs.

j. Inability to take AEDs independently.

2. If a patient passes the exclusion criteria, further review of the neuropsychological records will follow to select subjects based on the following inclusion criteria:

   a. Adult patients between 18-59 years old.

   b. Full Scale IQ ≥ 70.

   c. A formal diagnosis of epilepsy with focal/localization-related and/or generalized seizures[22] as confirmed by medical records.

   d. Completion of GPT and/or SDMT as part of the neuropsychological evaluation during admission for V-EEG monitoring and characterization of seizures at NYUCEC.

3. After meeting the above criteria, a review of medical records will follow to select those who have been prescribed the same AED regimen for at least one year at the time of the neuropsychological evaluation. This will complete the selection of subjects for the current study.

C. PREDICTORS

The following predictors will be selected from medical and/or neuropsychological records, and coded for statistical analysis:

1. Years of seizures (continuous variable).

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[22] Commission of ILAE, 1989.

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2. Years of AED treatment (continuous variable).
3. Number of AEDs in regimen at the time of the neuropsychological evaluation,
    a. One AED
    b. Two AEDs
    c. Three AEDs
4. Based on the AED regimen, type of therapy will be coded as:
    a. One AED = monotherapy
    b. More than one AED = polytherapy
5. The primary mechanisms of action of the AED regimen will be coded into seven levels based on a review of the literature (Kwan et al., 2001; Armijo et al., 2005; Meldrum, 1996; Coulter, 1997). Each subject's AED regimen will be classified by whether their "primary" action[23] involves:
    a. Blockade of the Na^+ channel only
    b. Blockade of the Ca^{2+} channel only
    c. Enhancement of GABAergic inhibition
    d. Blockade of both Na^+ and Ca^{2+} channels
    e. Synergistic mechanisms involving blockade of Na^+ and Ca^{2+} channels, blockade of ionotropic glutamate receptors, and enhancement of GABAergic inhibition
    f. Blockade of both Na^+ and Ca^{2+} channels, and enhancement of GABAergic inhibition
    g. Blockade of the Na^+ channel and enhancement of GABAergic inhibition

[23] As opposed to secondary mechanisms.

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6. Based on the above mechanisms of action, the number of ion channels targeted per AED regimen will be coded as:
    a. 1 ion channel
    b. 2 ion channel
    c. 3 ion channel
    d. 4 ion channel
7. Demographic variables
    a. Age
    b. Gender
    c. Handedness
    d. Years of education
    e. FSIQ scores

D. OUTCOME VARIABLES

The following three outcome variables will be selected from a review of neuropsychological records:

1. Two outcome variables will consist of bilateral performance on GPT, as measured by the number of seconds required to correctly insert all 25 pegs. Raw scores and standardized scores will be selected, the latter of which will be used for statistical analysis (variable names = PEGDT and PEGNDT).
2. One outcome variable will consist of the number of correct matches of symbols to numeral on the SDMT within the time limit. Raw scores and standardized scores will be selected, the latter of which will be used for statistical analysis (variable name = SDMT LN).

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In some instances, both GPT and SDMT were previously administered to the same patient to provide additional support for confirmation or exclusion of cognitive decline. Among the 164 subjects selected for the study:

1. Sixty-seven were administered only GPT
2. Sixty-six were administered only SDMT
3. Thirty-one were administered both tests (Figure 4)

Despite the discrepancy in test administration, independent samples t-tests showed that the difference in performance between all 164 subjects on GPT (N = 67), SDMT (N = 66), and both GPT and SDMT (N = 31) was not statistically significant. While the subjects who were administered GPT performed better (dominant hand mean = 35.21, SD = 13.75, SEM = 1.68) than those who were administered both GPT and SDMT (dominant hand mean = 30.68, SD = 13.60, SEM = 2.44), the difference was not statistically significant [dominant t(96) = 1.52, p = .13] (Table 6).

Similarly, the difference in performance between subjects who were given SDMT versus those who were given both GPT and SDMT was not statistically significant [*t*(95) -.086, p = .93] (Table 7). Therefore, it was feasible to use both GPT (N = 67 + 31 = 98) and SDMT (N = 66 + 31 = 97) as measures of fine motor dexterity[24] in all data analyses.

E. STATISTICAL PROCEDURES

All statistical analyses will be completed using the Statistical Package for the Social Sciences – version 11.0 (SPSS - 11.0), which is a common and commercially available computer software package for statistics (SPSS, 2001).

An alpha level of .05 will be used for all statistical analysis, and effect size will be

[24] As opposed to separating all subjects into three groups such as "GPT" versus "SDMT" versus "GPT + SDMT."

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calculated for the results of t-tests using the following equation: $\sqrt{\frac{t2}{t2+df}}$ (Rosnow & Rosenthal, 2005, p.328).

1. Normality of distribution

All raw scores for GPT and SDMT were previously converted to standardized T-scores ($\mu = 50$, $\sigma = 10$) based on established guidelines (Heaton et al., 1992; Smith, 1993) for clinical interpretation.

All standardized T-scores will be evaluated for non-normal distributions by dividing the skewness statistic from the standard error of the skewness statistic, and normal distribution is obtained if the quotient does not exceed ± 1.96 (Tabachnick & Fidell, 2001; Field, 2005).

Using this method to evaluate the normality of distribution, non-dominant hand T-scores on GPT (PEGNDT) are normally distributed, while dominant-hand T-scores on GPT (PEGDT) and raw scores on SDMT are both positively skewed. However, PEGDT will not be statistically transformed for two reasons: a) the skewness quotient for PEGDT is 2.04, which is only .08 above the cut-off value of ± 1.96; and b) to facilitate clinical interpretation and remain consistent with existing literature, T-scores are preferred over other standardized values.

The only statistical transformation will involve raw scores from SDMT (skewness quotient = 2.58), which will undergo a logarithmic transformation to base e[25] to obtain a normal distribution, according to the guidelines set forth in Tabachnick & Fidell (2001).

Consequently, the outcome variables entered into all statistical analyses will consist of bilateral T-scores from GPT (PEGDT and PEGNDT), and the logarithmically-

[25] Also known as natural logarithm.

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transformed scores from SDMT (SDMT LN), except for hypothesis 1a in which only T-scores are used for one-sample t-tests to compare means to normative data.

2. Statistical tests

Hypotheses 1a, which stated that patients with epilepsy would show reduced fine motor dexterity compared to normative means (Heaton et al., 1992), will be tested using one-sample t-tests to compare average performance on GPT and SDMT to normative data ($\mu = 50$, $\sigma = 10$).

Hypothesis 1b, which stated that years of seizure would be negatively correlated with fine motor dexterity, will be tested using bivariate Pearson's correlation.

Hypothesis 2a, which stated that years of overall AED treatment would be negatively correlated with fine motor dexterity, will be tested using bivariate Pearson's correlation.

Hypothesis 2b, which stated that mechanisms of action of AEDs would contribute to varying degrees of fine motor impairment, will be tested using a one-way analysis of variance (ANOVA) and post-hoc testing procedures.

Hypothesis 2c, which stated that which stated that the number of ion channels targeted by AEDs regimen would contribute to varying degrees of fine motor impairment, will be tested using a one-way ANOVA and post-hoc testing procedures.

Hypothesis 2d, which stated that patients on monotherapy would show better fine motor dexterity than patients on polytherapy, will be tested using independent samples t-test.

Bivariate Pearson's correlations will be performed to examine the relationship between the continuous predictors and the outcome variables. Point-biserial correlations

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(r_{pb}) will be used for dichotomous predictors (e.g., monotherapy versus polytherapy, and gender).

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III. RESULTS

A. DEMOGRAPHIC PROFILE

All subjects were fluent in English and did not demonstrate difficulty comprehending task instructions. Among the 164 subjects, 151 were right-handed according to self-report and hand preference for SDMT (a written task).

The subjects administered either GPT or SDMT were comparable in age, education level, overall intellectual functioning, and handedness, with slightly more women than men who were administered either test.

For the subjects who were administered GPT (N = 98), the average age was 35.9 ± 10.9 years and ranged from 18 to 56 years old. The average years of education were 13.8 ± 2.9 and ranged from 4 to 20 years. The average FSIQ was 95.5 ± 13.8. Fifty-six of these subjects were women, and 90 were right-handed.

For the subjects who were administered SDMT (N = 97), the average age was 35.9 ± 10.0 years, and ranged from 18 to 58 years old. The average years of education were 14.5 ± 2.4 and ranged from 7 to 20 years. The average Full Scale IQ was 98.7 ± 13.2. Fifty-seven of these subjects were women, and 90 were right-handed. See Tables 8 and 9 for the demographic profile of the sample.

Data for seizure diagnosis were available for 150 subjects. The diagnoses for the remaining 14 subjects were unavailable at the time of data collection. Among the 150 subjects, 33 had generalized seizures, 59 had partial/focal seizures, and 58 had partial/focal seizures with secondary generalizations. See Figures 5 – 6 for all 164 subjects, Figures 7 - 8 for the subjects administered GPT, and Figures 9 – 10 for the subjects administered SDMT.

AEDs = antiepileptic drugs; **GPT** = Grooved Pegboard Test; **PEGDT** = Dominant T-scores on GPT; **PEGNDT** = non-dominant T-scores on GPT; **SDMT** = Symbol Digit Modalities Test, **SDMTLN** = natural logarithm for SDMT raw scores; **SD** (or ±) = standard deviation; **SEM** = standard error of the mean

B. RELATIONSHIP BETWEEN PREDICTORS AND OUTCOME

Bivariate Pearson's correlations were performed to examine the intercorrelations among predictor variables, as well as the relationships of the predictors to the outcome variables (Table 10).

C. HYPOTHESIS TESTING

1. Overall performance of the study sample (hypotheses 1a)

To determine if the study sample demonstrated reduced fine motor dexterity compared to normative means (Heaton et al., 1992; Smith, 1993), one-sample t-tests using T-scores from GPT and SDMT[26] showed that the average performance on both tests was significantly below the normative mean (50 ±10). The average performance on GPT was 33.78 ± 13.79 (SEM = 1.39) for the dominant hand, and 34.98 ± 12.17 (SEM = 1.23) for the non-dominant hand. In other words, the average performance on the GPT was in the borderline range at the 5th percentile. The average performance on SDMT was 38.11 ± 14.25 (SEM = 1.45), which was in the low average range at the 12th percentile (Kirk, 1990) (Table 11).

Dominant-hand performance on GPT correlated with non-dominant hand performance ($r(96) = .75$, $p = .000$), as well as with performance on SDMT ($r(29) = .40$, $p = .03$). This suggested that the performance of one hand related to the other on the GPT, and additionally, dominant-hand performance on the GPT was related to performance on the SDMT (Table 12).

2. Years of seizures and of AED treatment (hypotheses 1b and 2a)

The average number of years of seizures was 16.35 ± 12.08 (SEM = .95) and the

[26] This is the only instance in which T-scores from SDMT were used in order to compare performance to GPT. All subsequent analyses used the transformed values of SDMT ("SDMTLN").

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average number of years of overall AED treatment was 4.69 ± 5.82 (SEM = .47). To determine if the outcome variables in the study sample correlated with the number of years of epilepsy (hypothesis 1b) and of AED treatment (hypothesis 2a), bivariate Pearson's correlations were calculated.

Results indicated no significant relationship between fine motor dexterity and years of seizure [PEGDT, r (94) = -.04, p = .70, PEGNDT, r (94) = -.04, p = .66, SDMTLN, r (93) = -.12, p = .25], and years of AED treatment [PEGDT, r (88) = -.05, p = .63, PEGNDT, r (88) = -.01, p = .96, SDMTLN, r (88) = -.01, p = .95]. These correlations remained nonsignificant after excluding outliers from the analyses (e.g., 7 subjects who experienced seizures for over 40 years, and 6 subjects who were treated with AEDs for more than 14 years) (Table 13).

In regards to its relationship with other predictors, years of seizure were correlated with years of AED treatment (r (148) = .35, p = .000), which was expected given that AEDs were frequently prescribed as the first-line treatment following seizure onset, hence the longer the years of seizure experience, the longer the AED treatment (Table 10).

Years of seizure also correlated with age of seizure onset (r (159) = -.64, p = .000), which in turn correlated with years of AED treatment (r (149) = -.26, p = .000). Hence, the younger the age of seizure onset, the longer the years of seizure experience, as well as years of AED treatment (Table 10).

3. Mechanisms of action of AEDs (hypothesis 2b)

Table 14 shows the performance on GPT and SDMT according to mechanisms of action. Figures 11 – 12 show the distribution of subjects for GPT and SDMT, and

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Figures 13 – 15 show the means and standard errors for PEGDT, PEGNDT, and SDMTLN.

Overall findings supported the role of specific mechanisms[27] of action on the performance of GPT only. Mechanisms of action correlated with bilateral performance on the GPT [PEGDT r(96) = -.26, p = .00; PEGNDT r(96) = -.35, p = .00], but not with SDMT (Table 15).

A one-way ANOVA showed a significant effect of mechanisms of action on non-dominant performance only [F(6, 91) = 2.70, p = .018]. Post-hoc testing using Tukey HSD revealed a significant difference in mean performance between the Na^+ group and the Na^+ + GABA group, with the Na^+ group (Mean = 40.47 ± 13.00, SEM = 2.30) significantly outperforming the Na^+ + GABA group (Mean = 27.36 ± 12.30, SEM = 3.71) in nondominant performance on GPT (Tables 16 - 17).

Exploratory analyses of Na^+ and GABAergic mechanisms on non-dominant performance of GPT were performed. Data from all 164 subjects were re-coded to exclude other mechanisms (i.e., blockade of Ca^{2+} channels), which reduced the seven levels of measurement to four, which were: a) Na^+-channel blockers only; b) GABAergic enhancers only; c) the combination of Na^+-channel blockers and GABAergic enhancers (Na^++ GABA); and d) neither Na^+ nor GABAergic mechanisms. A one-way ANOVA and post-hoc testing procedures reduced the alpha level from .018 to .009, which reduced the chances of a Type I error (Tables 18 - 19). This corroborated the findings from the previous ANOVA.

Table 20 shows the AED regimens involving blockade of Na^+ channels, enhancement of GABAergic inhibition, and both mechanisms for the corresponding

[27] Please refer to the Method section, predictor #5 (page 43-44) for the levels of the mechanisms.
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subjects who were administered GPT. Figures 16 – 17 show the means and standard errors for bilateral performance on GPT.

It was noted that the subjects in the Na^++ GABA group experienced longer years of seizures [r(90) = .21, p = .043], and their first seizures at younger ages [r(90) = -.21, p = .042] than the subjects in monotherapy with either a Na^+-channel blocker or GABAergic enhancer (Tables 21-22).

4. The number of ion channels (hypothesis 2c)

A one-way ANOVA revealed no statistical significance for the number of ion channels targeted by the AED regimen on fine motor dexterity (Table 23). Hence, any variability in fine motor impairment as measured by GPT and SDMT could not be attributed to the number of ion channels targeted by the AED regimen (Tables 23).

5. Type of AED therapy: monotherapy versus polytherapy (hypothesis 2d)

An independent samples t-test showed that the subjects in monotherapy performed significantly better than those in polytherapy on all three outcome variables [PEGDT $t(96) = 3.55$, p = .001, effect size = .34; PEGNDT $t(96) = 3.73$, p = .000, effect size = .36; SDMT $t(95) = 2.01$, p = .048, effect size = .20]. See Table 24, and Figures 18 - 20.

The age of subjects was not significantly related to the type of AED therapy. The average age of subjects in monotherapy was 37.68 ± 9.95, whereas the average age of subjects in polytherapy was 34.96 ± 10.85 (Table 25). Other variables such as years of seizure or of AED treatment also did not correlate with the type of AED therapy.

A one-way ANOVA showed a significant effect of the one-AED regimen on bilateral performance of GPT [dominant F(2, 94) = 5.15, p = .008; non-dominant F(2, 94)

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= 5.82, p = .004]. Post-hoc testing showed that subjects on the one-AED regimen significantly outperformed those on two- or three-AED regimen, with no significant difference between the two- and three-AEDs regimens. These findings provided further support for monotherapy over polytherapy in bilateral fine motor dexterity (hypothesis 2d) as measured by GPT (Tables 26 – 28, and Figures 21 – 22).

D. DEMOGRAPHIC VARIABLES

Demographic variables that correlated with performance on GPT and SDMT were gender, years of education, and FSIQ.

1. Gender

An independent samples t-test revealed a significant effect of gender on dominant-hand performance of GPT [$t(96) = 2.32$, p = .02, effect size = .23)], with men (M = 37.43 ± 13.87, SEM = 2.14) significantly outperforming women (M = 31.04 ± 13.20, SEM = 1.76) (Tables 29 - 30).

2. Education and FSIQ

Years of education correlated with Full Scale IQ [r(153) = .50, p = .000] (Table 10), and they correlated with performance on both GPT and SDMT, suggesting that fine motor dexterity was associated with higher education level and intellectual functioning. Years of education correlated higher with performance on SDMT [r(95) = .42, p = .000] than on GPT [PEGDT r(96) = .19, p = .030; PEGNDT r(96) = .20, p = .020], whereas FSIQ uniformly correlated with all outcome variables [PEGDT r(89) = .42, p = .000; PEGNDT r(89) = .44, p = .000; SDMT r(92) = .43, p = .000] (Table 31).

AEDs = antiepileptic drugs; **GPT** = Grooved Pegboard Test; **PEGDT** = Dominant T-scores on GPT; **PEGNDT** = non-dominant T-scores on GPT; **SDMT** = Symbol Digit Modalities Test, **SDMTLN** = natural logarithm for SDMT raw scores; **SD** (or ±) = standard deviation; **SEM** = standard error of the mean

IV. DISCUSSION

The current study sought to bridge some gaps in the literature on the behavioral effects of AEDs, specifically by exploring the extent to which their mechanisms of action contributed to fine motor difficulty. Other predictive factors examined were the duration of seizures and of AED treatment, and the type of AED therapy (e.g., monotherapy versus polytherapy). Overall findings indicated the significance of specific AED mechanisms of action, the type of AED therapy, and specific demographic variables on fine motor dexterity.

A. OVERALL PERFORMANCE (hypothesis 1a)

Overall performance in patients with epilepsy on both GPT and SDMT was below that of published normative data (Heaton et al., 1992; Smith, 1993), and ranged from borderline to low average, respectively. This was consistent with previous findings (Lendt et al., 2002; Weglage et al., 1997; Thompson & Trimble, 1982, 1983; Trimble & Thompson, 1984; Reynolds & Trimble, 1985; Trimble, 1987; Smith et al., 1987; Dodrill & Temkin, 1989; Meador et al., 1990, 1991, 1995, 1998, 1999, 2003, 2005; Dodrill & Wilensky, 1992; Meador, 2002; Prevey et al., 1998; Brodie et al., 1987; Smith et al., 1986; Aldenkamp & Vermeulen, 1995; Beckung & Uvebrant, 1993; Braathen et al., 1997) and supported hypothesis 1a.

It is generally accepted that a greater than 10% advantage in the dominant hand indicates the presence of an ipsilateral lesion, whereas a lower than 10% advantage in the dominant hand reflects a contralateral lesion (Boll, 1981; Reitan & Wolfson, 1993). This pattern of fine motor impairment was absent in the predominantly right-handed subjects in the current study, with respect to their performance on GPT, since the average

performance was in the borderline range, bilaterally.

The discrepancy between the mean performance on GPT and SDMT may be attributed to the fact that GPT was more challenging and sensitive to fine motor impairment than SDMT, which measured additionally abilities such as sustained attention.

Nevertheless, SDMT was included in the current study due to its relative sensitivity to detect motor slowing, a skill that was also measured by GPT (Ho, Sahakian, Brown, Barker, Hodges, Ane, Snowden, Thompson, Esmonde, Gentry, Moore, Bodner, 2000). Also, independent samples t-tests showed that the difference in performance between the subjects who were administered GPT, SDMT, or both measures was not statistically significant. Therefore, it was feasible to use both GPT and SDMT as measures of fine motor dexterity in all data analyses, even though SDMT measured additionally abilities such as sustained attention.

B. YEARS OF SEIZURE AND OF AED TREATMENT (hypotheses 1b and 2a)

Years of seizure, and of AED treatment, did not account for any variability in fine motor impairment or overall intellectual functioning, which was inconsistent with the literature (Dodrill, 2004). This suggested that other factors are involved, one of which may be the primary mechanism of action of the AED regimen, as explained in further detail in the next section.

C. MECHANISMS OF ACTION OF AEDS (hypothesis 2b)

An unexpected finding involved two mechanisms of action, namely the blockade of Na^+ channels and the enhancement of GABAergic inhibition, whose combination was associated with fine motor impairment in the non-dominant hand on GPT.

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AED regimens consisting of only Na^+-channel blockers (e.g., CBZ) was associated with higher performance than regimens consisting of both a Na^+-channel blocker and a GABAergic enhancer (i.e., OXC and GBP). This result indicated the advantage of Na^+-channel blockers over its combination with another AED that enhanced GABAergic inhibition. This supported hypothesis 2b and was consistent with previous studies, which suggested that AEDs with primary mechanism of action at the Na^+ channel were associated with less cognitive effects[28] compared to AEDs with other primary mechanisms (Sankar & Holmes, 2004). A brief review of these two mechanisms of action is provided in the next section[29].

1. Blockade of voltage-gated Na^+ channels

AEDs whose primary[30] mechanism of action blocked voltage-gated Na^+ channels were PHT, CBZ, LMT, and OXC[31] (Kwan et al., 2001; Armijo et al., 2005; Coulter, 1997). These four AEDs shared several features in their primary mechanism at voltage-gated Na^+ channels.

First, their voltage- and use-dependent features resulted in the selective blockade of high-frequency and repetitive neuronal firing, hence they inhibited the spread of seizure activity without interfering with normal physiologic processes (Perucca, 2005; Bang & Goa, 2004; Kuo, 1998; Kuo & Bean, 1994, Kuo & Lu, 1997). Secondly, their mechanisms of action were mutually-exclusive as illustrated by their one-to-one

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[28] Except at overtly neurotoxic doses (Sankar & Holmes, 2004).
[29] Further information is available in the literature review.
[30] As opposed to secondary mechanisms at other voltage- or ligand-gated channels.
[31] Although other AEDs also inhibited Na^+ currents (e.g., zonisamide, topiramate, and felbamate), they were considered "polymechanistic" (Leppik, 2000) in that their primary mechanisms were not at the Na^+ channels (Table 5).

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binding[32] to a common receptor on the extracellular side of the Na^+ channel (Kuo, 1998).

Thirdly, they bind to this receptor at a slow rate, which had two important implications: a) their binding caused little or no alteration in the time course of the Na^+ currents, and preserved normal resting and action potentials, and other physiologic neurotransmission; and b) once bound to the receptor, the recovery from the blockade was slow, which delayed the reactivation of the channel, prolonged the antiepileptic action, and prevented the release of glutamate (Rogawski & Löscher, 2004; Meador & Baker, 1997).

A fourth feature shared by CBZ, PHT, LMT, and OXC may explain their advantage in minimizing fine motor impairment compared to AEDs with other primary mechanisms of action. It has been suggested that these Na^+-channel blockers prevented the initiation and propagation of action potentials in hyperexcitable neurons at the beginning phases of the seizure activity, which minimized the amount of neuronal injury caused by seizure activity (please refer to section B in the literature review) and subsequent cognitive impairment. This was in contrast to AEDs with other mechanisms of action, which typically controlled seizures at later phases by blocking excessive Ca^{2+} entry into depolarized neurons, preventing release of glutamate, and/or enhancing GABAergic inhibition. Consequently, their mechanisms of action occurred after the onset of seizures, which may have already caused some degree of neuronal injury. After consulting with a number of experts in this subject matter (C. B. Dodrill, A. Ettinger, & E. Perucca, personal communications, February 24, 2006), this speculation remains a possibility. Further investigation is necessary due to the paucity of studies exploring this

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[32] As opposed to double-occupancy, in which the channel is simultaneously occupied by two different drug molecules (Kuo, 1998).

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relationship.

2. Enhancement of GABAergic inhibition

AEDs whose primary mechanism enhanced GABAergic inhibition were VPA, TGB, GBP, and PRM (Kwan et al., 2001; Armijo et al., 2005; Coulter, 1997).

The primary mechanism of action of AEDs such as VPA, TGB, GBP, and PRM enhanced GABAergic inhibition by preventing neuronal and glial reuptake of GABA (e.g., TGB), increasing the synthesis and nonvesicular release of GABA (e.g., GBP), increasing GABA-stimulated chloride Cl^- flux into neurons (e.g., PRM), or interfering with the metabolic breakdown of GABA (e.g., VPA) (Kwan et al., 2001; Armijo et al., 2005; Sills & Brodie, 2001). Unlike the Na^+ channel-blockers, their mechanisms had little in common other than in augmentation of GABA through their actions on the postsynaptic $GABA_A$ receptor, with the exception of GBP, which has an undescribed mechanism. In the current study, these mechanisms did not contribute to the variability in fine motor functioning.

Some researchers consider these mechanisms detrimental to neuropsychological functioning due to their side effects (e.g., cognitive slowing), which may reduce vigilance that is necessary to perform any neuropsychological test (Sankar & Holmes, 2004). This relationship remains to be confirmed due to the broad range of actions for the AEDs in this category (i.e., VPA also blocks voltage-gated Na^+ channels) (Kwan et al., 2001).

3. AED combinations involving Na^+ channel-blockers and GABAergic enhancers

The subjects treated with this combination of AEDs experienced significantly longer years of seizures, and their first seizures at younger ages, than the subjects who were in monotherapy with either Na^+-channel blockers or GABAergic enhancers. This

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suggested that these variables pertaining to their seizures, combined with a regimen consisting of both Na^+-channel blockers and GABAergic enhancers, may contribute to the fine motor difficulty revealed in the current sample of patients.

Since regimens containing only Na^+-channel blockers were associated with better fine motor dexterity than when combined with GABAergic enhancers, this suggested a negative "add-on" effect of GABAergic enhancers, particularly in patients with long history of seizures who experienced their first seizures at younger ages. GABAergic enhancers' consistent disruption of attention or vigilance has been suggested in the literature, which reported that GBP or VPA were associated with the most consistent disruption (Shannon & Love, 2005; Sankar & Holmes, 2004). Although this effect of GABAergic enhancers in monotherapy was not evident in the current study due to the small sample (N = 3), its combination with Na^+-channel blockers, coupled with the patients' seizure history (e.g., years of seizures and age of seizure onset), may be associated with fine motor difficulty as measured by GPT. The lack of significance of this combination regimen on the performance of SDMT may be attributed to the small sample of patients treated with this regimen (N = 7).

Although the number of subjects treated with this combination of AEDs was only 11, it was sufficient for statistical significance, whereas other AED combinations with a higher number of subjects (e.g., 17 subjects with regimen consisting of Na^+-channel and Ca^{2+}-channel blockers) did not achieve statistical significance. Hence the significance of AED regimens containing Na^+-channel blockers and GABAergic enhancers on fine motor impairment was supported despite the relatively small sample size.

Despite the association of GABAergic enhancers to the impairment of attention or

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vigilance, some studies suggested that its combination with a Na^+-channel blocker may still be efficacious in the treatment of epilepsy (Lawthom & Smith, 2003; Leppik, 2000; Deckers et al., 2000) and may be preferable over other AED combinations, such as one with similar mechanisms of action, which has been associated with cognitive effects (e.g., carbamazepine and phenytoin, which are both Na^+ channel-blockers) (Deckers et al., 2000).

D. THE NUMBER OF ION CHANNELS (hypothesis 2c)

Exploratory analyses to determine if the number of ion channels targeted by an AED regimen contributed to variability in fine motor impairment revealed no statistical significance, therefore excluded this variable as a predictor of fine motor impairment.

E. TYPE OF AED THERAPY: monotherapy versus polytherapy (hypothesis 2d)

The type of AED therapy accounted for the variability in the performance on both GPT and SDMT, with monotherapy being superior to polytherapy on all outcome variables. This finding was corroborated by the lack of statistical significance between the two- and three-AEDs regimens. Hence a regimen with three AEDs did not significantly reduce fine motor dexterity any more than a regimen with two AEDs, but both regimens are associated with significant difficulty in comparison to monotherapy.

The disadvantage of polytherapy may also be attributed to the variables associated with the patients' seizures, since patients on polytherapy most likely experienced higher severity and/or frequency of seizures that were uncontrolled by monotherapy, hence their fine motor difficulty may have been exacerbated by their seizures as well as their AED regimens. Since data on seizure frequency and severity were unavailable from the current study sample, further study is necessary.

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According to the current findings on AED's mechanisms of action, fine motor difficulty may be associated with synergistic mechanisms between specific AEDs, which raises the theory of rational polytherapy. In standard clinical practice, a patient is placed on polytherapy after failure with one or two monotherapy trials to control seizures. The criteria for selecting AEDs in such circumstances vary due to factors such as the clinician's comfort level with an AED (Brodie & Kwan, 2001), the ability to optimize dosage (Perucca, Dulac, Shorvon, & Tomson, 2001), and the AEDs' interaction with other medications in co-morbid conditions such as migraine, mood disorders, and sleep disturbance (Perucca et al., 2000).

On the other hand, the guidelines for rational polytherapy suggested that AED combinations be selected based on the following criteria: a) they had different mechanisms of action; b) they did not have complex or vague pharmacodynamic or pharmacokinetic interactions (e.g., felbamate with PHT); c) they had the lowest potential for adverse effects; and d) they were prescribed at the lowest possible dosages to control seizures (Lawthom & Smith, 2003; Leppik, 2000; Ferrendelli, 1995; Richens, 1995; Deckers et al., 2000). See Table 32 for the recommended AED combinations.

It is interesting to note that although the current findings supported monotherapy over polytherapy in minimizing fine motor impairment, the difference between the two types of AED therapy may be marginal. Some AEDs contained active metabolites (e.g., OXC's active metabolites include PHT) while others contained no active metabolites but had multiple mechanisms of action (e.g., topiramate has no active metabolite but works on all four mechanisms of action) (Leppik, 2000). Therefore monotherapy may actually resemble polytherapy when consisting of an AED with active metabolites or multiple

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mechanisms of action. This may explain the failure of monotherapy for some patients with epilepsy, and emphasized the importance of considering mechanisms of action when devising an AED regimen for monotherapy, which would ensure maximal response and efficacy (Table 32).

F. OTHER VARIABLES

1. Gender

Gender correlated with dominant-hand performance on GPT, with men outperforming women. This was an unexpected finding and inconsistent with the literature, which stated the opposite effect of gender on the performance on GPT (Ruff & Parker, 1993; Schmidt, Oliveira, Rocha, & Abreu-Villaca, 2000). Further exploration of the relationships between gender and age, education, FSIQ, years of seizure, years of AED treatment, type of therapy, and diagnosis (e.g., generalized vs. partial/focal seizures) did not explain men's advantage on GPT. Also, there were slightly more women than men who performed both tests (e.g., GPT = 42 men and 56 women, SDMT = 40 men and 57 women), therefore the variability in performance between the sexes could not be a function of unequal cell sizes. One possibility may lie in the patients' seizure histories, with higher severity and/or frequency of seizures in women than in men.

2. Years of education and Full Scale IQ

FSIQ and the years of education contributed to varying degrees of fine motor difficulty as measured by GPT and SDMT. Education was a stronger predictor of success on SDMT than on GPT, while FSIQ correlated with performance on both measures uniformly. Overall this pattern of functioning was consistent with the

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literature, particularly with respect to the theory of cognitive reserve, which stated that individuals with higher education and occupational attainments develop cognitive impairment associated with neurologic disorders (e.g., Alzheimer's disease) at a slower rate than those with less education and occupational attainments (Stern, Albert, Tang, & Tsai, 1999).

Patients with epilepsy are likely to have cognitive impairment associated with the disorder itself, given that medial temporal lesions account for a large proportion of epileptogenic foci and frequently cause permanent neuronal damage (Pai & Tsai, 2005), and that cognitive impairment has been documented in patients before the initiation of any AED treatment (Pulliainen, Kuikka, & Jokelainen, 2000). However, those with higher cognitive reserve (e.g., higher FSIQ and education levels) may process tasks in a more efficient manner by either using a brain network more efficiently, or engaging alternate brain networks or cognitive strategies, in response to increased demand, compared to individuals with less cognitive reserve (Stern, 2003).

3. Age

While age did not account for significant variability in fine motor impairment, the average age of the subjects in monotherapy, which demonstrated to be favorable to polytherapy, was slightly older than the subjects in polytherapy, although the difference was nonsignificant. The age difference in subjects across mechanisms of action was also nonsignificant, therefore excluding this variable as a predictor of performance.

G. STRENGTHS OF THE CURRENT STUDY

1. Mechanisms of action of AEDs

Despite the abundant studies performed on the cognitive effects associated with

AEDs, this study bridged a gap in the literature by examining the extent to which AEDs' mechanisms of action contributed to fine motor impairment in patients with epilepsy. Although the classification of AEDs' mechanisms of action remains to be confirmed, partially due to the continuous emergence of new information, the current study utilized a system that encompassed reliable sources in an attempt to elucidate the relationship between AEDs' mechanisms of action and fine motor impairment, which would assist in treatment planning for patients with epilepsy or other disorders that incorporate AEDs in their treatment.

2. Type of AED therapy

With respect to the relationship between the type of AED therapy and fine motor impairment, the current findings replicated those in the epilepsy literature, which supported the use of monotherapy to minimize cognitive effects, as well as strengthened the validity of the data. In addition, the sample size per therapy type (mono- versus polytherapy) was sufficient to generate adequate power and reduce the chances of making a Type I error (Cohen, 1992). Furthermore, this study bridged a gap in the literature by examining the variability accounted by the number of AEDs in polytherapy, and revealed no significant differences between the use of two or three AEDs in a regimen on fine motor impairment. Lastly, the active metabolites (e.g., VPA) and multiple mechanisms of action (e.g., LMT) of the AEDs that are commonly used in monotherapy should be considered, which may minimize the adverse effects associated with polytherapy, or failure with monotherapy.

3. Absence of effects from co-morbid conditions

Since this study employed strict inclusion criteria to select all subjects (see

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Methods section), fine motor impairment could not be attributed to the effects of other medications or co-morbid conditions.

4. Met the assumptions of parametric tests

Although there were unequal cell sizes for mechanisms of action, all data from the study sample met the assumptions of parametric tests. They derived from normally distributed populations with homogeneous variances, in that the variance of one variable was stable at all levels of the other variable. This was tested using the Levene's tests, which were non-significant and hence the difference between the variances was zero (Tabachnick & Fidell, 2001; Field, 2005).

H. LIMITATIONS

1. Sample size

Although the total sample size in the current study was adequate (N = 164), the cell size for each mechanism of action was not sufficient for multivariate analyses (e.g., multiple regression, analysis of co-variance), particularly as it pertained to mechanisms involving GABA, therefore limiting the predictive power of the data. However, all data demonstrated homogeneity of variance using Levene's test, which showed that the difference between the variances was zero, thereby supporting the validity of the statistical analyses (Tabachnick & Fidell, 2001; Field, 2005). Nevertheless, future investigations in the mechanisms of action of AEDs should incorporate larger cell sizes for each level of the predictor in order to perform multivariate analyses. A minimum sample size of 50 + 8k (k = the number of predictors) is necessary to test the overall fit of the regression model (e.g., R^2), and a minimum sample size of 104 + k is necessary to test

the individual predictors within the model (e.g., b-values of the model) (Cohen, 1992; Green, 1991).

2. Variables associated with diagnosis and AEDs

Although the mechanisms involving Na^+-channel blockers and GABAergic enhancers significant correlated to longer years of seizure experience and younger ages of seizure onset, the number of subjects treated with this combination was only 11, which limited the generalization of this finding. Future investigation should actively recruit more subjects with such regimen to confirm its relationship with fine motor impairment.

The current study did not take into account the severity and frequency of seizures, as well as the number of toxic episodes from AEDs[33], because they were not consistently available or recorded. Future studies should control for these variables when examining the cognitive effects of AEDs.

Variability existed in regards to the point of AED discontinuation[34] and the beginning of neuropsychological evaluation[35], which presented as confounding variables due to the discrepancies in AEDs' pharmacodynamic actions, which may or may not have had residual motor effects. Future exploration should utilize a uniform protocol to discontinue AEDs and begin neuropsychological evaluation.

I. SUMMARY AND CLINICAL IMPLICATIONS

Overall performance on GPT and SDMT was over one standard deviation below the normative means, with lower scores on GPT than SDMT. This disparity may be

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33 The therapeutic range varies depending on the specific AED.

34 Some patients were discontinued from treatment during the first few days of their admission, while others were discontinued later, due to the titration schedule for their regimens.

35 Due to unpredictable variables such as patient fatigue, medical procedures (i.e., MRI) that delayed the evaluation or were incompatible with the examiner's availability, etc…

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attributed to the fact that SDMT[36] was not as sensitive to fine motor difficulty as GPT, hence the difficulty detected by GPT was not consistent compared to performance on SDMT.

Overall findings supported four of the six hypotheses and suggested that fine motor impairment in patients with epilepsy may be partially attributed to AED's mechanisms of action and the type of therapy. Specifically, patients treated with both Na^+-channel blockers and GABAergic enhancers demonstrated significantly more fine motor impairment than patients treated with only Na^+-channel blockers. In addition, those with significant impairment also experienced longer years of seizure with younger ages of seizure onset. With respect to the type of AED therapy, monotherapy was associated with better outcome than polytherapy on all measures. Lastly, the significance of education level and intellectual functioning on fine motor dexterity supported the theory of cognitive reserve in neurologic disorders.

These findings suggest the importance of considering synergistic mechanisms of action when devising an AED regimen for patients with epilepsy, especially since certain AEDs are reportedly more useful than others for different stages of seizure activity: a seizure may be suppressed in its initiation by one AED (e.g., CBZ, a Na^+ channel-blocker), and in its propagation by another (e.g., GBP to enhance GABAergic inhibition) (Kwan et al., 2001; P. Kwan, personal communication, February 21, 2006). Variables associated with seizure history should continue to be included in evaluating the cognitive effects of AEDs. While monotherapy remained advantageous over polytherapy in minimizing fine motor impairment, an AED's active metabolites and additional mechanisms of action should be considered (e.g., OXC's active metabolites include

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[36] SDMT additionally measured other cognitive abilities (e.g., visual attention).
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PHT). Based on the current findings, the use of CBZ or LMT in monotherapy was more advantageous than a combination of both LMT, OXC, and GBP (Table 20).

AED's mechanisms of action, the type of therapy, and the recommended guidelines for rational polytherapy may be used to plan appropriate regimens for patients with epilepsy, as well as patients with other neurologic and/or psychiatric disorders (e.g., mood disorder, brain tumor, neuropathic pain, migraines), given AEDs broad range of indication (Rogawski & Löscher, 2004). This would maximize efficacy and minimize cognitive effects such as fine motor impairment, the presence of which affects a patient's quality of life.

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Table 1. International Classification of Epileptic Seizures (Commission, 1989).

Generalized seizures

Tonic clonic seizures (includes variations beginning with a clonic or myoclonic phase)
Clonic seizures
- Without tonic features
- With tonic features

Typical absence seizures
Atypical absence seizures
Myoclonic absence seizures
Tonic seizures
Spasms
Myoclonic seizures
Eyelid myoclonia
- Without absences
- With absences

Myoclonic atonic seizures
Negative myoclonus
Atonic seizures
Reflex seizures in generalized epilepsy syndromes

Focal ("localization-related") seizures[37]

Focal sensory seizures
- With elementary sensory symptoms (e.g., occipital and parietal lobe seizures)
- With experiential sensory symptoms (e.g., temporoparietooccipital junction seizures)

Focal motor seizures
- With elementary clonic motor signs
- With asymmetric tonic motor seizures (e.g., supplementary motor seizures)
- With typical (temporal lobe) automatisms (e.g., mesial temporal lobe seizures)
- With hyperkinetic automatisms
- With focal negative myoclonus
- With inhibitory motor seizures

Gelastic seizures
Hemiclonic seizures
Secondarily generalized seizures
Reflex seizures in focal epilepsy syndromes

Continuous seizure types

Generalized status epilepticus
- Generalized tonic clonic status epilepticus
- Clonic status epilepticus

[37] The 1989 Classification of Epilepsies and Epileptic Syndromes replaced the term "partial" with "localization-related." The new term has been cumbersome therefore is not consistently used. The Task Force of the ILAE is now proposing that the terms partial and localization-related be replaced with the older term "focal," which remains in common use. "It must be strongly emphasized, however, that the term focal does not mean that the epileptogenic region is a small, well-delineated focus of neuronal pathology; focal seizures, as well as focal syndromes, are almost always due to diffuse, and at times widespread, areas of cerebral dysfunction" (Fisher et al. of the ILAE, 2005, p. 798).

Table 1 (Cont.). International Classification of Epileptic Seizures (Commission, 1989).

Continuous seizure types (c*ont.*)

- Absence status epilepticus
- Tonic status epilepticus
- Myoclonic status epilepticus

Focal status epilepticus

- Epilepsia partialis continua of Kojevnikov
- Aura continua
- Limbic status epilepticus (psychomotor status)
- Hemiconvulsive status with hemiparesis

Precipitating stimuli for reflex seizures

Visual stimuli

- Flickering light: color to be specified when possible
- Patterns
- Other visual stimuli

Thinking
Music
Eating
Praxis
Somatosensory
Proprioceptive
Reading
Hot water
Startle

Table 2. Annotated International Classification of Epileptic Seizures (American Epilepsy Society, 2004).

I. **Localization-related seizures (formerly known as partial seizures)**

- **A. Simple partial seizures (consciousness not impaired)**
  1. with motor symptoms
  2. with somatosensory or special sensory symptoms
  3. with autonomic symptoms
  4. with psychic symptoms
- **B. Complex partial seizures (with impairment of consciousness)**
  1. beginning as simple partial seizures and progressing to impairment of consciousness
     a. without automatisms
     b. with automatisms
  2. with impairment of consciousness at onset
     a. without automatisms
     b. with automatisms
- **C. Partial seizures (simple or complex), secondarily generalized**

II. Generalized seizures (bilaterally symmetric, without localized onset)

- **A. Absence seizures**
  a. true absence ("petit mal")
  b. atypical absence
- **B. Myoclonic seizures**
- **C. Clonic seizures**
- **D. Tonic seizures**
- **E. Tonic-clonic seizures ("grand mal")**
- **F. Atonic seizures**

III. Unclassified seizures

Table 3. Pharmacological treatments of epilepsy over time (Schachter, 2004).

YEAR	NAME OF ANTIEPILEPTIC DRUG (AEDs)
1850	Bromides – introduced to treat seizures in epilepsy.
1910	Phenobarbital (Luminal®) – originally used to induce sedation, its antiepileptic properties were soon immediate. Phenobarbital is the oldest AED in modern clinical use.
1937	Phenytoin (Dilantin®) – approved by FDA for partial and tonic-clonic seizures, and for status epilepticus.
1954	Primidone (Mysoline®) approved by FDA for generalized tonic-clonic seizures, nocturnal myoclonic seizures, simple partial seizures, and complex partial seizures.
1958	Ethosuximide (Zarontin®) approved by FDA for atypical absence seizures with or without tonic-clonic or myoclonic seizures.
1963	Sodium valproate (Depakote®) approved by FDA for a wide range of seizures.
1974	Carbamazepine (Tegretol®) approved by FDA for a wide range of seizures.
1993	Felbamate (Felbatol®) and gabapentin (Neurontin®) approved by FDA as second-line/add-on treatments in epilepsy.
1995	Lamotrigine (Lamictal®) approved by FDA for a wide range of seizures.
1997	Topiramate (Topamax®) and Tiagabine (Gabitril®) approved by FDA for prevention of seizures.
1999	Levetiracetam (Keppra®) approved by FDA for prevention of seizures.
2000	Oxcarbazepine (Trileptal®) and zonisamide (Zonegran®) approved by FDA for prevention of seizures.

Table 4. Generic and brand names of commonly-prescribed antiepileptic drugs.

GENERIC NAME	BRAND NAMES
Carbamazepine (CBZ)	Tegretol, Carbatrol, Carbagen SR, Mazepine, Tegrital, Teril, and Timonil
Ethosuximide (ESX)	Zarontin
Felbamate (FBM)	Felbatol, Taloxa
Gabapentin (GBP)	Neurontin
Lamotrigine (LMT)	Lamictal
Levetiracetam (LEV)	Keppra
Oxcarbazepine (OXC)	Trileptal
Phenobarbital (PB)	Phenobarbital
Phenytoin (PHT)	Dilantin, Epanutin, Phenytek
Primidone (PRM)	Mysoline
Tiagabine (TGB)	Gabitril
Topiramate (TPM)	Topamax
Valproic acid (VPA)	Depakote, Depakene, Convulex, Depakine, Orfiril, Valporal, and Valprosid
Vigabatrin (VGB)	Sabril (not approved for use in the U.S. due to its effects on vision)
Zonisamide (ZNM)	Zonegran

Table 5. Mechanisms of action of AEDs (Kwan et al., 2001; Meldrum, 1996; Coulter, 1997; & Armijo et al., 2005).

Sodium-Channel Blockers	**Enhancers of GABAergic inhibition**	**Glutamate Blockers**	**Calcium Channels^{++}**
CBZ			
PHT			
Oxcarbazepine			
Lamotrigine			
Zonisamide			Zonisamide*****
	VPA		
Felbamate	Felbamate	Felbamate (NMDA)	Felbamate^{+}
Topiramate	Topiramate	Topiramate (AMPA/KA)	Topiramate
	Tiagabine (GABA-T)		
			Ethosuximide*****
			Levetiracetam^{+}
	Gabapentin (↑ GABA turnover)		
	Primidone		

***** T-type calcium channels [low-threshold] $^{+}$ High voltage-activated Ca^{2+} channel (HVACC): "N-type"
$^{++}$ All 6 types of Ca^{2+} channels (L, N, T, P, Q, R) are high threshold except T-type.

Figure 1. Mechanisms of actions of antiepileptic drugs at excitatory and inhibitory synapses (Rho & Sankar, 1999).

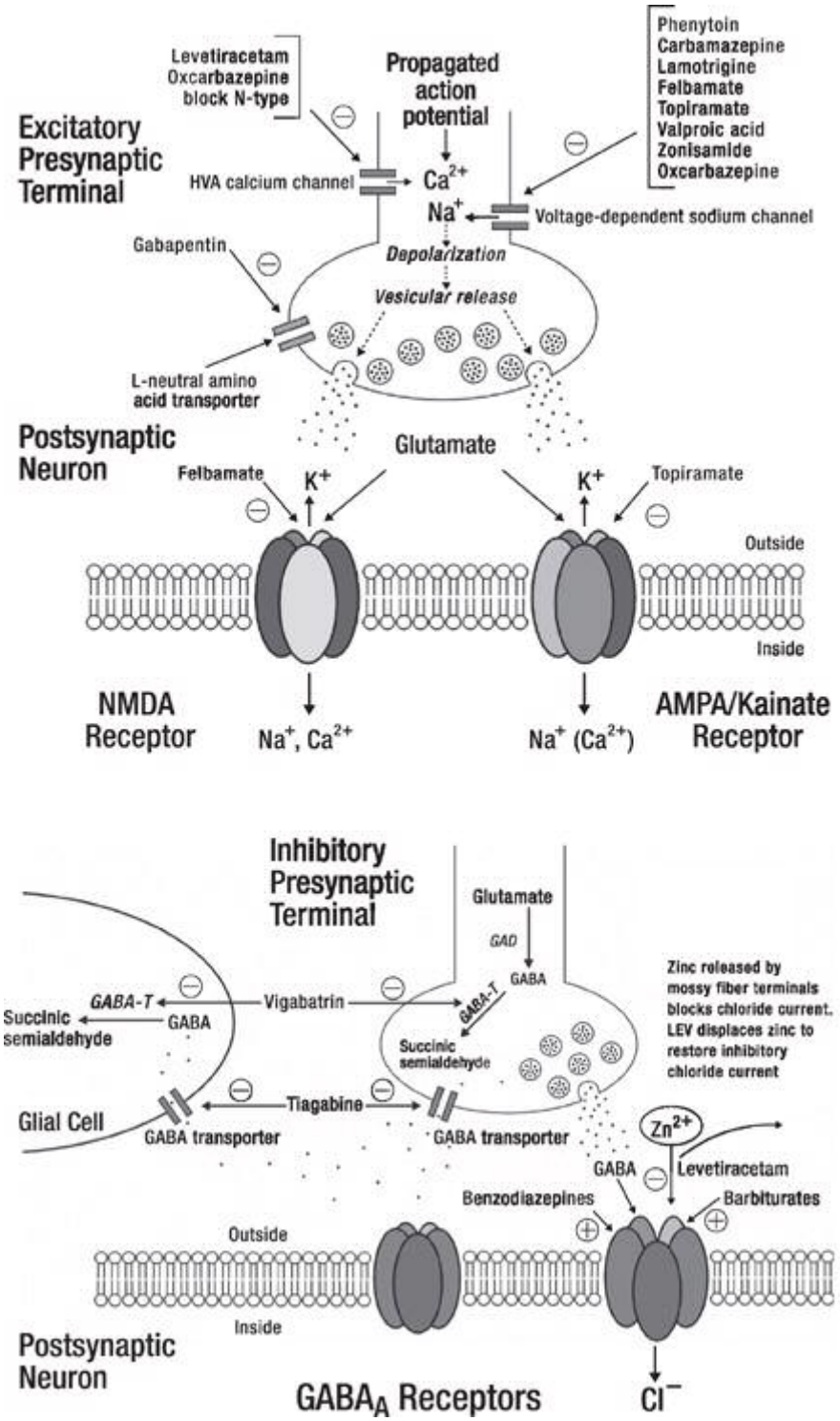


Figure 2. Grooved Pegboard Test (GPT)[38] (Heaton et al., 1992; Lezak, 2004).

(Adapted from http://www.lafayetteinstrument.com/evaldexterity.htm)

[38] The pegboard consists of 25 equidistant holes in a 5 X 5 matrix with randomly-oriented slots. Each peg, which has a ridge along one side, must be rotated with only one hand to match the slot in the pegboard before it can be inserted. The goal is to insert a peg into each hole as quickly as possible, starting at the top row from left to right until all 25 holes are filled. The time required to complete this task with each hand is recorded.

Figure 3. Symbol Digit Modalities Test[39,40] (SDMT) (Smith, 1993).

Reference Key

(	—	⊢	⌐	⊣	>	+	)	÷
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**

(	⊣	—	(	⊢	>	⌐	—	⊣
	PRACTICE TRIAL							
⊢	>	(	+	⌐	÷	⊣	)	+
⌐	÷	⊣	(	+	⊣	⊢	—	>
)	⊣	⊢	>	(	÷	+	⌐	—
÷	—	(	⊣	>	⊢	)	+	)
(	>	⌐	÷	—	+	⊣	)	⊢
+	⊣	)	—	(	>	÷	⊢	⌐
⊣	÷	—	⌐	+	⊢	)	>	(

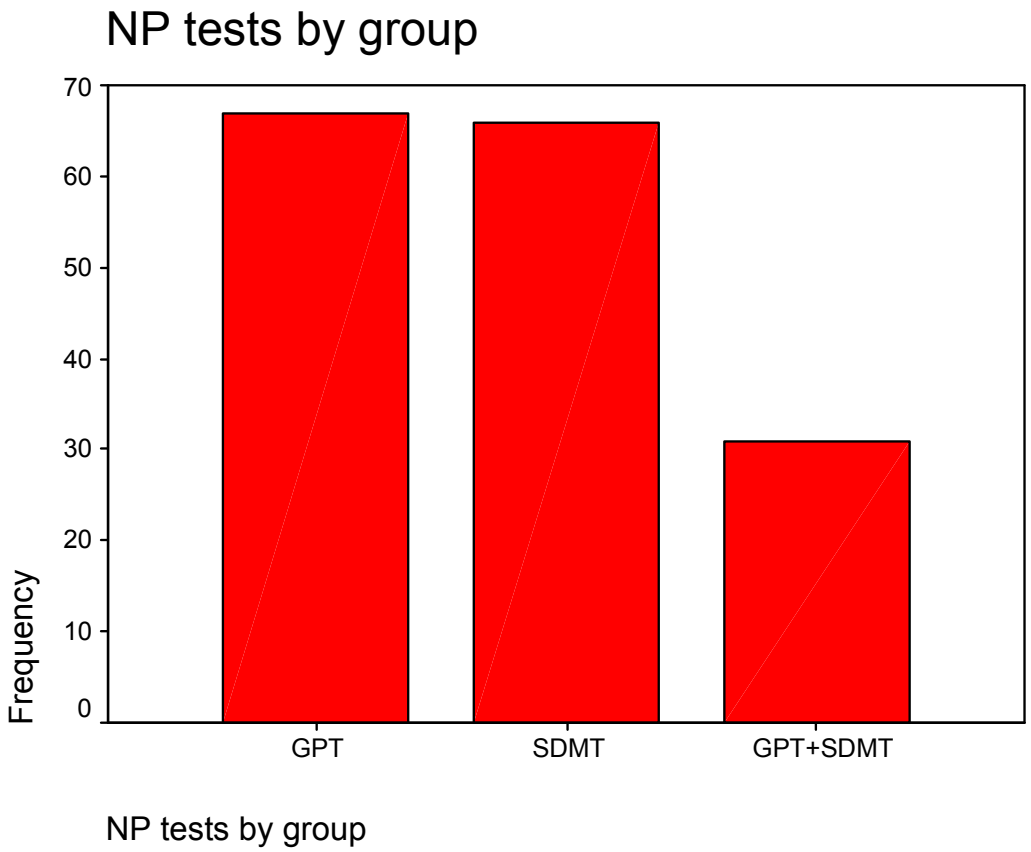
[39] All symbols, numbers, and the number of rows in this illustration differ from the copyrighted version. Reproduction rights for the actual SDMT will be obtained for the purpose of publication.

[40] The goal is to identify nine different symbols corresponding to the numbers 1 through 9 using a reference key, and write as many correct matches as possible within a 90-second period. Using the dominant hand, an un-timed practice trial is provided, followed by a timed test trial, and the variable measured is the total number of correct matches within the time limit.

Figure 4. The number of subjects administered GPT only, SDMT only, and both GPT and SDMT.

NP tests by group

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	GPT	67	40.9	40.9	40.9
	SDMT	66	40.2	40.2	81.1
	GPT+SDMT	31	18.9	18.9	100.0
	Total	164	100.0	100.0	



NP tests = Neuropsychological tests
GPT = Grooved Pegboard Test.
SDMT = Symbol Digit Modalities Test.

Table 6. Independent samples t-test for subjects administered GPT only, or GPT and SDMT. *Top*: means and SD on GPT. *Bottom*: results of the independent samples t-test.

Group Statistics

	NP tests by group	N	Mean	Std. Deviation	Std. Error Mean
Dominant T	GPT	67	35.21	13.748	1.680
	GPT+SDMT	31	30.68	13.598	2.442
Nondominant T	GPT	67	35.31	13.127	1.604
	GPT+SDMT	31	33.55	11.544	2.073

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Dominant T-score	Equal variances assumed	.012	.913	1.523	96	.131	4.53	2.976	-1.376	10.439
	Equal variances not assumed			1.529	59.084	.132	4.53	2.964	-1.399	10.462
Nondominant T-score	Equal variances assumed	.000	.984	.642	96	.522	1.77	2.749	-3.691	7.221
	Equal variances not assumed			.673	65.912	.503	1.77	2.621	-3.468	6.998

GPT = Grooved Pegboard Test; **SDMT** = Symbol Digit Modalities Test, **Dominant T** = Dominant T-scores on GPT; **Nondominant T** = non-dominant T-scores on GPT; **SDMTLN** = natural logarithm for SDMT raw scores.

Table 7. Independent samples t-test for subjects administered SDMT only, or GPT and SDMT. *Top*: means and SD on SDMT. *Bottom*: results of the independent samples t-test.

Group Statistics

	NP tests by group	N	Mean	Std. Deviation	Std. Error Mean
SDMT LN	SDMT	66	3.56817	.360989	.044435
	GPT+SDMT	31	3.57534	.426212	.076550

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
SDMT LN	Equal variances assumed	1.551	.216	-.086	95	.932	-.00718	.083347	-.17264	.15829
	Equal variances not assumed			-.081	50.953	.936	-.00718	.088512	-.18488	.17052

GPT = Grooved Pegboard Test; **SDMT** = Symbol Digit Modalities Test, **Dominant T** = Dominant T-scores on GPT; **Nondominant T** = non-dominant T-scores on GPT; **SDMTLN** = natural logarithm for SDMT raw scores.

Table 8. Demographic profile of subjects administered GPT (N = 98) and SDMT (N = 97).

Demographic variable	GPT Mean (SD)	SEM	SDMT Mean (SD)	SEM
Age	35.90 (10.94)	.82	35.91 (9.97)	1.01
Years of education	13.83 (2.85)	.21	14.54 (2.40)	.24
Full Scale IQ	95.47 (13.82)	1.11	98.70 (13.24)	1.37
Years of AED Tx	4.70 (6.56)	.47	5.16 (6.93)	.73
Number of AEDs (range 1-3)	1.77 (0.76)	.06	1.53 (0.71)	.07
Years of seizure	17.16 (12.34)	.95	16.11 (12.65)	1.30
Age of seizure onset	18.89 (12.99)	.98	20.07 (11.77)	1.20
Male	37.43 (13.87)*	2.14	3.56 (0.38)+	.06
Female	31.04 (13.20)	1.76	3.57(0.37)	.05

*GPT: male N = 42, female N = 56
+SDMT: male N = 40, female N = 57

SD = Standard Deviation
SEM = Standard Error of the Mean
GPT = Grooved Pegboard Test
SDMT = Symbol Digit Modalities Test

Table 9. Handedness of subjects on GPT and SDMT.

Handedness	**GPT**	**SDMT**
Left	8	7
Right	90	90
Total	98	97

Figure 5. Diagnostic profile of all subjects (N = 164).

	Frequency	Percent
Generalized	33	20.1
Partial/Focal	59	36.0
Partial/Focal-Generalized	58	35.4
Total	150	91.5
Unavailable data	14	8.5
Total	164	100.0

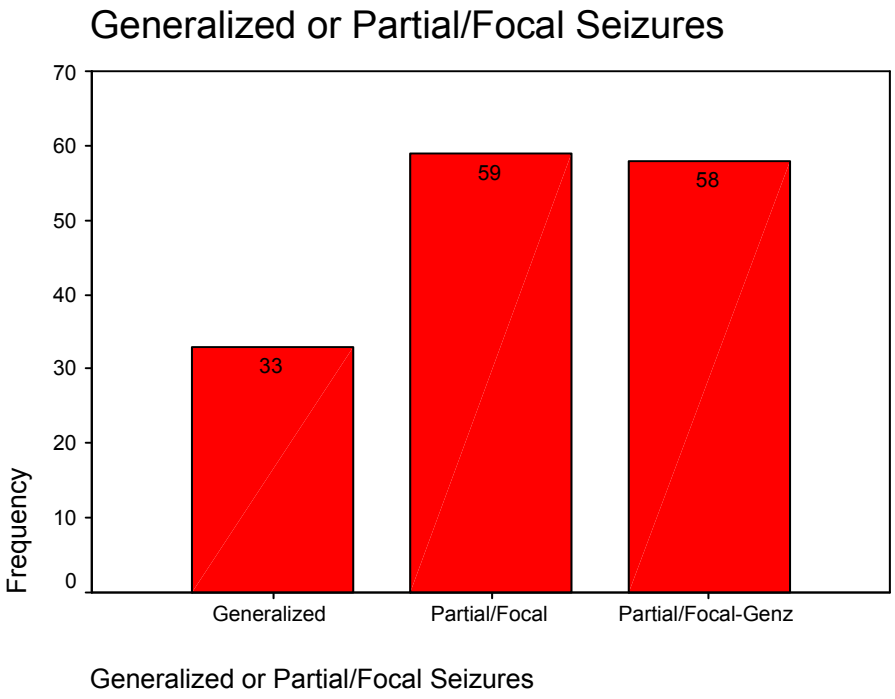


Figure 6. Hemisphere of seizure origin for all subjects (N = 164).

	Frequency	Percent
Left	73	44.5
Right	32	19.5
Both	35	21.3
Unclear	24	14.6
Total	164	100.0

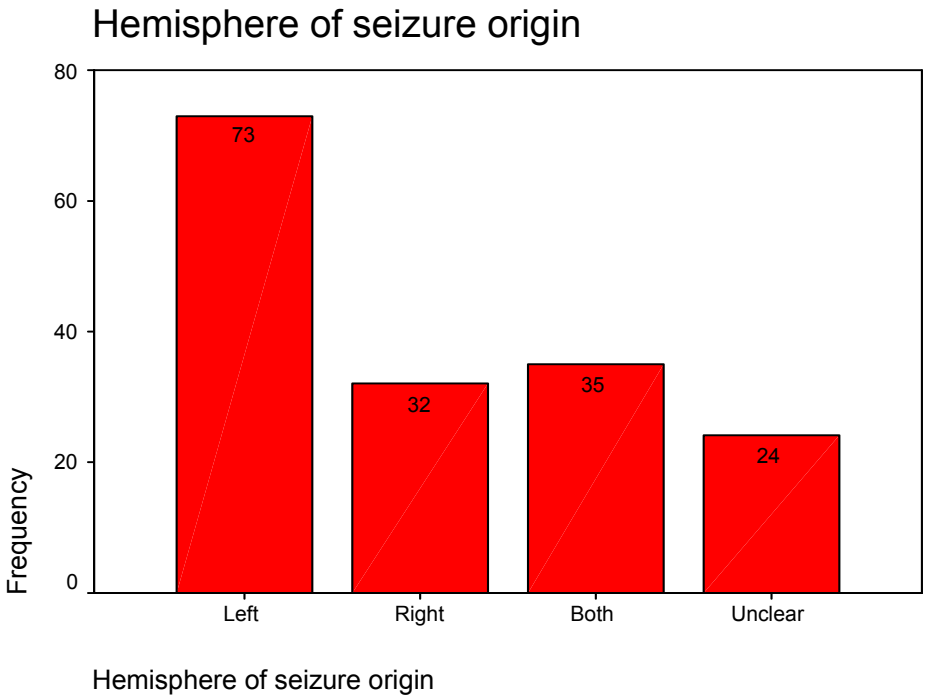
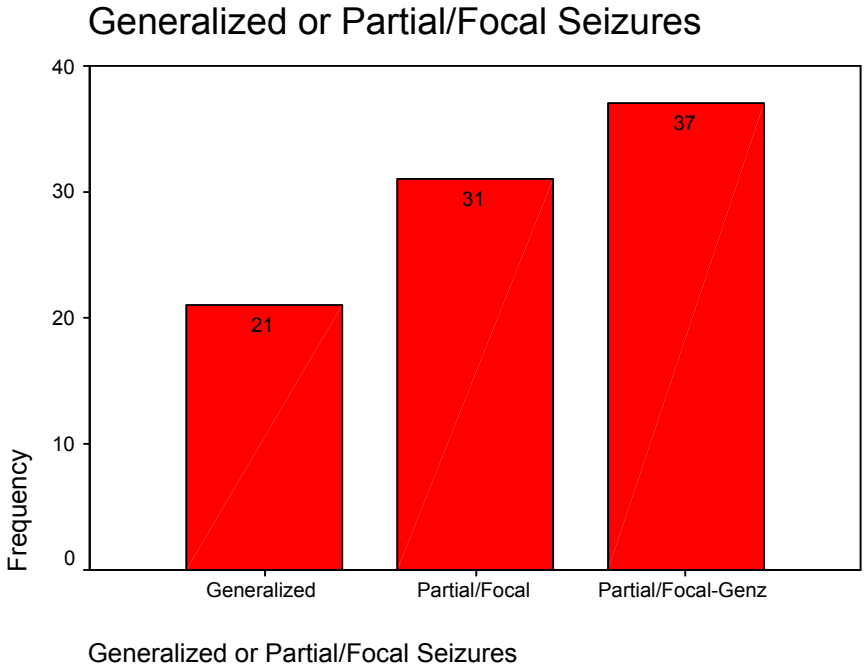


Figure 7. Diagnostic profile of subjects administered GPT (N = 98).

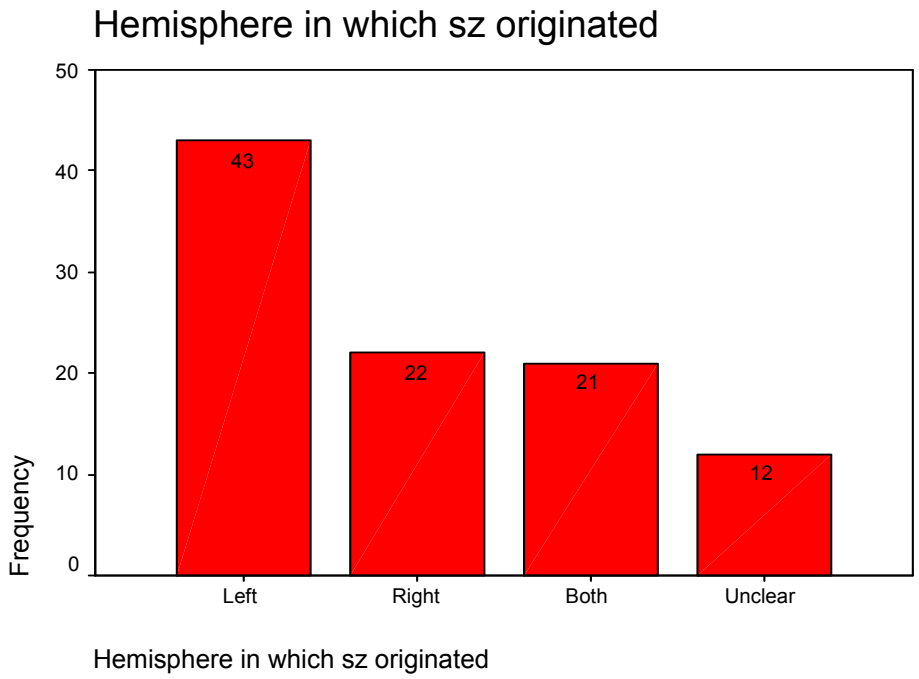
	Frequency	Percent
Generalized	21	21.4
Partial/Focal	31	31.6
Partial/Focal-Generalized	37	37.8
Unavailable data	9	9.2
Total	98	100.0



GPT = Grooved Pegboard Test

Figure 8. Hemisphere of seizure origin for subjects administered GPT (N = 98).

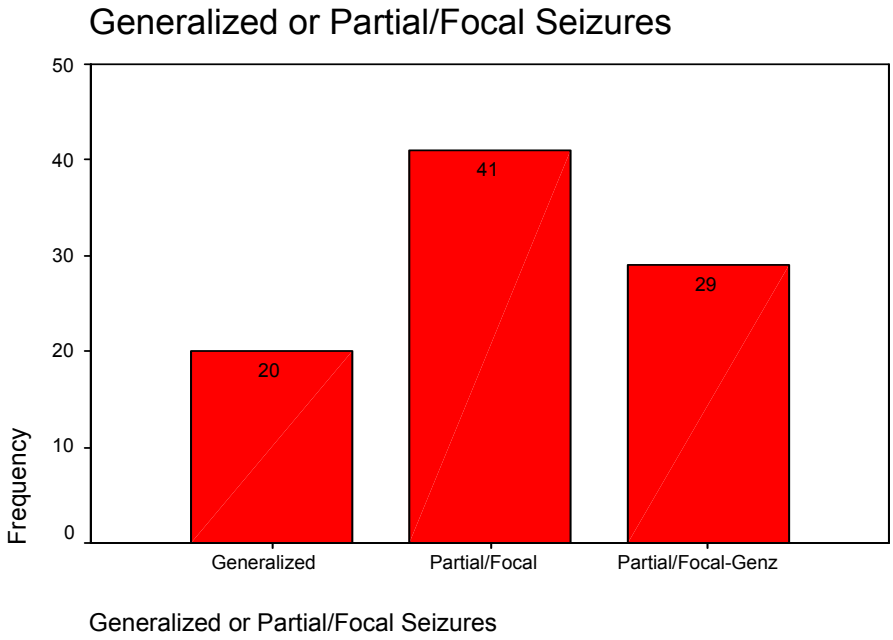
	Frequency	Percent
Left	43	43.9
Right	22	22.4
Both	21	21.4
Unclear	12	12.2
Total	98	100.0



GPT = Grooved Pegboard Test

Figure 9. Diagnostic profile of subjects administered SDMT (N = 97).

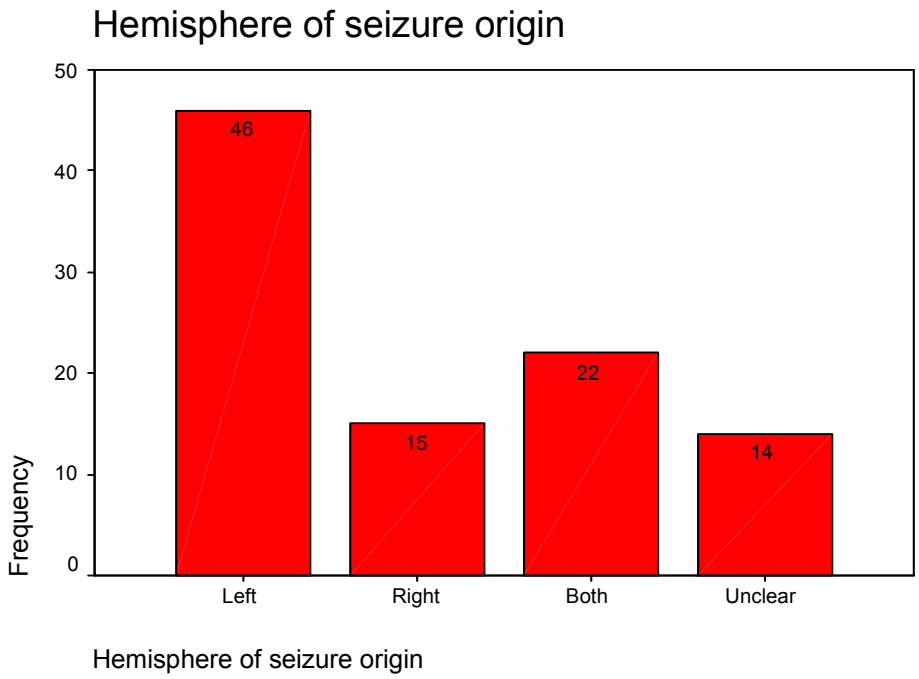
	Frequency	Percent
Generalized	20	20.6
Partial/Focal	41	42.3
Partial/Focal-Generalized	29	29.9
Unavailable data	7	7.2
Total	97	100.0



SDMT = Symbol Digit Modalities Test

Figure 10. Hemisphere of seizure origin for subjects administered SDMT (N = 97).

	Frequency	Percent
Left	46	47.4
Right	15	15.5
Both	22	22.7
Unclear	14	14.4
Total	97	100.0



SDMT = Symbol Digit Modalities Test

Table 10. Pearson product-moment correlation coefficients (PC; 2-tailed) of all variables for all subjects (N = 164).

		Age	Edu	SzYrs	AEDYrs	Dx	AgeSzons	Hem Orig	MOA	#AEDs	FSIQ	PEGDT	PEGNDT	SDMT LN
Age	PC	1												
	Sig.	.												
	N	164												
Edu	PC	.032	1											
	Sig.	.680	.											
	N	164	164											
SzYrs	PC	**.383****	-.023	1										
	Sig.	**.000**	.776	.										
	N	161	161	161										
AEDYrs	PC	.099	.027	**.350****	1									
	Sig.	.222	.743	**.000**	.									
	N	153	153	150	153									
Dx	PC	-.058	.050	-.108	-.097	1								
	Sig.	.464	.522	.173	.235	.								
	N	164	164	161	153	164								
AgeSzOns	PC	**.457****	.052	**-.644****	**-.257****	.077	1							
	Sig.	**.000**	.508	**.000**	**.001**	.327	.							
	N	162	162	161	151	162	162							
Hem Orig	PC	-.008	-.074	-.039	-.135	**.380****	.041	1						
	Sig.	.915	.348	.626	.097	**.000**	.608	.						
	N	164	164	161	153	164	162	164						
MOA	PC	-.145	-.081	.152	.095	.067	**-.261****	-.025	1					
	Sig.	.064	.300	.055	.243	.391	**.001**	.748	.					
	N	164	164	161	153	164	162	164	164					

Table 10 (Cont.). Pearson product-moment correlation coefficients (PC; 2-tailed) of all variables for all subjects (N = 164).

		Age	Edu	SzYrs	AEDYrs	Dx	AgeSzons	Hem Orig	MOA	#AEDs	FSIQ	PEGDT	PEGNDT	SDMTLN
#AEDs	PC	-.132	-.094	.131	-.079	-.038	**-.239****	-.067	**.659****	1				
	Sig.	.096	.233	.101	.334	.632	**.002**	.399	**.000**	.				
	N	161	161	158	150	161	159	161	161	161				
FSIQ	PC	-.115	**.497****	-.012	.065	.124	-.059	.136	-.077	-.069	1			
	Sig.	.153	**.000**	.879	.434	.125	.466	.092	.342	.395	.			
	N	155	155	152	145	155	153	155	155	154	155			
PEGDT	PC	-.001	.190	-.039	-.051	-.025	.030	-.034	**-.264****	**-.291****	**.425****	1		
	Sig.	.989	.061	.703	.633	.806	.771	.741	**.009**	**.004**	**.000**	.		
	N	98	98	96	90	98	96	98	98	97	91	98		
PEGNDT	PC	.032	**.201***	-.045	.005	-.044	.068	-.020	**-.350****	**-.309****	**.440****	**.752****	1	
	Sig.	.757	**.047**	.661	.964	.667	.512	.848	**.000**	**.002**	**.000**	**.000**	.	
	N	98	98	96	90	98	96	98	98	97	91	98	98	
SDMTLN	PC	-.149	**.420****	-.118	.007	.047	.020	.082	-.074	-.168	**.427****	**.403***	.305	1
	Sig.	.145	**.000**	.254	.951	.647	.848	.423	.473	.103	**.000**	**.025**	.095	.
	N	97	97	95	90	97	96	97	97	95	94	31	31	97

*Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed).

#AEDs = number of AEDs in regimen; AEDYrs = Years of antiepileptic drug (AEDs) treatment; AgeSzOns = Age of seizure onset; Dx = Diagnosis; Edu = Years of education; FSIQ = Full Scale IQ; GPT = Grooved Pegboard Test; Hem Orig = Hemisphere of seizure origin; MOA = mechanisms of action; PEGDT = dominant-hand T-score on GPT; PEGNDT = non-dominant hand T-score on GPT; SDMT = Symbol Digit Modalities Test; SDMTLN = natural logarithm of SDMT raw scores; SzYrs = Years of seizures.

Table 11. Descriptive data on GPT and SDMT (T-score mean = 50, SD = 10).

	PEGDT	PEGNDT	SDMTTS*	SDMT LN
N	98	98	97	97
Range	63	59	60	1
Minimum	9	12	20	3
Maximum	72	71	80	4
Mean	33.78	34.98	38.11	3.57
SEM	1.39	1.23	1.45	.04
SD	13.79	12.17	14.25	.38
Variance	190.27	148.30	203.12	.14
Skewness	.49	.40	.62	-.11
Std. Error (skewness)	.24	.24	.24	.24
Kurtosis	-.16	.28	.16	-.921
Std. Error (kurtosis)	.48	.48	.45	.48

SD = Standard Deviation
SEM = Standard Error of the Mean
GPT = Grooved Pegboard Test
PEGDT = Dominant T-scores on GPT
PEGNDT = Non-dominant T-scores on GPT
SDMT = Symbol Digit Modalities Test
SDMTTS* T-scores on SDMT, which are displayed only for comparison to GPT T-scores and not used in statistical analyses due to its non-normal distribution. SDMTLN will be used instead.
SDMTLN = Natural logarithm for SDMT raw scores

Table 12. Pearson product-moment correlation coefficients between outcome variables

	N	Mean	SD	SEM
PEGDT	98	33.78	13.79	1.39
PEGNDT	98	34.98	12.18	1.23
SDMT LN	97	3.57	.38	.04

	PEGDT	PEGNDT	SDMT LN
PEGDT	1	.752**	.403*
Sig. (2-tailed)	.	.000	.025
N	98	98	31
PEGNDT	.752**	1	.305
Sig. (2-tailed)	.000	.	.095
N	98	98	31
SDMT LN	.403*	.305	1
Sig. (2-tailed)	.025	.095	.
N	31	31	97

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

SD = Standard Deviation
SEM = Standard Error of the Mean
GPT = Grooved Pegboard Test
SDMT = Symbol Digit Modalities Test
PEGDT = Dominant T-scores on GPT
PEGNDT= Non-dominant T-scores on GPT
SDMTLN = Natural logarithm for SDMT raw scores

Table 13. Pearson product-moment correlation coefficients for years of seizure, years of AED treatment, and outcome.

	N	Mean	SD	SEM	Variance	Skewness (SE)	Kurtosis (SE)	Range
Years of seizures	161	16.35	12.08	.95	145.84	.80 (.19)	-.14 (.38)	1-51
Years of AED	153	4.69	5.82	.47	33.91	4.24 (.20)	26.36 (.39)	1-50
PEGDT	98	33.78	13.79	1.39				
PEGNDT	98	34.98	12.18	1.23				
SDMT LN	97	3.57	.38	.04				

	PEGDT	PEGNDT	SDMT LN
Years of seizures	-.039	-.045	-.118
Sig. (2-tailed)	.703	.661	.254
N	96	96	95
Years of AED	-.051	.005	.007
Sig. (2-tailed)	.633	.964	.951
N	90	90	90

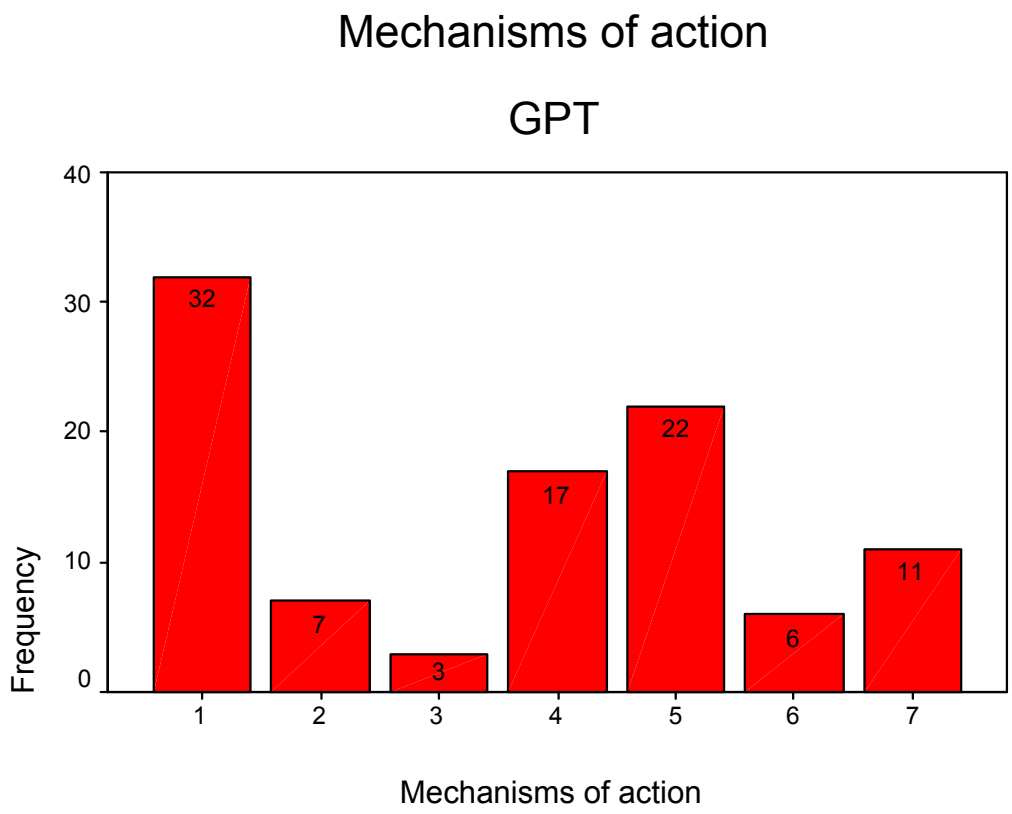
SD = Standard Deviation
SE = Standard Error
SEM = Standard Error of the Mean
GPT = Grooved Pegboard Test
SDMT = Symbol Digit Modalities Test
PEGDT = Dominant T-scores on GPT
PEGNDT = Non-dominant T-scores on GPT
SDMTLN = Natural logarithm for SDMT raw scores

Table 14. Means, SD, and SEM on GPT and SDMT by mechanisms of action.

		N	Mean	SD	SEM	95% Confidence Interval		Min.	Max.
						Lower	Upper		
PEGDT	Na	32	38.38	14.39	2.54	33.18	43.57	10	72
	Ca	7	35.43	8.96	3.39	27.14	43.72	27	52
	GABA	3	38.00	17.06	9.85	-4.38	80.38	19	52
	Na+Ca	17	30.76	12.44	3.02	24.37	37.16	17	54
	Na+Ca+GABA+Glu	22	32.77	13.33	2.84	26.86	38.68	9	58
	Na+Ca+GABA	6	27.00	11.10	4.53	15.35	38.65	12	44
	Na+GABA	11	28.55	16.26	4.90	17.62	39.47	11	70
	Total	98	33.78	13.79	1.39	31.01	36.54	9	72
PEGNDT	Na	32	40.47	13.00	2.30	35.78	45.16	12	71
	Ca	7	38.14	9.67	3.65	29.20	47.08	26	52
	GABA	3	31.33	7.02	4.05	13.89	48.78	24	38
	Na+Ca	17	31.06	11.84	2.87	24.97	37.15	12	56
	Na+Ca+GABA+Glu	22	34.91	10.01	2.13	30.47	39.35	16	50
	Na+Ca+GABA	6	29.17	9.45	3.86	19.25	39.09	20	46
	Na+GABA	11	27.36	12.30	3.71	19.10	35.63	12	54
	Total	98	34.98	12.18	1.23	32.54	37.42	12	71
SDMT LN	Na	38	3.58	.42	.07	3.44	3.72	3	4
	Ca	7	3.74	.49	.18	3.29	4.19	3	4
	GABA	14	3.55	.35	.09	3.35	3.76	3	4
	Na+Ca	8	3.71	.24	.08	3.51	3.90	3	4
	Na+Ca+GABA+Glu	19	3.49	.33	.08	3.33	3.65	3	4
	Na+Ca+GABA	4	3.30	.35	.18	2.74	3.86	3	4
	Na+GABA	7	3.62	.31	.12	3.33	3.91	3	4
	Total	97	3.57	.38	.04	3.49	3.65	3	4

Na = Blockade of Na^+ channel(s) only; **Ca** = Blockade of Ca^{2+} channel(s) only; **GABA** = Enhancement of GABAergic inhibition; **Na+Ca** = Blockade of both Na^+ and Ca^{2+} channels; **Na+Ca+GABA+Glu** = Blockade of Na^+, Ca^{2+}, & glutamate, as well as enhancement of GABAergic inhibition; **Na+Ca+GABA** = Blockade of both Na^+ and Ca^{2+} channels, and enhancement of GABAergic inhibition; **Na+GABA** = Blockade of the Na^+ channel and enhancement of GABAergic inhibition; **GPT** = Grooved Pegboard Test; **SDMT** = Symbol Digit Modalities Test; **PEGDT** = Dominant T-scores on GPT; **PEGNDT** = Non-dominant T-scores on GPT; **SDMTLN** = Natural logarithm for SDMT raw scores; **SD** = Standard Deviation; **SEM** = Standard Error of the Mean.

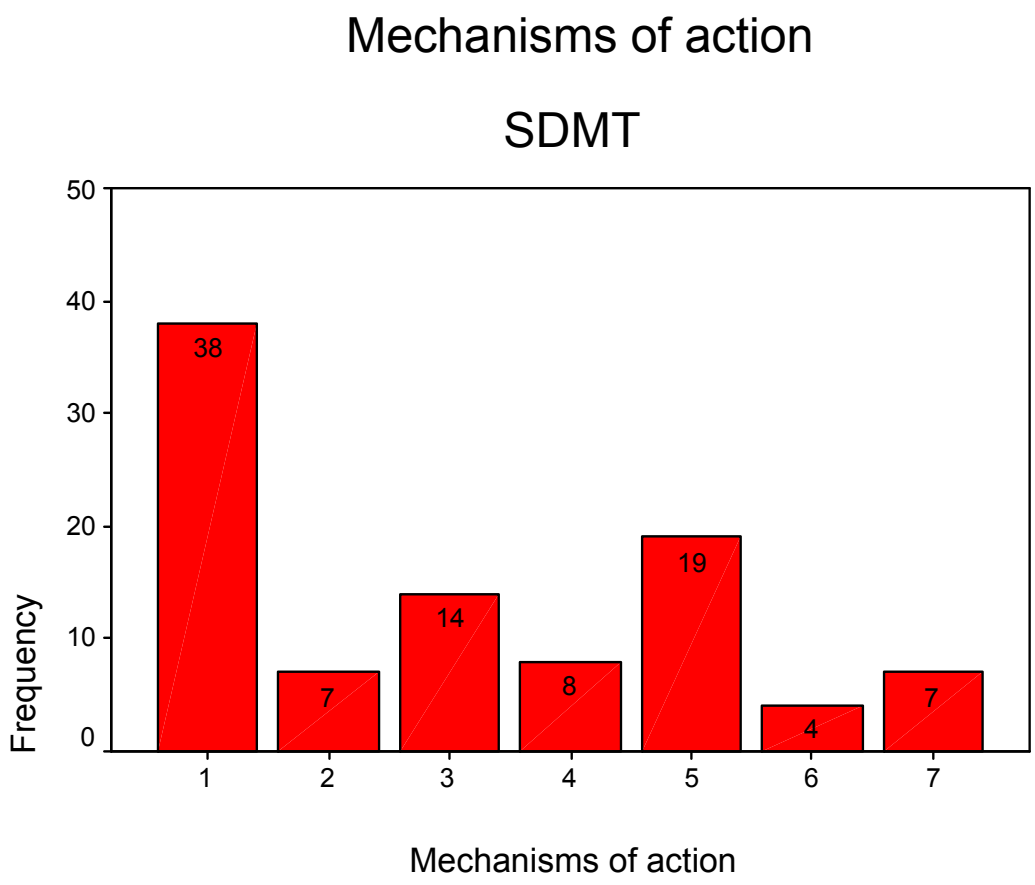
Figure 11. The number of subjects administered GPT (N = 98) according to mechanisms of action.



GPT = Grooved Pegboard Test

1 = Na - Blockade of Na^+ channel(s) only
2 = Ca - Blockade of Ca^{2+} channel(s) only
3 = GABA - Enhancement of GABAergic inhibition
4 = Na + Ca - Blockade of both Na^+ and Ca^{2+} channels
5 = Na + Ca + GABA + Glu - Synergistic mechanisms involving blockade of Na^+ and Ca^{2+} channels, blockade of ionotropic glutamate receptors, and enhancement of GABAergic inhibition
6 = Na + Ca + GABA - Blockade of both Na^+ and Ca^{2+} channels, and enhancement of GABAergic inhibition
7 = Na + GABA - Blockade of the Na^+ channel and enhancement of GABAergic inhibition

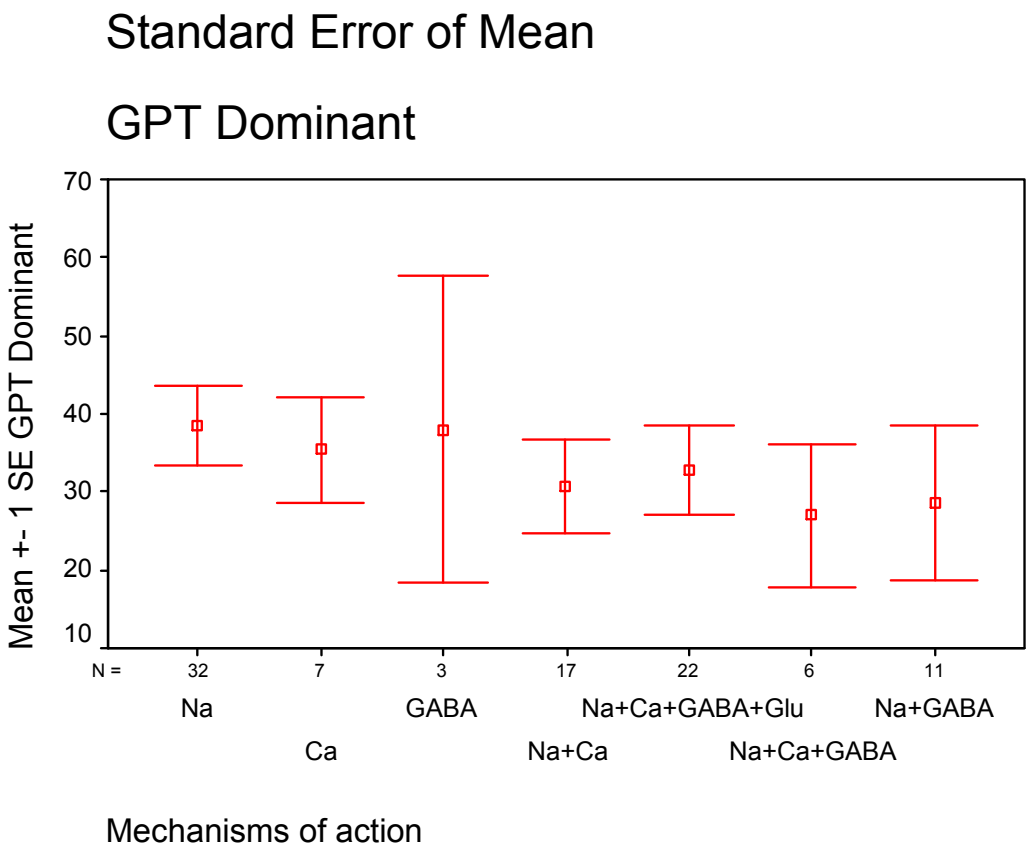
Figure 12. The number of subjects administered SDMT (N = 97) according to mechanisms of action.



SDMT = Symbol Digit Modalities Test

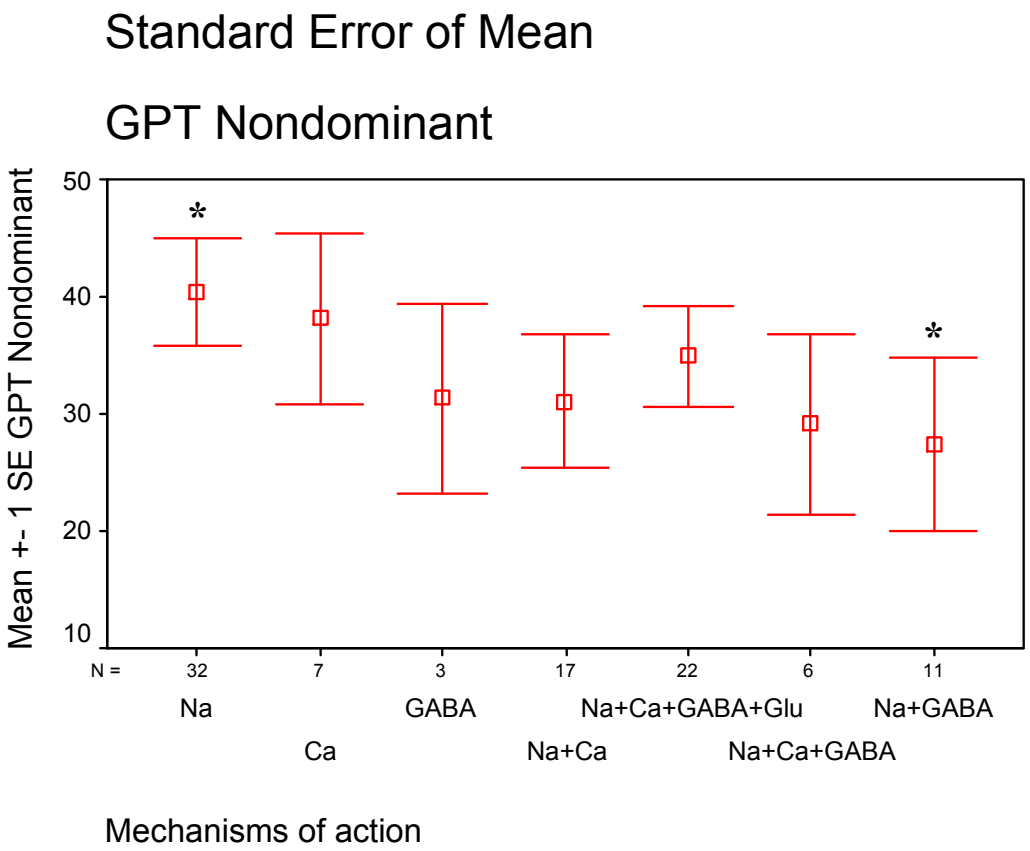
1 = Na - Blockade of Na^+ channel(s) only
2 = Ca - Blockade of Ca^{2+} channel(s) only
3 = GABA - Enhancement of GABAergic inhibition
4 = Na + Ca - Blockade of both Na^+ and Ca^{2+} channels
5 = Na + Ca + GABA + Glu - Synergistic mechanisms involving blockade of Na^+ and Ca^{2+} channels, blockade of ionotropic glutamate receptors, and enhancement of GABAergic inhibition
6 = Na + Ca + GABA - Blockade of both Na^+ and Ca^{2+} channels, and enhancement of GABAergic inhibition
7 = Na + GABA - Blockade of the Na^+ channel and enhancement of GABAergic inhibition

Figure 13. Standard error of the mean for GPT-dominant (N = 98) by mechanisms of action. Mean performance is indicated by the boxes.



Na =	Blockade of Na+ channel(s) only
Ca =	Blockade of Ca2+ channel(s) only
GABA =	Enhancement of GABAergic inhibition
Na+Ca =	Blockade of both Na+ and Ca2+ channels
Na+Ca+GABA+Glu =	Blockade of Na+, Ca2+, & glutamate, as well as enhancement of GABAergic Inhibition
Na+Ca+GABA =	Blockade of both Na+ and Ca2+ channels, and enhancement of GABAergic inhibition
Na+GABA =	Blockade of the Na+ channel and enhancement of GABAergic inhibition
GPT =	Grooved Pegboard Test

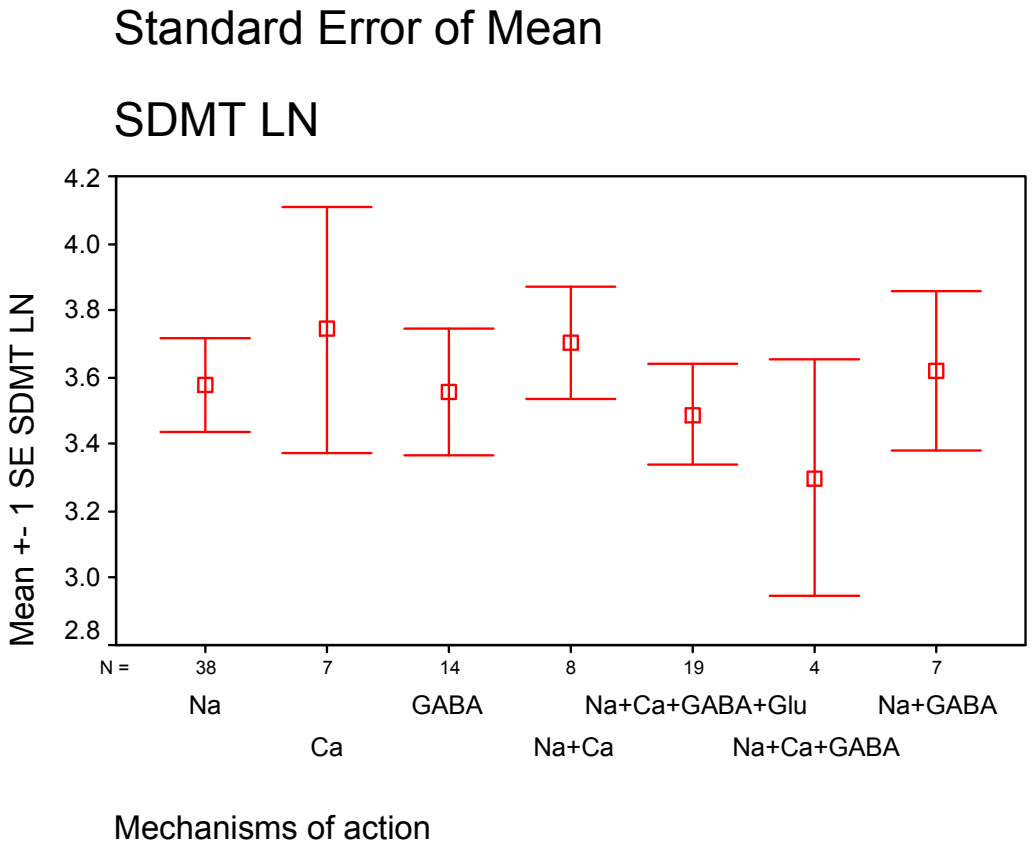
Figure 14. Standard error of the mean for GPT non-dominant (N = 98) by mechanisms of action. Mean performance is indicated by the boxes.



* = The mean difference is significant at the .05 level

Na =	Blockade of Na+ channel(s) only
Ca =	Blockade of Ca2+ channel(s) only
GABA =	Enhancement of GABAergic inhibition
Na+Ca =	Blockade of both Na+ and Ca2+ channels
Na+Ca+GABA+Glu =	Blockade of Na+, Ca2+, & glutamate, as well as enhancement of GABAergic Inhibition
Na+Ca+GABA =	Blockade of both Na+ and Ca2+ channels, and enhancement of GABAergic inhibition
Na+GABA =	Blockade of the Na+ channel and enhancement of GABAergic inhibition
GPT =	Grooved Pegboard Test

Figure 15. Standard error of the mean for SDMT (N = 97) by mechanisms of action. Mean performance is indicated by the boxes.



Na =	Blockade of Na+ channel(s) only
Ca =	Blockade of Ca2+ channel(s) only
GABA =	Enhancement of GABAergic inhibition
Na+Ca =	Blockade of both Na+ and Ca2+ channels
Na+Ca+GABA+Glu =	Blockade of Na+, Ca2+, & glutamate, as well as enhancement of GABAergic Inhibition
Na+Ca+GABA =	Blockade of both Na+ and Ca2+ channels, and enhancement of GABAergic inhibition
Na+GABA =	Blockade of the Na+ channel and enhancement of GABAergic inhibition
SDMTLN =	Natural logarithm for SDMT raw scores

Table 15. Means and SD (top) and Pearson product-moment correlation coefficients (bottom) for mechanisms of action and outcome variables.

	N	Mean	SD	SEM
Mechanisms of action (MOA)	164	3.16	2.10	.16
PEGDT	98	33.78	13.79	1.39
PEGNDT	98	34.98	12.18	1.23
SDMT LN	97	3.57	.38	.04

	PEGDT	PEGNDT	SDMT LN
Mechanisms of action (MOA)	-.264**	-.350**	-.074
Sig. (2-tailed)	.009	.000	.473
N	98	98	97

** Correlation is significant at the 0.01 level (2-tailed).

SD = Standard Deviation
SEM = Standard Error of the Mean
GPT = Grooved Pegboard Test
SDMT = Symbol Digit Modalities Test
PEGDT = Dominant T-scores on GPT
PEGNDT = Non-dominant T-scores on GPT
SDMTLN = Natural logarithm for SDMT raw scores

Table 16. ANOVA for mechanisms of action on outcome.

Test of Homogeneity of Variances

	Levene Statistic	df1	df2	Sig.
GPT Dominant	.489	6	91	.815
GPT Nondominant	.450	6	91	.843
SDMT LN	1.943	6	90	.082

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
GPT Dominant	Between Groups	1502.197	6	250.366	1.344	.246
	Within Groups	16954.864	91	186.317		
	Total	18457.061	97			
GPT Nondominant	Between Groups	2176.328	6	362.721	2.703	.018
	Within Groups	12209.631	91	134.172		
	Total	14385.959	97			
SDMT LN	Between Groups	.797	6	.133	.911	.491
	Within Groups	13.124	90	.146		
	Total	13.921	96			

Robust Tests of Equality of Means

		Statistic[a]	df1	df2	Sig.
GPT Dominant	Brown-Forsythe	1.351	6	24.043	.274
GPT Nondominant	Brown-Forsythe	3.296	6	60.932	.007
SDMT LN	Brown-Forsythe	1.008	6	38.558	.434

a. Asymptotically F distributed.

GPT = Grooved Pegboard Test
SDMTLN = Natural logarithm for SDMT raw scores

Table 17 Multiple comparisons for mechanisms of action and **non-dominant GPT.**

Multiple Comparisons

							95% Confidence Interval	
Dependent Variable		(I) Mechanisms of action	(J) Mechanisms of action	Mean Difference (I-J)	Std. Error	Sig.	Lower Bound	Upper Bound
PEGNDT	Tukey	Na	Ca	2.33	4.833	.999	-12.25	16.90
	HSD		GABA	9.14	6.994	.847	-11.95	30.22
			Na+Ca	9.41	3.476	.108	-1.07	19.89
			Na+Ca+GABA+Glu	5.56	3.208	.596	-4.11	15.23
			Na+Ca+GABA	11.30	5.153	.309	-4.24	26.84
			Na+GABA	13.11*	4.048	.027	.90	25.31
		Ca	Na	-2.33	4.833	.999	-16.90	12.25
			GABA	6.81	7.993	.979	-17.29	30.91
			Na+Ca	7.08	5.202	.820	-8.60	22.77
			Na+Ca+GABA+Glu	3.23	5.027	.995	-11.92	18.39
			Na+Ca+GABA	8.98	6.444	.804	-10.46	28.41
			Na+GABA	10.78	5.600	.470	-6.11	27.67
		GABA	Na	-9.14	6.994	.847	-30.22	11.95
			Ca	-6.81	7.993	.979	-30.91	17.29
			Na+Ca	.27	7.254	1.000	-21.60	22.15
			Na+Ca+GABA+Glu	-3.58	7.129	.999	-25.07	17.92
			Na+Ca+GABA	2.17	8.191	1.000	-22.53	26.86
			Na+GABA	3.97	7.545	.998	-18.78	26.72
		Na+Ca	Na	-9.41	3.476	.108	-19.89	1.07
			Ca	-7.08	5.202	.820	-22.77	8.60
			GABA	-.27	7.254	1.000	-22.15	21.60
			Na+Ca+GABA+Glu	-3.85	3.740	.946	-15.13	7.43
			Na+Ca+GABA	1.89	5.500	1.000	-14.69	18.48
			Na+GABA	3.70	4.482	.982	-9.82	17.21
		Na+Ca+GABA+Glu	Na	-5.56	3.208	.596	-15.23	4.11
			Ca	-3.23	5.027	.995	-18.39	11.92
			GABA	3.58	7.129	.999	-17.92	25.07
			Na+Ca	3.85	3.740	.946	-7.43	15.13
			Na+Ca+GABA	5.74	5.335	.933	-10.34	21.83
			Na+GABA	7.55	4.277	.575	-5.35	20.44
		Na+Ca+GABA	Na	-11.30	5.153	.309	-26.84	4.24
			Ca	-8.98	6.444	.804	-28.41	10.46
			GABA	-2.17	8.191	1.000	-26.86	22.53
			Na+Ca	-1.89	5.500	1.000	-18.48	14.69
			Na+Ca+GABA+Glu	-5.74	5.335	.933	-21.83	10.34
			Na+GABA	1.80	5.879	1.000	-15.92	19.53
		Na+GABA	Na	-13.11	4.048	.027	-25.31	-.90
			Ca	-10.78	5.600	.470	-27.67	6.11
			GABA	-3.97	7.545	.998	-26.72	18.78
			Na+Ca	-3.70	4.482	.982	-17.21	9.82

* The mean difference is significant at the .05 level.

Table 17 (Cont.). Multiple comparisons for mechanisms of action and **non-dominant GPT**.

Na =	Blockade of Na+ channel(s) only
Ca =	Blockade of Ca2+ channel(s) only
GABA =	Enhancement of GABAergic inhibition
Na+Ca =	Blockade of both Na+ and Ca2+ channels
Na+Ca+GABA+Glu =	Blockade of Na+, Ca2+, & glutamate, as well as enhancement of GABAergic Inhibition
Na+Ca+GABA =	Blockade of both Na+ and Ca2+ channels, and enhancement of GABAergic inhibition
Na+GABA =	Blockade of the Na+ channel and enhancement of GABAergic inhibition
GPT =	Grooved Pegboard Test

Table 18. ANOVA for Na versus GABAergic mechanisms of action on **non-dominant GPT.**

ANOVA

GPT Nondominant

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	1768.086	3	589.362	4.391	.006
Within Groups	12617.873	94	134.233		
Total	14385.959	97			

Na = Blockade of Na+ channel(s) only
GABA = Enhancement of GABAergic inhibition
GPT = Grooved Pegboard Test

Table 19. Multiple comparisons for Na versus GABAergic mechanisms and **non-dominant GPT.**

						95% Confidence Interval	
	(I) Na, GABA, or Na+GABA	**(J) Na, GABA, or Na+GABA**	**Mean Difference (I-J)**	**Std. Error**	**Sig.**	**Lower Bound**	**Upper Bound**
Tukey HSD	Other	Na-only	-7.05*	2.603	.040	-13.85	-.24
		GABA only	2.09	6.879	.990	-15.90	20.08
		Na+GABA	6.06	3.845	.397	-4.00	16.12
	Na-only	Other	7.05*	2.603	.040	.24	13.85
		GABA only	9.14	6.996	.562	-9.16	27.43
		Na+GABA	13.11*	4.049	.009	2.51	23.70
	GABA only	Other	-2.09	6.879	.990	-20.08	15.90
		Na-only	-9.14	6.996	.562	-27.43	9.16
		Na+GABA	3.97	7.546	.953	-15.77	23.71
	Na+GABA	Other	-6.06	3.845	.397	-16.12	4.00
		Na-only	-13.11*	4.049	.009	-23.70	-2.51
		GABA only	-3.97	7.546	.953	-23.71	15.77

* The mean difference is significant at the .05 level.

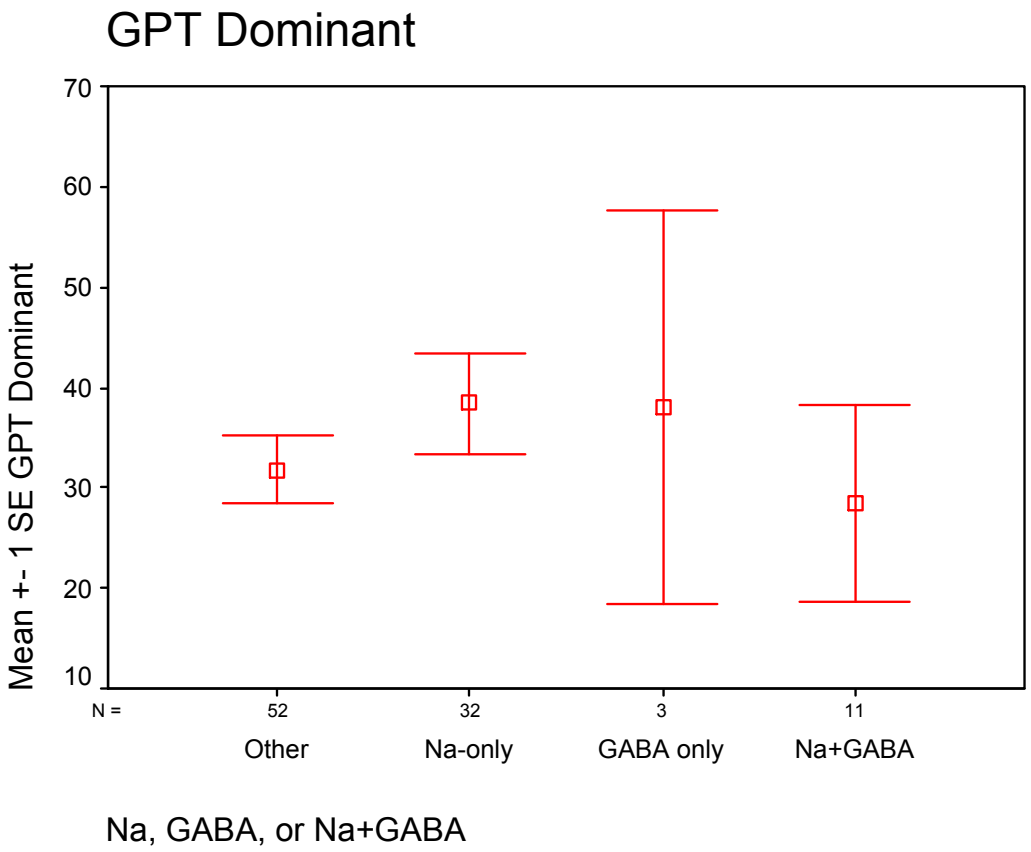
Na = Blockade of Na+ channel(s) only
GABA = Enhancement of GABAergic inhibition
Na+GABA = Blockade of the Na+ channel and enhancement of GABAergic inhibition
GPT = Grooved Pegboard Test

Table 20. AED regimens involving blockade of Na^+ channels, enhancement of GABAergic inhibition, and both mechanisms, for subjects administered GPT (see "Table 14" for the number of subjects treated with other AED regimens).

Blockade of Na^+ channels	**N**	**Enhancement of GABA**	**N**	**Blockade of Na^+ and Enhancement of GABA**	**N**
CBZ	10	VPA + GBP	1	OXC + GBP	1
LMT	7	VPA	2	PRM + OXC	1
PHT	6			LMT + OXC+ GBP	3
OXC	5			PHT + GBP	3
PHT + LMT + CBZ	1			TGB + LMT	1
LMT + CBZ	2			VPA + CBZ	1
PHT + CBZ	1			GBP + CBZ	1
Total	**32**	**Total**	**3**	**Total**	**11**

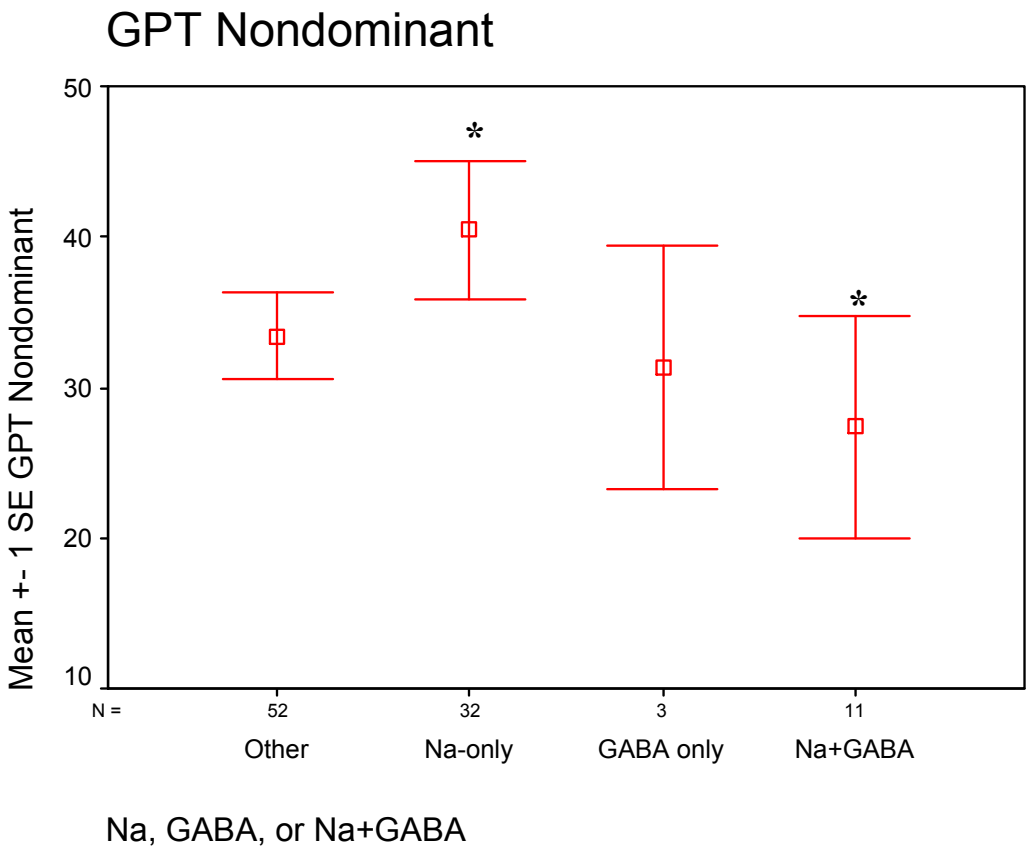
CBZ = carbamazepine (Tegretol)
GBP = gabapentin (Neurontin)
GPT = Grooved Pegboard Test
LMT = lamotrigine (Lamictal)
OXC = oxcarbazepine (Trileptal)
PHT = phenytoin (Dilantin)
PRM = primidone (Mysoline)
TGB = tiagabine (Gabritril)
VPA = valproic acid (Depakote)

Figure 16. Standard error of the mean for **GPT-dominant** (N = 98) by Na versus GABAergic mechanisms. Mean performance is indicated by the boxes.



Na =	Blockade of Na+ channel(s) only
GABA =	Enhancement of GABAergic inhibition
Na+GABA =	Blockade of the Na+ channel and enhancement of GABAergic inhibition
GPT =	Grooved Pegboard Test

Figure 17. Standard error of the mean for **GPT non-dominant** (N = 98) by Na versus GABAergic mechanisms. Mean performance is indicated by the boxes.



* =	The mean difference is significant at the .05 level
Na =	Blockade of Na+ channel(s) only
GABA =	Enhancement of GABAergic inhibition
Na+GABA =	Blockade of the Na+ channel and enhancement of GABAergic inhibition
GPT =	Grooved Pegboard Test

Table 21. Means and SD of demographic variables by Na^+ channel-blockers and GABAergic enhancers.

	N	Mean	SD	SEM
Age	93	37.52	10.39	1.08
Years of edu	93	14.30	2.69	.28
Years of seizures	92	15.78	11.54	1.20
Years of AED Tx	87	5.97	7.03	.75
Age of seizure onset	92	21.79	12.92	1.35
Hemisphere sz origin	93	2.16	1.18	.12
Generalized or Focal/Partial	83	2.08	.78	.09
Type of AED Therapy	93	.30	.46	.05
Number of AEDs	93	1.35	.62	.06
New Old Combo AEDs	93	1.91	.67	.07
Full Scale IQ	90	97.36	13.82	1.46
Na+GABA	93	1.53	.79	.08

Table 22. Pearson product-moment correlation coefficients of combination regimen of Na^+ channel-blockers and GABAergic enhancers to demographic variables.

	Na+GABA
Gender	.095
Sig. (2-tailed)	.367
N	93
Age	-.025
Sig. (2-tailed)	.810
N	93
Years of edu	-.042
Sig. (2-tailed)	.688
N	93
Years of seizures	.211*
Sig. (2-tailed)	.043
N	92
Years of AED Tx	.190
Sig. (2-tailed)	.078
N	87
Age of seizure onset	-.212*
Sig. (2-tailed)	.042
N	92
Hemisphere sz origin	.020
Sig. (2-tailed)	.846
N	93
Generalized or Focal/Partial	-.151
Sig. (2-tailed)	.172
N	83
Type of AED Therapy	.637**
Sig. (2-tailed)	.000
N	93
Number of AEDs	.633**
Sig. (2-tailed)	.000
N	93
New Old Combo AEDs	.372**
Sig. (2-tailed)	.000
N	93
Full Scale IQ	.005
Sig. (2-tailed)	.962
N	90

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

Table 23. ANOVA for number of ion channels targeted by AED regimen and outcome. This page: means and SD. Next page: results from Levene's test and ANOVA.

Descriptives

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Min.	Max.
						Lower Bound	Upper Bound		
GPT Dominant	1 ion channel	13	37.92	10.579	2.934	31.53	44.32	24	59
	2 ion channels	18	34.06	14.069	3.316	27.06	41.05	10	64
	3 ion channels	38	32.71	14.465	2.347	27.96	37.47	11	72
	4 ion channels	29	33.14	14.302	2.656	27.70	38.58	9	70
	Total	98	33.78	13.794	1.393	31.01	36.54	9	72
GPT Nondominant	1 ion channel	13	39.31	8.321	2.308	34.28	44.34	26	52
	2 ion channels	18	34.83	12.330	2.906	28.70	40.96	12	54
	3 ion channels	38	35.11	13.669	2.217	30.61	39.60	12	71
	4 ion channels	29	32.97	11.488	2.133	28.60	37.34	12	54
	Total	98	34.98	12.178	1.230	32.54	37.42	12	71
SDMT LN	1 ion channel	16	3.60	.438	.110	3.37	3.84	3	4
	2 ion channels	21	3.68	.381	.083	3.51	3.85	3	4
	3 ion channels	41	3.58	.346	.054	3.47	3.69	3	4
	4 ion channels	19	3.40	.375	.086	3.22	3.58	3	4
	Total	97	3.57	.381	.039	3.49	3.65	3	4

ANOVA = Analysis of Variance
GPT = Grooved Pegboard Test
GPT Dominant = Dominant T-scores on GPT
GPT Nondominant = Non-dominant T-scores on GPT
SDMTLN = Natural logarithm for SDMT raw scores

Table 23 (Cont.). ANOVA for number of ion channels targeted by AED regimen and outcome. Top: results from Levene's test. Bottom: ANOVA.

Test of Homogeneity of Variances

	Levene Statistic	df1	df2	Sig.
GPT Dominant	.644	3	94	.588
GPT Nondominant	.892	3	94	.448
SDMT LN	.771	3	93	.513

Robust Tests of Equality of Means

		Statistic[a]	df1	df2	Sig.
GPT Dominant	Brown-Forsythe	.527	3	80.370	.665
GPT Nondominant	Brown-Forsythe	.925	3	82.015	.432
SDMT LN	Brown-Forsythe	1.785	3	65.245	.159

a. Asymptotically F distributed.

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
GPT Dominant	Between Groups	279.930	3	93.310	.483	.695
	Within Groups	18177.132	94	193.374		
	Total	18457.061	97			
GPT Nondominant	Between Groups	362.145	3	120.715	.809	.492
	Within Groups	14023.814	94	149.190		
	Total	14385.959	97			
SDMT LN	Between Groups	.814	3	.271	1.926	.131
	Within Groups	13.107	93	.141		
	Total	13.921	96			

ANOVA = Analysis of Variance
GPT = Grooved Pegboard Test
GPT Dominant = Dominant T-scores on GPT
GPT Nondominant = Non-dominant T-scores on GPT

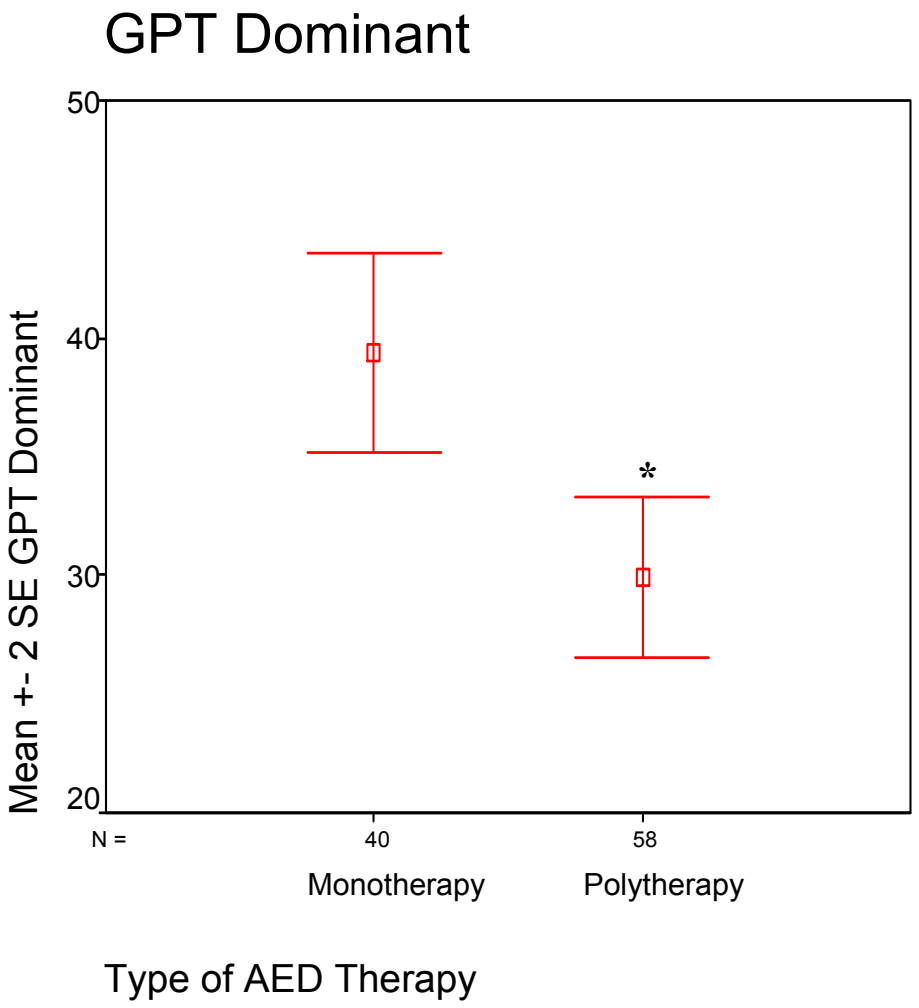
Table 24. Independent samples t-test: type of therapy on outcome. Top: means and SD. Bottom: results from independent samples t-test.

	Type of Therapy	N	Mean	SD	SEM
PEGDT	Monotherapy	40	39.40	13.37	2.11
	Polytherapy	58	29.90	12.81	1.68
PEGNDT	Monotherapy	40	40.17	11.89	1.88
	Polytherapy	58	31.40	11.12	1.46
SDMT LN	Monotherapy	56	3.64	.39	.05
	Polytherapy	41	3.48	.36	.05

		Levene's Test for Equality of Variances		t-test for Equality of Means					95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
PEGDT	Equal variances assumed	.000	.993	3.547	96	.001	9.50	2.680	4.184	14.823
PEGNDT	Equal variances assumed	.003	.958	3.734	96	.000	8.78	2.351	4.112	13.445
SDMT LN	Equal variances assumed	.170	.681	2.007	95	.048	.15470	.077064	.001712	.307696

SD = Standard Deviation; **SEM** = Standard Error of the Mean; **GPT** = Grooved Pegboard Test; **SDMT** = Symbol Digit Modalities Test; **PEGDT** = Dominant T-scores on GPT; **PEGNDT** = Non-dominant T-scores on GPT; **SDMTLN** = Natural logarithm for SDMT raw scores.

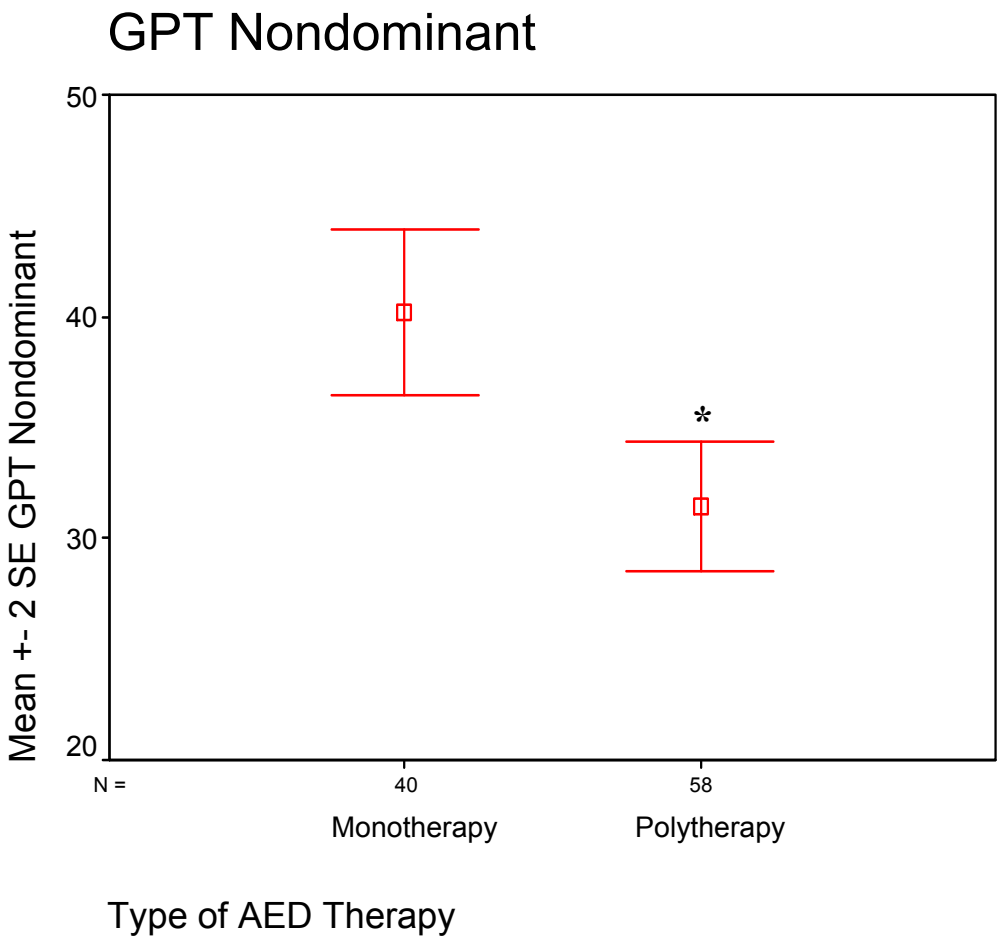
Figure 18. Standard error of the mean for GPT-**dominant** (N = 98) by type of therapy.



* = The mean difference is significant at the .05 level

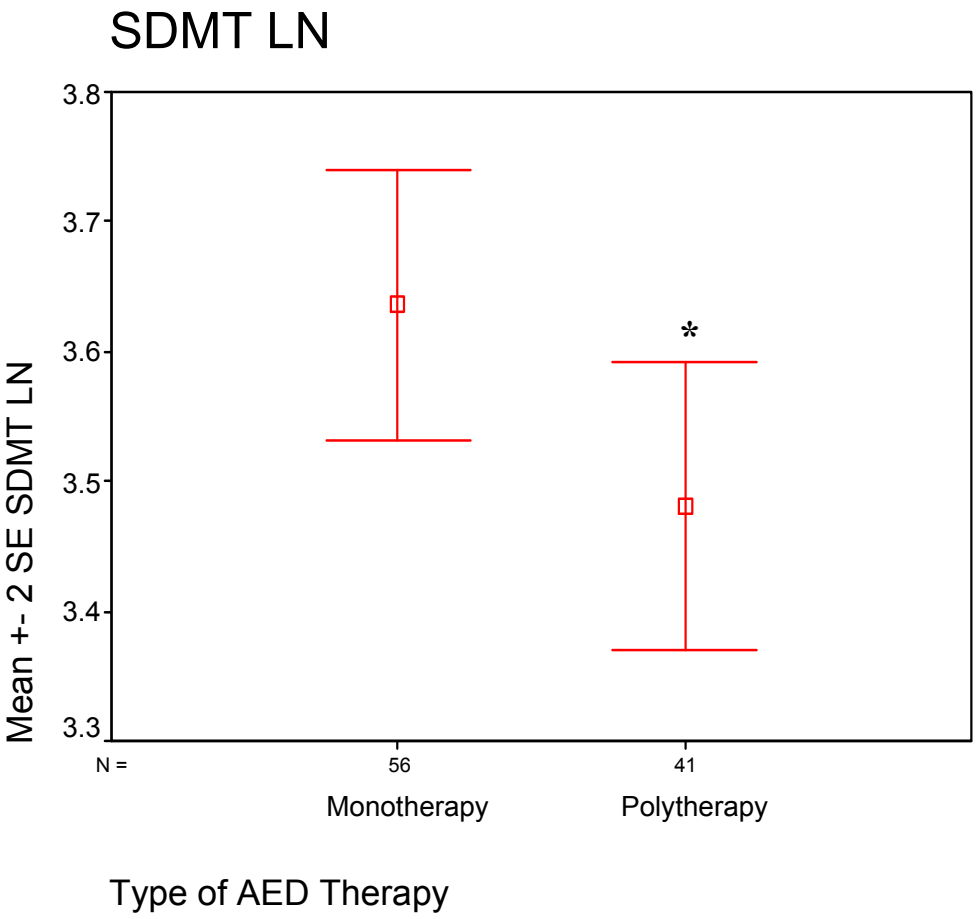
AED = Antiepileptic Drug

Figure 19. Standard error of the mean for GPT **non-dominant** (N = 98) by type of therapy.



* = The mean difference is significant at the .05 level
AED = Antiepileptic Drug

Figure 20. Standard error of the mean for SDMTLN (N = 97) by type of therapy.



* = The mean difference is significant at the .05 level
AED = Antiepileptic Drug
SDMTLN = Natural logarithm for SDMT raw scores.

Table 25. Independent Samples t-test for age by type of therapy for subjects administered GPT only (N = 98).

	N	Mean	SD	SEM
Age - monotherapy group	40	37.68	9.95	1.06
Age - polytherapy group	58	34.96	10.85	1.24
Age (total for GPT)	98	35.90	10.94	.47

		Levene's Test for Equality of Variances		t-test for Equality of Means				95% C.I. of Difference	
		F	Sig.	t	df	Sig.	MD	Lower	Upper
Age	Equal variances assumed	1.066	.304	2.447	96	.16	2.72	-1.28	6.72

MD = Mean Difference
SD = Standard Deviation
SED = Standard Error of the Difference
SEM = Standard Error of the Mean
GPT = Grooved Pegboard Test

Table 26. Means and SD by number of AEDs in regimen. Top: means and SD. Bottom: results from Levene's test.

		N	Mean	SD	SEM	95% Confidence Interval		Min.	Max.
						Lower	Upper		
PEGDT	1 AED	41	38.90	13.58	2.12	34.62	43.19	10	72
	2 AEDs	38	30.47	13.42	2.18	26.06	34.88	11	70
	3 AEDs	19	29.32	11.90	2.73	23.58	35.05	9	53
	Total	98	33.78	13.79	1.39	31.01	36.54	9	72
PEGNDT	1 AED	41	39.78	12.01	1.88	35.99	43.57	12	71
	2 AEDs	38	31.89	11.00	1.78	28.28	35.51	12	56
	3 AEDs	19	30.79	11.78	2.70	25.11	36.47	12	50
	Total	98	34.98	12.18	1.23	32.54	37.42	12	71
SDMT LN	1 AED	9	3.78	.45	.150	3.44	4.13	3	4
	2 AEDs	13	3.55	.38	.107	3.32	3.79	3	4
	3 AEDs	9	3.40	.41	.138	3.08	3.72	3	4
	Total	31	3.58	.43	.077	3.42	3.73	3	4

Test of Homogeneity of Variances

	Levene Statistic	df1	df2	Sig.
PEGDT	.206	2	95	.814
PEGNDT	.085	2	95	.919
SDMT LN	.168	2	28	.846

AED = Antiepileptic Drug
SD = Standard Deviation
SEM = Standard Error of the Mean
GPT = Grooved Pegboard Test
SDMT = Symbol Digit Modalities Test
PEGDT = Dominant T-scores on GPT
PEGNDT = Non-dominant T-scores on GPT
SDMTLN = Natural logarithm for SDMT raw scores

Table 27. ANOVA for the number of AEDs in regimen.

		Sum of Squares	df	Mean Square	F	Sig.
PEGDT	Between Groups	1809.93	2	904.96	5.15	.008
	Within Groups	16529.82	94	175.85		
	Total	18339.75	96			
PEGNDT	Between Groups	1564.66	2	782.33	5.82	.004
	Within Groups	12623.86	94	134.30		
	Total	14188.51	96			
SDMT LN	Between Groups	.47	2	.24	1.66	.196
	Within Groups	13.11	92	.14		
	Total	13.58	94			

Robust Tests of Equality of Means

		Statistic	df1	df2	Sig.
PEGDT	Brown-Forsythe	5.639	2	82.095	.005
PEGNDT	Brown-Forsythe	6.077	2	71.401	.004
SDMT LN	Brown-Forsythe	1.889	2	24.438	.173

a Asymptotically F distributed.

GPT = Grooved Pegboard Test
PEGDT = Dominant T-scores on GPT
PEGNDT = Non-dominant T-scores on GPT
SDMT = Symbol Digit Modalities Test
SDMTLN = Natural logarithm for SDMT raw scores

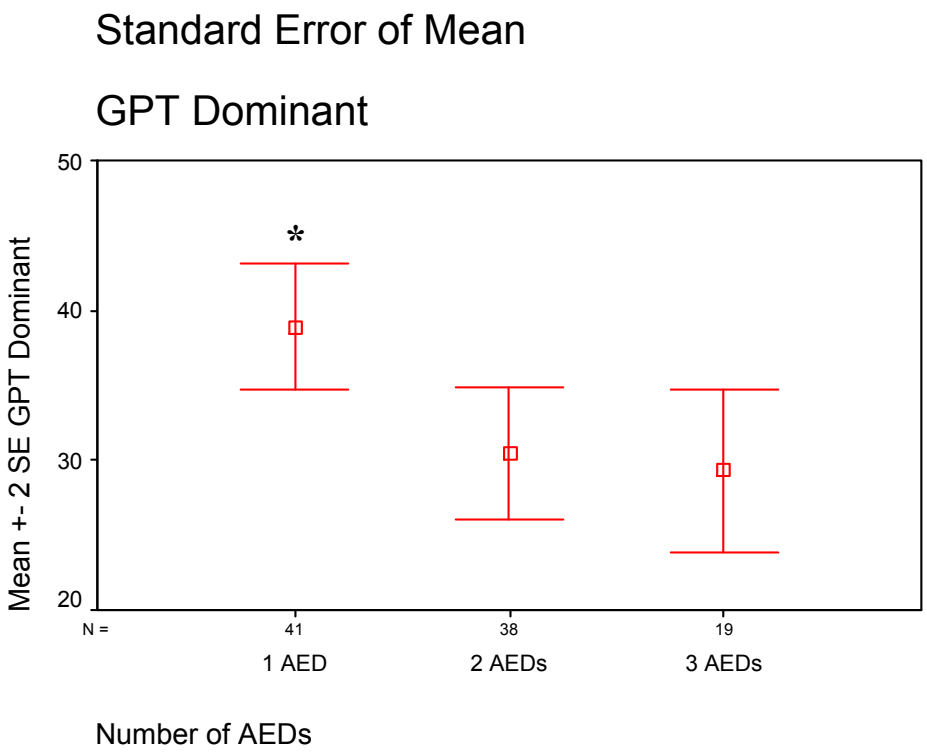
Table 28. Multiple comparisons between the number of AEDs in regimen and performance on GPT.

							95% Confidence Interval	
Dependent Variable		**(I) Number of AEDs**	**(J) Number of AEDs**	**Mean Difference (I-J)**	**Std. Error**	**Sig.**	**Lower Bound**	**Upper Bound**
PEGDT	**Tukey HSD**	1 AED	2 AEDs	8.43*	2.97	.015	1.34	15.51
			3 AEDs	9.59*	3.67	.028	.86	18.32
		2 AEDs	1 AED	-8.43*	2.97	.015	-15.51	-1.34
			3 AEDs	1.16	3.71	.948	-7.68	10.00
		3 AEDs	1 AED	-9.59*	3.67	.028	-18.32	-.86
			2 AEDs	-1.16	3.71	.948	-10.00	7.68
PEGNDT	**Tukey HSD**	1 AED	2 AEDs	7.89*	2.61	.009	1.68	14.10
			3 AEDs	8.99*	3.21	.017	1.34	16.64
		2 AEDs	1 AED	-7.89*	2.61	.009	-14.10	-1.68
			3 AEDs	1.11	3.25	.938	-6.64	8.85
		3 AEDs	1 AED	-8.99*	3.21	.017	-16.64	-1.34
			2 AEDs	-1.11	3.25	.938	-8.85	6.64

* The mean difference is significant at the .05 level.

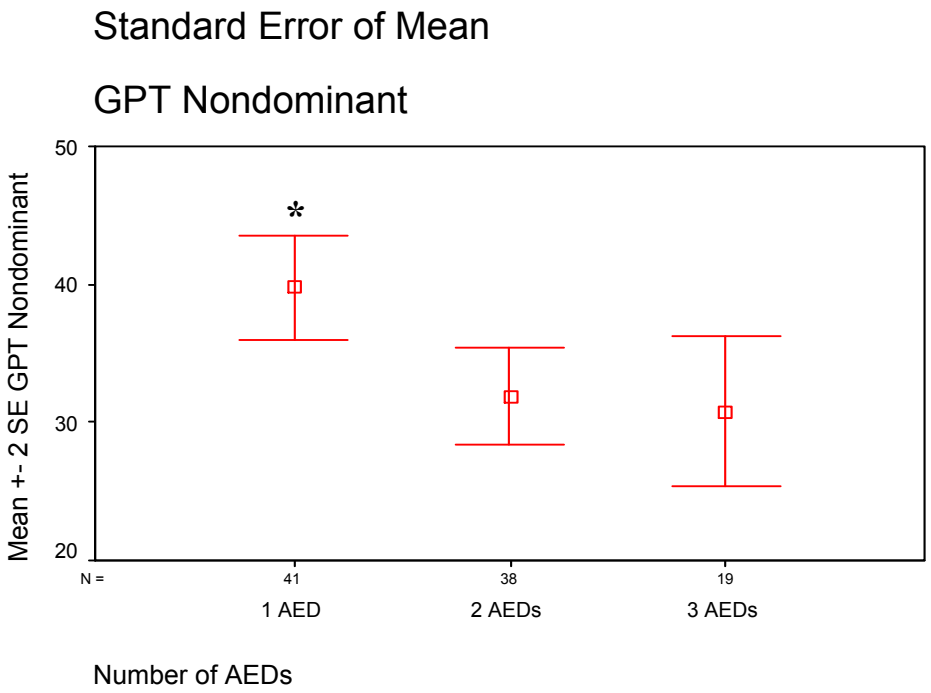
GPT = Grooved Pegboard Test
PEGDT = Dominant T-scores on GPT
PEGNDT = Non-dominant T-scores on GPT

Figure 21. Standard error of the mean for GPT-**dominant** (N = 98) by the number of AEDs. Mean performance is indicated by the boxes.



* = The mean difference is significant at the .05 level
GPT = Grooved Pegboard Test

Figure 22. Standard error of the mean for GPT **non-dominant** (N = 98) by the number of AEDs. Mean performance is indicated by the boxes.



* = The mean difference is significant at the .05 level

GPT = Grooved Pegboard Test

Table 29. Means and SD on GPT and SDMT by gender

	Gender	N	Mean	SD	SEM
PEGDT	Male	42	37.43	13.87	2.14
	Female	56	31.04	13.20	1.76
PEGNDT	Male	42	37.24	10.88	1.68
	Female	56	33.29	12.90	1.72
SDMT LN	Male	40	3.56	.39	.06
	Female	57	3.57	.38	.05

SD = Standard Deviation
SEM = Standard Error of the Mean
GPT = Grooved Pegboard Test
SDMT = Symbol Digit Modalities Test
PEGDT = Dominant T-scores on GPT
PEGNDT = Non-dominant T-scores on GPT
SDMTLN = Natural logarithm for SDMT raw scores

Table 30. Independent samples t-test for gender and outcome.

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
PEGDT	Equal variances assumed	.065	.799	2.321	96	.022	6.39	2.754	.926	11.860
	Equal variances not assumed			2.305	86.039	.024	6.39	2.774	.879	11.907
PEGNDT	Equal variances assumed	.390	.534	1.603	96	.112	3.95	2.466	-.943	8.847
	Equal variances not assumed			1.642	94.635	.104	3.95	2.407	-.825	8.730
SDMT LN	Equal variances assumed	.079	.779	-.137	95	.891	-.01	.079	-.168	.146
	Equal variances not assumed			-.136	82.850	.892	-.01	.079	-.168	.147

GPT = Grooved Pegboard Test
SDMT = Symbol Digit Modalities Test
PEGDT = Dominant T-scores on GPT
PEGNDT = Non-dominant T-scores on GPT
SDMTLN = Natural logarithm for SDMT raw scores

Table 31. Pearson product-moment correlation coefficients of demographic variables and outcome.

	PEGDT	PEGNDT	SDMT LN
Age	-.001	.032	-.149
Sig. (2-tailed)	.495	.378	.072
N	98	98	97
Years of edu	.190*	.201*	.420**
Sig. (2-tailed)	.030	.023	.000
N	98	98	97
Full Scale IQ	.425**	.440**	.427**
Sig. (2-tailed)	.000	.000	.000
N	91	91	94

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).

SD = Standard Deviation
SEM = Standard Error of the Mean
GPT = Grooved Pegboard Test
SDMT = Symbol Digit Modalities Test
PEGDT = Dominant T-scores on GPT
PEGNDT = Non-dominant T-scores on GPT
SDMTLN = Natural logarithm for SDMT raw scores

Table 32. Suggested AED combinations based on their interactions, mechanisms of action, and side effects (adapted from Leppik, 2000; Deckers et al., 2000).

AED COMBINATIONS BY DRUG INTERACTIONS	**RATIONALE**
Most useful	
GBP with any AED	No drug interactions
VPA with LMT	VPA inhibits metabolism of LMT, thereby reducing dose and cost
Least useful	
CBZ with PHT	PHT increases metabolism of CBZ, thereby increasing CBZ dosages
VPA with PHT	CYP450 system
AED COMBINATIONS (2 AEDS ONLY) BY MECHANISMS OF ACTION	**RATIONALE**
Most useful	
CBZ/LMT/PHT with GBP/LEV/TGB/TPM/VPA	Widely different mechanisms of action, increased efficacy and tolerability
Least useful	
CBZ and PHT	Similar mechanisms of action
TGB and GBP	Similar mechanisms of action
AED COMBINATIONS BY SIDE EFFECTS	**RATIONALE**
Possibly useful	
VPA with FBM or TPM	Weight loss caused by FBM and TPM may compensate for the weight gain by VPA
Least useful	
CBZ and VPA in pregnant women	VPA and CBZ may increase risk for spina bifida; VPA inhibits metabolism of 10,11 CBZ epoxide, which also may be teratogenic

CBZ = carbamazepine (Tegretol)
FBM = felbamate (Felbatol)
GBP = gabapentin (Neurontin)
LEV = levetiracetam (Keppra)
LMT = lamotrigine (Lamictal)
OXC = oxcarbazepine (Trileptal)
PHT = phenytoin (Dilantin)
PRM = primidone (Mysoline)
TGB = tiagabine (Gabitril)
TPM = topiramate (Topamax)
VPA = valproic acid (Depakote)
ZNM = zonisamide (Zonegran)

References

Al Rajeh, S., Awada, A., Bademosi, O., & Ogunniyi, A. (2001). The prevalence of epilepsy and other seizure disorders in an Arab population: a community-based study. *Seizure, 10*(6), 410–414.

Aldenkamp, A.P., & Vermeulen, J. (1995). Phenytoin and carbamazepine: differential effects on cognitive function. *Seizure, 4*(2), 95-104.

Alioğlu, Z., Sari, A., Velioğlu, S.K., & Ozmenoğlu, M. (2000). Cerebellar atrophy following acute phenytoin intoxication. *Journal of Neuroradiology, 27*(1), 52-55.

American Epilepsy Society (2004). Epilepsy education program. http://www.aesnet.org.

Anderson, A.E., Adams, J.P., Varga, A.W., Selcher, J.C., Feng, J., Trzaskos, J.M., & Sweatt, J.D. (2000). Essential role for ERK MAPK activation and K+ channel phosphorylation in the kainate model of epilepsy [Abstract]. *Society for Neuroscience Abstracts, 26,* 1836.

Annegers, J.F., Rocca, W.A., & Hauser, W.A. (1996). Causes of epilepsy: contributions of the Rochester epidemiology project. *Mayo Clinic Proceedings, 71*(6), 570-5.

Armijo, J.A., Shushtarian, M., Valdizan, E.M., Cuadrado, A., de las Cuevas, I., & Adin, J. (2005). Ion channels and epilepsy. *Current Pharmacological Designs, 11*(15), 1975-2003.

Aumann, T.D. (2002). Cerebello-thalamic synapses and motor adaptation. *Cerebellum, 1*(1), 69-77.

Babb, T.L., & Brown, W.J. (1987). Pathological Findings in Epilepsy. In: J. Engel Jr. (Ed.), *Surgical treatment of the epilepsies* (pp. 511-540). New York: Raven Press.

Bang, L.M., & Goa, K.L. (2004). Spotlight on oxcarbazepine in epilepsy. CNS Drugs, *18*(1), 57-61.

Baraban, J.M., Fiore, R., Sanghera, J.S., Paddon, H.B., & Pelech, S. (1993). Identification of p42 mitogen-activated protein kinase as a tyrosine kinase substrate activated by maximal electroconvulsive shock in hippocampus. *Journal of Neurochemistry, 60,* 330–336.

Beckung, E., & Uvebrant, P. (1993). Motor and sensory impairments in children with intractable epilepsy. *Epilepsia, 34*(5), 924-929.

Bell, G.S., & Sander, J.W. (2001). The epidemiology of epilepsy: the size of the problem. *Seizure, 10,* 306–314.

Berkovic, S.F., & Scheffer, I.E. (2001). Genetics of the epilepsies. *Epilepsia, 42*(Suppl. 5), 16-23.

Binder, D.K., Routbort, M.J., & McNamara, J.O. (1999). Immunohistochemical evidence of seizure-induced activation of trk receptors in the mossy fiber pathway of adult rat hippocampus. *Journal of Neuroscience, 19*(11), 4616-4626.

Boll, T.J. (1981). The Halstead-Reitan Neuropsychological Battery. In: S.B. Filskov and T.J. Boll (Eds.). Handbook of clinical neuropsychology. New York, NY: Wiley-Interscience.

Botez, M.I., Attig, E., & Vezina, J.L. (1988). Cerebellar atrophy in epileptic patients. Canadian *Journal of Neurological Sciences, 15*(3), 299-303.

Botez, M.I., Botez, T., Elie, R., & Attig, E. (1989). Role of the cerebellum in complex human behavior. *Italian Journal of Neurological Sciences, 10*(3), 291-300.

Braathen, G., von Bahr, L., & Theorell, K. (1997). Motor impairments in children with epilepsy treated with carbamazepine. *Acta Paediatrica, 86*(4), 372-376.

Brodie, M.J., & Kwan, P. (2001). The star systems: overview and use in determining antiepileptic drug choice. *CNS Drugs, 15*(1), 1-12.

Brodie, M.J., McPhail, E., Macphee, G.J., Larkin, J.G., & Gray, J.M. (1987). Psychomotor impairment and anticonvulsant therapy in adult epileptic patients. *European Journal of Clinical Pharmacology, 31*(6), 655-660.

Brunbech, L., & Sabers, A. (2002). Effect of antiepileptic drugs on cognitive function in individuals with epilepsy: a comparative review of newer versus older agents. *Drugs, 62*(4), 593-604.

Cavazos, J.E., Golarai, G., & Sutula, T.P. (1991). Mossy fiber synaptic reorganization induced by kindling: time course of development, progression, and permanence. *Journal of Neuroscience, 11*(9), 2795–2803.

Chang, B.S., & Lowenstein, D.H. (2003). Epilepsy. *New England Journal of Medicine, 349*(13), 1257-1266.

Cohen, A.F., Ashby, L., Crowley, D., Land, G., Peck, A.W., & Miller, A.A. (1985). Lamotrigine (BW430C), a potential anticonvulsant, effects on the central nervous system in comparison with phenytoin and diazepam. *British Journal of Clinical Pharmacology, 20*(6), 619-629.

Cohen, J. (1992). *A power primer. Psychological Bulletin, 112,* 155-159.

Cole, A.J., Koh, S., Zheng, Y. (2002). Are seizures harmful: what can we learn from animal models? *Progress in Brain Research, 135,* 13-23.

Cole, A.J., Saffen, D.W., Baraban, J.M., & Worley, P.F. (1989). Rapid increase of an immediate early gene messenger RNA in hippocampal neurons by synaptic NMDA receptor activation. *Nature, 340,* 474–476.

Commission on Classification and Terminology of the International League Against Epilepsy. (1981). Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia, 22*(4), 489-501.

Commission on Classification and Terminology of the International League Against Epilepsy. (1989). Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia, 30*(4), 389-399.

Corsellis, J.A.N., & Meldrum, B.S. (1976). Epilepsy. In W. Blackwood, & J.A.N. Corsellis (Eds.), *Greenfield's neuropathology* (pp. 771–795). London: Edward Arnold.

Cosford, N.D., Meinke, P.T., Stauderman, K.A., & Hess, S.D. (2002). Recent advances in the modulation of voltage-gated ion channels for the treatment of epilepsy. *Current Drug Targets - CNS Neurological Disorder, 1*(1), 81-104.

Coulter, D. A. (1997). Antiepileptic drug cellular mechanisms of action: where does lamotrigine fit in? *Journal of Child Neurology, 12*(suppl. 1), S2– S9.

Crooks, R., Mitchell, T., & Thom, M. (2000). Patterns of cerebellar atrophy in patients with chronic epilepsy: a quantitative neuropathological study. *Epilepsy Research, 41*(1), 63-73.

Dam, M. (1970). Number of Purkinje cells in patients with grand mal epilepsy treated with diphenylhydantoin. *Epilepsia, 11,* 313–320.

Danscher, G. (1981). Histochemical demonstration of heavy metals. A revised version of the sulphide silver method suitable for both light and electronmicroscopy. *Histochemistry, 71*(1), 1-16.

Deckers, C.L., Czuczwar, S.J., Hekster, Y.A., Keyser, A., Kubova, H., Meinardi, H., Patsalos, P.N., Renier, W.O., & Van Rijn, C.M. (2000). Selection of antiepileptic drug polytherapy based on mechanisms of action: the evidence reviewed. *Epilepsia, 41*(11), 1364-1374.

Deichmann, M. (1998). Nonverbal intelligence and the speed/accuracy trade-off in children with diabetes: A longitudinal follow-up. *Dissertation Abstracts International: Section B: The Sciences and Engineering, 59*(1-B), 0433.

Demakis, G., Mercury, M., Sweet, J., Rezak, M., Eller, T., & Vergenz, S. (2002). Motor and cognitive sequelae of unilateral pallidotomy in intractable Parkinson's disease: Electronic measurement of motor steadiness is a useful outcome. *Journal of Clinical and Experimental Neuropsychology, 24*(5), 655–663.

Devinsky, O., & Tarulli, A. (2002). Progressive cognitive and behavioral changes in epilepsy. In O. Devinsky, L. Westbrook (Eds.), *Epilepsy and developmental disabilities* (pp. 133-149). Boston: Butterworth-Heinemann.

Dichter, M.A. (1994). Emerging insights into mechanisms of epilepsy: Implications for new antiepileptic drug development. *Epilepsia, 35*(Suppl. 4), S51-S57.

Dodrill, C.B. (2002). Progressive cognitive decline in adolescents and adults with epilepsy. *Progress in Brain Research, 135,* 399-407.

Dodrill, C.B. (2004). Neuropsychological effects of seizures. *Epilepsy & Behavior, 5*(Suppl. 1), S21-24

Dodrill, C.B., & Temkin, N.R. (1989). Motor speed is a contaminating factor in evaluating the "cognitive" effects of phenytoin. *Epilepsia, 30*(4), 453-457.

Dodrill, C.B., & Troupin, A.S. (1977). Psychotropic effects of carbamazepine in epilepsy: a double-blind comparison with phenytoin. *Neurology, 27*(11), 1023-1028.

Dodrill, C.B., & Troupin, A.S. (1991). Neuropsychological effects of carbamazepine and phenytoin: a reanalysis. *Neurology, 41*(1), 141-143.

Dodrill, C.B., & Wilensky, A.J. (1992). Neuropsychological abilities before and after 5 years of stable antiepileptic drug therapy. *Epilepsia, 33*(2), 327-334.

Drane, D.L., & Meador, K.J. (2002). Cognitive and behavioral effects of antiepileptic drugs. *Epilepsy & Behavior, 3*(5S), 49-53.

Engel, J. (2001). A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology. *Epilepsia, 42*(6), 796-803.

Engel, J. Jr., Kuhl, D.E., Phelps, M.E., & Mazziotta, J.C. (1982). Interictal cerebral glucose metabolism in partial epilepsy and its relation to EEG changes. *Annals of Neurology, 12,* 510–517.

Engel, J. Jr. (1989). *Seizures and epilepsy.* Philadelphia: F.A. Davis.

Engel, J. Jr. (1990). The Hans Berger lecture. Functional explorations of the human epileptic brain and their therapeutic implications. *Electroencephalography and clinical neurophysiology, 76*(4), 296-316.

Engel, J. Jr. (1991). Neurochemical disturbances in epilepsy: relationship to behavior. In O. Devinsky & W.H. Theodore (Eds.), *Epilepsy and Behavior,* (pp. 336-343). New York: Wiley-Liss.

Ferrendelli, J.A. (1995). Relating pharmacology to clinical practice: the pharmacologic basis of rational polypharmacy. *Neurology, 45*(3 Suppl 2), S12-6.

Field, A. P. (2005). Discovering statistics using SPSS (2nd ed.). London: Sage.

Fisher, R.S., van Emde, Boas W., Blume, W., Elger, C., Genton, P., Lee, P., & Engel, J. Jr. (2005). Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia, 46*(4), 470-472.

Food and Drug Administration (FDA) (2006). http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

Friedman, L.K. (1998). Selective reduction of GluR2 protein in adult hippocampal CA3 neurons following status epilepticus but prior to cell loss. *Hippocampus, 8*(5), 511-525.

Futami, T., Kano, M., Sento, S., & Shinoda, Y. (1986). Synaptic organization of the cerebello-thalamo-cerebral pathway in the cat. III. Cerebellar input to corticofugal neurons destined for different subcortical nuclei in areas 4 and 6. *Neuroscience Research, 3*(4), 321-344.

Gall, C., Lauterborn, J., Isackson, P., & White, J. (1990). Seizures, neuropeptide regulation, and mRNA expression in the hippocampus. *Progress in Brain Research, 83,* 371–390.

Germano, E., Gagliano, A., Magazu, A., Sferro, C., Calarese, T., Mannarino, E., & Calamoneri, F. (2005). Benign childhood epilepsy with occipital paroxysms: neuropsychological findings. *Epilepsy Research, 64*(3), 137-150.

Ghez, C. (1991). The cerebellum. In E.R. Kandel, J.H. Schwartz & T.M. Jessel (Eds.), *Principles of Neural Science,* (3rd ed., pp. 626-646). New York: Elsevier.

Gloor, P. (1991). Mesial temporal sclerosis: historical background and an overview from a modern perspective. In H. Luders (ed.), *Epilepsy surgery* (pp. 689–703). New York: Raven Press.

Goddard, G.V. (1967). Development of epileptic seizures through brain stimulation at low intensity. *Nature, 214*(92), 1020-1021.

Golden, C. J. (1978). Diagnosis and rehabilitation in clinical neuropsychology. Springfield, IL: C.C. Thomas.

Goldstein, G. (1974). The use of clinical neuropsychological methods in the lateralization of brain lesions. In S. J. Dimon & J. G. Beaumont (Eds.), *Hemisphere function in the human brain.* New York: Halsted Press.

Gomes, M.M., Zeitoune, R.G., Kropf, L.A., & Beeck, E.S. (2002). A house-to-house survey of epileptic seizures in an urban community of Rio de Janeiro, Brazil. *Arquivos de Neuro-Psiquiatria, 60,* 708–711.

Graves, T.D., & Hanna, M.G. (2005). Neurological channelopathies. *Postgraduate Medical Journal, 81*(951), 20-32.

Green, S. B. (1991) How many subjects does it take to do a regression analysis? *Multivariate Behavioral Research, 26,* 499-510.

Haaland, K. Y., & Delaney, H. D. (1981). Motor deficits after left or right hemisphere damage due to stroke or tumor. *Neuropsychologia, 19,* 17–27.

Haaland, K. Y., Cleeland, C. S., & Carr, D. (1977). Motor performance after unilateral hemisphere damage in patients with tumor. *Archives of Neurology, 34,* 556–559.

Hamandi, K., & Sander, J.W. (2006). Pregabalin: A new antiepileptic drug for refractory epilepsy. *Seizure, 15*(2), 73-78.

Harley, J. P., Leuthold, C. A., Matthews, C. G., & Bergs, L. E. (1980). *Wisconsin Neuropsychological Test Battery T-score Norms for Older Veterans Administration Medical Center Patients.* Madison, WI: Department of Neurology, University of Wisconsin Medical School.

Hauptmann, A. (1912). Luminal bei Epilepsie (Introduction of phenobarbitone in the treatment of epilepsy). *Münchener medizinische Wochenschrift, 59,* 1907-1909.

Heaton, R. K., Grant, I., & Matthews, C. G. (1992). *Comprehensive norms for an expanded Halstead-Reitan Battery.* Odessa, FL: Psychological Assessment Resources.

Heidary, H., & Tomasch, J. (1969). Neuron numbers and perykarion areas in the human cerebellar nuclei. *Acta Anatomica (Basel), 74*, 290-296.

Ho, A.K., Sahakian, B.J., Brown, R.G., Barker, R.A., Hodges, J.R., Ane, M.N., Snowden, J., Thompson, J., Esmonde, T., Gentry, R., Moore, J.W., & Bodner, T. NEST-HD Consortium. (2003). Profile of cognitive progression in early Huntington's disease. *Neurology, 61*(12), 1702-1706.

Holmes, G. (1939). The cerebellum of man. *Brain*, *62*, 1-30.

Holmes, G.L. (1997). Epilepsy in the developing brain: Lessons from the laboratory and clinic. *Epilepsia, 38,* 12-30.

Honn, V., Para, M., Whitacre, C., & Bornstein, R. (1999). Effect of exercise on neuropsychological performance in asymptomatic HIV infection. *AIDS and Behavior, 3*(1), 67–74.

Horne, M. K., & Butler, E. G. (1995). The role of the cerebello-thalamo-cortical pathway in skilled movement. *Progress in Neurobiology, 46*(2-3), 199-213.

Ivry, R. B. & Keele, S. W. (1989). Timing functions of the cerebellum. *Journal of Cognitive Neuroscience, 1*(2), 136-152.

Jeljeli, M., Strazielle, C., Caston, J., & Lalonde, R. (2003). Effects of ventrolateral-ventromedial thalamic lesions on motor coordination and spatial orientation in rats. *Neuroscience Research, 47(3),* 309-16.

Julien, R.M. (2001). *A primer on drug action: a concise, nontechnical guide to the actions, uses, and side effects of psychoactive drugs* (revised and updated). New York: Henry Holt and Company.

Kandel, E. R., & Siegelbaum, S.A. (2000). Synaptic integration. In E. R. Kandel, J. H. Schwartz, & T. M. Jessel (Eds.), Principles of neural science (4th ed., pp.207-227). New York: McGraw-Hill.

Kelland, D. Z., Lewis, R., & Gurevitch, D. (1992). Evaluation of the repeatable cognitive-perceptual-motor battery: Reliability, validity, and sensitivity to Diazepam. *Journal of Clinical and Experimental Neuropsychology, 14,* 65.

Kelso, A.R., & Cock, H.R. (2005). Advances in epilepsy. *British Medical Bulletin, 21*(72), 135-148.

Kirk, R.E. (1990). *Statistics: an introduction* (3rd ed.). Orlando, FL: Holt Rinehart & Winston.

Kolodny, E.H. (2001). Metabolic and genetic disorders. In: O. Devinsky & L.E. Westbrook (Eds.), *Epilepsy and Developmental Disabilities* (pp. 17–22). Boston, MA: Butterworth-Heinemann; 2001.

Kotsopoulos, I.A., van Merode, T., Kessels, F.G., de Krom, M.C., & Knottnerus, J.A. (2002). Systematic review and meta-analysis of incidence studies of epilepsy and unprovoked seizures. *Epilepsia, 43*(11), 1402-1409.

Kullmann, D.M. (2002). The neuronal channelopathies. *Brain, 125*(Pt 6), 1177-1195.

Kuo, C.C. (1998). A common anticonvulsant binding site for phenytoin, carbamazepine, and lamotrigine in neuronal Na+ channels. *Molecular Pharmacology, 54*(4), 712-721.

Kuo, C.C., & Bean, B.P. (1994). Slow binding of phenytoin to inactivated sodium channels in rat hippocampal neurons. *Molecular Pharmacology, 46*(4), 716-725.

Kuo, C.C., & Lu, L. (1997). Characterization of lamotrigine inhibition of Na+ channels in rat hippocampal neurones. *British Journal of Pharmacology, 121*(6), 1231-1238.

Kwan, P., & Brodie, M.J. (2002). Refractory epilepsy: a progressive, intractable but preventable condition? *Seizure, 11*(2), 77-84.

Kwan, P., Sills, G.J., & Brodie, M.J. (2001). The mechanisms of action of commonly used antiepileptic drugs. *Pharmacology and Therapeutics, 90,* 21-34.

Lawthom, C., & Smith, P.E.M. (2003). What is the role of polytherapy in the treatment of epilepsy? *The Journal of the Royal College of Physicians of Edinburgh, 33*(Suppl. 11), 22-30.

Lendt, M., Gleissner, U., Helmstaedter, C., Sassen, R., Clusmann, H., Elger, C.E. (2002). Neuropsychological Outcome in Children after Frontal Lobe Epilepsy Surgery. *Epilepsy and Behavior, 3*(1), 51-59.

Lennox, W.G. (1942). Brain injury, drugs, and environment as causes of mental decay in epilepsy. *American Journal of Psychiatry, 99,* 174-180.

Leppik, I.E. (2000). Monotherapy and polypharmacy. *Neurology, 55*(11 Suppl. 3), S25-29.

Lerche, H., Jurkat-Rott, K., Lehmann-Horn, F. (2001). Ion channels and epilepsy. *American Journal of Medical Genetics, 106*(2), 146-159.

Levy, R.H., Mattson, R.H., & Meldrum, B.S. (1995). *Antiepileptic drugs* (4th ed.). New York: Raven Press.

Lewis, R., & Kupke, T. (1992). Intermanual differences on skilled and unskilled motor tasks in non-lateralized brain dysfunction. *The Clincial Neuropsychologist, 6,* 374–382.

Lezak, M. D. (2004). Neuropsychological assessment (4th ed.). New York: Oxford University Press.

Liu, R.S., Lemieux, L., Bell, G.S., Sisodiya, S.M., Bartlett, P.A., Shorvon, S.D., Sander, J.W., & Duncan, J.S. (2005). Cerebral damage in epilepsy: a population-based longitudinal quantitative MRI study. *Epilepsia, 46*(9), 1482-1494.

Loiseau, P. (2001). Seizure Precipitants. In E. Wyllie. *The treatment of Epilepsy Principles and Practice* (3rd ed., pp. 93-97). Philadelphia, PA: Lippincott Williams & Wilkins.

Löscher, W. (1997). Animal models of intractable epilepsy. *Progress in Neurobiology, 53*(2), 239-58.

Lothman, E.W. (1993). The neurobiology of epileptiform discharges. *American Journal of EEG Technology, 33,* 93-112.

Lukyanetz, E.A., Shkryl, V.M., & Kostyuk, P.G. (2002). Selective blockade of N-type calcium channels by levetiracetam. *Epilepsia, 43*(1), 9-18.

Lynch, B.A., Lambeng, N., Nocka, K., Kensel-Hammes, P., Bajjalieh, S.M., Matagne, A., & Fuks, B. (2004). The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. *Proceedings of the National Academy of Sciences of the United States of America, 101,* 9861–9866.

MacDonald, B.K., Cockerell, O.C., Sander, J.W., Shorvon, S.D. (2000). Incidence and lifetime prevalence of neurological disorders in a prospective community based study in the UK. *Brain, 123*, 665-676.

Macdonald, R. L., & Kelly, K. M. (1995). Antiepileptic drug mechanisms of action. *Epilepsia, 36*(suppl. 2), S2–S12.

Madsen, T.M., Greisen, M.H., Nielsen, S.M., Bolwig, T.G., & Mikkelsen, J.D. (2000). Electroconvulsive stimuli enhance both neuropeptide Y receptor Y1 and Y2 messenger RNA expression and levels of binding in the rat hippocampus. *Neuroscience, 98*(1), 33–39.

Manto, M.U., & Bosse, P. (2003). Directional tuning of speed-related activation for reaching in the vertical plane in cerebellar ataxia. *Neurological Research, 25*(5), 434-444.

Margerison, J.H., & Corsellis, J.A.N. (1966). Epilepsy and the temporal lobes: a clinical encephalographic and neuropathological study of the brain in epilepsy, with particular reference to the temporal lobes. *Brain, 89*, 499–530.

Martin, R., Kuzniecky, R., Ho, S., Hetherington, H., Pan, J., Sinclair, K., Gilliam, F., & Faught, E. (1999). Cognitive effects of topiramate, gabapentin, and lamotrigine in healthy young adults. *Neurology, 52*(2), 321-327.

Matthews, C. G., & Klove, H. (1964). *Instruction Manual for the Adult Neuropsychology Test Battery*. Madison, WI: University of Wisconsin Medical School.

Mattson, R.H., & Cramer, J. (1997). The choice of antiepileptic drugs in focal epilepsy. In: E. Wyllie (ed.). *The treatment of epilepsy: Principles and practice* (pp. 771-778). Baltimore, MD: Williams & Wilkins.

Mattson, R.H., Cramer, J.A., & Collins, J.F. (1992). A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. The Department of Veterans Affairs Epilepsy Cooperative Study No. 264 Group. *New England Journal of Medicine, 327,* 765-771.

Mattson, R.H., Cramer, J.A., Collins, J.F., Smith, D.B., Delgado-Escueta, A.V., Browne, T.R., Williamson, P.D., Treiman, D.M., McNamara, J.O., & McCutchen, C.B. (1985). Comparison of carbamazepine, phenobarbital, phenytoin, and primidone

in partial and secondarily generalized tonic-clonic seizures. *New England Journal of Medicine, 313*(3), 145-151.

Mazarati, A.M., & Wasterlain, C.G. (1997). Blockers of NMDA receptor restore paired-pulse inhibition in the rat dentate gyrus lesioned by perforant path stimulation. *Neuroscience Letters, 234*(2-3), 135-138.

McLain, L.W., Jr, Martin, J.T., & Allen, J.H. (1980). Cerebellar degeneration due to chronic phenytoin therapy. *Annals of Neurology, 7*(1), 18-23.

Meador, K.J. (1998). Cognitive and behavioral assessments in AED trials. *Advances in Neurology, 76*, 231-238.

Meador, K.J. (2002). Cognitive outcomes and predictive factors in epilepsy. *Neurology, 58*(8 Suppl. 5), S21-6.

Meador, K.J., & Baker, G.A. (1997). Behavioral and cognitive effects of lamotrigine. *Journal of Child Neurology, 12*(Suppl. 1), S44-S47.

Meador, K.J., Loring, D.W., Abney, O.L., Allen, M.E., Moore, E.E., Zamrini, E.Y., & King, D.W. (1993). Effects of carbamazepine and phenytoin on EEG and memory in healthy adults. *Epilepsia, 34*(1), 153-157.

Meador, K.J., Loring, D.W., Allen, M.E., Zamrini, E.Y., Moore, E.E., Abney, O.L., & King, D.W. (1991). Comparative cognitive effects of carbamazepine and phenytoin in healthy adults. *Neurology, 41*(10), 1537-1540.

Meador, K.J., Loring, D.W., Huh, K., Gallagher, B.B., & King, D.W. (1990). Comparative cognitive effects of anticonvulsants. *Neurology, 40*(3 Pt 1), 391-394.

Meador, K.J., Loring, D.W., Hulihan, J.F., Kamin, M., & Karim, R. (2003). CAPSS-027 Study Group. Differential cognitive and behavioral effects of topiramate and valproate. *Neurology, 60*(9), 1483-1488.

Meador, K.J., Loring, D.W., Moore, E.E., Thompson, W.O., Nichols, M.E., Oberzan, R.E., Durkin, M.W., Gallagher, B.B., & King, D.W. (1995). Comparative cognitive effects of phenobarbital, phenytoin, and valproate in healthy adults. *Neurology, 45*(8), 1494-1499.

Meador, K.J., Loring, D.W., Ray, P.G., Murro, A.M., King, D.W., Nichols, M.E., Deer, E.M., & Goff, W.T. (1999). Differential cognitive effects of carbamazepine and gabapentin. *Epilepsia, 40*(9), 1279-1285.

Meador, K.J., Loring, D.W., Vahle, V.J., Ray, P.G., Werz, M.A., Fessler, A.J., Ogrocki, P., Schoenberg, M.R., Miller, J.M., Kustra, R.P. (2005). Cognitive and behavioral effects of lamotrigine and topiramate in healthy volunteers. *Neurology, 64*(12), 2108-2114.

Meiri, H., Spira, G., Sammar, M., Namir, M., Schwartz, A., Komoriya, A., Kosower, E.M., & Palti, Y. (1987). Mapping a region associated with Na channel inactivation using antibodies to a synthetic peptide corresponding to a part of the channel. Proceedings of the National Academy of Sciences USA, 84(14), 5058-5062.

Meldrum, B. S. (1996). Update on the mechanism of action of antiepileptic drugs. *Epilepsia, 37*(suppl. 6), S4–S11.

Meldrum, B.S. (1981). Metabolic effects of prolonged epileptic seizures and the causation of epileptic brain damage. In Metabolic Disorders of the Nervous System, pp. 175-187. F. C. Rose (Ed.). London: Pitman.

Meldrum, B.S. (1983). Metabolic factors during prolonged seizures and their relation to nerve cell death. *Advances in Neurology, 34*, 261-75.

Meldrum, B.S. (1995). Excitatory amino acid receptors and their role in epilepsy and cerebral ischemia. *Annals of the New York Academy of Sciences, 757,* 492-505.

Meldrum, B.S., Bruton, C.J. (1992). Epilepsy. In: J.H. Adams, & L.W. Duchen (Eds.). *Greenfield's neuropathology* (5th Ed) p. 1246–83. London: Edward Arnold.

Meldrum, B.S., Vigouroux, R.A., Brierley, J.B. (1973). Systemic factors and epileptic brain damage. *Archives in Neurology, 29,* 82–87.

Miller, N. (1999). A neuropsychological investigation of visual–perceptual and visuo-motor abilities in very low-birthweight children. *Dissertation Abstracts International: Section B: The Sciences and Engineering, 59*(9-B), 5140.

Morgan, J.I., Cohen, D.R., Hempstead, J.L. & Curran, T. (1987). Mapping patterns of c-fos expression in the central nervous system after seizure. *Science 237*(4811), 192–197.

Nadkarni, S., LaJoie, J., & Devinsky, O. (2005). Current treatments of epilepsy. *Neurology, 64*(12 Suppl. 3), S2-11.

Nadkarni, S., & Devinsky, O. (2005). Psychotropic effects of antiepileptic drugs. *Epilepsy Current, 5*(5), 176-181.

Ney, G. C., Lantos, G., Barr, W. B., & Schaul, N. (1994). Cerebellar atrophy in patients with long-term phenytoin exposure and epilepsy. *Archives of Neurology, 51*(8), 767-771.

Ohmori, H., Ogura, H., Yasuda, M., Nakamura, S., Hatta, T., Kawano, K., Michikawa, T., Yamashita, K., & Mikoshiba, K. (1999). Developmental neurotoxicity of phenytoin on granule cells and Purkinje cells in mouse cerebellum. *Journal of Neurochemistry, 72*(4), 1497-1506.

Ojemann, L.M., Ojemann, G.A., Dodrill, C.B., Crawford, C.A., Holmes, M.D., Dudley, D.L. (2001). Language disturbances as side effects of topiramate and zonisamide therapy. *Epilepsy Behavior, 2*(6), 579-584.

Olafsson, E., & Hauser, W.A. (1999). Prevalence of epilepsy in rural Iceland: a population-based study. Epilepsia, 40, 1529–1534.

Olsen, R.W., & Sapp, D.W. (1995). Neuroactive steroid modulation of $GABA_A$ receptors. In: $GABA_A$ receptors and anxiety: from neurobiology to treatment. G. Bigio, E. Sanna, & E. Costa (Eds.). New York, NY: Raven Press, 57-74.

Onal, A.E., Tumerdem, Y., Ozturk, M.K., Gurses, C., Baykan, B., Gokyigit, A., & Ozel, S. (2002). Epilepsy prevalence in a rural area in Istanbul. *Seizure, 11*(6), 397-401.

Ortinski, P., & Meador, K.J. (2004). Cognitive side effects of antiepileptic drugs. *Epilepsy Behavior,* (5 Suppl. 1), S60-65.

Pai, M.C., & Tsai, J.J. (2005). Is cognitive reserve applicable to epilepsy? The effect of educational level on the cognitive decline after onset of epilepsy. *Epilepsia, 46*(Suppl. 1), 7-10.

Pal, S., Sombati, S., Limbrick, D.D. Jr., & DeLorenzo, R.J. (1999). In vitro status epilepticus causes sustained elevation of intracellular calcium levels in hippocampal neurons. *Brain Research, 851*(1-2), 20-31.

Parent, A. (1996). Carpenter's human neuroanatomy (9th ed). Baltimore, MD: Williams and Wilkins.

Patrylo, P.R., Schweitzer, J.S., & Dudek, F.E. (1999). Abnormal responses to perforant path stimulation in the dentate gyrus of slices from rats with kainate-induced epilepsy and mossy fiber reorganization. *Epilepsy Research, 36*(1), 31–42.

Patsalos, P.N., Froscher, W., Pisani, F., & van Rijn, C.M. (2002). The importance of drug interactions in epilepsy therapy. *Epilepsia, 43*(4), 365-385.

Perucca, E. (1993). The clinical pharmacology of the new antiepileptic drugs. *Pharmacological Research, 28,* 89-106.

Perucca, E. (2005). An introduction to antiepileptic drugs. *Epilepsia, 46*(Suppl. 4), 31-37.

Perucca, E., Beghi, E., Dulac, O., Shorvon, S., & Tomson, T. (2000). Assessing risk to benefit ratio in antiepileptic drug therapy. *Epilepsy Research, 41*(2), 107-139.

Perucca, E., Dulac, O., Shorvon, S., & Tomson, T. (2001). Harnessing the clinical potential of antiepileptic drug therapy: dosage optimisation. *CNS Drugs, 15*(8), 609-621.

Pisani, A., Bonsi, P., Martella, G., De Persis, C., Costa, C., Pisani, F., Bernardi, G., & Calabresi, P. (2004). Intracellular calcium increase in epileptiform activity: modulation by levetiracetam and lamotrigine. *Epilepsia, 45*(7), 719-728.

Placencia, M., Shorvon, S.D., & Paredes, V. (1992). Epileptic seizures in an Andean region of Ecuador: incidence and prevalence and regional variation. *Brain, 115,* 771–782.

Placencia, M., Shorvon, S.D., Paredes, V., Bimos, C., Sander, J.W., Suarez, J., & Cascante, S.M. (1992). Epileptic seizures in an Andean region of Ecuador. Incidence and prevalence and regional variation. *Brain, 115*(3), 771-782.

Prasad, A.N., Prasad, C., & Stafstrom, C.E. (1999). Recent advances in the genetics of epilepsy: insights from human and animal studies. *Epilepsia, 40,* 1329-1352.

Prevey, M.L., Delaney, R.C., & Cramer, J.A. (1996). Effect of valproate on cognitive functioning. Comparison with carbamazepine. The Department of Veterans Affairs Epilepsy Cooperative Study 264 Group. *Archives Neurology, 53,* 1008-1016.

Prevey, M.L., Delaney, R.C., Cramer, J.A., & Mattson, R.H. (1998). Complex partial and secondarily generalized seizure patients: cognitive functioning prior to treatment with antiepileptic medication. VA Epilepsy Cooperative Study 264 Group. *Epilepsy Research, 30*(1), 1-9.

Prevey, M.L., Delaney, R.C., Cramer, J.A., Cattanach, L., Collins, J.F., & Mattson, R.H. (1996). Effect of valproate on cognitive functioning. Comparison with carbamazepine. The Department of Veterans Affairs Epilepsy Cooperative Study 264 Group. *Archives of Neurology, 53*(10), 1008-1016.

Pulliainen, V., Kuikka, P., & Jokelainen, M. (2000). Motor and cognitive functions in newly diagnosed adult seizure patients before antiepileptic medication. *Acta Neurologica Scandinavia, 101*(2), 73-78.

Raza, M., Pal, S., Rafiq, A., & DeLorenzo, R.J. (2001). Long-term alteration of calcium homeostatic mechanisms in the pilocarpine model of temporal lobe epilepsy. *Brain Research, 903*(1-2), 1-12.

Reitan, R. M., & Wolfson, D. (1993). *The Halstead-Reitan Neuropsychological Test Battery: Theory and clinical interpretation.* Tucson, AZ: Neuropsychology Press.

Reynolds, E. H., & Shorvon, S. D. (1981). Monotherapy or polytherapy for epilepsy. *Epilepsia, 22,* 1–10.

Reynolds, E.H., & Trimble, M.R. (1985). Adverse neuropsychiatric effects of anticonvulsant drugs. *Drugs, 29*(6), 570-81.

Rho, J.M., & Sankar, R. (1999). The pharmacologic basis of antiepileptic drug action. *Epilepsia, 40*(11), 1471-83.

Richens, A. (1995). Rational polypharmacy. *Seizure, 4,* 211-214.

Rocca, W.A., Savettieri, G., Anderson, D.W., Meneghini, F., Grigoletto, F., Morgante, L., Reggio, A., Salemi, G., Patti, F., & Di Perri, R. (2001). Sicilian Neuro-Epidemiologic Study (SNES) Group. Door-to-door prevalence survey of epilepsy in three Sicilian municipalities. *Neuroepidemiology, 20*(4), 237-241.

Rogawski, M.A., & Loscher, W. (2004). The neurobiology of antiepileptic drugs. *Nature Reviews Neuroscience, 5*(7), 553-564.

Roll, P., & Szepetowski, P. (2002). Epilepsy and ionic channels. *Epileptic Disorders, 4*(3), 165-72.

Rosnow, R. L., & Rosenthal, R. (2005). *Beginning behavioral research: A conceptual primer* (5th ed.). Englewood Cliffs, NJ: Pearson/Prentice Hall.

Ruff, R.M., & Parker, S.B. (1993). Gender- and age-specific changes in motor speed and eye-hand coordination in adults: normative values for the Finger Tapping and Grooved Pegboard Tests. *Perceptual and Motor Skills, 76*(3 Pt. 2), 1219-1230.

Rwiza, H.T., Kilonzo, G.P., Haule, J., Matuja, W.B., Mteza, I., Mbena, P., Kilima, P.M., Mwaluko, G., Mwang'ombola, R., & Mwaijande, F. (1992). Prevalence and incidence of epilepsy in Ulanga, a rural Tanzanian district: a community-based study. *Epilepsia, 33*(6), 1051-6.

Saffen, D.W., Cole, A.J., Worley, P.F., Christy, B.A., Ryder, K., & Baraban, J.M. (1988). Convulsant-induced increase in transcription factor messenger RNAs in rat brain. *Proceedings of the National Academy of Sciences, 85,* 7795–7799.

Sander, J.W. (2003). The epidemiology of epilepsy revisited. *Current Opinions in Neurology, 16*(2), 165-170.

Sander, J.W. (2004). The use of antiepileptic drugs--principles and practice. *Epilepsia, 45*(Suppl. 6), 28-34.

Sander, J.W., & Shorvon, S.D. (1996). Epidemiology of the epilepsies. *Journal of Neurology, Neurosurgery and Psychiatry, 61,* 433–443.

Sankar, R., & Holmes, G.L. (2004). Mechanisms of action for the commonly used antiepileptic drugs: relevance to antiepileptic drug-associated neurobehavioral adverse effects. *Journal of Child Neurology, 19*(Suppl. 1), S6-14.

Schachter, S. C. (1995). Review of the mechanisms of action of antiepileptic drugs. *CNS Drugs, 4,* 469–477.

Schachter, S. C. (2004). History of epilepsy. Retrieved October 1, 2005, from http://www.epilepsy.com/epilepsy/history.html.

Schauble, B., & Cascino, G.D. (2003). Advances in neuroimaging: management of partial epileptic syndromes. *Neurosurgical Review, 26*(4), 233-46.

Schauwecker, P.E., & Steward, O. (1997). Genetic determinants of susceptibility to excitotoxic cell death: implications for gene targeting approaches. *Proceedings of the National Academy Sciences, U.S.A., 94*(8), 4103-4108.

Scheyer, R.H., & Cramer, J.A. (1990). Pharmacokinetics of antiepileptic drugs. *Seminars in Neurology, 10,* 414-421.

Schmidt, S.L., Oliveira, R.M., Rocha, F.R., & Abreu-Villaca, Y. (2000). Influences of handedness and gender on the grooved pegboard test. *Brain and Cognition, 44*(3), 445-454.

Schwartz, R.D. (1988). The GABAA receptor-gated ion channel: biochemical and pharmacological studies of structure and function. *Biochemical Pharmacology, 37,* 3369–3375.

Schwob, J.E., Fuller, T., Price, J.L., & Olney, J.W. (1980). Widespread patterns of neuronal damage following systemic or intracerebral injections of kainic acid: a histological study. *Neuroscience 5,* 991–1014.

Shannon, H.E., & Love, P.L. (2005). Effects of antiepileptic drugs on attention as assessed by a five-choice serial reaction time task in rats. *Epilepsy & Behavior, 7*(4), 620-628.

Shakkottai, V.G., Chou, C.H., Oddo, S., Sailer, C.A., Knaus, H.G., Gutman, G.A., Barish, M.E., LaFerla, F.M., & Chandy, K.G. (2004). Enhanced neuronal excitability in the absence of neurodegeneration induces cerebellar ataxia. *Journal of Clinical Investigation, 113*(4), 582-90.

Shinoda, Y., Kano, M., & Futami, T. (1985). Synaptic organization of the cerebello-thalamo-cerebral pathway in the cat. I. Projection of individual cerebellar nuclei to single pyramidal tract neurons in areas 4 and 6. *Neuroscience Research, 2*(3), 133-156.

Shorvon, S. D., & Reynolds, E. H. (1977). Unnecessary polypharmacy for epilepsy. *British Medical Journal, 1,* 1635–1637.

Shorvon, S. D., & Reynolds, E. H. (1979). Reduction of polypharmacy for epilepsy. *British Medical Journal, 2,* 1023–1025.

Siegelbaum, S.A., & Koester, J. (2000). Ion channels. In E. R. Kandel, J. H. Schwartz, & T. M. Jessel (Eds.), *Principles of neural science,* (4th ed) (pp.105-123). New York, NY: McGraw-Hill.

Sills, G.J., & Brodie, M.J. (2001). Update on the mechanisms of action of antiepileptic drugs. *Epileptic Disorders, 3*(4), 165-72.

Sloviter, R.S. (1994). On the relationship between neuropathology and pathophysiology in the epileptic hippocampus of humans and experimental animals. *Hippocampus 4*(3), 250–253.

Smith, A (1993). *Symbol Digit Modalities Test Manual.* Los Angeles, CA: Western Psychological Services.

Smith, D.B., Craft, B.R., Collins, J., Mattson, R.H., & Cramer, J.A. (1986). Behavioral characteristics of epilepsy patients compared with normal controls. *Epilepsia, 27*(6), 760-768.

Smith, D.B., Mattson, R.H., Cramer, J.A., Collins, J.F., Novelly, R.A., & Craft, B. (1987). Results of a nationwide Veterans Administration Cooperative Study

comparing the efficacy and toxicity of carbamazepine, phenobarbital, phenytoin, and primidone. *Epilepsia, 28*(Suppl. 3), S50-8.

Soderpalm, B. (2002). Anticonvulsants: aspects of their mechanisms of action. *European Journal of Pain, 6*(Suppl A), 3-9.

Soldin, S.J., Wang, E., Verjee, Z., & Elin, R.J (2003). Phenytoin overview--metabolite interference in some immunoassays could be clinically important: results of a College of American Pathologists study. *Archives of Pathology and Laboratory Medicine, 127*(12), 1623-1625.

Somerfeld-Ziskind E, Ziskind E (1940). Effect of phenobarbital on the mentality of epileptic patients. *Archives of Neurology and Psychiatry, 43,* 70-79.

Spreen, O., & Strauss, E. (1998). *A compendium of neuropsychological tests* (2nd ed.). New York, NY: Oxford University Press.

SPSS, Inc. (2001). Statistical Package for the Social Sciences, Standard Version, Release 11.0.0. Palo Alto, CA.

Stafstrom, C.E., & Tempel, B.L. (2000). Epilepsy genes: the link between molecular dysfunction and pathophysiology. *Mental retardation and developmental disabilities research reviews, 6,* 281-292.

Stefan, H., Halasz, P., Gil-Nagel, A., Shorvon, S., Bauer, G., Ben-Menachem, E., Perucca, E., Wieser, H.G., & Steinlein, O. (2001). Recent advances in the diagnosis and treatment of epilepsy. *European Journal of Neurology, 8*(6), 519-539.

Stern, Y., Albert, S., Tang, M.X., & Tsai, W.Y. (1999). Rate of memory decline in AD is related to education and occupation: cognitive reserve? *Neurology, 53*(9), 1942-1947.

Stern, Y. (2003). The concept of cognitive reserve: a catalyst for research. *Journal of Clinical and Experimental Neuropsychology, 25*(5), 589–593.

Stolze, H., Klebe, S., Petersen, G., Raethjen, J., Wenzelburger, R., Witt, K., & Deuschl, G. (2002). Typical features of cerebellar ataxic gait. *Journal of Neurology, Neurosurgery, and Psychiatry*, *73*(3), 310-312.

Sutula, T.P., He, X.X., Cavazos, J., & Scott, G. (1988). Synaptic reorganization in the hippocampus induced by abnormal functional activity. *Science, 239*(4844), 1147–1150.

Tabachnick, B. G., & Fidell, L. S. (2001). Using Multivariate Statistics (4th ed). Boston, MA: Allyn and Bacon.

Tallent, M.K., & Siggins, G.R. (1999). Somatostatin acts in CA1 and CA3 to reduce hippocampal epileptiform activity. *Journal of Neurophysiology, 81*(4), 1626-1635.

Tan, E.K., Chan, L.L., & Auchus, A.P. (2001). Phenytoin cerebellopathy without epilepsy. *Acta Neurologica Scandinavia, 4*(1), 61-62.

Tauck, D.L., Nadler, J.V. (1985). Evidence of functional mossy fiber sprouting in hippocampal formation of kainic acid-treated rats. *Journal of Neuroscience, 5*(4), 1016-1022.

Temkin, O. (1971). *The falling sickness: a history of epilepsy from the Greeks to the beginnings of modern neurology* (2nd Rev edition). The Johns Hopkins University Press.

Theodore, W.H., Fishbein, D., Dietz, M., Baldwin, P., & Deitz, M. (1987). Complex partial seizures: cerebellar metabolism. *Epilepsia, 28*(4), 319-23.

Theodore, W.H. (1995). Phenytoin and cerebellar atrophy. *Archives of Neurology, 52*(3), 232.

Thompson, P.J., & Trimble, M.R. (1982). Anticonvulsant drugs and cognitive functions. *Epilepsia, 23*(5), 531-544.

Thompson, P.J., & Trimble, M.R. (1983). Anticonvulsant serum levels: relationship to impairments of cognitive functioning. *Journal of Neurology, Neurosurgery and Psychiatry, 46*(3), 227-233.

Tien, R.D., & Ashdown, B.C. (1992). Crossed cerebellar diaschisis and crossed cerebellar atrophy: correlation of MR findings, clinical symptoms, and supratentorial diseases in 26 patients. *American Journal of Roentgenology, 158,* 1155–1159.

Tiffen, J. (1968). *Purdue Pegboard Examiner's Manual.* Rosemont, IL: London House.

Toescu, E.C. (1998). Apoptosis and cell death in neuronal cells: where does Ca^{2+} fit in? *Cell Calcium, 24*(5-6), 387-403.

Trimble, M.R. (1987). Anticonvulsant drugs and cognitive function: a review of the literature. *Epilepsia, 28*(Suppl. 3), S37-45.

Trimble, M.R., & Thompson, P.J. (1984). Sodium valproate and cognitive function. *Epilepsia, 25*(Suppl. 1), S60-4.

Upton, N. (1994). Mechanisms of action of new antiepileptic drugs: rational design and serendipitous findings. *Trends in Pharmacological Sciences, 15,* 456–463.

Vezzani, A., Sperk, G., & Colmers, W.F. (1999). Neuropeptide Y: emerging evidence for a functional role in seizure modulation. *Trends in Neurosciences, 22*(1), 25–30.

Wasterlain, C.G., & Shirasaka, Y. (1994). Seizures, brain damage and brain development. *Brain and Development, 16*(4), 279-95.

Wechsler, D. (1955). Manual for the Wechsler Adult Intelligence Scale (WAIS). New York, NY: The Psychological Corporation.

Wechsler, D. (1997). Wechsler adult intelligence scale-third edition. San Antonio, TX: The Psychological Corporation.

Wechsler, D. (1999). Wechsler Abbreviated Scale of Intelligence. San Antonio, TX: The Psychological Corporation.

Weglage, J., Demsky, A., Pietsch, M., & Kurlemann, G. (1997). Neuropsychological, intellectual, and behavioral findings in patients with centrotemporal spikes with and without seizures. *Developmental Medicine and Child Neurology, 39*(10), 646-651.

Weimer, A., Schatz, A., Lincoln, A., Ballantyne, A., & Trauner, D. (2001). ‘‘Motor’’ impairment in Asperger syndrome: Evidence for a deficit in proprioception. *Journal of Developmental and Behavioral Pediatrics, 22*(2), 92–101.

Westbrook, G.L. (2000). Seizures and epilepsy. In E.R. Kandel, J.H. Schwartz & T.M. Jessel (Eds.), *Principles of Neural Science,* (4th ed., pp.910-935). New York: Elsevier.

White, H. S. (1999). Comparative anticonvulsant and mechanistic profile of established and newer antiepileptic drugs. *Epilepsia, 40*(suppl. 5), S2– S10.

White, H.S. (2002). Animal models of epileptogenesis. Neurology, 59(9 Suppl. 5), S7-S14.

Wilder-Willis, K., Sax, K., Rosenberg, H., Fleck, D., Shear, P., & Strakowski, S. (2001). Persistent attentional dysfunction in remitted bipolar disorder. *Bipolar Disorders, 3*(2), 58–62.

World Health Organization (2005). Atlas: Epilepsy Care in the World. http://www.who.int/mental_health/neurology/epilepsy_atlas_introdion.pdf

Wuarin, J-P., & Dudek, F.E. (1996). Electrographic seizures and new recurrent excitatory circuits in the dentate gyrus of hippocampal slices from kainate-treated epileptic rats. *Journal of Neuroscience, 16*(14), 4438–4448.

Yang, Y., Tandon, P., Liu, Z., Sarkisian, M.R., Stafstrom, C.E., & Holmes, G.L. (1998). Synaptic reorganization following kainic acid-induced seizures during development. *Brain Res Dev Brain Res, 107*(2), 169-177.

Yogeeswari, P., Ragavendran, J.V., Thirumurugan, R., Saxena, A., & Sriram, D. (2004). Ion channels as important targets for antiepileptic drug design. *Current Drug Targets, 5*(7), 589-602.

Yoshida, M, Yajima, K., & Uno, M. (1966). Different activation of the 2 types of the pyramidal tract neurones through the cerebello-thalamocortical pathway. *Experientia, 22*(5), 331-332.

Zarrelli, M.M., Beghi, E., Rocca, W.A., & Hauser, W.A. (1999). Incidence of epileptic syndromes in Rochester, Minnesota: 1980–1984. *Epilepsia, 40,* 1708–1714.