

Comparison of the Effects of Sensorimotor
Rhythm and Slow Cortical Potential
Neurofeedback in Epilepsy

by

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Statement

I declare that the work presented in this thesis is my own. No portion of this work was submitted in support of an application for another degree of this or any other university, or institute of learning.

I declare editorial assistance was used exclusively for proofreading, spelling, grammar, and punctuation.

Diana Martinez Huerta MD, M.Sc.

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Abbreviations

AED	Anti-epileptic drugs
AST	Attention switching task
CNV	Contingent negative variation
DC	Direct current
DBS	Deep brain stimulation
EEG	Electroencephalogram
EPSPs	Excitatory postsynaptic potentials
ERP	Event related potential
GABA	Gamma amino butyric acid
ILAE	International league against epilepsy
LTM	Long term memory
PRS	Post reinforcement synchronization
QEEG	Quantitative electroencephalogram
QOL	Quality of life
SF	Seizure frequency
SSS	Seizure severity scale
SMR	Sensorimotor rhythm
SCP	Slow cortical potentials
SD	Standard deviation

Abstract

Current conventional epilepsy treatments do not always aim to improve epilepsy comorbidities. For a treatment to be effective, is not necessary for it to keep the patient seizure-free; it is sufficient to show improvement in functions to help people who suffer from epilepsy to become more independent and productive in life. There is an urgent need to explore non- pharmaceutical/non-invasive interventions that can help in that regard. The earlier patients are treated with this condition, the more likely it is to prevent severe disabilities over time.

Neurofeedback is a self-modulatory brain activity oscillatory intervention that previous researchers have found to reduce seizure frequency in patients with epilepsy. The aim of this work was to compare two Neurofeedback techniques that have shown some efficacy in improving symptoms in epilepsy. The novelty of this study is to explore further and included clinical, neurophysiological and cognitive outcomes in order to assess in more detail the effectiveness epilepsy comorbidities.

Forty-four patients, between the ages of 12 and 18 years, and diagnosed with focal epilepsy, divided randomly in to three groups: sensorimotor rhythm (SMR) training, slow cortical potential (SCP) training, and control. The patients completed 25 sessions of intervention.

The results showed that the SMR group training had an advantage in improving reaction time compared with SCP and control. Regression analysis revealed a significant correlation between the patients who learned to modify their brain activity in the SMR

group and improving reaction time in two different tasks. In addition, the quality of life scale significantly improved in all three groups.

The study supplies preliminary data to support that SMR neurofeedback training as an intervention should further be explored as a therapeutic option for children who suffer from focal epilepsy.

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Chapter 1 Overview

The understanding of the human brain is one of the more complex subjects in science, philosophy, and even spirituality. Scientists are accelerating the pace of discoveries each day due to advancements in technology, yet we still are far from a complete comprehension of the mechanisms of the integrative function of the human brain. Many neurological and psychiatric conditions are still considered mysterious entities and, in some cases, their unknown etiology makes it even harder to diagnose and select the most effective treatment and interventions. Furthermore, neurological and psychiatric drug trials are failing phase III studies, and the number of patients searching for alternative therapeutic options is increasing every day. For these reasons, there is a deep interest within neuroscience to explore and understand better the mechanisms and efficacy of interventions that could have a positive effect on brain disorders. This study explored the use of newer interventions applied to one of the more complex and stigmatized neurological disorders. These interventions are worth studying because they could provide further therapeutic options to people suffering from this condition.

The following sections feature a thorough review of the pathology of epilepsy, its complexity, and the stigma attached to this neurological disease. This study introduces the background of a condition with a high incidence in the population, which is associated with a heavy burden to society due to the significant incidence of disability that is usually associated with epilepsy. Among the difficulties for patients suffering from epilepsy are the iatrogenic effects of the pharmacological regimen required to stabilize the condition.

The multi-drug approach promotes the development of severe comorbidities (cognitive, psychological and neurological), while decreasing quality of life.

Conventional treatments for epilepsy focus on pharmacological interventions, while finding the right drug, or the combination of them, to decrease seizure activity is the main goal for many medical specialists. Unfortunately, not all individuals with epilepsy respond adequately to conventional pharmacological treatments.

It is important to note that, in clinical experience, no pharmacological intervention aims to improve the comorbidities associated with the side effects of drug treatment, which contributes to the dysfunction of those being treated for epilepsy. These drug iatrogenic effects place heavy burden on the personal, social and emotional life of those being treated. It is, therefore of interest to explore innovative non-pharmacological interventions that could improve not only seizure control but also the comorbidities (clinical, cognitive and neurophysiological) present in individuals with epilepsy.

Neurofeedback is a form of brain computer interphase intervention studied for the last four decades. Sterman et al found the first condition tested using this intervention was epilepsy in early 1970s, and showed preliminary positive results in seizure control (Sterman, Wyrwicka, & Howe, 1969). Researchers were enthusiastic about the efficacious effects of this intervention. Unfortunately, after some initial trials, interest in studying neurofeedback methods and methodologies decreased as researchers began focusing more on behavioral conditions, leaving a gap between neurological research and neurofeedback applications. Another reason why research interest waned in neurological application of neurofeedback was the complexity of designing appropriate control randomized studies in

epilepsy. Additionally, few researchers in the medical community were interested in exploring non-pharmacological interventions, which led to a lack of financial support, making it harder for established scientists to continue in this line of research.

Some professionals practicing in the field of neurological rehabilitation experience constant frustration and concern for patients with epilepsy, considering the various comorbidities and the side effects of the drugs as a part of their treatment regimen. Individuals suffering from epilepsy often indicate that the seizures are less of an issue in their lives compared with the comorbidities and how there are few interventions to help them in that regard.

The unique contribution of this study is the evaluation of the physiological and behavioural effects of neurofeedback for the treatment of children and adolescents with focal epilepsy. There are two neurofeedback modalities—sensorimotor (SMR) and slow cortical potentials (SCP)—that have been employed and studied that have demonstrated some beneficial effects in epilepsy. This study compared these modalities and evaluated their impact in young patients with focal epilepsy. Of special interest is that it has been well reported that the earlier a patient receives intervention with resultant improved function, the better the prognosis (Cioni, Inguaggiato, & Sgandurra, 2016).

This study comprehensively and critically examined the available literature to provide the necessary background to better understand the epilepsies in the context of neurofeedback applications. It begins with a review of epilepsy as a pathological entity, the complexity of the neurophysiological components, and the basis of the complex

comorbidities. The different types of epilepsy and etiologies are reviewed, but this study focuses on patients with focal epilepsy.

The statement of purpose of this study was to compare two neurofeedback modalities and explore the clinical, neurophysiological and cognitive outcomes of each in order to better inform decisions about which intervention is more appropriate for children who suffer from focal epilepsy.

Research Aim, Objectives and Hypotheses

The aim of this study was to examine two neurofeedback interventions to explore their clinical, neurophysiological, and cognitive effects among children with focal epilepsy.

The research objectives were

1. To examine the clinical, neurophysiological, and cognitive effects of neurofeedback on children with focal epilepsy.
2. To explore differences between neurofeedback techniques (SMR or SCP) on clinical, neurophysiological, and cognitive functions in children with focal epilepsy.
3. To examine which area of evaluation (clinical, neurophysiological and cognitive) has more effect using neurofeedback on children with focal epilepsy.
4. To explore if there is a specific type of neurofeedback from which children with epilepsy will benefit the most.
5. To explore if there are associations between how the participant learn with neurofeedback and specific variables.

The research hypotheses were the following:

1. The type of intervention, active intervention (SMR or SCP), would provide significantly greater effects in clinical, neurophysiological, and cognitive functions of epilepsy relative to controls.
2. Significant differences exist between the means of the clinical, neurophysiological, and cognitive measures across three-time intervals (at the beginning of intervention (baseline), after the last session of intervention was concluded, and three months after the conclusion of the intervention).
3. Significant differences exist between the means of the groups (SMR, SCP, and control).

The novelty of the present study is the exploratory outcome of variables that include clinical, neurophysiological and cognitive functions that are part of comorbidities in epilepsy. This study compared two neurofeedback modalities that are recognized as possibly effective in epilepsy.

Also, the age of the participants (children) is something that this study offers, as most of previous research done with neurofeedback and epilepsy is on adult population.

Chapter 2 Epilepsy Background

Epilepsy is considered one of the oldest neurological conditions and is characterized by recurrent seizures. It is important to define the difference between a seizure and epilepsy (Howell, Harvey, & Archer, 2016). A *seizure* is a clinically discernible event that results from the synchronous and excessive discharge of neurons in the cerebral cortex. It has the capability to manifest itself in any part of the brain depending on how fast and far it grows. In contrast, *epilepsy* is defined as the tendency to have recurring unprovoked seizures (Engel, 2008)

Over the years, many researchers have attempted to describe this disorder. The International League Against Epilepsy (ILAE) successfully improved these descriptions (Trinka et al., 2015). The ILAE provided the most impactful definition of epilepsy for this research: “A brain disorder characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition” (Fisher et al., 2005, p. 471).

Epilepsy onset occurs with a bimodal lifetime distribution having two distinct modes. The first peak is encountered during the initial two decades of life (epilepsy which is secondary to genetic and congenital aetiologies), whereas the second peak typically arrives over 60 years of age, resulting in late seizures after a stroke or tumour (Hauser, Annegers, & Kurland, 1993). The prevalence of active epilepsy is 0.5–1%. It is also estimated that 2–5% of the population above the age of 70 will experience an epileptic seizure once in their lifetime (Behr, Goltzene, Kosmalski, Hirsch, & Ryvlin, 2016). The rate of epilepsy’s growth is slightly higher in men than in women (Thurman et al., 2011). It

is essential to evaluate the impact of this disease if confronted during the early years of life because the earlier that doctors treat this disorder, the better the outcome for the patient (García-Peñas, Fournier-Del Castillo, & Domínguez-Carral, 2014). Therefore, epilepsy is a condition considered as a worldwide health problem, which justifies the development of more research to explore interventions and to improve the comorbidities of patients that suffer from epilepsy.

Epilepsy and Seizure Classification

It is important to classify seizures to get a better understanding of their localisation and focal distribution and to provide a basis for prognosis providing the best possible treatment for the patient. The ILAE has been trying for years to create a simpler and more comprehensible classification since previous classifications were more confusing and less accurate (Fisher et al., 2017). The most recent classification in 2015–2016 was based on more scientific and clinical knowledge. The first objective was to classify the initial manifestation of the seizure, which can be focal or generalized. The symptoms presented during the seizure are then classified as motor or non-motor (sensory, cognitive, emotional or autonomic). Finally, the classification considers the state of awareness. The ILAE defined a focal seizure as “originated within networks limited to one hemisphere and discretely localized or more widely distributed; maybe originated in subcortical structures,” and a generalized seizure as “originated at some point within, and rapidly engaging, bilaterally distributed networks” (Berg et al., 2010). A third group of seizures contains

those of an unknown onset with motor and non-motor symptomatology. Figure 1 shows the most updated ILAE seizure classification differentiating each category.

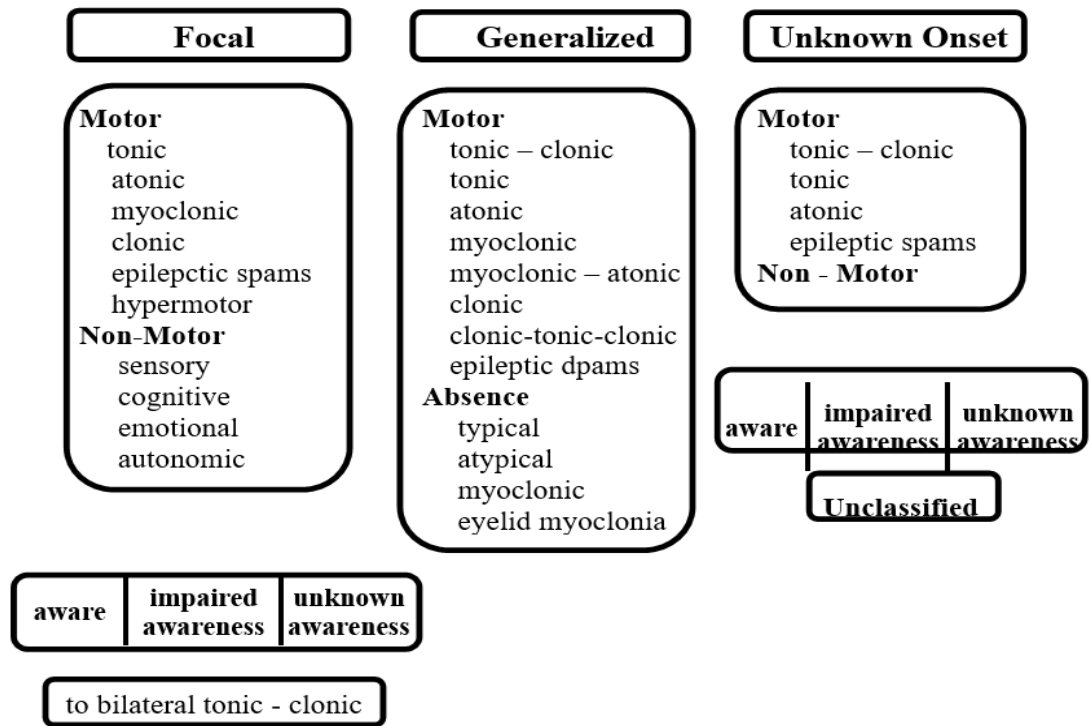


Figure 1. International League Against Epilepsy seizure classification 2017, *Epilepsy Foundation* <<http://www.epilepsy.com/article/2017/12/2017-revised-classification-seizures>>

Shorvon et al. (2011) proposed an etiological classification of epilepsy, as it is crucial for determining treatment and prognosis. The classification includes four categories: idiopathic, symptomatic, provoked and cryptogenic. Each category and subcategory with examples of pathologies that follow from them are described in Figure 2.

Main category	Subcategory	Examples ^a
Idiopathic epilepsy	Pure epilepsies due to single gene disorders	Benign familial neonatal convulsions; autosomal dominant nocturnal frontal lobe epilepsy; generalized epilepsy with febrile seizures plus; severe myoclonic epilepsy of childhood; benign adult familial myoclonic epilepsy
	Pure epilepsies with complex inheritance	Idiopathic generalized epilepsy (and its subtypes); benign partial epilepsies of childhood
Symptomatic epilepsy Predominately genetic or developmental causation	Childhood epilepsy syndromes	West syndrome; Lennox-Gastaut syndrome
	Progressive myoclonic epilepsies	Unverricht-Lundborg disease; Dentato-rubro-pallido-luysian atrophy; Lafora body disease; mitochondrial cytopathy; sialidosis; neuronal ceroid lipofuscinosis; myoclonus renal failure syndrome
	Neurocutaneous syndromes	Tuberous sclerosis; neurofibromatosis; Sturge-Weber syndrome
	Other neurologic single gene disorders	Angelman syndrome; lysosomal disorders; neuroacanthocytosis; organic acidurias and peroxisomal disorders; porphyria; pyridoxine-dependent epilepsy; Rett syndrome; Urea cycle disorders; Wilson disease; disorders of cobalamin and folate metabolism
	Disorders of chromosome function	Down syndrome; Fragile X syndrome; 4p-syndrome; isodicentric chromosome 15; ring chromosome 20
Predominately acquired causation	Developmental anomalies of cerebral structure	Hemimegalencephaly; focal cortical dysplasia; agyria-pachygyria-band spectrum; agenesis of corpus callosum; polymicrogyria; schizencephaly; periventricular nodular heterotopia; microcephaly; arachnoid cyst
	Hippocampal sclerosis	Hippocampal sclerosis
	Perinatal and infantile causes	Neonatal seizures; postneonatal seizures; cerebral palsy; vaccination and immunization
	Cerebral trauma	Open head injury; closed head injury; neurosurgery; epilepsy after epilepsy surgery; nonaccidental head injury in infants
	Cerebral tumor	Glioma; ganglioglioma and hamartoma; DNET; hypothalamic hamartoma; meningioma; secondary tumors
	Cerebral infection	Viral meningitis and encephalitis; bacterial meningitis and abscess; malaria; neurocysticercosis, tuberculosis; HIV
	Cerebrovascular disorders	Cerebral hemorrhage; cerebral infarction; degenerative vascular disease; arteriovenous malformation; cavernous hemangioma
	Cerebral immunologic disorders	Rasmussen encephalitis; SLE and collagen vascular disorders; inflammatory and immunologic disorders
Degenerative and other neurologic conditions	Alzheimer disease and other dementing disorders; multiple sclerosis and demyelinating disorders; hydrocephalus and porencephaly	
Provoked epilepsy	Provoking factors	Fever; menstrual cycle and catamenial epilepsy; sleep-wake cycle; metabolic and endocrine-induced seizures; drug-induced seizures; alcohol and toxin-induced seizures
	Reflex epilepsies	Photosensitive epilepsies; startle-induced epilepsies; reading epilepsy; auditory-induced epilepsy; eating epilepsy; hot-water epilepsy
Cryptogenic epilepsies ^b		

Figure 1. Etiological classification of epilepsy

To better understand the types of seizures and their complexity, it is important to mention that this research was concerned with focal epilepsy. The background research in neurofeedback has emphasized focal epilepsy. In addition, in generalized epilepsy there are several neurophysiological components that are difficult to control and measure with the evaluating tools used in this study.

Epilepsy Mechanisms

For a better understanding of the underlying mechanisms in epilepsy, it is important to consider the basic anatomy and neurophysiology of the cerebral cortex. The human cerebral cortex consists of six neuronal layers. The hippocampus, which is the oldest part of the cortex, is one region consisting of three layers, (Shipp et al., 2007). It is localized in the temporal lobe and considered an important structure in the pathophysiology of epilepsy, as this is the region common for dysplasia, which is the malformation of the cortical development (Schwartzkroin, 1994). The types of neurons in the cortex are differentiated by pyramidal neurons, most of which are a part of excitatory synapses; and interneurons, which have inhibitory synapses. Recurrent inhibition forms synapses on inhibitory neurons and creates a negative feedback loop, which decreases function and stabilizes their function.

The neurons are activated by an action potential that occurs due to the depolarization of the neuronal membrane. This is an all or none activity due to the diffusion of ions through the membrane (Barnett & Larkman, 2007). A hyperexcitable state occurs when there is an increase in excitatory synaptic activity, decrease in inhibitory activity, and change of the voltage-gated ion channels. Figure 3 shows the relationship between the modification of the voltage of the membrane and the influx of ions (Carlson, 1992). In epilepsy, it is crucial to understand this mechanism, as the influx of ions in the stabilization of the membrane is significant for proper functioning.

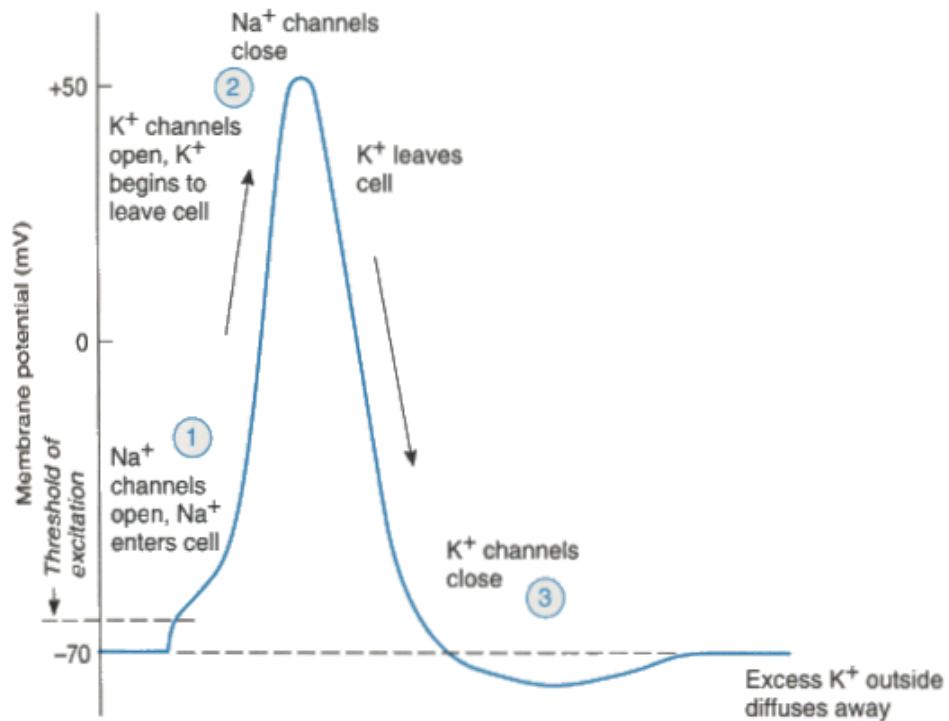


Figure 2. An action potential with the flow of ions (Carlson, 1992).

Another important component in the mechanism of epilepsy is the role of the neurotransmitter, the chemicals released at the presynaptic level and activated by a postsynaptic receptor. The main neurotransmitters are glutamate, gamma-amino-butyric acid (GABA), acetylcholine, norepinephrine, dopamine, serotonin and histamine. The most important excitatory neurotransmitter is glutamate and its postsynaptic receptors, such as alpha-amino-2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropanoic acid (AMPA), kainite receptors and alpha N-methyl-D-aspartate (NMDA), which are responsible for an adequate ion influx; agonism of these receptors can induce seizure activity (Pincus, 1992).

The inhibitory neurotransmitter GABA relates with two receptors: GABA-a and GABA-b. GABA-a receptors are permeable to chloride (Cl⁻), which hyperpolarizes the membrane and inhibit action potentials; whereas substances that are GABA-a agonist suppress seizure activity. GABA-b relates to the second messenger system and often results in the opening of potassium (K⁺) channels causing a hyperpolarization; GABA-b agonist exacerbates hyperexcitability and seizures (Treiman, 2001).

The electrical activity of the brain takes place in two environments: within the neuron (intrinsic) or in the extracellular space (extrinsic). The intrinsic mechanisms depend on the type, number and distribution of ligand-gated channels as these channels determine the directions, degree and rate of changes in the transmembrane potential and the extrinsic mechanism depends on extracellular ion concentrations as it varies the extracellular volume (Bromfield, Cavazos, & Sirven, 2006).

There are various factors underlying the pathophysiology of epileptogenesis that disrupt the imbalance of the excitation and inhibition of the neuronal activity, disturb extracellular ion homeostasis alter energy metabolism, change receptor functions and change transmitter uptake (Le Magueresse et al., 2013). There are major mechanisms of hyperexcitability of the neural network that are not exclusive, as between them they synergize in epilepsy: (a) selective loss of interneurons, (b) selective reorganization that creates recurrent excitatory connections and (c) loss of excitatory neurons that stimulate inhibitory neurons (Benini & Avoli, 2005).

Kindling is a phenomenon that explains epileptogenesis such as alterations within the glutamate channel, selective neuronal loss and axonal reorganization (Corcoran, 1989).

However, we still do not know of all the mechanisms that occur. Rather, we understand that continuous electrical chemical activation of a specific area of the brain involves long-lasting biochemical or structural changes that affect the central nervous system (CNS) (Bertram, 2007).

Epilepsy and Comorbidities

In contrast to recurrent seizures, epilepsy is usually diagnosed alongside other cognitive and behavioral issues that are more disabling than the seizures. Amongst epileptics, quality of life (QOL) is affected more by factors such as social life, family life, academic achievement, and professional achievement, than by seizures (Keezer, Sisodiya, & Sander, 2016).

Neurobehavioral comorbidities in epilepsy. Population-based and community-based studies documented the prevalence of neurobehavioral comorbidities in epilepsy, which are divided into psychiatric, cognitive, and social categories (Lin, Mula, & Hermann, 2012). Severe epileptic encephalopathy, which commences in early childhood, more frequently has complex comorbidities. According to the ILAE, “The epileptic activity itself may contribute to severe cognitive and behavioural impairment above and beyond the expected from the underlying pathology alone” (Berg et al., 2010). Roughly 75% of children diagnosed with epilepsy are affected with epileptic syndrome (Lennox-Gastaut, West, & Dravet). This syndrome gives rise to encephalopathy that may result in mental retardation and/or autism (Berg, 2011)

Psychiatric comorbidities. Various researchers, such as García-Peñas et al. (2014) and Aaberg et al. (2016), have documented that patients suffering from epilepsy may also

have mood disorders, anxiety disorders, and attention deficit hyperactive disorder (ADHD), as well as other psychiatric disorders (Aaberg et al., 2016). Tellez-Zenteno, Patten, Jette, Williams, and Wiebe (2007) found that patients who have experienced early presentation of epilepsy suffer from more evident comorbidities than people diagnosed later in life. These disorders also are associated with non-complicated epilepsy, though they are more common with complicated epilepsy (Tellez-Zenteno et al., 2007).

In a population-based study in England, Rai et al. (2012) found that one third of people with epilepsy met diagnostic criteria for anxiety and depressive disorders, compared with one in six in the general population without epilepsy. Kessler, Lane, Shahly, and Stang (2012) showed that the association of epilepsy with days of role impairment due to comorbidities is equivalent to 89.4 million days off annually among U.S. adults with epilepsy, which is significantly higher than among a healthy population.

Cognitive comorbidities. In a review of the literature concerning neurobehavioral comorbidities in the community-based investigation of paediatric epilepsy, Lin et al. (2012) found increased cognitive dysfunction in children with epilepsy, including uncomplicated epilepsy, when compared with healthy children. Table 3 presents the literature discussed in this review.

Table 1

Cognitive Comorbidities in Paediatric Epilepsy Population-Based Studies

Ellenberg, Hirtz, and Nelson, (1986)	IQ <70 in 27% of children with epilepsy (Ellenberg et al., 1986)
Berg et al. (2008)	Impaired non-verbal intelligence in 47% of children with epilepsy compared with 3% of healthy control individuals Impaired executive function on seven of eight tests in children with epilepsy compared with healthy control individuals IQ <80 in 25% of children with epilepsy (Berg et al., 2008)
Fastenau et al. (2009)	Children with epilepsy did worse than healthy control individuals on four of four cognitive domains (Fastenau et al., 2009)
Jones, Siddarth, Gurbani, Shields, W. and Caplan, R. (2010)	Children with epilepsy (uncomplicated) has lower verbal IQ, and learning than did healthy control individuals (Jones et al., 2010)

Other authors have shown that at least a quarter of all children diagnosed with epilepsy experience cognitive difficulties (Berg et al., 2008). Epileptic activity may restrict proper functioning and development of the brain by preventing adequate function of cortical networks (Berg et al., 2011). The age of onset and the number of seizures are two factors that associate positively with the extent of cognitive dysfunction (Vasconcellos et al., 2008)

Berg et al. (2011) examined the factors that may impact other functions in an epileptic patient, such as structural defects and the consequences of abnormal cognitive processes. One of the most common structural defects observed in children was deformity in the development of the cerebral cortex region of the brain (Berg & Scheffer, 2011). Such structural abnormalities hinder the proper functioning of the brain and result in several cognitive impairments. This disruption in intellectual and cognitive behavior is due

to the transient effects of seizures that last for a long period of time (Kim et al., 2016). Additionally, patients with mesial temporal lobe epilepsy (MTLE) experience progressive drops in cognitive function, an advanced effect of epilepsy. This leads to the thinning of the neocortex, which can degenerate memory in a span of four years (Hermann et al., 2006)

Taylor et al. (2010) further documented comorbidities among patients recently diagnosed with an epileptic disorder prior to starting antiepileptic drugs (AED) and compared those to a healthy population. The authors suggested that the cerebral deficiencies present in the patients preceded the commencement of epilepsy as the scores were expressively low in all cognitive areas. The patients tested with fewer seizures experienced the same effects, indicating that AED were not the primary source of their deterioration (Taylor et al., 2010)

Social comorbidities. The social aspects of epilepsy are important factors that affect the QOL of patients with epilepsy. Discrimination within society can often be more challenging than the disease itself (Viteva & Semerdjieva, 2015). In many countries, the laws reflect a lack of understanding of the social dimension of epilepsy. For example, epilepsy in China and India is generally regarded as a reason to forbid or terminate a marriage. Until 1970, the law in the United Kingdom prohibited people with epilepsy from marrying (Kilinç & Campbell, 2009). In the United States, until 1970, individuals with epilepsy were denied access to restaurants, theatres, and recreation centres. The stigma of this disorder may affect patients who seek treatment, as they may feel ashamed to ask for help (Pan, Gupta, Wyllie, Lüders, & Bingaman, 2004)

As a medical diagnosis, epilepsy may serve as a stigmatizing social label (Jacoby, Johnson, & Chadwick, 2015). In previous eras, people with epilepsy have been viewed as possessed by demons, infectious, or insane, leading individuals to hide their condition socially (Sleeth, Drake, Labiner, & Chong, 2016). Patients experiencing social non-acceptance may develop anxiety, low self-esteem, hostility, and maladaptive behaviors (e.g., dependency, rigidity, anger, and aggression) that affect their QOL (Livneh & Antonak, 2005).

Economically, epilepsy treatments are quite costly. Substantial funds are required to pay for medication, treatment procedures, lack of productivity, and premature death. People with epilepsy face financial crises, and often have limited access to health services and insurance. These individuals have no chance of obtaining a driver's license and may face difficulty securing employment. As such, the ideal treatment for epilepsy disorder includes proper psychological, financial and social support (Stefan et al., 2014)

Early diagnosis and treatment is essential as the most significant neurodevelopmental changes occur during childhood and adolescence. These changes impact patients' lives academically, emotionally, and economically. Early diagnosis and intervention may reverse some cognitive injuries. For example, patients may recover their development quotient through successful surgical treatment (Freitag & Tuxhorn, 2005; Jonas et al., 2004).

Psychological comorbidities. The factors responsible for the psychological influence of epilepsy on the child and family's everyday life suggested by Camfield, Breau, and Camfield (2001) include: (a) the discipline of the brain disorder, (b) the availability of

the medical administration, (c) the significance of the disease to the child and family socially, (d) boundaries on the family's events, (e) difficulty and innate coping mechanisms and (f) the extent of assets and social livelihood available to deal with epilepsy (Camfield et al., 2001). The difficulty of the situation stems from the fact that the arrival of sporadic and unpredictable conditions resulting from epilepsy can cause mental distress to parents. The difficulty of the situation can affect the child's confidence (Rodenburg, Wagner, Austin, Kerr, & Dunn, 2011). It can also affect parenting duties and create family difficulties. Thornton et al. (2008) observed that children with poor control and prognosis pose obstacles that affect family dynamics. Additionally, children diagnosed with epilepsy experience lower self-esteem that affects their relationships with friend and relatives (Sturniolo & Galletti, 1994)

Quality of Life and Epilepsy

Epilepsy negatively impacts the QOL of a patient (Lai et al., 2015). If the condition begins during childhood, the patient may develop a dependent personality with severe disabilities that impact social development and the ability to live independently. It is often difficult for people outside of the environment of epilepsy to understand how this disorder may lead to disabilities, as the patient may look normal and not present all related issues in public settings.

Vickery et al. measured quality of life in research to evaluate the efficacy of medical, surgical, and rehabilitative interventions, to provide an indicator of quality of care, health care and health behavior, comparison of impairments across the disease and evaluation of the cost-benefit ratio (Vickrey, 1993). While QOL generally includes life

satisfaction, self-esteem, well-being, health, and happiness (Frank-Stromborg, 1988), QOL is the state of overall health that includes the domains of physical, social, psychological, vocational and economic well-being (Spencer & Hunt, 1996)

Hosseini, Mokhtari, Momeni, Vossoughi, and Barekatian (2016) reviewed extensive literature on the QOL for patients suffering from epilepsy. Epilepsy affects mortality and distresses patients socially, psychologically, and cognitively. People suffering from epilepsy are uncertain about their life expectancy, and this affects their QOL significantly. Patients with epilepsy cannot predict when, where, and in which circumstance their seizures will erupt (Murray, 1993). In addition, patients may not know how each seizure will affect them, or if it will have damaging effects on their functioning. As such, once patients are diagnosed with epilepsy, they must learn to cope with the repercussions of seizures. They should be aware of the treatment required for them in these circumstances. Yet seeking psychological and emotional support may be challenging for the patients (Taylor, 1989).

Kwong et al. (2015) found that adolescents with epilepsy demonstrate higher rates of anxiety and depression when compared with adolescents who suffer from asthma (38.2% anxiety and 22.2% depression). The authors also found that polytherapy and older age were correlated with higher anxiety level. The results showed that key factors associated with depression among females were high seizure frequency and early age of onset (Kwong et al., 2015). The authors also found that the duration of epilepsy is another common component in both anxiety and depression.

Collings (1990) examined the impact of epilepsy on patients' well-being as well as social/family circumstances. The authors aimed to improve the evaluation and measurement of QOL among epileptic patients (Collings, 1990).

There are sufficient QOL scales to evaluate the outcome of treatments and interventions for epilepsy. For clinical use, generic scales have been developed to measure general health conditions. However, for epilepsy, the specific issues that affect certain areas of life are neglect in generic scales. Thus, disease-specific scales measure distinct aspects of this disease (Cowan & Baker, 2004).

Epilepsy and Therapeutic Interventions

It is important to understand the current therapeutic options available for patients with epilepsy in order to treat the condition adequately. This section, describes the various therapeutic interventions (Table 2), as well as the need for improved therapies for epilepsy.

Table 2

Available Therapeutic Interventions for Epilepsy, Efficacy and Negative Points

	Intervention	Efficacy	Negative points
Conventional	Antiepileptic drugs	70%	Cognitive decline Behavioural issues Systemic symptoms (renal, hepatic) Overmedication Addiction
	Surgery	56%	Invasive surgery Complications of surgery Expensive Cognitive issues Seizures relapse
Neuromodulation	Vagus nerve stimulation	57%	Invasive procedure Complications of surgery
	Deep brain stimulation	56%	Invasive procedure Complications of surgery
	Trigeminal nerve stimulation	40%	Not enough evidence
	Transcranial direct current stimulation	58%	Not enough evidence
Others	Repetitive transcranial magnetic stimulation	50%	Expensive Low availability
	Ketogenic diet	Unknown	Not possible to follow for long periods of time
	Acupuncture	Unknown	Not enough evidence

Antiepileptic drugs (AEDs). These drugs are used as a conventional treatment for epilepsy, and have a 70% success rate among newly diagnosed children and adults (Dwivedi, Singh, Kaleekal, Gupta, & Tripathi, 2015). However, it is a frequent practice to

overmedicate patients even if there is not much clinical improvement after the treatment is provided (Chuang et al., 2007). The risk and benefits of AED should be monitored continuously to control the frequency of seizure. In addition, it is also important to consider if the treatment is able to optimize cognitive, psychological and social functioning (Jovanovic, Jovic-Jakubi, & Stevanovic, 2015).

Side effects of AED are abundant and should be evaluated with respect to the treatment required for the patient. Approximately 90% of patients suffering from epilepsy experience an unwanted side effect of AED (Thomas, Koshy, Nair, & Sarma, 2005). Neurotransmitter systems, neuronal ion permeability, and other targets, are affected by AED. However, the precise mechanisms affected by AED are not fully understood because they are so complex. After undertaking a systematic review of the literature by (Piedad, Rickards, Besag, and Cavanna (2012), evidence of unfavourable effects of epilepsy documented including depression, anxiety, aggression, psychosis and sleep disorders. Thus, there is a need to look for alternative therapeutic options for epilepsy.

Surgery. Surgical options include resection of a brain lobe or specific brain structures such as temporal lobectomy, lesionectomy, hemispherectomy, and corpus colostomy. However, surgery is not always an effective treatment (Najm et al., 2013). The failure of the surgery could lead to adequate trials of seizures due to side-effects of AED (Asadi-Pooya et al., 2014). In the last decade, approximately 5% of the paediatric epilepsy population were candidates for surgery (Sugano & Arai, 2015). Typically, the patients who suffer from malformation of cortical development are better candidates for surgery. In 56% of cases, surgery is successful, defined as seizure free at 3 months follow up (Mühlebner et

al., 2014). The use of highly invasive techniques may severely affect neuropsychological functions and impede memory. Additionally, after five to ten years of surgery, in general, 50–60% of patients report experiencing seizures again (Kwan & Sperling, 2009)

It is also important to consider constraints associated with the monetary cost and the availability of the surgical option for such patients. In developing countries, over 40 million people suffer from epilepsy and access to accurate imaging studies, electrophysiology, metabolic testing, and state-of-the-art surgical equipment to perform surgery successfully may be limited (Asadi-Pooya et al., 2014).

Vagus nerve stimulation (VNS). This treatment is a nonpharmacological, moderate-risk surgical intervention option that aids epilepsy treatment. It is used for patients suffering from refractory epilepsy. It has a success rate of 57% (Rocha, 2013). The procedure consists of an implantation of a programmable signal generator in the chest cavity and an electrode that produces electrical stimulation over the vagus nerve (Schachter & Saper, 1998). One of the mechanisms of action is an increase of parasympathetic tone to reduce the cortical hyperexcitability and reduce seizures (Bodin et al., 2015).

Deep brain stimulation (DBS). This treatment uses intracerebral implantation to stimulate electrodes. The electrodes are connected to a subcutaneous pulse generator, and a pulse of electrical current is continuously delivered to the parts of the brain to be modulated. In epilepsy, anterior nucleus (AN) and centromedian nucleus of the thalamus are frequently stimulated. Kocabicak, Temel, Höllig, Falkenburger, and Tan (2015) found that 56% of patients reported a reduction in seizures after this treatment. However, DBS is

another invasive intervention and its risks and side effects must thus be evaluated (Halpern, Samadani, Litt, Jaggi, & Baltuch, 2008).

Trigeminal nerve stimulation (TNS). This is a non-invasive technique that uses neuromodulation principles. The mechanism is based on reducing cortical spiking and prolonging the refractory period of cortical pyramid neurons. Soss et al. (2015) studied this intervention in epilepsy and showed reduced cerebral blood flow and metabolism in the sensorimotor cortex, parietal cortex, and temporal cortex in images. In addition, positive response rates of 42% and 40.5% respectively have been observed in two clinical trials. Thereafter, a response rate of more than 30% reported after a six to twelve-month follow-up with those exposed to the intervention (Soss et al., 2015).

Transcranial direct current stimulation (TDCS). This treatment modulates cortical excitability via a non-invasive brain stimulation technique. A weak and constant electric current passes through two electrodes (anode and cathode) on the scalp. The cathode stimulation reduces cortical excitability, whereas the anodal stimulation increases it. The hyperpolarization occurrence is used in epilepsy for stimulation. In a recent systematic review, San-Juan et al. (2015) concluded that TDCS trials showcased preliminary safety and efficacy among animals and epileptic patients. The authors also found that there were benefits of this intervention over other neuromodulation therapies as well, as TDCS uses less expensive and compact equipment.

Repetitive transcranial magnetic stimulation (rTMS). This treatment aims to modulate cortical excitability. In rTMS, a magnetic current is applied to the surface of the scalp, which targets specific parts of the brain. Some clinical trials have shown that

stimulating the epilepsy foci produce a 50% success rate from rTMS treatment (Lefaucheur et al., 2014). However, rTMS requires costly equipment.

Ketogenic diet. Refractory epilepsy treated with a dietary option known as the ketogenic diet. In this diet, high amounts of fats, adequate quantities of protein, and low carbohydrates are consumed by patients. In refractory epilepsy, the body consumes more fat than carbohydrates. Thus, it requires the number of ketones to be increased in the bloodstream. The brain uses the ketones instead of glucose, and this mechanism helps in reducing seizure activity (Freeman, Kossoff, & Hartman, 2007).

Acupuncture. An alternative therapy to treat neurological disorders is acupuncture, a conventional Chinese form of therapy (Zhao, Rong, & Zhu, 2015). It is a safe and non-invasive intervention. Acupuncture stimulates the thalamus as it is the sensory brain regulator and connected with epilepsy genesis. Chen et al. (2014) showed that this intervention is associated with neuromodulatory techniques and can offer advantages to patients who suffer from refractory epilepsy.

Based on the information provided of the current therapeutic intervention for epilepsy, there is evidence that there are still clinical issues that are not fully resolved. In order to improve epilepsy and the comorbidities, there is need to explore less invasive treatments with fewer side effects and cost-effective interventions.

Conclusion

This chapter showed the general characteristics of epilepsy and the complexity of clinical presentation, as well as how limited, risky, costly, and severe the available

therapeutic interventions can be. These reasons justify an exploration of additional interventions that treat seizures and comorbidities as well as offer lower risk approaches that reduce side effects for this population.

Chapter 3 Introduction to Electroencephalogram

An electroencephalogram (EEG) is a recording of brain activity taken from scalp electrodes. The modernisation of the technology has led to its extensive use. Berger first studied EEG signals in 1929 (Jung & Berger, 1979) and since then neurological and psychiatric disorders, such as epilepsy, stroke, head injury, brain tumour, and sleep disorders, are diagnosed using EEG signals. The recorded activity results from action potentials that arise out of cortical neurons, which produce EEG rhythms. Excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs) are then stimulated and further produce pyramidal cells in the cortex. Subcortical structures such as the thalamus play an important role in understanding the origins of EEG rhythms (Mitzdorf, 1987).

The oscillations produced by the thalamo-cortical circuits instigate the firing of layer IV cortical neurons, and a dipole of negativity and positivity are created on the superficial layers of cortex. The electrodes produce fluctuations after reading these changes in potentials. The electrical activity measures the voltage differential between the two electrodes since the electrical activity needs to travel from one point to another point. Complex information processes can be measured by the EEG via the neural system in the central nervous system and the peripheral neural system (PNS) (Tyner, Knott, & Mayer, 1989).

For clinical practice, 20 electrodes are placed on the scalp in a specific localization in a 10/20 system (see Figure 4) (Knott, 1993). This is an international and standardized method to describe the localization of the electrodes on the scalp and is based on the relationship between location of an electrode and the underlying area of the cerebral cortex,

and electrode can record activity from 6 cm² of cortex. Frequency indicates how fast the waves oscillate, which is measured by the number of waves per second (Hz), while amplitude represents the power of these waves measured by microvolt (μV). High density EEGs with 123 additional electrodes provide high source location accuracy in epileptic patients (Meckes-Ferber, Roten, Kilpatrick, & O'Brien, 2004).

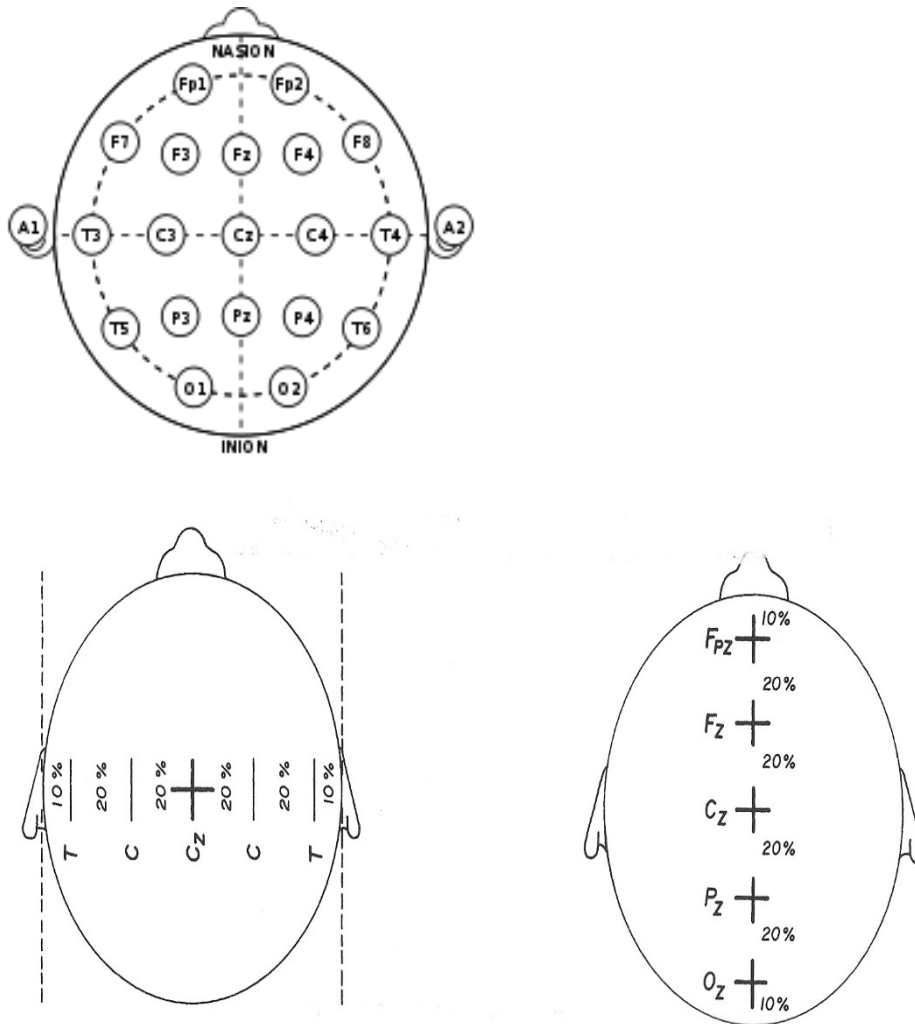


Figure 3. 10/20 system of electroencephalography electrode placement.

Electroencephalogram has developed from paper documentation to computer-based data analysis, display and storage. An analogue-digital converter (ADC) device can be used to convert the analogue EEG signal to digital values and save it in digital media, such as on hard discs or compact discs (Nuwer et al., 1998).

The Signal Processing of the EEG

The EEG signal has linear properties. For example, the activity between 10–300 μV can be easily assessed with physiological and electrical noises and artefacts from electrocardiogram (ECG), electrooculogram (EOG) and electromyogram (EMG).

Electroencephalogram is not a static process that relies on a physiological state. There are non-physiological artefacts that can contaminate the EEG, such as the 50/60 Hz artefact. Electrical devices such as TV stations, radio, pagers, telephones, or a cardiac pacemaker, can produce these artefacts. However, these artefacts can be easily eliminated using a notch filter and eliminated from analysis (Barlow, 1993). The EOG and ECG are the most challenging artefacts to remove because they overlap with the EEG amplitude.

The clinical application of EEG includes the diagnosis of seizure disorders, sleep disorders, altered levels of consciousness, infections and affective and behavioural disorders (Kupfer, Reynolds, Ulrich, Shaw, & Coble, 1982). Different frequency bands can be recognized in the EEG that relate to levels of alertness: delta (0–3+ Hz), theta (4–7+ Hz), alpha (8–13+ Hz), and beta (>14 Hz). Table 3 shows the EEG characteristics of each band (Niedermeyer, 1998). The posterior dominant rhythm (8–13 Hz in adults) is observed within the posterior head region, and the amplitude can be altered by having the eyes closed or open (see Figure 4). The activity can be synchronized and symmetrically organized via

an intrinsic pacemaker through the thalamus. Any abnormalities in the thalamic pacemaker indicates an irregularity in the central nervous system (Papazian, 1990).

Table 3

EEG Frequencies and Related Brain Activity

Frequency Band	Frequency Range (Hz)	Brain Activity
Delta	1-4	Sleep, unawareness, deep-unconsciousness
Theta	4-8	Unconsciousness, optima meditative state, distractibility.
Alpha	8-13	Alertness, deeply relax, recalling, optimal cognitive performance.
SMR	12-15	Mental alertness, physical relaxation
Beta	15-32	Focusing, sustained attention, alertness, excitement.
Gamma	32-40	Cognitive processing

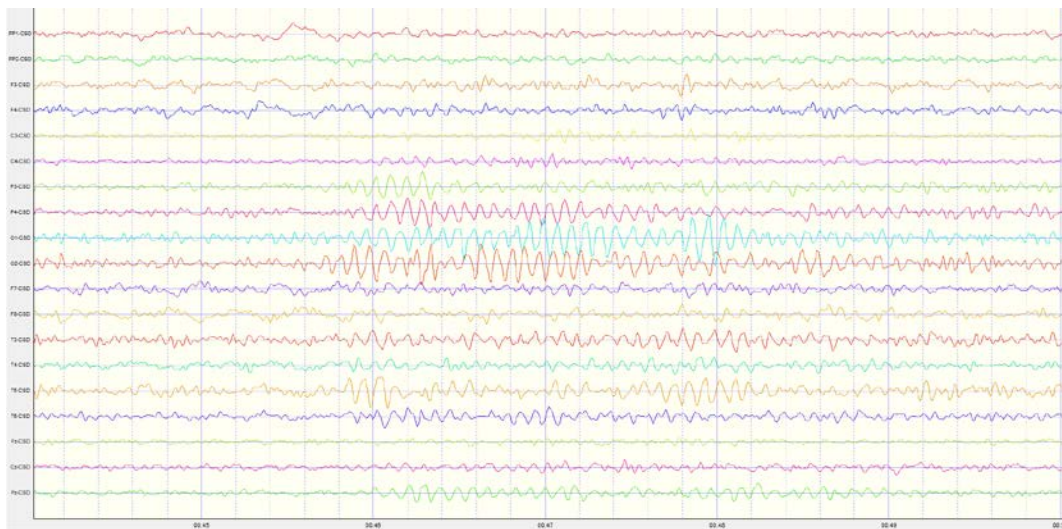


Figure 4. Normal adult electroencephalography with reactive activity during eyes closed (personal clinic data).

The neurophysiological mechanism of a focal seizure begins with a high amplitude, a recurring burst of activity, and hypersynchrony of a neuronal populations. If an appropriate number of neurons synchronise in a burst, it results in a spike discharge on the EEG (Perucca, Dubeau, & Gotman, 2014). A mechanism called paroxysmal depolarization shift is associated with the influx on Ca^{++} extracellular, which is related to an opening of Na^{+} channels and produces a repetitive action potential. Subsequently, hyperpolarization is associated with the GABA receptors and the presence and quantity of Cl^{-} or K^{+} ions. The propagation of the seizure occurs when there are enough neurons in surrounding areas that the central area is activated and producing a surrounding inhibition that spreads the seizure activity over cortical pathway (Kandel & Buzsáki, 1993). Once repetitive discharges happen, there is an increase of extracellular K^{+} ions and depolarized surrounding neurons. The build-up of Ca^{++} in presynaptic regions produces neurotransmitter turns and the depolarization of NMDA, which causes additional Ca^{++} and more neuronal activation (Eross et al., 2009).

Quantitative Electroencephalogram (QEEG)

The American Academy of Neurology defined the QEEG as “the mathematical processing of digitally recorded EEG in order to highlight specific waveforms components, transform the EEG in to a format or domain that elucidated relevant information, or associate numerical results with the EEG data for subsequent review or comparisons” (Nuwer, 1997). Novel techniques have been implemented to comprehensively assess brain function and connectivity. Linear and nonlinear methods as theory-based time series were implement. Fast Fourier transformation (FFT) has been one of the theorems used for this

purpose (see Appendix A for QEEG analysis methods). Fast Fourier transformation provides numeric values decomposing the waves into voltage of each frequency which provide power spectrum data driven from a QEEG analysis are the following: spectral analysis (frequency composition over given time); absolute power (power is the square of the EEG amplitude, mathematically it indicates the strength of the signal at the given frequencies interval); and coherence (analogous to cross-correlation in the frequency domain between activity in two channels) (Grin-Yatsenko, Baas, Ponomarev, & Kropotov, 2010).

High levels of split-half and test-retest reliability for the QEEG, as well as predictive validity, were demonstrated in a review of the literature by Hughes and John (2014). A QEEG greater than 0.9 correlation is considered reliable and has 40s seconds epoch. Predictive validity of QEEG was established by implementing replicable correlations that comprised of clinical measures and provided accurate predictions of the outcome and performance of neuropsychological tests. Content validity of QEEG established by constructing correlations with independent measures such as magnetic resonance imaging (MRI), positron emission tomography (PET) and single photon emission computed tomography (SPECT), the Glasgow Coma Score (GCS), and other neuropsychological tests. Thatcher Biver, and North (2003) found substantial correlations between the QEEG and independent measures, which related to attention deficit disorder, depression, and anxiety.

The innovations of the present study are the combination of clinical, neurological and psychological measures. Previous neurofeedback studies with epilepsy focused on

specific variables, such as seizure frequency, and did not examine the effects of intervention in young people who suffer from epilepsy

The main objective of using the QEEG as a neurological outcome for a neurofeedback study is to provide objective information about brain activity (absolute power and coherence) that can be compared over time. This objective data is not measurable in a conventional EEG as we only rely on visual analysis. In epilepsy, the use of QEEG can be valuable as seizure disorders are not localized anomalies in the cerebral cortex but rather dysfunctions within and between networks in cortical and subcortical structures (Pittau & Vulliemoz, 2015).

Walker (2008) found that 75% of patients suffering from intractable epilepsy witnessed proliferation in theta absolute power, in addition to a 50% rise in coherence within theta and beta bands. The author concluded that by lowering the absolute power of Theta and by decreasing the Theta and Beta coherences, seizures could be controlled more effectively. Birca et al. (2015) demonstrated that children with febrile seizures experience heightened Theta coherence in seizure prone state, which interferes with the process of brain maturation and in the development of interconnectivities in the brain. Kober et al. (2015) also demonstrated that healthy adults could voluntarily proliferate production of SMR absolute power and simultaneously reduce the Beta coherence. Sterman (1996) suggested that the reduction in coherence is an indication of reduced mutual interference which can perhaps boost stimulus processing. Thus, in this study, Theta and Beta coherences were analyzed.

Conclusion

This chapter covered the background of the EEG and QEEG as neurofeedback is an intervention based on EEG signal, but also because the study includes neurophysiological outcome measures, so it is important to have the background for the purpose of the study.

Also, there is more clear understanding of the rational of the variables used in this study to measure neurophysiological outcome.

Chapter 4 Neurofeedback Background

Neurofeedback, also known as a brain biofeedback, brain-computer interface (BCI), or brain-machine interfaces (BMI), is an intervention whereby the activity of the neuronal process is registered and regulated. Neuronal activity is measured and, in real-time, visual and auditory feedback is presented to self-regulate the electrical activity of specific brain structures that are related to a specific behavior and symptoms. As the patient is exposed to the intervention in repetitive sessions, different learning mechanisms are activated for the modification of the behaviors. For this reason, neurofeedback can be considered as endogenous neural stimulation (Shibata, Watanabe, Sasaki, & Kawato, 2011). Figure 8 illustrates the visual and auditory feedback compared with other neuroimaging methods and the feedback calculations.

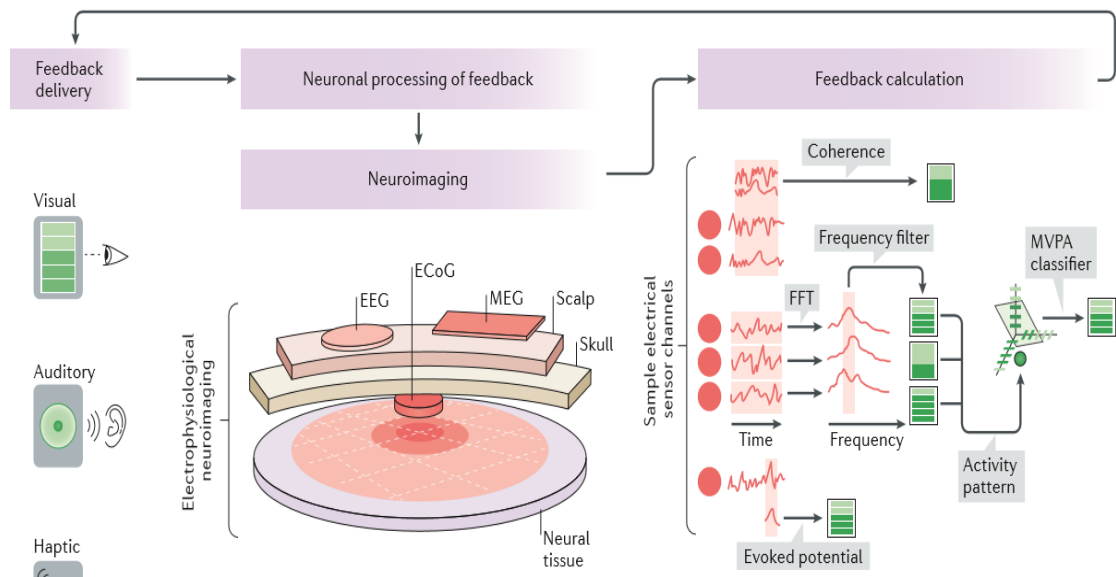


Figure 7. Overview of the procedure of neurofeedback. Adapted from Sitaram et al. (2016).

Neurofeedback begins with the observation of neural activity. Electrophysiological methods to detect such activity include electroencephalography (EEG), magnetoencephalography (MEG), and invasive electrocorticography (ECoG). Sample signals that are extracted from the sensor channels provide a qualitative representation of the difference in temporal resolution. Univariate approaches extract a signal from a single channel or region of interest as, for example, an evoked potential. Calculation of coherence or connectivity between two channels as a measure of functional connectivity is another common feedback method. Features from a set of sensors, such as the power at a frequency window or the level of activation, can be classified as multivariate patterns of activity (MVPAs). The calculated signal is then presented to the individual via visual and auditory feedback, allowing the user to alter neural function and complete the loop with neural processing of feedback.

Newer technology includes rt-fMRI (real time functional magnetic resonance imaging) neurofeedback, which showed to be accurate in modifying specific cortical activity of target brain regions. This exciting neuroimaging technique is the type of neurofeedback that has been shown to be more effective in effecting positive outcome in different neurobehavioral conditions (Kopel et al., 2017). For epilepsy, there is not enough evidence for the use of this technique, and unfortunately, it is a costly intervention. For this reason, the present study included the neurofeedback modalities that showed efficacy in the treatment of epilepsy.

Learning Theories in Neurofeedback

Neurofeedback emerged from learning theories, especially associative learning theory, which includes the notion of classical conditioning and operant conditioning (Strehl, 2014). Classical conditioning is a type of learning that involves the acquisition of elicited responses, while operant conditioning is a type of learning that involves the acquisition of emitted responses (Kirsch, Lynn, Vigorito, & Miller, 2004). In 1927, Pavlov conducted an experiment popularly known as classical conditioning, in which an unconditioned response (“inborn reflexes”) was generated as a result of an unconditioned stimulus (Pavlov, 1927). In that experiment, Pavlov used a dog and measured the effect of saliva during digestion. The meat powder was used as a stimulus for the dog while the saliva was the result of a conditioned stimulus. Pavlov observed that the dogs salivated even before the meat powder was presented in front of him. The dog salivated as he heard the sound of the steps of the person who brought the meat powder or after listening to the noise produced by the device that delivered the meat powder. The dog associated the ring of the bell to the delivery of meat powder and, after several rings, when the bell rang the dog produced saliva (Gantt, 1927)

Through this experiment, Pavlov demonstrated that when stimulus and response are linked, they can become the basis of learning. The meat powder was the unconditioned stimulus (UCS) and the dog’s salivation was the unconditioned response (UCR). The ringing of the bell was an auditory stimulus and acted as a neutral stimulus until the dog was conditioned to salivate after listening to the ringing. Thus, the bell became the conditioned stimulus (CS) that produced a conditioned response (CR). Hence, a

physiological function does not always require a learning process (e.g., salivation at the sight of food) using classical conditioning. In this process, the conditioned stimulus produces a conditioned response (e.g., saliva after hearing person's footsteps who brings food for the dog) (Pavlov, 2010).

Researchers working to understand better the mechanism of neurofeedback have explained how operant conditioning also implies a role in the intervention. By proposing the "law of effect," Thorndike and Skinner (1948) described operant conditioning on newly learned behaviors. Such behavior was not observed in Pavlov's studies on classical conditioning. Operant conditioning is based on a response that generates a substantial effect in a given situation. Such an effect usually contrasts with expectations; the responses produced thereafter have discomforting effects and are less likely to happen again (Skinner, 1960). The theory of operant conditioning thus increases the desired behavior and decreases the undesired behavior.

Typically, undesired behavior is punished and desired behavior is rewarded. A reward includes any situation in which the desired response is considered desirable and promotes an exact response under the same conditions. A punishment is an action that is given when an undesired response is discouraged. It prevents the occurrence of an undesirable event. If the frequency of reward or punishment increases or decreases, then the response is reinforced (Bauer & Gharabaghi, 2015). The reinforcement and punishment may be *positive* or *negative*. Positive reinforcement means providing a stimulus, and negative reinforcement indicates the removal or absence of the stimulus. Furthermore, extinction is induced by a lack of consequences following a particular behavior.

Neurofeedback learning involves an initial stage of fast change in performance and a late stage of more stable improvement as the skill is consolidated. VanLehn (1996) showed functional and structural changes in the dorsomedial striatum to be associated with the first stage, whereas such changes in the dorsolateral striatum are associated with the late stage.

Brain Activity Conditioning

Durup and Loomis (1935), Jasper and Shagass (1941) and Kamiya (1958) were pioneers in experimenting with human brain activity conditioning. These experiments showed that the human brain can be trained to produce specific brain activity voluntarily paired with a specific stimulus, at this moment without knowing that this could lead to a clinical use for neurological disorders.

Durup and Rouanet (1968) and Loomis et al. paired a low auditory tone with light stimulus that resulted in alpha blocking and extinction if the low tone was presented several times devoid of the light stimulus. Jasper and Shagass (1941) questioned whether alpha blocking was not simply an unconditional response to light, and demonstrated the voluntary control of EEG by associating with it a vocal stimulus. The authors instructed the participants voluntarily say sub-vocally “block” and press a button followed by a sub-vocal “stop” and release of the button. The button switched on the light, serving as the unconditioned response, associating the sub-vocal command with alpha blocking and hence becoming the conditioned response (Jasper & Shagass, 1941). Later, Kamiya (1958) demonstrated that the human brain can voluntarily discriminate between high and low amplitudes of EEG alpha rhythms when a trainer gave a command (Kamiya, 2011).

Regardless the light or vocal stimulus, these studies showed that the human brain activity can modify their activity following learning theories.

Sterman et al. (1969) conducted an animal experiment regarding classical conditioning of brain activity. Using cats, the authors synchronized EEG activity and behavioral manifestation of sleep. The cats were conditioned with a tone that rested in basal forebrain stimulation, and the CS was sleep preparatory behavior. Sterman et al. used variation in tone frequencies, and the conditioned response showed variation in resulting behavior. Other studies done on animals recently confirmed that monkeys and rodent were able to learn and modify their brain activity (Koralek et al., 2012)

This was the beginning of a series of studies from healthy participants and animals studies that provided the rational to use it later to treat neurological conditions that will be described in further chapters specifically related with epilepsy.

Types of Neurofeedback and Protocols

Varying types of neurofeedback intervention have been studied for the last 40 years in the attempt to improve the clinical symptoms of seizures. There are four main types of neurofeedback discussed in the literature. Table 4 describes these types and their most common application.

Table 4

Types of Neurofeedback and Clinical Applications

Neurofeedback Type	Channels	Clinical Applications
Frequency power	2-4	ADHD, anxiety, epilepsy, depression, insomnia, within others.
Slow cortical potentials	4	ADHD, epilepsy and migraines
Z score	2-19	Insomnia
LORETA	19	Addictions, depression, obsessive-compulsive disorder

The following sections explore frequency power (or sensory motor rhythm [SMR]) and slow cortical potentials neurofeedback in detail, as these comprise the two interventions investigated in this study.

Another type of neurofeedback, Z-score neurofeedback is a continuous comparison of variables of brain activity to a database to deliver continuous feedback (Áine, Kate, Graham, Jamie, & Michael, 2014). And low-resolution electromagnetic tomography (LORETA) neurofeedback is based on source localization images that provide more specific training targets (Cannon et al., 2006). As Table 4 illustrates, frequency power and slow cortical potentials are the types of neurofeedback that promise effects for epilepsy while the other types do not pertain to epilepsy.

It is also important to acknowledge the different protocols used in frequency power neurofeedback. The names of the protocols are based on the frequency bands that comprise the focus in reward specific frequency band training. Table 5 shows the different protocols

that have been studied and the disorders they treat (Marzbani, Marateb, & Mansourian, 2016).

Table 5

Frequency Power Neurofeedback Protocols and Indications

Protocol	Indications
Delta	Pain, sleep, headaches, emotional trauma, traumatic brain injury
Theta	Improve memory, promotes creativity meditation and improve sleep
Alpha	Pain, anxiety, improve memory, mental performance
Alpha/Theta	Anxiety, depression, addictions
Beta/SMR	Epilepsy, depression, sleep disorders, ADHD, improve cognitive process
Gamma	Improve memory and cognitive process

Neurofeedback and Epilepsy

Sensorimotor rhythms (SMR) and slow cortical potentials (SCPs) are two neurofeedback techniques that have demonstrated efficacy in dealing with epilepsy. The neurophysiology and justification for the use of each method in relation to epilepsy will be presented in the sections below. In addition, this chapter includes the background on the effect of each neurofeedback technique on clinical improvements in epilepsy, as well as discussion of neurofeedback and cognition. These discussions support exploring broader the effects in cognitive function such as attention task in epilepsy.

Sensorimotor Rhythm

Sterman et al. (1969) initiated the first clinical application of operant conditioning of EEG and conducted a series of investigations to understand learned suppression of a response., while examining the learned suppression of this response, it was important that a

specific EEG rhythm of a sensory motor cortex appeared above non-rhythmic, low-voltage background activity. This specific rhythm had a frequency of 12–20 Hz and spectral peak of 12–15 Hz, unlike any EEG sleep spindles. In Figure 9, 12-15Hz was denoted as SMR.

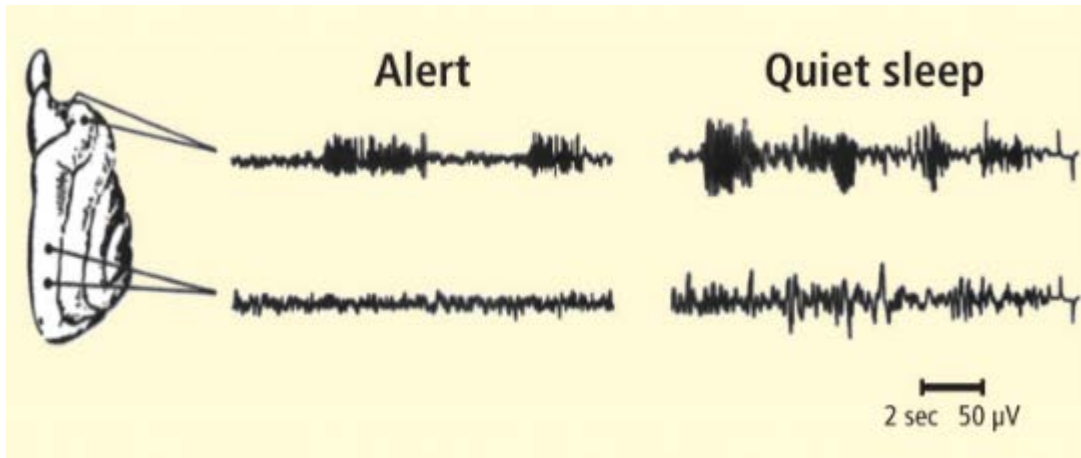


Figure 8. Electroencephalography samples from sensorimotor and parietal cortex in the cat during quiet wakefulness and quiet non-REM sleep. Both states are associated with a burst of 12-15 Hz (Serman, Howe, & Macdonald, 1970).

Neurophysiology of SMR. The ventrobasal nucleus of the thalamus (nVB) forms the foundation of SMR and is responsible for conducting afferent somatosensory information (Serman, 1972). Three types of neurons are known in the thalamic relay. First, thalamocortical neurons perform their functions in two different modes. The first mode acts as a relay cell for transmitting and assimilating ascending sensory input by depolarizing input volleys. In the second mode, it plays the role of an oscillatory cell by blocking the information from reaching the cortex while working in a collective rhythm (Lopes da Silva, Pijn, Velis, & Nijssen, 1997). Second, reticular nucleus neurons are responsible for providing restricted (hyperpolarizing) feedback control to the

thalamocortical neurons. Finally, local interneurons synchronize successful communications between thalamocortical neurons and the reticular nucleus (see Figure 10).

Thalamocortical Circuit

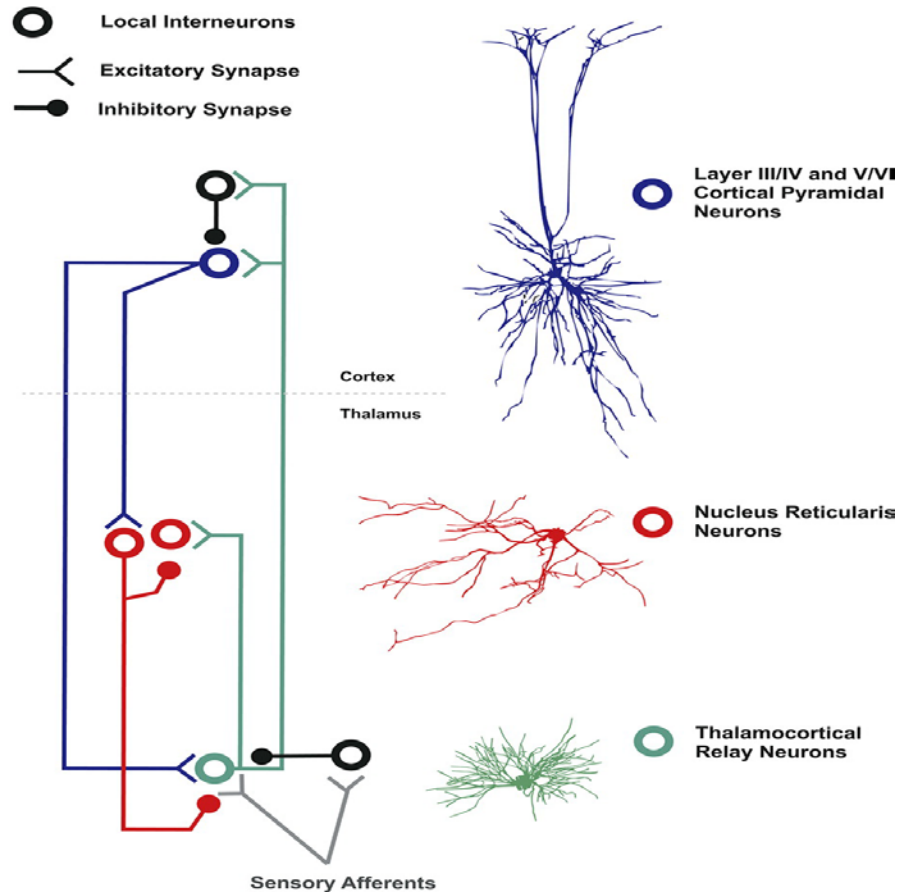


Figure 9. Thalamocortical circuit diagram (Khosravani & Zamponi, 2006).

The nVB firing patterns shift from fast and non-rhythmic (tonic) discharges to systematic, rhythmic bursts of discharges when conditioned SMR production takes place. Suppression of somatosensory information emerges from these discharges coupled with a reduction in muscle tone (Howe, 1973). When afferent somatosensory input is reduced, the nVB cells also hyperpolarize. A gradual depolarization is mediated by a slow calcium

influx that causes nVB neurons to discharge a burst of spikes. This is carried out to stabilize the level of inhibition. Thereafter, neuronal networks are connected to thalamic reticular nucleus (nRT) neurons and to the sensorimotor cortex. Additionally, if stimulated, the latter then leads to a GABAergic inhibition of VB relay cells, and again returns to a hyperpolarized state. Hence, a new cycle of slow depolarization will be initiated.

Rhythmic thalamocortical volleys and consequent cortical EEG oscillations occur when neuronal populations in the nVB, nRT and sensorimotor cortex are interrelated with each other (Serman & Egner, 2006). The oscillatory activity is largely influenced by nonspecific cholinergic and monoaminergic neuromodulation. In addition, SMR is initiated when the efferent motor and afferent somatosensory activity are reduced.

Comprehensively, neurotransmitters affect excitability levels of both the thalamic relay nuclei and the cortical areas that receive the relay signals. When a person walks, the neuromodulatory influences cortical projections and the nVB cells are depolarized. Also, the rhythmic bursting patterns are suppressed. Meanwhile, oscillations at SMR frequency are observed during behavioral stillness. Thus, SMR constitutes the dominant frequency of the integrated thalamocortical, somatosensory and somatomotor pathways.

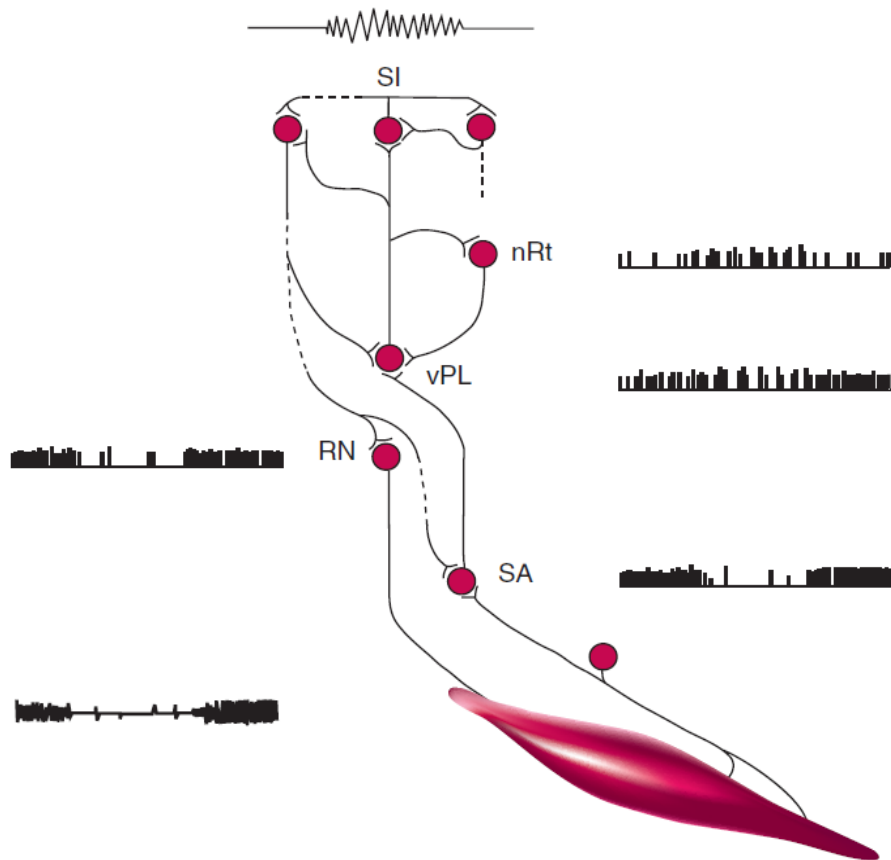


Figure 10. Overview of the neurophysiological changes associated with trained burst of the sensory motor rhythm in a cat.

Figure 10 illustrates an overview of the neurophysiological changes associated with a trained burst of SMR rhythm in a cat. On the effect side of the motor pathway, an abrupt decrease in muscle tone is seen together with a corresponding decrease in the firing rate of cells in the red nucleus and a suppression of the monosynaptic stretch reflex excitability. On the afferent side of the somatosensory pathways, a decrease in the firing rate of somatic afferent cells is accompanied by a shift to an interactive burst-silence pattern in cells of both the somatosensory relay nucleus of the thalamus and the thalamic nucleus reticularis,

resulting in rhythmic oscillation that can be recorded over the sensory cortex (Egner & Sterman, 2006).

Egner and Sterman (2006) related the production of field potentials at scalp level that exert influence on the thalamus with three integrative activities of the brain: vigilance, sensorimotor integration and cognitive integration. The vigilance system was coupled with diffused networks and specific centres in the brainstem. This system ascended and influenced the thalamic, subcortical and cortical centres. The sensorimotor system involved ascending touch and proprioceptive pathways and their projections to the thalamus and sensorimotor cortex, and the efferent from this cortical area. The vigilance system produced SMR, the 12–14 Hz rhythm over the sensorimotor strip. Cognitive integration involved a range of activities that process and integrate sensory inputs and motor responses (Egner & Sterman, 2006).

Egner and Sterman (2006) linked production of SMR, alpha and theta rhythms with the presence or absence of input, which arise from these systems on the thalamic oscillatory generators. When the influence of combinations of the three modalities is withdrawn from thalamus, then different oscillatory modes appear in it. Some prominent examples of the prototype involve initiating alpha rhythms by withdrawing brainstem cholinergic activity from the thalamus. The SMR rhythm appears when sensorimotor inputs are withdrawn from it. If cognitive processing is reduced (i.e., relaxed states without cognitive activity), then alpha appears. Furthermore, if vigilance is withdrawn (i.e., states of inattentive drowsiness), then theta appears. Thus, the underlying brain states of vigilance, cognitive processing and sensorimotor integration are attributed to the presence of these rhythms on

the EEG. Hence, it can be assumed that attentiveness intrinsically accompanies various conditions of SMR-associated stillness (including frequencies between 15–20 Hz) (Abarbanel, 2009).

SMR and Epilepsy

Tan et al. (2009) conducted a meta-analysis focused on analysing index studies using neurofeedback in epilepsy in various databases between 1990 and 2005. From 63 published studies, only 10 met the inclusion and exclusion criteria (i.e., were peer-review journal publications, provided full information on patient selection, utilized SMR or SCP and reported individual pre- and post-treatment seizure rates). These studies showed consistent positive results in treating refractory epilepsy participants. All studies reported decreased seizure incidence resulting from neurofeedback. The authors found that 64 out of 87 participants (74%) reported a reduction in weekly seizures. As the study involved small groups, sample heterogeneity was possible (Q test, $p = .18$), random effects were assumed, and the effect of intervention was statistically significant (Tan et al., 2009). Since Tan et al.'s meta-analysis, little research has been conducted on neurofeedback and epilepsy, mostly due to difficulties in the methodology in a clinical trial for epilepsy applications.

It is important to describe the first studies done by Sterman et al. (1969). After his study showing that a cat could learn to modify brain activity, Sterman started a non-related study to establish dose-response functions of highly epileptogenic drug compounds and used cats that had previously participated in SMR conditioning. These cats displayed elevated

epileptic seizure threshold when compared to untrained animals. The results suggested that SMR training inoculated the cats in avoiding seizures (Goff, Serman, & Allison, 1966)

Subsequently, Serman and Friar (1972) studied applied EEG operant conditioning to treat clinical disorders. The authors described a twenty-three-year-old female with a seven-year history of generalized tonic-clonic seizures. The patient encountered at least two major motor seizures per month. When three months training enhancement of 12-15 Hz was provided pertaining to EEG operant conditioning, the patient reported that the seizures terminated. Additionally, quantitative analysis of the EEG over this period disclosed a significant increase of the 12–15 Hz band and a corresponding decrease in slower activity. Hence, this patient was treated keeping in mind the requirements of an expanded multi-participant study. Finally, the patient was seizure free and her medications were reduced. Following the same authors, recruit another eight patients with intractable epilepsy (Serman & Friar, 1972). The training aimed at increasing their production of SMR activity, but also added an inhibition training of 4-7 Hz slow-wave activities. The participants' seizures were focal and after treating the participants for six to eight months, their medication was adjusted according to their condition at the end of the trial. Six out of eight patients reported post-conditioning reduction in seizure frequency; unfortunately, we can discuss here that the medications were adjusted, so the results may be questionable.

Several other authors have published interesting findings, which is illustrated in Table 6. In a recent review, Marzbani et al. (2016) summarized studies that were done on neurofeedback and epilepsy. All these studies showed 60-83% improvements in seizure reduction in patients with epilepsy. Although these studies were conducted on different

types of epilepsy (focal and or generalized), and medications were modified during the intervention, as well as other methodology limitations, we have enough information and valid rationale to continue exploring this intervention in epilepsy. This study differs in that it explored a younger population.

Table 6

Summary of Neurofeedback Treatment Studies on Epilepsy

Protocol	Neurofeedback protocol	Measuring results	Length of treatment	Age range
(Serman, McDonald, & Stone, 1974)	SMR (11-15Hz)	Seizure frequency, EEG	6-18 months	6-46
(Kaplan, 1975)	SMR	Seizure frequency	20-25 weeks	20-30
(Lubar & Bahler, 1976)	SMR	Seizure frequency	80-260 days	12-29
(Kuhlman & Allison, 1977)	SMR	Seizure frequency, EEG	24 sessions	17-42
(Serman & McDonald, 1978)	SMR	Seizure frequency	12 months	10-40
(Cott, Pavloski, & Black, 1979)	SMR	Seizure frequency, EEG	210 days	16-31
(Quy, Hutt, & Forrest, 1979)	SMR	Seizure frequency, EEG	12 months	23-49
(Lubar et al., 1981)	SMR	Seizure frequency, EEG	10 months	13-52
(Tozzo, Elfner, & May, 1988)	SMR	Seizure frequency	5 weeks	18-29
(Lantz & Serman, 1988)	SMR	Seizure frequency	8 months	18-45
(Andrews & Schonfeld, 1992)	SMR	Seizure frequency	6 months	20-40

SMR and Cognition

After observing initial improvement in epileptic patients, the effect of SMR neurofeedback in attention processing and learning difficulties was studied in detail. Shouse and Lubar (1979) applied protocols that were similar to previous studies to reduce hyperactivity among hyperkinetic children, demonstrating the utility and success of theta/SMR neurofeedback for treating attention deficit hyperactivity disorder (ADHD) (Shouse & Lubar, 1979). Lubar and Lubar (1984) also added beta (16–20Hz) to enhanced the attention. According to Monastra, Lubar, and Linden (2001), the rationale for this treatment was that the children with ADHD displayed abnormally low beta and elevated theta activity.

Additional studies have demonstrated that neurofeedback improves cognitive function in healthy individuals. For example, Vernon et al. (2003) examined SMR training in medical students, finding that it improved their cognition when compared against another group trained to enhance theta (4–7 Hz). The group that trained SMR showed development in semantic working memory and focused attention. In a similar study, Egner and Gruzelier (2004) examined a group of participants to enhanced SMR and as a result these participants improved their perceptual sensitivity and reduced omission error and reaction time variability. Moreover, the group that increased beta frequencies (15–18 Hz) witnessed improvement in their reaction time and the amplitude of P300 event-related potential (ERP). Both studies demonstrated that the specific control groups did not encounter any improvement with these processes in contrast to the SMR groups.

Egner and Gruzelier (2004) also used this intervention in healthy patients, and found that enhancing SMR activity associated with lessening commission error and enhanced perceptual sensitivity on the Test of Variable of Attention (TOVA). It also showed improvement in attention-related events and their associated potential. The authors concluded that SMR neurofeedback enhanced the attentional process in healthy participants.

As explained earlier, during the inactive focused and alert behavior, burst firing in the nVB to initiate SMR is done by attenuating somatosensory inputs. Humans show greater activity in the 11–15 Hz frequencies in the somatosensory cortex when they visually pay attention to the stimuli compared to the completion of a motor task (Mann, Serman, & Kaiser, 1996). As a result, by suppressing SMR, an interference with perceptual and integrative competence of information processing occurs. When SMR is conditioned, information processing decreases motor interference and improves cognitive functions (Vernon et al., 2003). Haarmann, Cameron, and Rucjkin (2002) supported the finding that promoting brain activity ranging within 10–14 Hz is associated with semantic processing. Beyond the neurofeedback literature, cortical activity in the range of 10–14 Hz was associated with semantic processing.

Slow Cortical Potentials

The slow cortical potentials (SCPs) belong to the family of event-related potentials and are denominated as direct current (DC) (Olcese & Faraguna, 2015). Unlike the oscillatory activity of the brain, evoked related potentials (ERPs) do not occur spontaneously, but over predictable a timeframe. After the onset of the stimulus, SCPs can

be observed from 500 ms with a duration ranging from 300 ms to several seconds. The timing of responding to a stimulus reveals various aspects of stimulus processing.

Neurophysiology of SCP

Walter (1967) first described the clinical significance of the contingent negative variation (CNV), which is the neurophysiological base of the SCP. The author recorded DC potentials just one second before the stimulus was presented and pressed the button; this was preceded by warnings of the stimulus. A slow change between the warning and the imperative stimulus was associated with amplitude coupled with behavioral significance (Walter, 1967). Figure 11 illustrates various cortical activations, out of which C is the most significant and considered the SCP generator due the excitatory postsynaptic potentials (EPSPs) in the apical dendrites, which have their source in deeper layers near the soma and also involve long-distance connections.

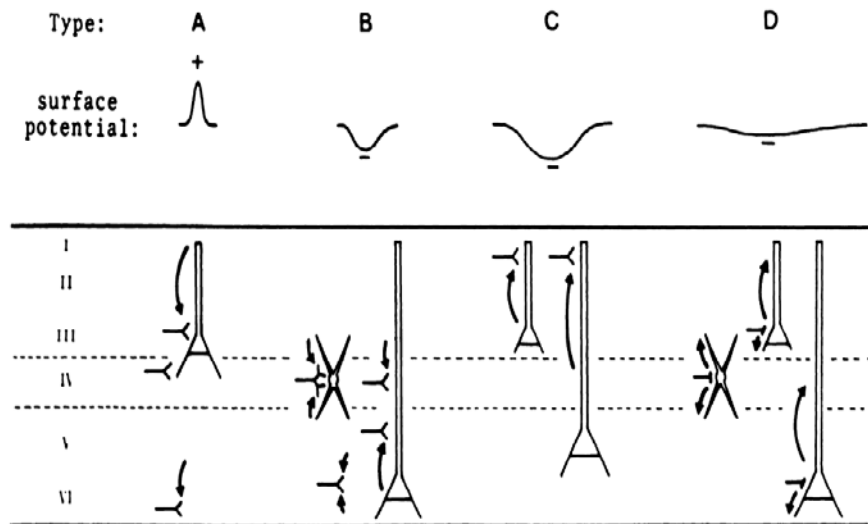


Figure 11. Diagram of four types of cortical activation (Müller-Preuss & Mitzdorf, 1984).

Potassium ions and glia also play a crucial role in the SCP generator. Neurons liberate K^+ so that the glial cells can be depolarized. The SCP amplitude, extracellular K^+ and depolarization glial are correlated and together represent neuronal activity. Pre- and postsynaptic currents, EPSPs and IPSPs all summate in the SCP generator (Cordingley & Somjen, 1978). Hence the SCP, which is close to the cell area, is generally produced by the neuroglia. However, when the SCP has been recorded from human scalp, the contribution of the glial has been considerably small. It is significant to consider the negative ions because they cannot cross the glial membrane. The glial cells play an important role in determining volume conduction (Rockstroh et al., 1987).

Additional neurochemical mechanisms are responsible for producing SCPs. Research has shown the role of dopaminergic and cholinergic projection to frontal neocortical regions in generating anticipatory negative SCPs (Bundy et al., 1980). Some evidence has proven the need for catecholamines for generating SCPs at cortical sites; cortical negativity is also produced by the inhibitory activity of the GABAergic neurons in the reticular nucleus of the thalamus. Reducing the activity of the dopaminergic-noradrenergic further reduces tonic and phasic inhibition from GABAergic neurons, and finally produces positive SCP. The implication of dopaminergic and cholinergic projection frontal neocortical regions in generating anticipatory negative SCPs has been observed from the evidence obtained from both humans and animals.

Generally, SCPs fluctuate and vary from being electrically negative to positive. Negative surface SCPs are a consequence of synchronous slow excitatory postsynaptic potentials in the apical dendrites of Layer 1 in the cortex. Positive fluctuations usually

represent the inhibition or reduction of prevailing negativities. Electrical negative shifts reflect the activity occurring in the large cell assemblies that are also responsible for planning and initiating a goal-directed behavior. In contrast, disfacilitation of excitation thresholds is considered as a positive shift in this direction (Haarmann et al., 2002).

SCP and Epilepsy

In order to understand the mechanism of SCP in epilepsy, we need to review the data on other neurological conditions. A CNV of lower amplitude can be caused by general brain lesions. Research has shown that the greater the brain damage, the lower the CNV amplitude (McCallum & Cummins, 1973). The thalamus holds an important place in the producing SCP. In one study, the SCPs were small or absent in a patient whose lesion invaded or distorted the thalamus (Purves & Low, 1978). Research has additionally shown a decrease in the CNV amplitude, either in depression or chronic anxiety in terms of mood disorders (McCallum & Walter, 1968).

The epilepsy model of SCPs has demonstrated that the amplitude of surface negativity is dependent on synchronisation of the afferent input to apical dendrites. However, this “output positivity” may be compensated by continued simultaneous synchronous afferent input to apical dendrites (Strehl, Birkle, Wörz, & Kotchoubey, 2014). These results suggest that negativity is an indicator of cortical excitability. In addition, the extreme potential amplitudes are related to overexcitability, which manifests itself in an epileptic seizure (Strehl et al., 2014).

Rockstroh, Elbert, Lutzenberger, and Birbaumer (1979) reported on a study conducted with 25 patients suffering from epilepsy, and particularly partial seizures (though

some patients with primary generalized seizures were also included in the study). Eighteen patients completed at least one year of follow up, and reported a significant decrease in seizure frequency when compared with baseline. Six patients were seizure free, seven patients reported reduction in seizure frequency from baseline, and only five patients reported no change in the incidences of seizure (T.Elbert, B. Rockstroh, W. Lutzenberger, 1980).

In another study, Kotchoubey et al. (2001) used self-regulated cortical potentials to train patients suffering from intractable epilepsy. The SCPs were compared with a new AED treatment and respiratory self-regulation. The main seizure type was partial, but patients who suffered from absence, myoclonic, and primary generalised tonic-clonic seizures were also included in the study. The results demonstrated a significant decrease in overall seizure rate for the SCP group and the antiepileptic group. No significant differences were visible between the two groups. Therefore, self-regulation of SCP was determined to be as effective a tool for controlling seizures as an addition to a new AED.

Several studies have showed that training SCP has significantly improved cognitive functions. In one study, when participants shifted between negative and positive SCP, they easily controlled their word processing (Pulvermuller, Mohr, Schleichert, & Veit, 2000), while the group that did not change their SCP did not report any development in their functionality (Vernon et al., 2003). In another recent study, the results showed training SCP in patients with epilepsy could bring statistically significant enhancement in Global IQ, as compared to respiratory biofeedback and the control group (Strehl, Kotchoubey, Martinetz, & Birbaumer, 2011). Finally, in the longest follow-up study conducted to date,

after being exposed to SCP neurofeedback, the findings of 6 out of 41 participants who completed the follow up showed that even after 10 years, seizure reduction was consistent (Strehl et al., 2014).

SCP and Cognition

SCPs are related to the attention preparation process. After the stimulus is presented, the input can hold the information for a few milliseconds. Thereafter, the pattern recognition filters the information in an evaluation process that registers the information in the long-term memory. These concurring steps produce a first nonspecific response; these steps are not necessary for conscious awareness. Preparation processes are viewed as facilitated performance (e.g., it shortens reaction time and increases error rate accuracy).

A psychological description further clarifies the processing stages identified by cognitive experimentation, namely that SCPs play an important role from the second stage onwards. Sensory and motor preparation are observed in due course in time and amplitude of negativity arising at 500 ms or later after presenting novel stimulus or the stimuli associated with response choices (automatized responses).

A negative feedback loop limits the amount of negativity that a cortical network exhibits. It produces or attenuates negativity after reaching a certain amplitude for a particular duration. These limitations are dependent on both the anatomic localisation of the SCP generators and on the history of training a particular patient pertaining to that particular task. Several studies have made use of two-stimulus designs coupled with varying difficulty of the related task.

Within the phasic tuning mechanisms, SCPs serve as a basis for attenuating regulation (Rockstroh et al., 1993). A consistent relationship between cortical negativity, reaction time, signal detection and short-term memory performance have been found in several studies (Birbaumer, Elbert, Canavan, & Rockstroh, 1990). Birbaumer et al. (1990) observed impaired regulation of SCP and reduced negativities in anticipating a task among children who suffer from attentional problems. Strehl et al. (2014) found that ADHD children displayed reduced inactive state and low-frequency power (0.1 Hz) and attenuated power during rest-task transitions. This varied significantly from healthy controls (Strehl et al., 2014). Attenuation of power was negatively correlated to task performance, wherein participants who felt weak made the fewest errors (Strehl et al., 2014). They exhibited variability and slower reaction times (Strehl et al., 2014). The above findings also supported the conceptualization of ADHD symptoms in the form of impaired excitation threshold regulation, characterized by reduced cortical negativity (Strehl et al., 2014). Therefore, the authors hypothesized that training ADHD participants to increase their negative SCP would increase their capacity to produce cortical activation. This mechanism was necessary for increasing their cognitive tasks and concentration (Strehl et al., 2014).

Using SCP as a treatment parameter for children suffering from ADHD can lead to significant reductions in ADHD symptoms and improved attention. It also produced changes in ERP and helped to obtain SCP feedback of the CNV. Studer et al. (2014) found that after providing SCP feedback training, healthy participation from adults augmented their CNV amplitude. Examination of EEG during SCP treatment also indicated that children suffering from ADHD could control SCPs. This skill remained stable even after

the end of two years of treatment. Neurofeedback therapy has proven to be an effective treatment for children; Studer et al. thus investigated whether SCP feedback can be an efficient treatment for adult ADHD participants.

It is the purpose of this study to compare two neurofeedback modalities and explore the outcomes of each, in order to inform better decisions about which intervention is more appropriate for children who suffer from focal epilepsy.

Conclusion

It was important to consider the neurophysiology of each intervention and the type and nature of each participant's epileptic symptoms. The intention of the study was to explore the effects of two neurofeedback modalities in clinical, neurophysiological and cognitive outcome and to compare the two modalities of neurofeedback and is important to acknowledge the background that existed until now about the two neurofeedback modalities and their results in epilepsy and cognition. No previous studies compares the QOL on both types of neurofeedback.

Chapter 5 Methodology

Participants

The randomized controlled study included 44 participants (22 male, 22 female). These participants were chosen on the basis of the following criteria. All participants were diagnosed with persistent focal epilepsy. Focal epilepsy indicates that the seizures originate within networks usually limited to one hemisphere. These seizures may be either discretely localized or more widely distributed (Berg & Millichap, 2013). The participants suffered from at least one seizure in the previous 6 months (Loddenkemper et al., 2005). Third, their age ranged between 12 and 18 years ($M = 14.8$ years, $SE = 2.28$ years). Participants' vision and hearing function was assessed using standardized tests, as this was an essential step in ascertaining the efficacy of the participants' visual and auditory feedback stimuli. The participants were asked to maintain stable doses of their medication throughout the trial and the subsequent 3-month follow up. Individuals with other neurological disorders or decompensated illness (e.g., diabetes, renal failure) were excluded from the study. Patients treated with Vigabatrin were excluded as this could lead to damage in visual processing (Lüders, Turnbull, & Kaffashi, 2009).

Participants were considered an opportunity sample in this study. Four local neurologists referred study participants who completed the eligibility criteria (see Appendix B). Those participants interested in being a part of the study received initial assessments. All evaluations were complete at the Biomedical Research Institute located in Aguascalientes, Mexico (see Appendix C).

Design

This study employed a stratified, randomized, parallel trial. Three homogenous groups of participants were categorized on the basis of their age and gender. The first group was included in the SMR protocol, the second group was included in the SCP protocol, and the third group was included in the sham control protocol as independent variables. The dependent variables were clinical, neurophysiological and cognitive measures. The *clinical* dependent variables were: seizure frequency (SF), seizure severity scale (SSS), and quality of life scale (QOLS). The *neurophysiological* dependent variables included quantitative electroencephalogram (QEEG) that include four variables: theta absolute power, SMR absolute power, theta coherence and beta coherence; and *cognitive* dependent variables were the attention switching test (AST) that include four variables: letter category reaction time, letter category error rate, letter counting reaction time and letter counting error rate.

Each participant was evaluated at the beginning of the intervention (baseline), after the last session of intervention was concluded (after five weeks of treatment) and at 3 months follow up, which is standard time for follow up in pharmacological studies (Pasha, Kamate, & Didagi, 2014). Twenty-five one-hour sessions of neurofeedback were conducted in the protocol, as this is the minimum requirement to measure effect (Sterman, 2000). Each session was conducted from Monday to Friday for five consecutive weeks.

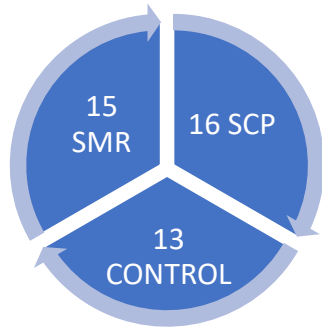


Figure 12. Participants (44 total) [SMR=Sensorimotor Rhythm; SCP=Slow Cortical Potentials].

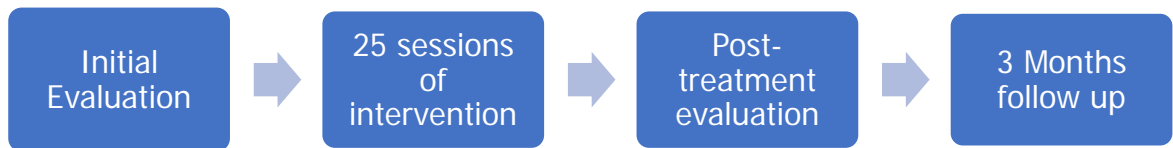


Figure 13. Design of the study.

Initial Evaluation	Post-treatment Evaluation	Final Evaluation "3 months follow up"
<ul style="list-style-type: none"> • SSS • QOL • QEEG • AST 	<ul style="list-style-type: none"> • SF • SSS • QEEG • AST 	<ul style="list-style-type: none"> • SF • SSS • QOL • QEEG • AST

Figure 14. Items included on each evaluation. [SSS=Seizure severity scale QOL=Quality of life QEEG=Quantitative electroencephalography AST=Attention switching task SF= Seizure frequency]

Procedure

Initial Assessment

An interview was conducted at the initial assessment. Background demographic information (e.g., data of birth, age and gender) was gathered. All participants belonged to the same nationality (Mexican). The potential participants also received complete medical and neurological examinations. All available EEG and imaging studies were used in order to document the diagnosis of focal epilepsy. In some cases, the localization of the foci was reported (see Appendix D). All previous and current medication were documented including start dates and doses given to the patient. At this point, the participants and their respective guardians signed the consent forms (see Appendices E & F). During this process, the purpose of the study and potential benefits were explained in detail. The participants were warned of potential risks in advance in order to avoid adverse reaction to the intervention. Detailed information was given about the randomization strategy. This strategy included the possibility of being assigned to a control group.

Experimental Measures

Clinical Measures

All questionnaires and scales were completed in a quiet room and ample time was given to think about each response. The primary care giver was responsible to respond to the questionnaires and scale. It was requirement for the same person to answer the questionnaires and scales.

Seizure frequency. Seizure frequency (SF) is considered the gold standard outcome when intervention in epilepsy is evaluated (Gilliam, 2002). There are various scales to evaluate the outcome of epileptic seizure from the ILAE (Wieser et al., 2008). For conducting evaluation on a year-by-year basis, the ILAE classification outcome assesses seizures per day instead of absolute number of seizures. There is another classification known as Engel's classification, which is used to assess postoperative outcome (Schachter & Schmidt, 1999). For this reason, these classifications were not appropriate to accomplish the objective of this study, as none of the scales register intensity and duration of the seizures, which are components that would be important to consider in a clinical intervention for epilepsy.

In this study, a seizure diary was included (see Appendix M). To evaluate SF, a diary was used to record more detailed clinical information. A format was designed for the diary wherein the parent or guardian could record the seizure experienced by the participant clinically during the period of assessment. Details such as date, time of the day, and intensity, duration, and time of recording of each seizure could be recorded in this diary by the parent or guardian (see Appendix M). Thereafter, the SF was compared during the intervention and follow up was provided to the participants. No baseline SF was collected as the participants were from a low educational and socioeconomic status and did not have a reliable measure of seizures before the study. Not all details mentioned in the diary were included in the data analysis.

Seizure severity scale. Seizure severity (SS) was evaluated by the revised Liverpool Seizure Severity Scale (Baker, Smith, Jacoby, Hayes, & Chadwick, 1998).

Chan, Zou, Wiebe, and Speechley (2015) demonstrated that the patients' perceptions regarding the severity of their seizure could be more significant than the seizure frequency to determine his/her psychosocial wellbeing. The rationale for including this scale in the study was due to the findings derived from previous studies that recommended evaluating the characteristics of the seizures.

In the context of clinical treatment, 50% reduction of seizure frequency was considered a successful outcome for epilepsy treatment (Wirrell, Wong-Kisiel, & Nickels, 2014). Each patient classified their seizure differently on the basis of the severity. Patients with severe epilepsy could distinguish between light and severe seizures using scales and by providing additional objective information (Smith, Baker, Dewey, Jacoby, & Chadwick, 1991). The Liverpool Seizure Severity Scale was used during this study to quantify the patients' perceptions of the changed pattern of the severity of the seizures during the course of the clinical trial. The Liverpool seizure severity scale consisted of 20 items in these categories: perception of control subscale (8 items) and perceived ictal/postictal severity subscale (11 items). Each item was scored on a one to four-point Likert response scale. For the purpose of this study, the total score of the scale was analyzed (see Appendix N). The scale was developed on the assumption that seizure severity is comprised of two factors: the perception of the patients to gain control of their seizures, and the perceived severity of the ictal (during the event or seizure) and postictal (posterior to the event or seizure) phenomena.

The post-ictal stage is a normal period that is dependent on the type of seizure and the transition from the ictal period. This stage involves a variety of symptoms. Brain

function might be low when the body recovers, or causes a prolonged period of unconsciousness that lasts from hours to days at a time. This phase may be further followed by a period of stupor or sleep, and, in rare cases, a period of prolonged generalized weakness. This condition is known as Todd's paralysis (Urrestarazu et al., 2002).

The present study investigated post-ictal modification with neurofeedback interventions. In the clinical practice, patients with epilepsy felt more distress from post-ictal disability in comparison to the seizure itself. Patients who suffered from refractory epilepsy treated with neurofeedback reported improvements in the post-ictal state before they experienced reduction in their seizure frequency.

The post-ictal state is considered the activity of inhibitory systems (adenosinergic systems, especially gamma-aminobutyric acid B receptors) that has been seen in the post-ictal cortex of rats. Also, there is intervention from the limbic system and the mu receptors (Kulick, Gutherz, Kondratyev, & Forcelli, 2014) The thalamus is important because it provides evidence of the major thalamocortical network in the post-ictal state, which is associated with the loss of consciousness (Penfield & Paine, 1955).

A previous section explained the role of the thalamo-cortical circuits during the neurofeedback intervention. It was hypothesized that by regulating these systems and circuits, the exacerbation of post-ictal symptoms could be prevented. Thus, there was a need to evaluate if neurofeedback can modify the severity of the post-ictal state.

Quality of life. Quality of life was evaluated by measuring and assessing the impact of the paediatric epilepsy scale (see Appendix O) (Camfield et al., 2001). This scale

was comprised of an 11-item questionnaire that is typically used in clinical trials for anticonvulsants. The children's guardians completed the questionnaire in order to measure the effects of their child's epilepsy on family life. The Jacoby scale is the precursor to the used scale, and some paediatric modification was introduced in the Jacoby scale (Kellett, Smith, Baker, & Chadwick, 1997). Each item on the questionnaire featured a severity score of 0 (not at all) to 3 (a lot). The higher the score, the more negative the impact of the item. The total score was computed as a sum and average. Items were categorized under various sections such as academic improvement, social adaptation and self-esteem. The assessment was included in the protocol as it was necessary to evaluate the psychosocial impact of epilepsy after implementing the intervention. Quality of life was also evaluated at baseline. In addition, a three-month follow-up visit was scheduled to detect differences among the QOL measures; this scale was not used immediately after the intervention as it was designed to be used after a three-month interval (Camfield et al., 2001).

Neurophysiological Measures

The EEG was recorded with a Neuronavigator 23-channel EEG amplifier along with an isolated computer interface (model NN-1 manufactures by J & J Engineering). The signals obtained by the EEG acquisition system were amplified. The signal was digitally processed by a quantitative topographic analysis system, band passed from 1-50Hz. This required an amplifier with specific features: good noise behavior, low leakage current, high common mode rejection ratio (CMRR), high input impedance, high power supply rejection ratio (PSRR), and high isolation mode rejection ratio (IMRR) (Binnie, 2003).

Data filters were required to analyze the data (high filter 50Hz, low filter 0.3Hz). Routine EEG is usually sampled at a frequency of ~250 Hz to remove the power line artefacts (50 or 60 Hz) (Nuwer et al., 1998). In order to record the EEG, a fitted electrode cap with leads was placed according to the International 10/20 System (see Appendix G). This system was applied to achieve a standardized 19-channel EEG recording. A referential recording was performed using the linked earlobes (see Appendix H).

Electrodes are found in varied shapes and sizes depending on the task or experimental conditions, such as surface electrodes, needle electrodes, sphenoid electrodes, subdural strip electrodes and depth electrodes. The most commonly used electrodes are surface electrodes which were attached to the skin with gel to monitor routine clinical EEG (Tong & Thakor, 2009). Before initiating the recording, an electrode impedance of less than five Kohms was required for all sites. The EEG signals were digitized at a particular rate or above 256 samples per second, band-pass filter between 0.5 and 35 Hz and for subsequent analysis. These responses could also be stored on a hard disk. For ten minutes, the participants were seated in a comfortable reclining chair. During this time, a recording was done with the participant's eyes closed for five minutes, after which they were asked to open their eyes for another five minutes.

QEEG analysis. Data were subjected to artefact detection and supplemented by visual review offline. The NeuroGuide database (Applied Neuroscience, Inc.) was used to analyse the artefact-free data (minimum 60 seconds) in offline mode. In addition, the dynamic normative database transformed EEG epoch into FFT algorithm and coherence measures (see Appendix I). The analysis was conducted using of absolute power on

Laplacian montage at Theta band (4–7Hz) and SMR band (12–15Hz) on central localization (Cz) of the sensorimotor area when the eyes were closed (see Appendices J–L). For all participants, during training the active electrode was placed on the Cz, for this reason the QEEG data analyzed on these sites.

To evaluate this data, various descriptive and statistical displays were used such as absolute power, relative power and connectivity of each clinical band and single Hertz evaluation. As a connectivity measure, the coherence within the Theta (4–7Hz) and Beta (12–15Hz) bands was calculated. Thus, in this study, I measured the coherence as a connectivity measure. Coherence measures the degree of association of frequency spectral between time series (Thornton, 2000). Thus, coherence was often interpreted as a measure of coupling and functional association between the two regions of the brain (Nunez, Srinivasan, & Fields, 2015). Coherence was considered a sensitive measure that revealed subtle aspects of the dynamic networks of the brain. These networks complement the data obtained by power spectral analyzes.

This study did not analyse frequencies greater than 40Hz, as the database used does not include analysis over 40 Hz.

Cognitive Measures

Attention switching test. The capability to behave adaptively in a complex world is one of the most important components of evaluating intelligence (Huepe & Salas, 2013). Another important component is to evaluate the ability to filter out the most important information at a particular moment. Additionally, attention is a cognitive function that can be used as an objective measure to assess the effectiveness of an intervention in the

treatment of a neurological condition. Cognitive switching is part of everyday life tasks; each task requires an appropriate configuration of mental resources, which is accompanied by a procedural scheme or task set (Kimberg, Aguirre, & D'Esposito, 2000). Furthermore, an external stimulus triggered by each task is presented in a combination of task set. These tasks sets are first acquired by trial and error and, thereafter, are stored in the memory. This technique requires a balance between endogenous control and exogenous influences; it further requires attention, classification, flexibility, and inhibition. As such, the switching task paradigm is used to evaluate effective and overall cognition such as attention, concentration, control, inhibition and memory (working memory), and hence provided a cognitive measure. It could perform other executive functions such as planning, organizing and sequencing (Monsell, 2003).

The attention-switching paradigm can evaluate the function of numerous regions of brain and especially the prefrontal cortex (specifically the medial and lateral regions). This is the region in which the neurofeedback intervention was located in this study (Cz) for their high connectivity with thalamo-cortical circuits and their reduction of hyperexcitability. For this reason, it is relevant to measure during this intervention a specific test that measure directly functions of specific structures of the brain.

This study used the Cedrus Corporation developed SuperLab 4.0 software in 2007 in San Pedro, CA, to conduct the experiments associated with attention switching in 60 trials (group of letters). A cue was presented to the participant (+ or Δ) before each stimulus. The + cue referred to the letters; if the stimuli showed an even number of letters (2 or 4), the participant had to press "A" key; if the stimuli presented an odd number of

letters (3 or 5) then the participant was required to press “L” key. The Δ cue referred to the type of letter—if the stimulus presented a vowel, the participant was supposed to press the “A” key; if the stimuli presented a consonant, the participant was supposed to press the “L” key. In each experiment, a random set of 30 even/odd and 30 vowel/consonant stimuli were presented. The stimuli comprised of 250 Arial fonts. To complete each experiment, an average duration of 2–3 minutes was allowed. The sum and average of reaction time (RT) in milliseconds and error rate (ER) was measured for each experiment. The even/odd numbers represented a letter-counting task and the vowel/consonants represented a letter-category task.

During this study, the test was administered in a silent room. The participants were required to sit on a comfortable chair at a distance of 30 cm from a 38-cm diagonal screen. While being seated on the chair, they could rest their arms on a desk while having close proximity to the keyboard. The instructions were provided clearly in detail until the participants understood all procedures involved in the intervention. Ten introductory stimuli were presented as test for practice. Once the participants completed the practice trial without any support, the actual test was performed. Thereafter, the results were exported to a Microsoft Excel spreadsheet for further analysis.

Intervention

Bio-Graph Infiniti Software was modified to standardize the functions for all groups. This software has the capability of capturing raw data to conduct accurate statistical analysis. Hardware ProComp Infiniti encoder (Thought Technology Ltd, Montreal, Canada) was implemented to enhance its power and flexibility in real time and

also to gain computerized biofeedback and data acquisition. Thus, in order to obtain the highest quality signal, this hardware enabled internal calibration. Thought Technology developed NFB equipment for several research studies. In addition, the technology also supported SCP intervention.

Before initiating the session, the participants were asked to sit in a comfortable chair in the office. The seizure diary was collected and the parents/guardians were asked if the participant reported any adverse reactions. In the first training session, the parent or guardians were allowed to remain present in the room when the instructions were explained. For the actual test, only the participant and technician were allowed in the room. Additionally, each time they earned points by accomplishing their expected goals, the participants were instructed to give to the stimuli to achieve their goals. Participants sat one metre away from a computer monitor and completed 30 minutes of actual training. The technician also allowed resting breaks for the participants to make sure that they remained attentive to the stimuli.

SMR intervention. Nuprep EEG skin prep gel from Weaver & Compan was use to prepare the skin to decrease impedance. Subsequently, Ten20 conductive paste from Weaver & Company was use to attach electrodes to the scalp or earlobes. Before training, impedance was less than 5 Khoms. The active electrode was set up in Channel A of the Pro-Infiniti encoder. The signal was amplified using the EEG-Z, and the electrode was located at Cz with reference to both earlobes. The pre-set parameters were as follows: inhibit theta (4–7Hz) at least 20% below their threshold, reinforce SMR (12–15Hz) 80% of the time and inhibit high beta (25–35 Hz) at least 20% below their threshold. A puzzle with

three bars representing each frequency band was used as a visual stimulus for the participants. One piece of the puzzle was open, and bars turned green whenever the participant achieved the parameters for 0.5 seconds. The auditory stimulus was a bell. In addition, by opening up subsequent puzzles, the participant could see a numerical reward of the points they earned. Samples of the screens are shown in Appendix T. The participants received feedback on their performance at the end of each session. The technician recorded the theta/SMR/high beta thresholds every five minutes and at the end of the session. The total rewards per session was also recorded. Recorded information was saved on a template in addition to the data for each session (see Appendix R).

SCP intervention. The first channel was used to set up the Pro Infiniti encoder. On the basis of previous research, the electrode was placed on Cz (Gevensleben et al., 2014). The reference electrodes were placed on both earlobes with the EEG-Z3 sensor (amplifier). Hence, to identify muscle artefact of the flicker, a second electrode was placed on the temporal area, which did not interfere with the EEG signal. Finally, as a reference the third electrode was placed on Pz.

The first 15 sessions were at 1:1 channel that inhibited 50% of the stimuli and rewarded 50% of the rest. The objective of this exercise was to allow a learning opportunity for the participants to control their inhibition and reward cortical shifts. The channel changed to 3:1 after 15 sessions, inhibiting 66% and rewarding 33%. Thereafter, the participant learned to inhibit negativity. Each session consisted of 75 trials. Appendix S illustrates the visual stimuli shown to the participants. Each trial included a balloon going up the screen if the goal was to activate the stimulus, or a submarine going down if

the goal was to inhibit the stimulus (see Appendix S). Baseline was recorded for two seconds and was followed by eight seconds of activation or inhibition training. If the participants were able to achieve the goals, at the end of each trial, they received visual and auditory stimuli. A few seconds were allowed between the test and trial. Small breaks were available depending on the needs of each participant. In order to remove muscle artefacts, participants were asked to avoid blinking during the 8-second trial. Instead, they could blink or close their eyes between the trials. Participants received feedback of their performance at the end of each session (Kübler & Birbaumer, 2008). In each session, inhibitions, activations, and total rewards were recorded.

Control intervention. The procedure of the control group was identical to the SMR group except for the fact that every participant watched a pre-recorded session. In every session, a different recording was shown (see Appendix T). In order to prevent unblinding, all procedures including the set-up time were kept identical. In this group, no information was recorded.

Randomization

Participants are categorized on the basis of their gender and were randomly assigned to one of the three groups in a ratio of 1:1:1. The research coordinator assigned the randomization sequence, and the researcher was blind during the experimental protocol.

Treatment of Blinding

Until the follow-up finished, the participants were blind to know which group they were assigned. The technicians and the coordinators were unblinded but the principal

investigator was blind while collecting and analyzing the data. Real intervention was offered at the end of the trial to the control group.

Statistical Analysis

The study aim was to examine two neurofeedback techniques to explore their clinical, neurophysiological, and cognitive effects among children with focal epilepsy. The statistical analyses used IBM SPSS Version 20 (IBM Corp, New York, NY, 2012). The data of each dependent variable was obtained in numerical data form. The last observation carry forward as an imputation method and intention-to-treat analysis was adopted in this study. A mixed 3x3 and 3x2 ANOVA was used with treatment as a between-participant variable with three levels (SMR, SCP, and control), and time as a within-participants variable with either two or three levels depending on the measure (pre-treatment, post-treatment, and follow up). A regression analysis was used to compare the changes in brain activity over the course of the session and Pearson correlation was to find association between neurofeedback learning and reaction time.

Sample size was calculated, as no preliminary data in this particular population intervention was available. The standard deviation estimated in the range/6 = $27/6 = 4.5$, that is the total range of a Gaussian distribution was six standard deviations. A sample size of 48 children had 80% power to detect a difference of 4.05 points between the groups when testing using repeated ANOVA's at the 0.05 level of significance. Thereafter, the participants' demographic and baseline characteristics are summarized. Trial competition,

withdrawal, exclusion, and protocol noncompliance were recorded. All medical history, medical information, and any other relevant baseline information were recorded.

Data Treatment

During the study required security and confidentiality of data was considered. Data management are performed in accordance with regulatory requirements of the clinical setting. This included the development and management of a database hosted in a locked external hard drive, administered by the research coordinator.

Ethical Considerations

The Ethics Committee of De Montfort University (United Kingdom) and the Biomedical Research Institute (Mexico) approved the study protocol (see Appendices U & V). Before commencing the trial, guardians of the participants provided written and informed consent that were reviewed and approved by the Ethics Committee. A signed and dated statement was sent to the research coordinator mentioning that the protocol was approved. All participants were informed that they could cease their participation at any point of time. Additionally, no compensation was offered for their participation.

The information clearly explained that if participants experienced any adverse reactions then they would be notified by the investigator immediately and the participant would be removed from the study, and his or her neurologist would be informed. Double copies of the consent forms were signed and the original copy rested with the participants' guardian or parents. The methodology of this study agreed to conduct this trial in

accordance with all laws, regulations and guidelines of the pertinent regulatory authorities by signing this clinical trial protocol. The trial was conducted according to the ethical principles set forth in the Declaration of Helsinki and other local regulatory requirements.

Conclusion

The methodology was designed based on previous neurofeedback studies (Sterman, Strehl, Fernandez). Rationale of the use of each measure was explained to fulfil the research questions and hypothesis. The procedures were covered on each of the neurofeedback interventions explaining in detail how every session was and how data was collected. In addition, the statistical analysis and ethical considerations are discussed.

Chapter 6 Results

Demographics

Forty-four participants completed the intervention and follow-up. Details of the demographics are shown in Appendix D. The summary in Table 7 illustrates that the groups were equally distributed on age, gender, and localization of the foci.

Table 7

Summary of Demographics: Gender, Age Mean (SD), Localization of the Epileptic Foci and ADE Monotherapy or Polytherapy

	SMR	SCP	Control
Male/female	7/8	9/7	6/7
Age, years	14.8 (2.33)	14.8 (2.3)	15 (2.3)
Foci UNK/localized	8/7	9/7	6/7
ADE mono/poly	9/6	13/3	8/5

Clinical Variables**Seizure Frequency**

A 3 x 2 mixed ANOVA was used to compare the effects of interventions on seizure frequency for all groups. There were no significant main effects ($p > .10$) or interaction effects ($p > .5$). There was no main effect of time [$F(1,41) = 1.88, MSe = 5.72, p = .18$] or group [$F(2,41) = 0.50, MSe = 90.39, p = .61$].

There was no significant interaction effect [$F(1,41) = 0.58, MSe = 5.72, p = .57$].

The seizure frequency post-intervention, and the follow-up mean scores of the SMR group, dropped from 3.60 ($SD = 12.850$) to 2.167 ($SD = 7.71$); the follow-up mean scores for the SCP group decreased from 1.75 ($SD = 6.213$) to 1.16 ($SD = 3.71$); for the control

group, the follow-up means scores also dropped from 0.38 to .31, which was the lowest of the three groups.

There was a consistent trend to reduction of seizures, being more prominent in the intervention groups (see Figure 16).

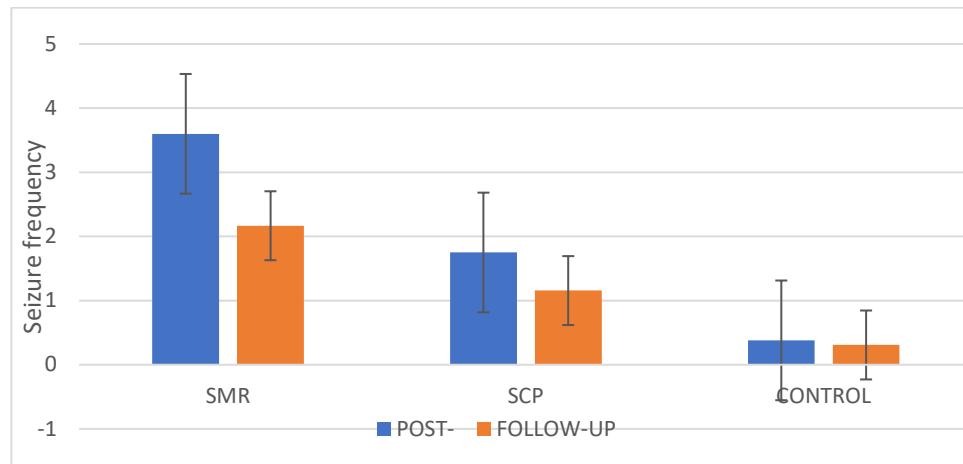


Figure 16. Mean seizure frequency by group post/follow-up. The error bars indicate standard error of the means.

Seizure Severity Scale

A Friedman non-parametric test was used for ordinal scale to compare the results from the seizure severity scale across the three treatment time points (pre, post, and follow-up). The test showed no significant differences in the seizure severity scale on any group for SMR ($\chi^2 = 2.8, p = .247$), SCP ($\chi^2 = 2.0, p = .368$) and control group ($\chi^2 = 2.0, p = .368$). There was a trend for the SMR group to present a reduction overtime of the seizure severity scale when compared with the SCP and control group that showed slight increase post-intervention and follow-up (see Figure 17).

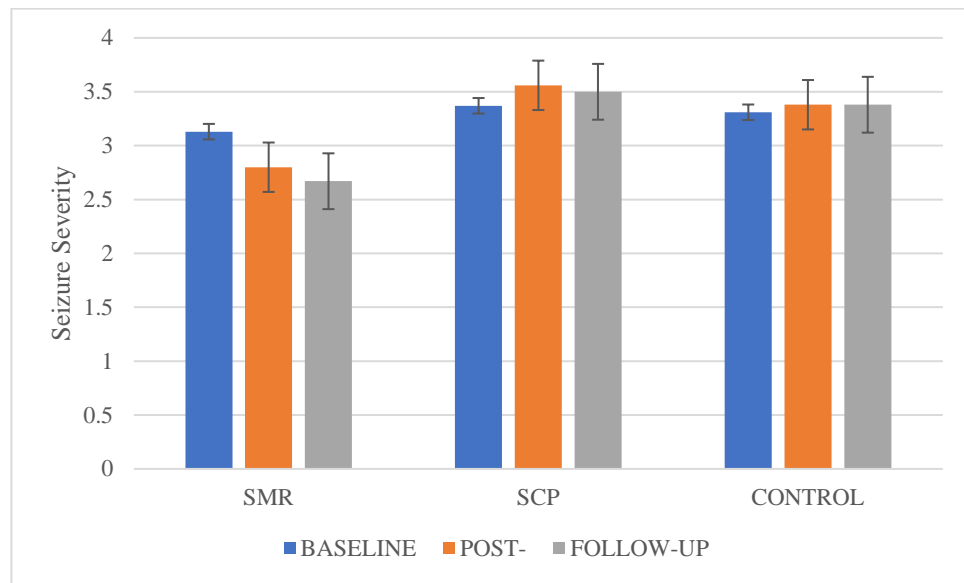


Figure 17. Means global seizure severity scale by groups pre/post/follow-up. The error bars indicate standard error of the means.

Quality of Life

A Wilcoxon-signed rank test, a non-parametric test for related samples, was used to compare the QOL score across two-time points (baseline and follow-up). The test showed a significant improvement in the QOL score for SMR ($Z=-3.035$, $p=.002$), and this change represented 1 percentage point over QOL score. The analysis revealed a significant improvement in the QOL score for SCP ($Z=-3.416$, $p=.001$), and the QOL score for the SCP group changed by 1.2 percentage points. For the control group, the analysis showed a significant improvement in the QOL score ($Z=-2.762$, $p=.006$), which changed by .92 percentage points. Figure 18 illustrates the mean by group baseline/follow-up.

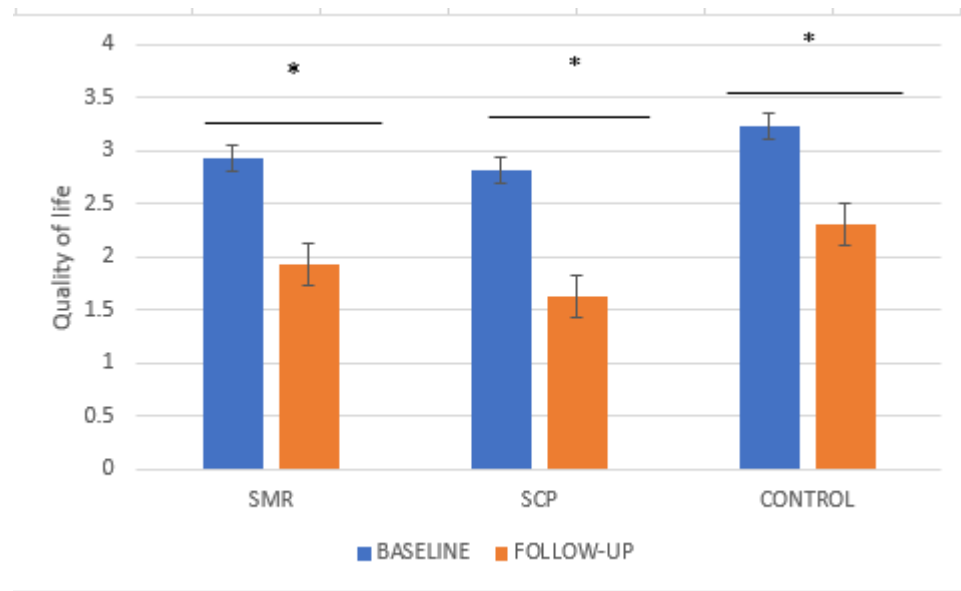


Figure 18. Graph of means QOL global score pre/follow-up by group. The error bars indicate standard error of the means, *statistical significant $<.05$.

Neurophysiological Variables

QEEG. A 3 x 3 mixed ANOVA was conducted for theta and SMR absolute power, and for theta and beta coherence. For *absolute power for theta* there was no main effect of time [$F(1,41) = 2.370$, $MSe = p = 0.106$], or group [$F(2,82) = 2.013$, $MSe = 936.22$, $p = .119$]. There was no significant interaction [$F(2,82) = 0.119$, $MSe = 465.10$, $p = .119$].

For *absolute power for SMR* there were no significant main effects ($p > .10$) or interaction effects ($p > .5$). There was no main effect of time [$F(1,41) = 1.944$, $MSe = 5.89$, $p = 0.156$], or group [$F(2,82) = 1.233$, $MSe = 8.8$, $p = .305$]. There was no significant interaction effect [$F(1,41) = 0.119$, $MSe = 7.2$, $p = .305$].

For *Theta coherence* there were no significant main effects ($p > .10$) or interaction effects ($p > .5$). There was no effect of time [$F(2,82) = 3.57$, $MSe = 2.79$, $p = 0.03$], or groups

[$F(4,82) = .727$, $MSe = .56$, $p = 0.57$]. There was no interaction effect [$F(2,82) = .72$, $MSe = .781$, $p = 0.48$].

For *beta coherence* there were no significant main effects ($p > .10$) or interaction effects ($p > .5$). There was no effect of time [$F(2,82) = .765$, $MSe = 2.02$, $p = .53$], or groups [$F(1,41) = 2.26$, $MSe = .63$, $p = 0.802$]. There was no interaction effect [$F(2,82) = .765$, $MSe = 64.4$, $p = .52$].

However, mean score for the SMR group showed a persistent decrease of the beta coherence throughout the intervention, while the other two groups responded in the opposite direction (post-treatment and then drop on the follow-up). Even though this result did not reveal statistical significance, the trends for the SMR group were as expected (see Figure 19) the SCP and control group increased beta coherence post-intervention and reduced for the follow-up.

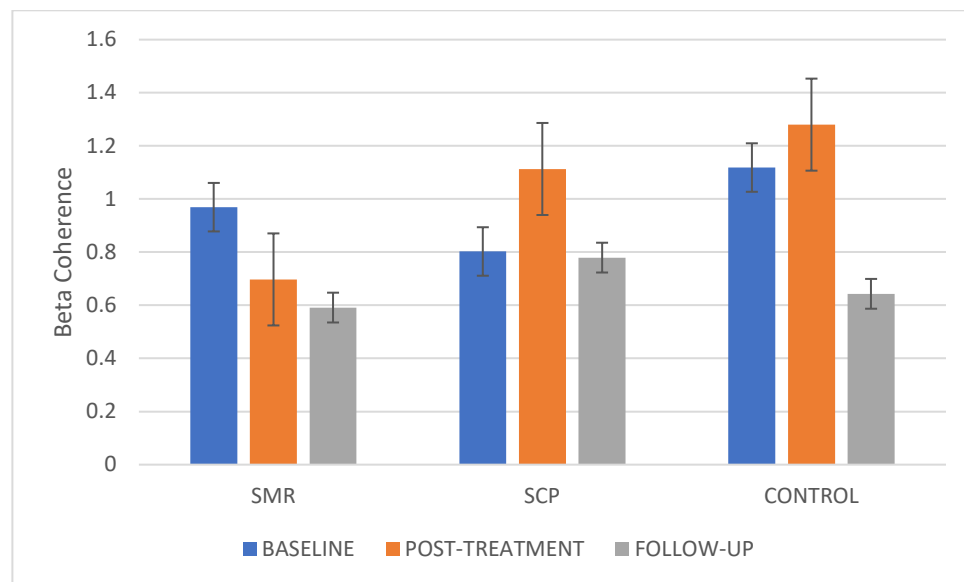


Figure 19. Mean beta coherence by group. The error bars indicate standard error of the means.

Cognitive Variables

The attention switching task was divided into four variables: letter category reaction time, letter category error rate, letter counting reaction time, and letter counting error rate. A 3 x 3 mixed ANOVA was conducted in all these variables.

For *letter category reaction time* within participants analysis showed a significant main effect of time [$F(2,82) = 7.043$, $MSe = 4.5$, $p = 0.006$, $\eta_p^2 = .147$], and for participant group there was a significant main effect as well [$F(4,82) = 3.319$, $MSe = .652$, $p = 0.046$, $\eta_p^2 = .139$]. There was no significant interaction effect [$F(2,82) = 1.35$, $MSe = .352$, $p = .269$],

There was a significant improvement from baseline to post-intervention ($p = .015$) and baseline of follow-up ($p = .041$). The SMR group showed significant improvement in the letter category reaction time from baseline to post-intervention compared with the other groups (see Figure 20).

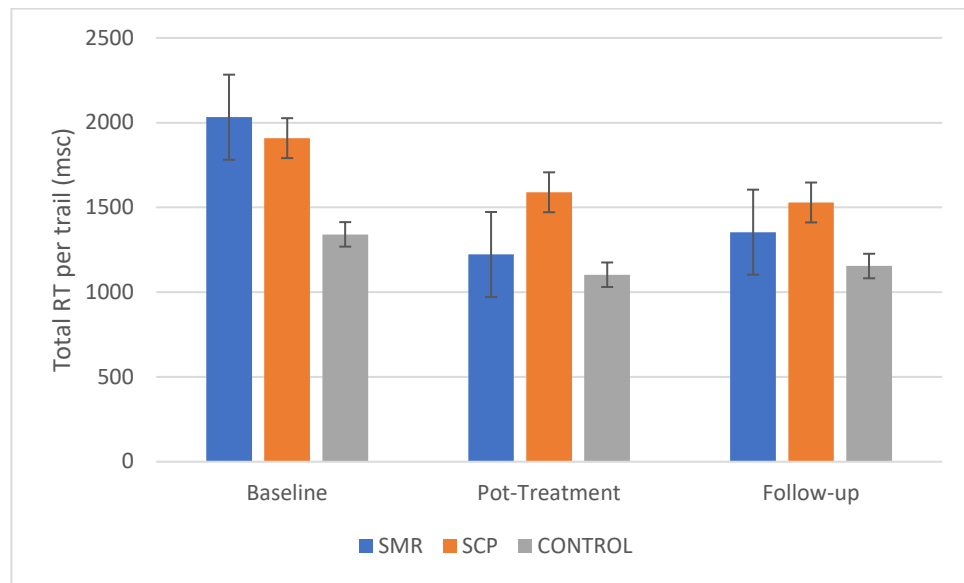


Figure 20. Total reaction time per trial by group. The error bars indicate standard error of the means. *statistical significant $<.05$.

The *letter counting reaction time* showed no significant interaction on time [$F(1,41) = 1.028, p = 0.367, MSe = 22.2$]; however, there was a significant interaction between groups [$F(2,82) = 11.346, MSe = 10.8, p = 0.000, \eta_p^2 = .217$] and no significance on the main effect [$F(2,82) = .737, MSe = 14.7, p = .569, \eta_p^2 = .139$]. Average reaction times for pre-intervention were significantly higher than the average reaction times for the post and follow-up timepoints. The SMR group showed significant improvement in the letter counting reaction time from baseline to post-intervention compared with the other groups (see Figure 21).

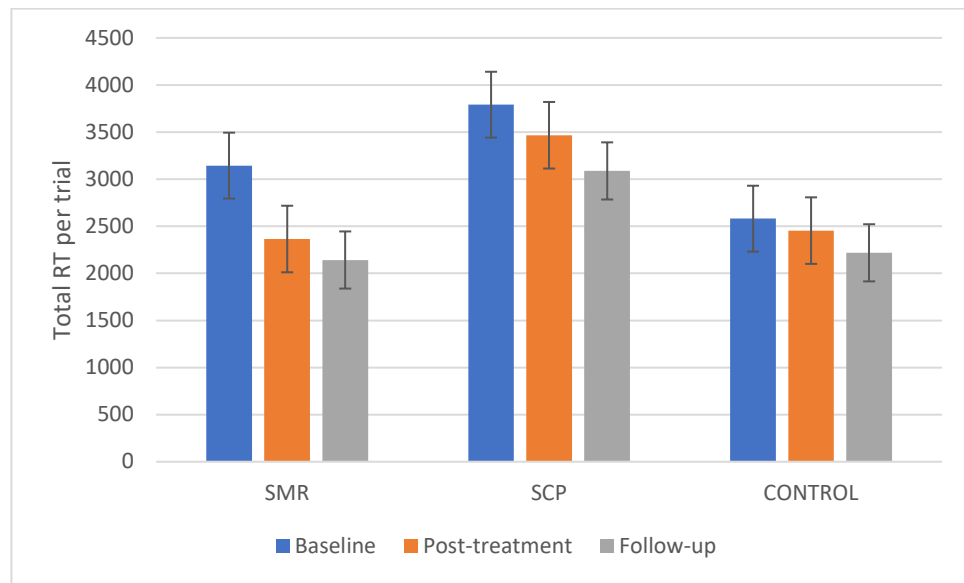


Figure 21. Total reaction time per trial by group. The error bars indicate standard error of the means. *statistical significant $<.05$.

Error rate in letter category there were no significant main effects ($p > .10$) or interaction effects ($p > .5$). There was no effect of time [$F(1,41) = 1.330$, $MSe = 52.6$, $p = 0.276$] or group [$F(2,82) = .849$, $MSe = 13.6$, $p = .482$] or interaction effect [$F(2,82) = .849$, $MSe = 16.05$, $p = .482$].

For *Error rate in letter counting* there were no significant main effects ($p > .10$) or interaction effects ($p > .5$). There was no effect of time [$F(1,41) = 1.504$, $MSe = 22.1$, $p = .228$, $\eta_p^2 = 0.35$] or group [$F(2,82) = 1.504$, $MSe = 10.8$, $p = .228$, $\eta_p^2 = 0.35$]. However, there was a significant interaction effect [$F(2,82) = .737$, $MSe = .564$, $p = .035$].

Neurofeedback Learning

In the SMR group, the neurofeedback learning was measured using the mean absolute power of theta and SMR of each session (25 sessions). This analysis explores the ability to learn to modify theta or SMR over sessions (reduce theta and increase SMR). A

regression analysis was used to evaluate the mean absolute power of theta over 25 sessions. As a group, sessions were not a significant predictor of theta absolute power showing a neutral relationship ($p = .909$) (see Figure 22).

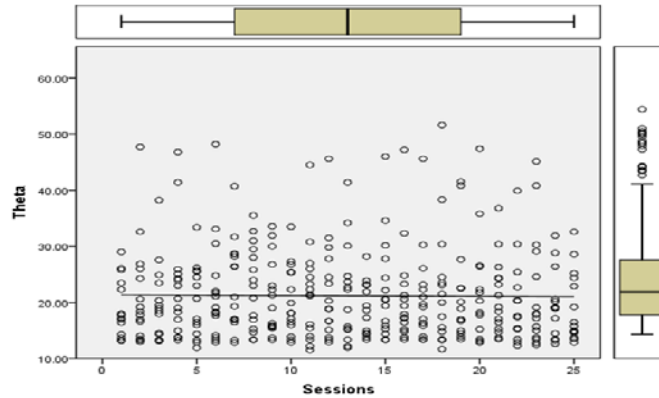


Figure 22. Scatterplot showed a linear regression of mean absolute theta over 25 sessions of the SMR group.

A regression analysis was used to evaluate the mean absolute power SMR over 25 sessions. As a group, sessions were not a significant predictor of SMR absolute power ($p=.916$). Even though there was no positive correlation, the effect of the outliers showed an effect due the variability over session. In this analysis, all participants (responders and non-responders) were included (see Figure 23). Only 50% of the participants were responders (participants that learn to modify their brain activity in the desired direction).

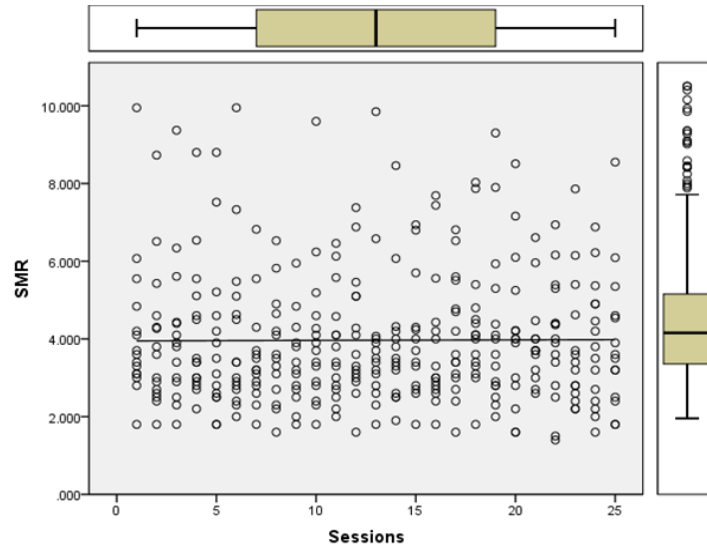


Figure 23. Scatterplot showed a linear regression of mean absolute SMR over 25 sessions of the SMR group.

In the SCP group, the neurofeedback learning was measured using the success number of successful trials by session. 80% of the participants were responders in this group. Regression analysis was used to evaluate the successful trial per session over 25 sessions. As a group, sessions were a significant predictor of total successful trials ($p < .001$). This indicates that the phenomenon of learning acquisition over the sessions was present. However, this information did not show significant improvements on other variables in the SCP group (see Figure 24).

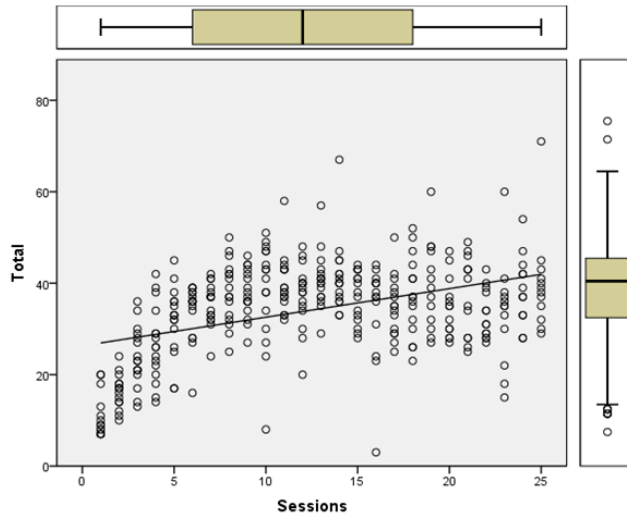


Figure 24. Scatterplot showed a positive regression of mean absolute theta over 25 sessions of the SCP group.

It is important to mention that the parameters used on the two groups are not equal as in SMR measures brain activity and the SCP is an objective reward.

Associations Between Neurofeedback Learning and Cognitive Functions

As only the SMR group showed the significant improvements in letter category reaction time improvement over time, the association between neurofeedback learning and cognitive function was analyzed in this group and this variable.

For the SMR group the mean difference in Theta between the first and last session and the mean difference in reaction time between the baseline and follow-up session were correlated.

Only theta showed a positive correlation ($r = .949$) between the relationship of theta and reaction time. The correlation was significant ($p = .017$). For the purpose of this correlation, only the participants who learned to reduce theta absolute power were included

(50% responders) (see Figure 25). The correlation was weak to determine the relationship between SMR and average reaction time per trail ($r=.063$) ($p = .846$).

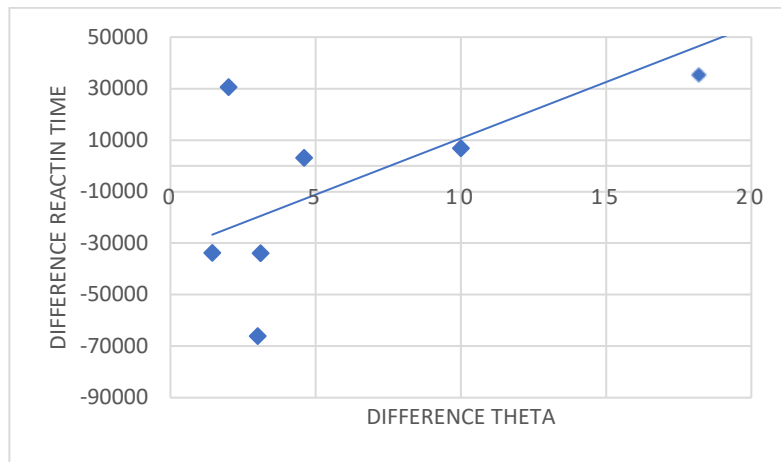


Figure 25. Scatterplot showed a positive correlation between the difference of average reaction time versus difference in theta.

Chapter 7 Discussion

The objective of this study was to evaluate the effect of two different types of neurofeedback on children with focal epilepsy. As was mentioned in the previous chapters, epilepsy is a complex condition with various comorbidities. These issues are poorly addressed during medical treatment, and are far more devastating than the seizures themselves. During this study, the exploratory outcomes were broader than those of previous studies of neurofeedback and epilepsy (Kotchoubey et al., 1996; Kotchoubey, Blankenhorn, Fröscher, Strehl, & Birbaumer, 1997; Nagai, 2011; Serman & Egner, 2006; Strehl, et al., 2014). The outcome of the present study expanded to clinical, neurophysiological, and cognitive measures comparing two neurofeedback modalities.

Clinical Outcome

Seizure Frequency

The results demonstrated a positive but non-significant trend in the reduction of seizure frequency among the groups. Although both active interventions showed a bigger reduction than the control group, the lack of statistical significance may be associated with the degree of variability in seizure events, which a minimum threshold in the number of seizures might be necessary to capture the real effect of the active interventions once the frequency is decreased. These results did not reach statistical significance in both active groups, even though a positive response was observed in seizure frequency. This could be a consequence of various factors: small sample size, standard protocol (reinforcing and inhibiting the same frequencies for all participants on the same location), number of

sessions, rate of non-responders, and the age of the participants. It is important to consider that the patients were exposed to research staff for a long period of time, hence leading to potential bonding and positive interactions between participant and researchers. All of this might have affected the development of placebo effect, which can be regarded as a form of “experimental subordination” consider when the participant wants to please the researcher based on his own expectation towards the experiment in the relationship with the researchers themselves. (Kienle & Kiene, 1997).

The clinical experience has shown that the more individualized the protocols are for patients with epilepsy, the more efficient and faster response to the intervention. This study did not consider individualized protocols. Previous research has utilized a standard protocol over the sensorimotor cortex (Tan et al., 2009). The number of sessions also can be a factor, even if most researchers suggested that 25 sessions could be enough to consolidate neural circuits, there are many other neurofeedback and epilepsy studies that did a long-term intervention (10-12 months) (Serman & Egner, 2006). The age of the participants in this study is younger than any other study that has been published with Neurofeedback and epilepsy (Schwartz, 1973). The changes of brain activity and chemical changes through adolescent will be discussed below.

For the clinical interpretation, to have a positive trend of in the reduction of seizures is an important factor and worth exploring. Both active intervention groups showed a positive trend in seizure reduction that could be considered in future studies.

Improvements of the control group is also expected, since the placebo effect of epilepsy is well known to be as high as 20%. In addition, this effect is as high 45-62% in

other neurological conditions (Bittar & Nascimento, 2015). The placebo effect observed during this study will be discussed in detail below.

Seizure Severity

The seizure severity did not demonstrate any statistically noteworthy variation among the groups due the same reasons mentioned above (small sample size; standard protocol, number of sessions, rate of non-responders and age of participants). The SMR group exhibited a tendency of reduced severity in seizure shortly after the intervention was provided, and this status was maintained during the follow-up period. Indicating that the effect of the neurophysiological process remained for many days after the intervention. Again, the modifications in the SCP were not evident, perhaps because of the underpower sample size, or because the participants were in controlled environment that involved pharmacological treatment.

In addition, it was important to consider the impact of age on seizure severity and seizure frequency. Previous studies included participants who fell into the adult age range while in this study included children suffering from epilepsy. Evidence showed that variation of brain activity is maximized during adolescence. Changes in white matter, grey matter, GABAergic systems and neurotransmitter systems are more evident in the age range of the participants in this study (Craiu, 2013).

The clinical experience showed that when used individualized protocols the first improvement in seizures we can observe is the seizure severity. In the following order; reduction of the post-ictal state, then more presence of aura or anticipation of the seizure so

the person can find a safe place to be during the seizure, finally a conscious control over the seizure, and seizure reduction as a result. These are consistent clinical observations that are encouraging for future researchers to consider.

Quality of Life

One of the main objectives of any medical treatment should be to improve the daily life of those patients who suffer from a specific medical condition. Patients with epilepsy undergo treatment not necessarily due the seizures but to improve their lives.

Unfortunately, once the patient is seizure-free, their physician typically does not offer other interventions to improve their QOL. Other interventions that can be offered include psychological, psychiatric, and social counselling. The options for treatment should also include multidisciplinary work and early intervention. Regrettably, as many cases are complicated, many institutions do not feel capable of providing treatment. Few settings offer cognitive training as an important intervention to treat epilepsy (Vermeulen, Alpherts, & Aldenkamp, 1993). It is important to notice how control or support in relation to emotional stress can dramatically improve the progress of epilepsy and that a group therapy intervention can reduce SF up to 70% (Williams, Gold, Shrout, Shaffer, & Adams, 1979). Other researchers also found that psychoeducational intervention can reduce seizures (Oosterhuis, 1994).

With this evidence, there is support for the importance of valuing all the aspects that a neurofeedback intervention can offer to a person with epilepsy. Any other intervention treats single symptoms, while neurofeedback broadly treats comorbidities that affect epilepsy.

Jacoby et al. reviewed QOL in various AED studies and compared patients in standard or new epileptic drugs. The study involved 2,437 participants and a two-year follow-up and did not find consistent differences in QOL outcomes between groups. In addition, the authors found that the individual response to a drug is more important for QOL than type of drug given to the patient. Also, proposed that the most significant improvement in QOL is the early withdrawal of medication after seizure remission, treatment for single seizure and early epilepsy (Jacoby et al., 2015)

In this study, the results revealed a statistical significant improvement in QOL among the three intervention groups. The QOL scale measured health, relationships, social life, academics, self-esteem, and family activities; even if the results only measure the sum of all of these, all areas were greatly improved in all three groups. The control group showed significant improvement as the placebo effect was strong in relation to this variable.

Previous studies exploring the effects of expensive interventions versus placebo-controlled groups, have revealed strong placebo responses; for example in patients with knee osteoarthritis and vertebral fractures (Moseley et al., 2002; Wali et al., 2017). It is possible that expectations regarding treatment are affected by the exposure and presence of impressive and expensive medical apparatus. These factors must have a profound influence on complex emotional and cognitive interactions to the point that pain is controlled and function improved even in the presence of structural and mechanical problems. It has been demonstrated that neural networks involving placebo responses extend its activation pattern beyond their anatomical and functional circuitry boundaries. For instance, sham analgesic

interventions not only activate the rostral anterior cingulate and the periaqueductal grey area where analgesic opioid receptors are stimulated to promote analgesic responses, but also the dorsolateral prefrontal cortex and the nucleus accumbens where expectations and reward responses are modulated respectively (Zubieta & Stohler, 2009). The placebo effect will be discussed in further details later on.

It is probable that a person diagnosed with epilepsy and treated with neurofeedback has would improve their QOL based on these results, and this can be considered an important contribution to the field and patients. The QOL scale was measured only on two occasions as the specifications of the use of the scale is that cannot be used more often than three months apart. The scales were compared three months after intervention and the improvements were significant.

It is important to consider the factor of social desirability as in the consent form mentioned that the intervention may offer some improvements (T. J Kaptchuk et al., 2008). This is the likely reason why the control group had significant improvement in the QOL scale. For a clinical trial, it is important to acknowledge the power of this effect and value it.

There is a possibility that when participants attempted to recover function of the body organ that is responsible for their disability, and they actively work on this intervention, they can achieve a better QOL outcome in comparison to passive intervention (AED).

Neurophysiological Outcome

Many researchers have studied the impact of neurofeedback on EEG. All the studies addressed the behavioral outcome of the participants (Arns, Conners, & Kraemer, 2013). Thus, there emerged an understanding that when brain receives training, such action can be correlated with clinical outcomes. Several researchers demonstrated that no significant changes in absolute power of the brain were seen, although improvement in coherence was observed (Mosanezhad Jeddi, & Nazari, 2013). Also they hypothesized that modification of coherence occurs prior to the modification of the absolute power. This phenomenon occurs due to neuroplasticity through networks rather than in the single sites. Legarda, McMahon, Othmer, and Othmer (2011) proposed that the reinforcement challenge during neurofeedback aims to regulate the *set point* of arousal level in an individual. It also aimed to reach a long-term stability in the habitual arousal state of individuals. In this process, enhanced stability was accomplished because the challenge led to a system of resting state networks. During this stage the nervous system network coherence was revealed when feedback was received while shifting the signals.

The present study did not demonstrate statistical significant improvement either in absolute power or coherence; only the SMR group showed a positive trend on beta coherence. This could be due to small sample size, number of sessions, rate of non-responders, age of participants, and standard protocol.

Up to today, there is still a lot of controversy about the changes in, or improvement of, QEEG measure after neurofeedback (Simkin, 2016). Empirical and clinical experience are showing that by using adequate procedures and analysis it is possible to achieve

changes in QEEG measures, for research purposes are more difficult to standardize this procedure.

Cognitive Outcomes

There are no therapeutic interventions for epilepsy that can impact more than one neurological symptom. Seizure frequency can be reduced with AED, but other neurological and psychiatric side effects prevail. In order to obtain productive and active life, cognitive enhancement is of utmost importance for epileptic patients.

The active sensor was located in the primary sensorimotor cortex (Cz) among all the participants of the intervention groups. Binkofski et al. (2002) showed functional studies confirmed that this particular region of brain was related to movement organisation, understanding, anticipation, organisation, planning, imitation, social behaviour, motor response, and inhibition. All these functions are involved in performing attention switching tasks.

The SMR group demonstrated significant improvement in reducing the reaction time of two variables; letter category and letter counting task, thereby showcasing improvement in time after the follow up. The SCP and control group did not show this pattern. This could be due to the technical limitations of the SCP procedure as explained below.

It is important to mention here that the SMR group showed an advantage over the other two groups and placebo effect did not apply here as other variables did. So, it has been demonstrated that the placebo effect is more evident in subjective measure than objective measures (Wechsler et al., 2011).

Neurofeedback Learning and Associations

Even though it was not one of the objectives of this study, focusing on neurofeedback responders versus non-responders was important in order to separate them for the correlation analysis. In the SMR group, 50% were responders versus 80% in the SCP group; the parameter are not compatible, so it not possible to do an exact comparison for the two groups in this regard. Even though the SCP group had more learners, it did not show statistical significance for any variable other than QOL. This may be due the technical issues that are explained below in the limitation section.

The only variable that showed significant positive correlation was the SMR group responders between the mean difference of absolute power theta over training and reaction time. There was not a statistically significant correlation between SMR and reaction time and this can be due to neurophysiological effect that is evident during neurofeedback which is easier to learn to reduce theta than reinforce SMR (Mohammadi, Malmir, Khaleghi, & Aminiorani, 2015). This positive correlation between reduction of absolute power theta over training with reduction of reaction time is what as expected neurophysiologically as theta can be a predictor of cognitive performance (Hermens et al., 2005).

Placebo

The results showed statistically significant positive effects in the QOL measures in the control group. Placebo effects are known to be larger for medical devices and

technology and for invasive treatments (T J Kaptchuk, Goldman, Stone, & Stason, 2000) . Researchers have observed that various neurobiological and psychobiological mechanisms are involved in the placebo effect, especially through the neural circuitry associated with reward. Furthermore, positive responses to placebo have been shown to involve networks associated with expectations to the treatment (Bittar & Nascimento, 2015; Colloca & Miller, 2011). Similarly, the two most prevalent psychological models that explain placebo effects are based on theories of expectancy and conditioning. Expectancy is usually thought of as a consciously accessible belief in the effectiveness of a therapy, while conditioning posits that previous experience taking (and benefitting from) effective medication or intervention (unconditioned stimulus) conditions an individual to experience benefit (conditioned response) in response to taking a pill or being exposed to a medical procedure (conditioned stimulus). These findings and models represent a complex system that responds and reacts to the presence of a fake or sham intervention (Albring et al., 2014).

Jütte (2013) argued that since ancient times, the placebo effect recognized as an element of medical praxis. Physicians from the Roman Empire knew that some bizarre forms of treatment were effective. Treatment for epileptic seizures then included peculiar interventions such as pouring bile of dark vulture in old wine, or drinking blood mixed with incense, lamb bile, honey or ashes from a weasel. Alternatively, rainwater collected in a human skullcap in supine position could be consumed. Seizures were also controlled by picking up pebbles from a swallows' nest and hanging those pebbles around the neck of the person suffering from epilepsy. Incredibly, all these treatments provided relief from seizures as reported in historic medical documents (Jütte, 2013).

What these bizarre treatments arguably represent is the construct of a healing ritual associated with the care of a malady (Ted J. Kaptchuk, 2002). If the intervention has positive results, patients will associate that response with the ritual and the intervention. Thus, the conditioning goes beyond the simple act of drinking a repugnant pottage that may have a strong conditioning effect due to sensory overload, or to a very ineffective intervention such as collecting and drinking water in a skull. Instead, the whole experience is enhanced by the complexity of the ritual, its symbols and human interaction with the healer. Medical rituals have a strong effect on therapeutic responses. Studies in analgesia response have shown that hidden injections, which is when medication is administered by an automatized infusion pump, are significantly less effective and less variable compared with open injections in full view of the patient, suggesting that part of the clinical response and its variability was due to non-specific factors (exposure to the medical ritual of a nurse providing a painful injection to mitigate a painful condition) (Amanzio, Pollo, Maggi, & Benedetti, 2001; Colloca & Benedetti, 2005) .

In the study reported here, it could be argued that both the real neurofeedback interventions and the sham group carried a strong medical ritual experience. The experimental procedures represented the contemporary technological equivalent of an ancient remedy, and this resulted in expectations regarding the intervention that were similar to treatment expectancy observed in medical praxis. Moreover, the uncertainty of being randomized to either of the experimental groups may have influenced the response to subjective outcomes. Previous work showed that for patients with Parkinson's disease, expectations of dopamine release enhanced reward learning and modulated learning-related

signals in the striatum and the ventromedial prefrontal cortex (Schmidt, Braun, Wager, & Shohamy, 2014). These effects were selective to learning from reward, showing that patient's expectations shape their learning and affect their placebo response.

Shapiro and Shapiro (2000) reviewed information regarding medication and procedures that were available across different historical eras, cultures, and societies. The authors found that even bizarre medical interventions that remain ineffective were believed by patients to be effective. This belief was reinforced with the event that comprised of real clinical improvements. These improvements were seen as normal remission or progress of the illness itself among the epileptic patients. When patients presented anxiety at that time the symptoms were relieved, or a true psychobiological placebo effect could be observed.

The *placebo effect* is a positive outcome that results a sham intervention. These improvements are a consequence of various factors, such as spontaneous improvement, statistical regression to the mean, psychosocial factors, biases, and co-interventions. The real *placebo effect* is the significant improvement that occurs due to psychosocial factors (Finniss, Kaptchuk, Miller, & Benedetti, 2010). Thus, it can be referred to as the improvement in the group that received placebo and can be elucidated that the placebo effect can improve the condition even if the cause is unknown to the patient. It can be a spontaneous regression of the symptom, a real active involvement of the brain while it anticipates the outcome, or it might also represent a biased report of the patient who aims to please the doctor, researcher, or family members (Benedetti, 2014).

Lately, many scientists have tried to distinguish the placebo effect from other phenomena that were observed in the clinical trials. In modern medical practice, a placebo

effect is registered only when positive outcome is measured on a sham group. Such studies emphasize the interaction between mind and body, a research area with particular significance in psychotherapy (Piersma & White, 1985).

Brody (2000) defined the placebo effect as a change in the body, or the body-mind unit. This effect occurred as a consequence of the symbolic significance which one attributed to an event or object in the healing environment (Brody, 2000). The therapeutic context of placebo effect induced expectations which, in turn, gave rise to experience and behavior (Price et al., 1999).

Understanding the placebo effect poses a challenge, because many mechanisms vary in the medical condition and therapeutic interventions. When conscious physiological functions are involved, expectations and anticipations of clinical benefits become prominent. Another crucial mechanism is anticipation of future outcomes (Tracey, 2010). Expectations drive cognitive readjustment of behavior. Positive expectation is also involved in adopting particular behavior. In addition, Staud and Price (2008) argue that memory, motivation, and the meaning of the experience related to illness prompt further expectations, leading to placebo effects.

From a neuroscientific viewpoint, expectations of a future event are associated with many structures and process of the brain. Neuronal networks of reward mechanism are linked with all types of responses, such as cognitive, emotional, and motor responses. In order to modulate behavioral responses, dopaminergic cells in the brain's ventral tegmental area are coupled with projections to the nucleus accumbens of the ventral basal ganglia that respond to the anticipated reward (Mogenson & Yang, 1991).

Any medical treatment or intervention that is performed in routine medical practice has two components, one related to the specific effects of the treatment itself and the other related to the perception that the therapy is being administered (Donald D Price, Finniss, & Benedetti, 2008). This is particularly the case when the therapy or intervention involves such a complicated set of processes as used in the current study, such as attaching electrodes to the head, calibrating computer software, presenting the animated stimulus with visual and auditory cues, and, importantly the constant presence of a therapist interacting with the patient. In this research protocol, the control group was presented with the same “rituals” of a modern technological therapy, and was also in the presence of the research technician mimicking the application of what was supposed to be an active therapy. Today there is increasing evidence that beliefs and expectations, which are associated to the therapeutic procedure *per se*, can play a salient role in human health, and placebos can mimic, enhance, and mask the beneficial responses to pharmacological agents or medical interventions associated with technology (Benedetti & Amanzio, 2011). Arguably, the patient-technician interaction played a role in the psychosocial context around the experimental procedure. It seems reasonable that patients in the control group were not responding to the sham pre-recorded session presented on the computer screen, but rather, they were responding to the symbolic significance of being part of an experiment involving fancy technology. Moerman (Daniel E Moerman & Jonas, 2002) proposed replacing the term “placebo response” with “meaning response”, thus highlighting that what matters is not the inert treatment or sham intervention *per se*, but rather the meaning of the surrounding context and of the therapeutic ritual. This meaning

response is enhanced by patient's beliefs and the expectancy that the intervention will provide a positive effect, a bias inherent in any clinical trial and a major source of "statistical noise" when comparing the effects of an intervention among experimental groups (D E Moerman & Jonas, 2000). Moreover, the human interaction associated with the experimental procedures might have had a special boosting effect on the placebo response, as patients with epilepsy usually are marginalized and disaffected. For such patients, a bonding with the experimenter might have served as surrogate of meaningful social relationship, otherwise not present in their daily life.

It is important to consider that the strongest placebo response was observed in the QoL outcome, which is considered a subjective measurement and prone to be influenced by patient's expectations and beliefs regarding the experimental procedures. In contrast, with other measures, specifically the objective measurements as in the case of physiological variables or cognitive performance metrics, the control group did not show that level of response when compared with the active interventions. The same degree of responsiveness to subjective measurements in the control or sham group can be observed on pain, anxiety, or sleep scales, but this effect disappears when objective measurements are applied.

These findings demonstrated that a dynamic and "ritualistic" intervention may have a strong effect on the sham or control group, especially when parents are responding to the QoL questionnaire. It is not only these pediatric patients who are reporting improvements in their life, but also the parental perception of such improvements driven by their own expectations to the intervention generating a placebo by proxy response that has been

described in pediatric trials (Burkart et al., 2017) (Coghill, Banaschewski, Soutullo, Cottingham, & Zuddas, 2017).

Placebo in Epilepsy

Like other neurological diseases, epilepsy is a condition that is subject to placebo effect on randomized clinical trials. As is the case of increased placebo response observed in depression, anxiety and smoking cessation trials (Fava, Evins, Dorer, & Schoenfeld, 2003). Thus, a thoughtful approach to the placebo response and behavior in epilepsy is essential in order to explore the effectiveness of interventions among epileptic patients.

Rheims, Cucherat, Arzimanoglou, and Ryvlin (2008) argue that regression to the mean may have had a significant effect on the outcomes of a study as participants may have been likely to enroll in trials when the seizure increased momentarily, and thereafter the seizures returned to baseline levels when the placebo or treatment had some effect. There was evidence of the previous trial which mentioned that placebo response was more evident among children (Rheims et al., 2008).

Goldenholz, Moss, Scott, Auh, and Theodore (2015) evaluated three major placebo mechanisms in epilepsy: regression to the mean (statistical phenomenon when a variable showed extreme results in the first measurement there is a tendency of the second measurement to be closer to the average), ongoing improvement (natural history of the disease), and information bias (individual interpretation of the information about the trial).

These researchers were able to gather more data about the effect of this mechanism of placebo in epilepsy and medical devices.

The present study revealed a significant placebo effect with regard to QOL. The QOL is a self-report measurement of wellbeing. However, the results from this instrument are subjective and easily influenced by the responder's physical and mental conditions at the time the questionnaire is being filled in. The placebo effect is usually weaker when objective measurements are used as main outcomes. In a study investigating the effects of lidocaine injection for chronic lower-back pain, the sham injection group showed significantly better clinical responses, measured by the self-reported visual analog scale for pain (VAS), when compared to the standard treatment group (analgesic medication and physical therapy). However, this effect reversed for the sham injection group when the outcome was the pain pressure threshold, which is an objective measurement of pain tolerance expressed in kilogram pressure force over square centimeter (Kgf/cm²) (Albring et al., 2014).

If we consider those functions that affect the daily course of action when patients are diagnosed with epilepsy, then bringing improvement in them will be beneficial.

There is evidence that the placebo has greater strength in comparison to medical devices than pharmaceutical interventions, as the participants were actually involved in activities that could improve their condition. This is another benefit of these interventions (Redberg, 2014).

Limitations of the Study

The small sample size is a significant limitation of this study, as this is considered a pilot study that will require further trials. There are other important limitations of the study design as some of the variables were measured only twice instead of three as the rest. The population was of low socioeconomic status and did not provide information prior to the study. In addition, the participants had difficulties understanding the questions of the subjective questions measures and scales.

Another significant limitation for the SCP group was differences in the methodology compared with previous SCP studies. The average number of trials in previous SCP studies were 125 trials (Kotchoubey et al., 2001). In the present study, the total training period was for 30 minutes and 75 trials. The rationale for choosing this duration of training was that an average participant could remain attentive and cooperative only for 30 minutes. Thus, only 75 trials per session were conducted for the purpose of this research. In previous studies sessions were arranged in blocks and homework was given to the participants of the study (Strehl et al., 2010). There is a possibility that if the study had been conducted using more trials, then more modifications of these variables might have been observed.

The present study used standardized neurofeedback protocols as previous researchers had done. For future studies, it would be useful to consider individualized protocols for stronger effects. It is also important to consider that not all the epilepsy foci were identifiable for this study. This could be considered a weakness, which would suggest the inclusion of patients with well localized epilepsy foci, hopefully on the same location.

The consent form mentioned the possibility of experiencing benefits from participating in this study and could be considering a social desirability effect that affected the subjective measures. This statement is part of the required consent form and ethical considerations during a clinical trial and thus cannot be excluded. This factor of offering gentle attention, empathy, more duration of interaction are factors that are not avoidable and we expect some effect from them (T. J Kaptchuk et al., 2008)

Another limitation of this study was the lack of measure for expectations. Boot, Simons, Stothart, & Stutts (2013) (Boot, Simons, Stothart, & Stutts, 2013) explain the failure to control for expectations is a common problem in mental health and cognitive studies. They propose alternative methodology designs to find clearly effects of the interventions

Conclusions

This research presented preliminary data comparing the effects of two neurofeedback modalities on children with focal epilepsy. The novelty of this study was to broadly explore clinical, neurophysiological, and cognitive outcomes that no previous researchers have explored. The age of the participants (children and adolescents) is a strength of this study as all previous research was done on adults.

The first contribution to the field that it demonstrated that this is a safe, non-pharmaceutical, non-invasive intervention that should be more explored as a treatment for epilepsy. Safety is an important issue when considering a therapeutic intervention, and no side effects were reported during the study in any of the 44 patients,

The SMR group showed improvement in reaction time, which suggests that there is an effect on cognition that can be very helpful in everyday life activities. Also, there was a positive improvement in the SMR group that were able to learn to modify their brain activity and improve the reaction time during the attention task. Seizure frequency and seizure severity did not show statistically significant improvement, but it is important to mention that the trends were positive for the SMR group in these two variables. In addition, the seizure frequency did not increase, which illustrates the stability of epilepsy through the intervention. Quality of life improved in all patients, including the control group, which could be due to a strong placebo effect. This study showed long lasting effects until the follow-up evaluation. The results of this study also showed SMR neurofeedback has some advantages over SCP.

Considering the few interventions to help comorbidities at the same time as seizure frequency it is important to continue exploring this intervention in larger groups of people with epilepsy at different ages and with different types of epilepsy. Keeping in view the complexity of brain malfunction, there is also a need to try several interventions to improve comorbidities in epilepsy. More importantly, interventions should be developed that can help a patient and do not cause any harm to their well-being.

Based on the results of this study, continued research on neurofeedback as an intervention to improve comorbidities in epilepsy would be beneficial.

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Appendix A

QEEG Analysis Method

The QEEG analysis are classified in to linear and non-linear approaches, and there are dependants in which the analysis is based: time, frequency and time-frequency.

In the following section the different theories are explained for deeper understanding of the analysis.

Time Domain Methods

The EEG signal can be analysed mathematically using different domains. The time domain in EEG modelling has been categorized in to two methods: (Thakor & Tong, 2004).

- a) *Parametric methods*: this method assume that the EEG signal created by equations, but with none define coefficients. The autoregressive model and the sinusoidal model are used for the analysis. The most known model of classical sinusoidal model is the Fourier transform (FT), which characterises the EEG with a series of waves
- b) *Non parametric methods*: This method studies directly the wave form by measuring the variety in amplitude. Another parameter to study is the wave

energy; there is a direct way to evaluate the strength change inside the signal (Abásolo, Simons, Morgado da Silva, Tononi, & Vyazovskiy, 2015).

Frequency Analysis Methods

EEG frequency analysis or also known as power spectral analysis. The purpose is to divide the EEG signal in various frequency bands: Delta wave (0.5~4 Hz), Theta wave (4~8 Hz), Alpha wave (8~12 Hz), Beta1 (12~18 Hz), and Beta2 (18~30 Hz).

Spectral analysis has been in use as a diagnostic instrument. To measure the Spectral can find directly the PSD (power spectrum density) or the DFT (discrete fourier transform) which is fast algorithm of FFT (Juhász, Kamondi, & Szirmai, 2009). The

power spectrum can be found by $\|X(k)\|^2 = P(k)$.

FFT-based spectral estimation is used then it is expected that the signal is stationary and do not change fast, and the limits ate the resolution and leakage effect (Muthuswamy & Thakor, 1998).

Time-Frequency Analysis Methods

The EEG signal is active, time fluctuating, temporary (spikes/bursts). These signals are, in general, non-stationary, and get disturbed by external noise. This analysis is needed due a pathological EEG.

To analyse epileptic EEG time-frequency analysis should be used. For localization of the source there is the need to find the increase of time resolution and short time (STFT) to increase the time resolution; where the signal is first measured around a time instant t , and the Fourier transform is calculated for each time. STFT is based on FFT so that the time resolution does not continue elevated. STFT suffers from interchange between its window length and its frequency resolution.

$$STFT(\omega, t) = \int_{-\infty}^{\infty} x(\tau)g(\tau - t)e^{-j\omega\tau} d\tau,$$

Appendix B

Criteria Checklist

Participant _____ No. _____

Inclusion Criteria	Si	No
Participant must be on the age range of 12-18 years old		
Diagnosed with focal epilepsy		
Don't have any other neurological disorder such as autism, ADHD, cerebral palsy, etc.		
Have at least 2 seizures in the last 6 months.		
Normal vision and audition		
Follow instructions		
No modification of medication during the trail and three months of follow up.		
Signed consent and assent form		
Availability for 25 sessions of intervention. One hour Monday-Friday)		
Exclusion Criteria		
Taking Vigabatrim		
Diagnosed with a systemic decompensated disease (diabetes, etc.)		

Appendix C

Initial Assessment Checklist

Participant ID	Date
Initial Assessment	
Introduction	
Contact info	
Clinical History	
Medication	
Criteria checklist	
Preparation for the EEG	
Consent forms	
Neurological Evaluation	
Review of medical records	
EEG procedure	
Attention switching test	
Seizure diary	
Protocol assignment	
Head measurements	

Appendix D

Localisation of the Foci/demographics

No.	CONDITION	GENDER	AGE	LOCALIZATION	AED 1	D/24H	AED2	D/24H	AED3	D/24H
1	SMR	M	18	UNK	NA					
2	SMR	F	15	TL	CBZ	600	LM	200		
3	SMR	M	13	TL	OX	600				
4	SMR	F	17	UNK	VA	1200	CBZ	900		
5	SCP	F	12	UNK	VA	1500				
6	SCP	F	13	UNK	VA	900	LV	2000	TP	300
7	Control	M	12	TL	VA	600	LM	200	CBZ	200
8	Control	F	13	UNK	VA	800				
9	Control	M	16	T/P	CBZ	200	LV	1000	DZ	10
10	SMR	F	14	T	PH	100	LM	100		
11	SCP	M	18	UNK	LV	1000				
12	SMR	F	12	P	VA	800				
13	SCP	M	15	T	VA	1200				
14	Control	M	12	P	LM	200				
15	SCP	M	12	UNK	NA					
16	SCP	M	12	T	PH	800				
17	SMR	M	12	TL	LV	1000	DZ	10	VA	600
18	SCP	F	12	UNK	VA	600				
19	Control	F	13	UNK	VA	800				
20	SMR	M	18	UNK	VA	800				
21	SMR	F	17	UNK	VA	600				
22	SCP	M	14	UNK	PH	200				
23	SCP	F	15	UNK	VA	500				
24	SMR	M	16	TL	VA	1400				
25	Control	F	18	UNK	VA	400				
26	Control	F	18	UNK	VA	800				
27	Control	F	14	T	VA	600	OX	600	LV	1000
28	SMR	F	18	UNK	VA	600	LV	1000		
29	SCP	M	18	TL	LV	1000				
30	Control	M	15	T	VA	800	PHY	200		
31	SMR	M	13	UNK	VA	400				
32	SCP	M	16	T	CBZ	800	DZ	5		
33	SCP	F	14	T	NA					
34	SMR	F	14	TL	VA	600	CBZ	100		
35	Control	M	15	T	LV	1000				
36	SCP	M	16	P	VA	1200	CBZ	400		
37	SMR	M	13	UNK	PH	200				
38	SCP	M	15	T	VA	400				
39	Control	F	13	TR	CBZ	200				
40	SCP	F	18	UNK	VA	800				
41	SCP	F	18	UNK	VA	1200				
42	SMR	F	12	UNK	CBZ	250				
43	Control	F	18	UNK	VA	600	CBZ	200		
44	Control	M	18	UNK	CBZ	300				

Note: Condition, gender, age localization of the epilepsy foci (UN: unknown, TL: temporal left, TR: tempolra right, P:parietal), AED (NA: non, CBZ: carbamazepine, OX: oxacarbazepine, VA: Valproate sodium, LV: levetiracepam PH; phenobarbital, LM: lamotrigine, DZ: diazepam).

Appendix E

Consent Form

Title: Effects of Sensory Motor Rhythm and Slow Cortical Potential Neurofeedback in Epilepsy: A comparative study

Researcher: Principal Investigator: Diana Martinez, M.D., M.Sc.

Aim: The purpose of the study is to investigate if there are any benefits of Neurofeedback in patients with epilepsy and compare the two modalities.

Background: Previous studies have showed that the human is able to learn how to control physiological functions such as blood pressure, heart rate, body temperature and brain activity. Now we know that is possible for your son/daughter to learn to control their brain activity with an intervention known as Neurofeedback. There are previous studies that doing such an epileptic patient can have some benefits. But we are not sure how much or in which areas. This is the reason why the investigator wants to ask for your permission so your son/daughter can participate in this study.

Inclusion criteria: Your son/daughter need to fill the following requirement to participate.

- Diagnosed with focal epilepsy.
- Ages between 12-18 years-old.
- Do not have any other neurological diagnosis (autism, developmental delay).
- Normal hearing and vision.
- No need of changes in medication during the trail and three months follow up.
- Availability to complete 25 sessions of intervention.

Exclusion Criteria:

- If taking Vigabatrin.
- Other neurological condition.

Anticipated Benefits: It is important to understand that this is an investigation study and no a specific treatment for your son/daughter. Even though, based in previous experience and research had showed improvements in patients with epilepsy. If there are benefits with this collaboration Neurofeedback can be used for more patients with epilepsy.

Procedures: Your child will be evaluated to begin the Neurofeedback intervention, at the end of 25 sessions and after three months of follow up. These evaluations will include questionnaires, attention test and EEG. You will need to fill a diary and bring it every day of session and during the follow up.

During the Neurofeedback sessions your child will have some electrodes in the head, while they look to a screen; every time their brain activity works better they will see a visual and

auditory reward. The total time of a session is 60 minutes including set up time. None of these procedures are invasive.

Three Study Groups: This study includes three groups. Two of them will be exposing to one type of Neurofeedback and the third one will receive a sham intervention. The assignment to the groups will be random and blinded to the principal investigator. In case your child is in the sham group; Neurofeedback intervention can be provided at the end of the three months follow up at any cost.

Possible Risks:

- There are no significant or dangerous side effects for participating in this study.
- The equipment doesn't use electrical current to your child's brain.
- The electrodes in their head can be somehow uncomfortable.
- There are some skins that can react to the contact of the electrodes.
- Your child can experience some tiredness or light headache as if they just perform 60 minutes of cognitive effort.

Options to Reduce the Possible Inconveniences: The session will be terminated immediately if your child experiences any uncomfortable situation. The session will continue only if your child feels normal and they agreed.

The skin rash disappeared once the electrodes are removed.

Alternatives to Participate: Be aware that there are other therapeutic alternatives for your son/daughter:

- Antiepileptic drugs.
- Surgery.
- Vagal stimulator.
- Ketogenic diet.

Emergency: There will be emergency services if there is any situation that needed. Not related illness need to be treated my physician.

Compensation: This study does not offer any compensation to the participants.

Privacy and Confidentiality: Only investigator of this study will review information about your son/daughter. Any information will be share with other professions without your permission only if your child is at any risk of request for law.

Participation and Termination: Your child participation in this study is voluntary. If you chose not to let your child participate you are free to do so. If you decide to participate you can stop at any time.

Termination Consequences: There is any consequence if your child interrupts their participation in the study.

New Information: The investigator will communicate any new information about the results of the study or if there are other optional treatments for your son/daughter.

Signing this form your child can interrupt their participating at any moment. If you have any questions you can contact the investigator.

Diana Martínez MD (researcher) Tel. (449) 9180701

I have read (or somebody read it to me) all the information in this form and I have asked all my questions. All my questions have been answered. I agreed my son/daughter will participate in this study.

NAME SUBJECT _____
SIGNATURE _____
DATE _____

FATHER'S NAME _____
SIGNATURE _____
DATE _____

MOTHER'S NAME _____
SIGNATURE _____
DATE _____

WITNESS NO. 1 _____
SIGNATURE _____
DATE _____
ADDRESS _____
RELATION WITH
SUBJECT _____

WITNESS NO. 2 _____
SIGNATURE _____
DATE _____
ADDRESS _____
RELATION WITH
SUBJECT _____

Appendix F

Child Consent Form

(For children 12 to 18 years-old)

Dear _____
Name of participant

The researcher of this study, Dr. Diana Martinez had explained to your parents about your participation in this project.

The reason we call it project is because we are looking for what's to find a new options to help your seizures and to improve your life. We are not sure if we will be able to do it; this is why we call it research.

We won't ask you to do something that would be uncomfortable.

You will wear a cap with some bottoms on the scalp; these bottoms will give us information about your brain and you will see in a screen some stimuli that you will learn how to manipulate them.

The researchers will teach you how to do it. This we call Neurofeedback.

Please talk to your family member before you decide if you want to participate in this study. We will ask your parents' permission for your participation but you can decide. If your parents said yes, you can say no.

You don't have to participate if you don't want to; this is your own choice. You can stop your participation at any time.

You can ask all questions that you need and the researcher will help you at any time.

Signing this you agreed with your participation in this study.

Participant Name _____

Signature _____

Date _____

Witness No. 1 _____

Signature _____

Date _____

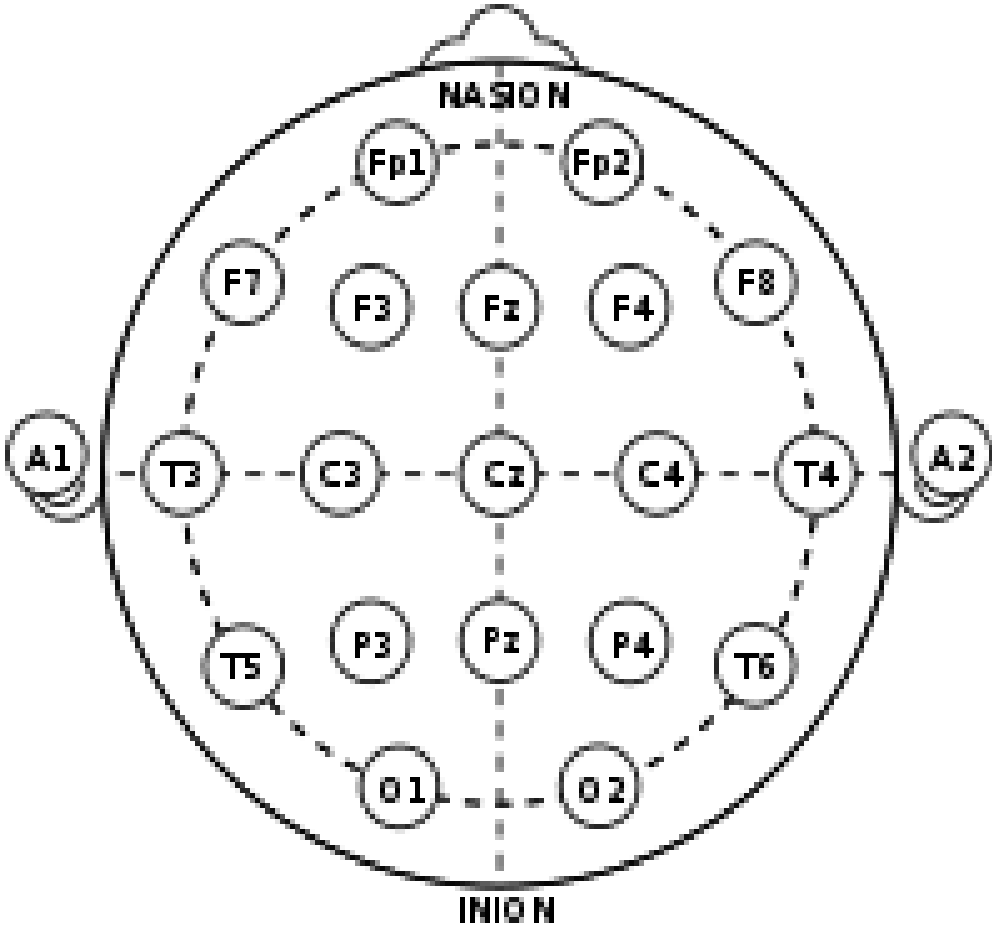
Address _____

Relationship with participant _____

Witness No. 2 _____
Signature _____
Date _____
Address _____
Relationship with participant _____

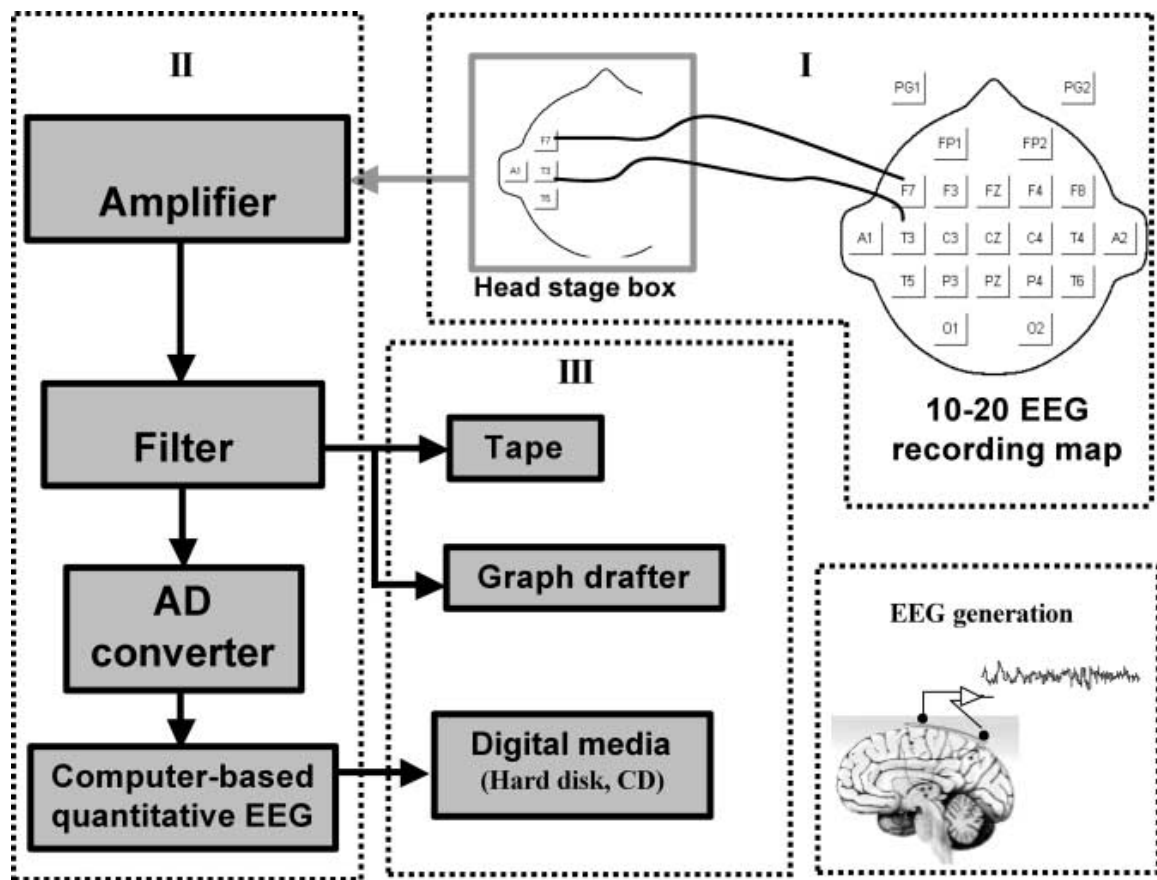
Appendix G

Electrode Localisation 10/20 System



Appendix H

Diagram of EEG Recording and Quantitative System



Note: (I) Headstage and electrodes, (II) preprocessing and qEEG, and (III) data storage system. The right bottom box illustrates the principle of rhythmical scalp EEG activities.

Appendix I

FFT Coherence

Montage: Laplacian				EEG ID: DAIEC2					
FFT Coherence									
Intrahemispheric: LEFT				Intrahemispheric: RIGHT					
	DELTA	THETA	ALPHA	BETA		DELTA	THETA	ALPHA	BETA
FP1 F3	0.70	0.54	16.98	1.39	FP2 F4	11.79	13.65	36.29	2.46
FP1 C3	3.36	2.88	3.29	0.12	FP2 C4	0.96	0.91	9.67	0.10
FP1 P3	21.98	8.84	34.37	2.81	FP2 P4	7.55	6.38	28.60	2.95
FP1 O1	0.36	1.78	8.52	1.67	FP2 O2	1.36	1.24	17.62	1.95
FP1 F7	2.95	2.17	4.53	1.66	FP2 F8	53.66	43.05	14.66	20.23
FP1 T3	7.66	1.65	8.95	1.31	FP2 T4	28.98	25.11	48.65	27.75
FP1 T5	2.41	1.80	3.94	1.72	FP2 T6	7.21	11.43	22.58	18.07
F3 C3	1.31	2.81	0.07	0.14	F4 C4	0.89	1.18	14.16	0.04
F3 P3	17.20	18.79	37.65	6.51	F4 P4	18.40	21.63	40.18	4.28
F3 O1	0.01	0.23	1.53	0.02	F4 O2	3.05	1.34	19.81	0.75
F3 F7	0.65	5.21	0.56	1.91	F4 F8	13.41	11.47	7.16	4.01
F3 T3	3.22	1.15	3.54	0.31	F4 T4	6.88	3.69	24.10	3.78
F3 T5	0.23	2.81	10.08	1.44	F4 T6	1.38	5.03	18.34	3.43
C3 P3	3.83	1.01	0.70	0.32	C4 P4	11.63	7.91	24.33	0.54
C3 O1	30.66	20.17	15.99	2.87	C4 O2	46.79	40.19	52.94	12.24
C3 F7	7.76	0.90	4.12	2.28	C4 F8	2.28	2.13	11.75	1.35
C3 T3	16.05	3.40	1.24	0.04	C4 T4	29.19	19.62	37.02	9.16
C3 T5	6.22	0.54	2.33	0.20	C4 T6	0.03	3.61	20.94	0.79
P3 O1	2.89	0.19	3.30	0.20	P4 O2	27.00	20.51	49.58	16.06
P3 F7	10.97	6.07	17.01	2.67	P4 F8	2.07	1.86	26.41	7.31
P3 T3	36.04	12.61	34.13	4.53	P4 T4	30.33	13.33	44.28	9.28
P3 T5	7.32	2.06	25.27	6.94	P4 T6	1.54	8.73	40.95	10.93
O1 F7	2.94	3.01	8.66	1.50	O2 F8	1.52	2.94	17.25	2.76
O1 T3	12.05	9.82	10.65	1.38	O2 T4	27.14	26.48	51.38	19.17
O1 T5	1.25	7.63	3.78	0.69	O2 T6	4.20	12.20	28.45	2.99
F7 T3	11.44	9.77	26.91	0.62	F8 T4	2.45	0.17	10.87	0.16
F7 T5	7.32	9.91	2.98	5.26	F8 T6	0.29	2.92	37.93	15.62
T3 T5	10.12	8.41	5.44	1.12	T4 T6	20.79	41.24	38.92	31.28
Interhemispheric: HOMOLOGOUS PAIRS									
	DELTA	THETA	ALPHA	BETA		DELTA	THETA	ALPHA	BETA
FP1 FP2	7.67	2.57	26.15	1.81	F3 F4	34.55	42.82	59.03	26.38
C3 C4	0.21	0.65	1.76	0.18	P3 P4	71.75	52.05	76.20	28.58
O1 O2	16.35	23.07	16.99	33.35	F7 F8	3.39	1.71	2.09	6.41
T3 T4	32.17	17.72	38.68	4.39	T5 T6	7.24	1.23	5.50	0.09

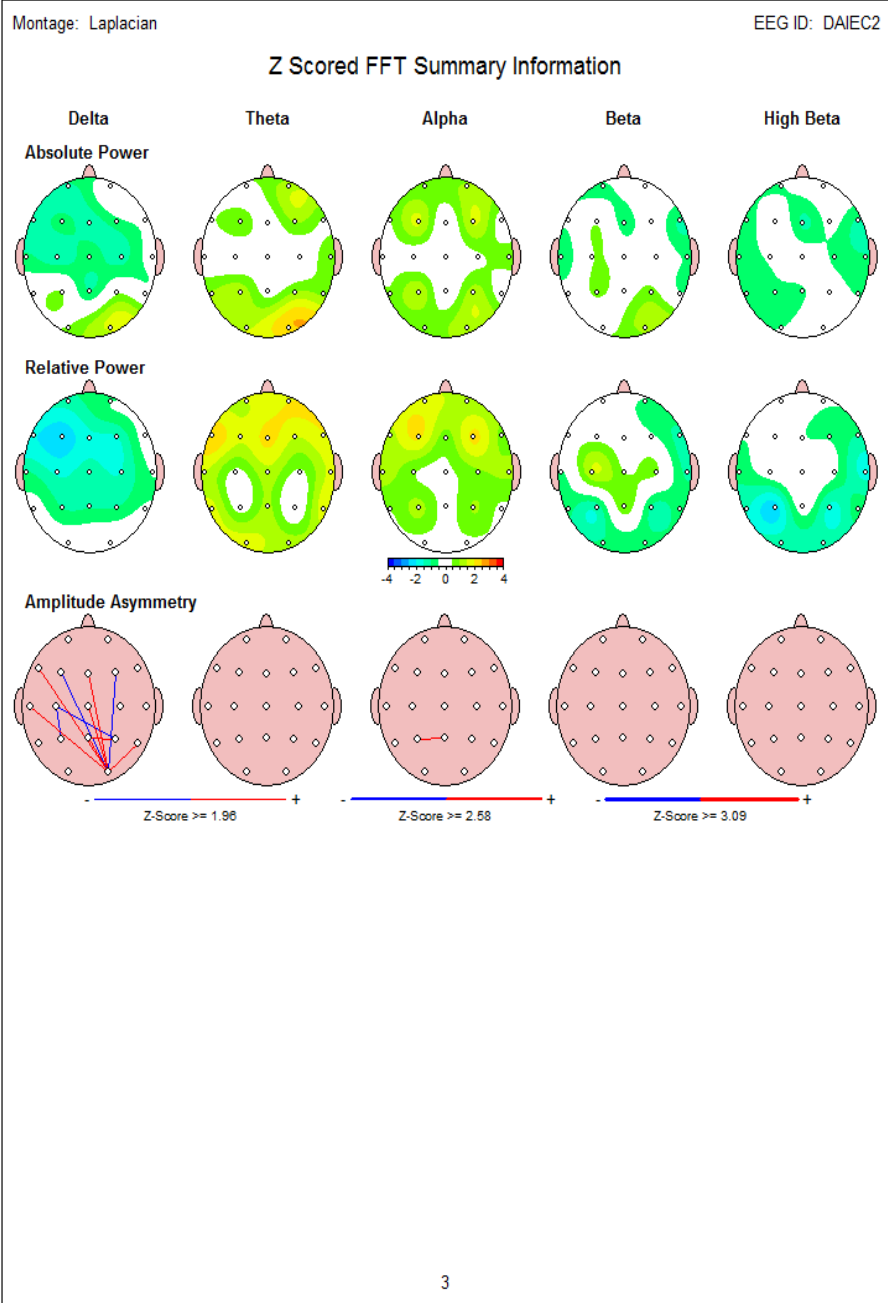
Appendix J

FFT Absolute Power (uA Sq)

Montage: Laplacian		EEG ID: DAIEC2						
FFT Absolute Power (uA Sq)								
Intrahemispheric: LEFT								
	DELTA	THETA	ALPHA	BETA	HIGH BETA	BETA 1	BETA 2	BETA 3
FP1 - CSD	215.23	197.34	194.88	114.10	33.94	39.41	25.75	48.94
F3 - CSD	305.73	524.01	468.76	335.07	64.78	146.83	80.94	107.31
C3 - CSD	73.34	121.74	182.67	240.42	24.21	117.98	32.10	90.33
P3 - CSD	557.46	785.03	2682.09	411.12	20.57	231.50	87.29	92.34
O1 - CSD	804.37	1269.51	2273.86	543.28	36.34	266.70	106.19	170.39
F7 - CSD	210.96	302.27	283.69	172.05	30.70	69.41	34.87	67.77
T3 - CSD	199.24	230.57	346.32	140.83	23.64	68.17	27.96	44.69
T5 - CSD	440.67	681.31	753.69	252.82	19.72	129.72	54.64	68.46
Intrahemispheric: RIGHT								
	DELTA	THETA	ALPHA	BETA	HIGH BETA	BETA 1	BETA 2	BETA 3
FP2 - CSD	555.82	478.30	364.61	188.40	53.22	76.87	40.09	71.43
F4 - CSD	356.34	558.46	520.93	282.17	49.71	125.02	57.97	99.17
C4 - CSD	81.43	135.14	300.43	201.04	21.45	91.95	31.24	77.85
P4 - CSD	565.19	731.09	3243.72	506.02	31.98	288.00	93.39	124.63
O2 - CSD	1748.53	2524.40	5138.57	1149.24	70.63	548.52	241.66	359.06
F8 - CSD	435.53	344.51	222.83	114.35	23.92	46.67	25.24	42.44
T4 - CSD	395.17	523.53	788.22	218.00	20.99	125.10	38.99	51.91
T6 - CSD	426.60	849.69	1135.82	295.60	30.93	153.30	63.97	78.32
Intrahemispheric: CENTER								
	DELTA	THETA	ALPHA	BETA	HIGH BETA	BETA 1	BETA 2	BETA 3
Fz - CSD	118.19	210.36	107.72	79.94	11.59	37.86	18.24	23.85
Cz - CSD	185.40	341.23	273.53	198.47	36.49	83.94	33.68	80.86
Pz - CSD	114.36	234.70	387.10	205.63	14.82	123.23	37.46	44.95

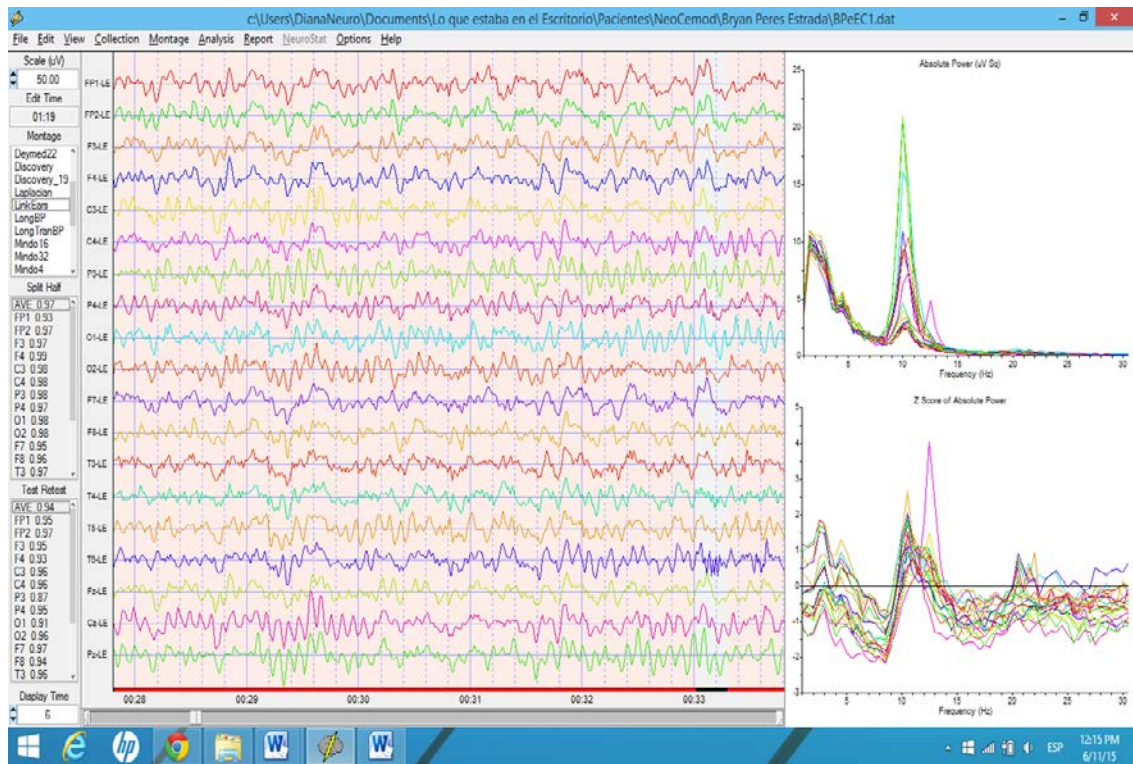
Appendix K

Z Score FFT Summary Map



Appendix L

Screenshot Raw EEG, Spectral Absolute Power and Spectral Z Score Absolute Power



Appendix M
Seizure Diary

Date:

Participant #

Day	Frequency	Duration	Intensity	Recovery
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
Day	Frequency	Duration	Intensity	Recovery
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
Day	Frequency	Duration	Intensity	Recovery
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				

Note: Frequency: How many seizures per day. Parents need to list them individually, so they can describe the duration intensity and reco from each seizure. *Duration:* Total time in seconds of the seizure. Family members need to have a clock close all the time to time e seizure. Include time of the day or night that the seizure happened. *Intensity:* Rate the degree of each seizure from 0 to 5; being 5 the most intense seizure the participant has ever had and 0 weak. *Reco:* Total time that the participant takes to recover all functions (language, mobility, behavior, attention, eye contact, awareness, etc). This time includes any sleeping time the patient needed after the seizure.

Appendix N

Liverpool Seizure Severity Scale

Item	Variable
Percept subscale	
1	Timing (specific or any time of day)
2	Ability to predict seizures
3	Ability to 'fight off' attacks
4	Presence of an aura
5	Perceived control over attacks
6	Clustering or random occurrence
7	Seizures in sleep only
8	Prevention of normal activities
Ictal/postictal subscale	
9	Perceived overall severity
10	Loss of consciousness
11	Degree of postictal confusion
12	Duration of postictal confusion
13	Falling to the ground
14	Postictal headache
15	Postictal sleepiness
16	Incontinence
17	Tongue biting
18	Injury other than tongue biting
19	Time to full recovery
20	Lip smacking or fidgeting

Items 1–4, 6, 7, 13–18 and 20: response categories; always, usually, sometimes, never.

Item 5: response categories; very good, fairly good, little control, no control.

Item 8: response categories; all of them, lot of them, few of them, none of them.

Item 9: response categories; very severe, severe, mild, very mild.

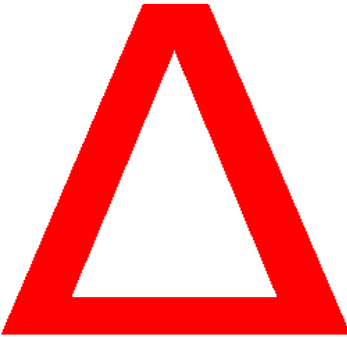
Item 11: response categories; very confused, fairly confused, slightly confused, not at all confused.

Items 10 and 12: response categories; <1 min, 1–2 min, 2–5 min, >5 min.

Item 19: response categories; <1 min, 1–5 min, 6–60 min, >60 min.

Appendix P

Screenshot SuperLab Cue



Appendix Q

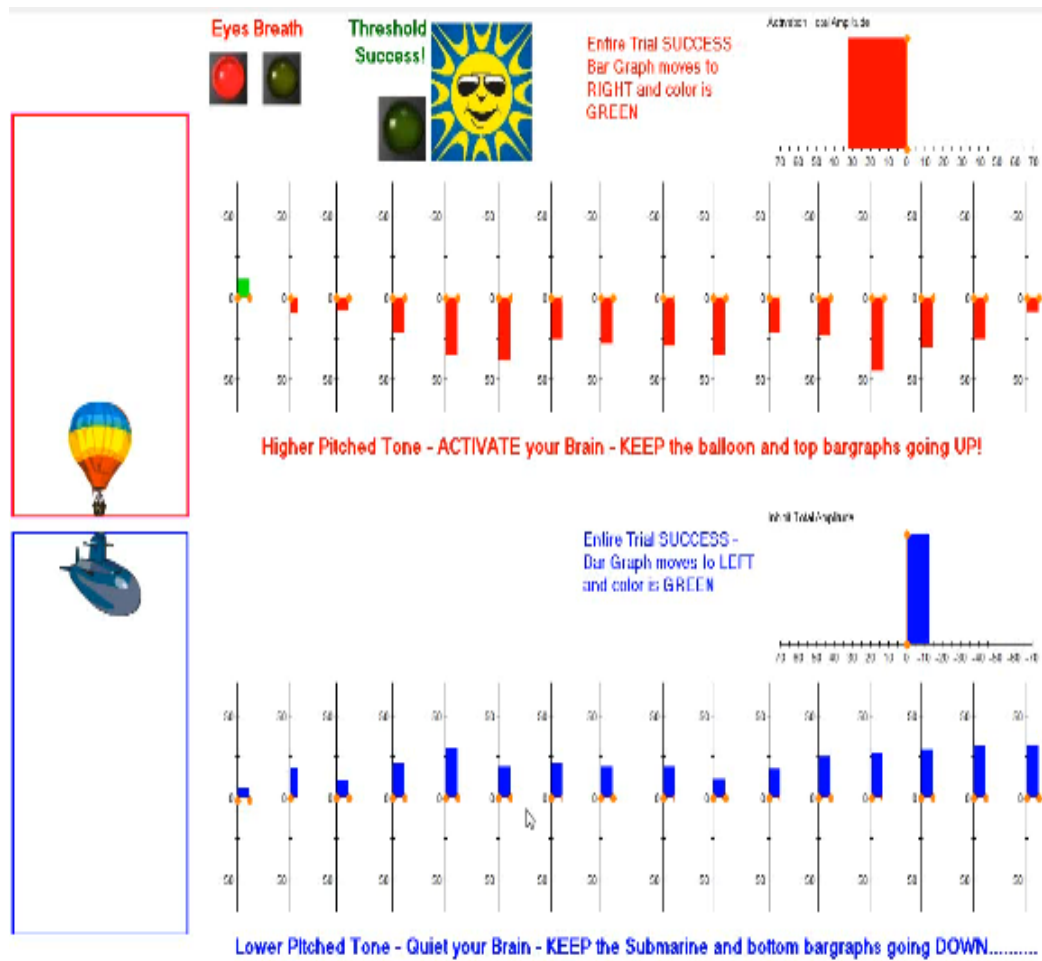
Screenshot SuperLab Stimulus

AAAA

CC

Appendix S

Screenshot SCP Intervention



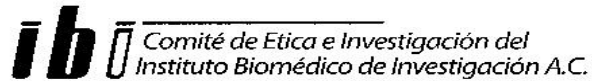
Appendix T

Screenshot SMR and Control Intervention

The screenshot displays a user interface for a neurofeedback session. On the left, a black panel contains the text "Can you complete all the" in yellow. The central area features a photograph of yellow and red flowers. To the right, a black panel shows a "Completed" counter with a large green "0" and the text "Number of" above another large green "0". Below the flower image, there are three vertical progress bars. The first bar, labeled "Focus on the", is green and reaches 100%. The second bar, labeled "Keep your muscles", is red and reaches 30%. The third bar, labeled "Keep your muscles", is green and reaches 100%. The y-axis for the first and third bars ranges from 0 to 100, while the y-axis for the second bar ranges from 0 to 30.

Appendix U

IRB Approval – Lic. González



Aguascalientes, Ags a 06 de Septiembre de 2010.

Dra. Diana Martínez
Investigador principal
Instituto Biomédico de Investigación, A.C

REF: Efectos Anticonvulsivos y Cognoscitivos de la Neuroretroalimentación

Por este conducto hago de su conocimiento que la siguiente documentación del estudio arriba mencionado fue presentada y revisada por el Comité de Ética e Investigación del Instituto Biomédico de Investigación, A.C quien dictaminó su **TOTAL APROBACION** el día 06 de Septiembre de 2010.

- Protocolo Efectos y Cognoscitivos de la Neuroretroalimentación en pacientes con epilepsia
- Asentimiento Informado Proyecto de investigación con Neuroretroalimentación para controlar convulsiones y mejorar cognición (niños de 8 a 18 años de edad)
- Consentimiento Informado Efectos anticonvulsivos

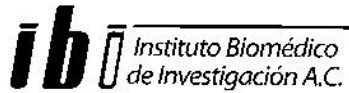
Sin mas por el momento y agradeciendo la atención que sirva dar a la presente me despido no sin antes hacerle llegar un cordial saludo.

Atentamente,

Lic. Gustavo Talamantes González
Presidente
Comité de Ética e Investigación Instituto Biomédico de Investigación, A.C
c.c.p Dr. Sarug Reyes Morales (Sub- Investigador)

Appendix V

IRB Approval – Dr. Morales



Aguascalientes, Ags. a 02 de Septiembre de 2010.

Srita. Norma Adriana García Díaz,
Secretaria Técnica del Comité de Ética e Investigación
Instituto Biomédico de Investigación, A.C.
P R E S E N T E

Re: "Efectos Anticonvulsivos y Cognoscitivos de la Neuroretroalimentación en pacientes con epilepsia."


Estimada Srita. García Díaz:

Por medio de la presente envío a Usted con referencia al protocolo arriba mencionado, para su conocimiento por parte del Comité de Ética e Investigación del Instituto Biomédico de Investigación, A.C., el siguiente documento:

- Protocolo "Efectos Anticonvulsivos y Cognitivos de la NRA, Diana Martínez M.D., M.Sc.
- Asentimiento Informado, proyecto de investigación con Neuroretroalimentación para controlar convulsiones y mejorar cognición en niños de 8 a 18 años de edad.
- Consentimiento Informado, Efectos anticonvulsivos y cognoscitivos de la Neuroretroalimentación en pacientes con epilepsia.

Sin más por el momento, agradezco de antemano su atención.

Atentamente



Dr. Sarug Reyes Morales
Sub-Investigador Principal

c.c.p Dra. Diana Martínez Investigadora Principal

Comité de Ética e Investigación del
Instituto Biomédico de Investigación A.C.

03 SET. 2010

SOMETIDO
Cpe. Macías.

