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Research Article

Treatment of Drug-Resistant Epilepsy with Neurofeedback in a Pediatric Population in Ivory Coast: A Pilot Study

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Abstract

This study concerns the treatment of drug-resistant epilepsy in the pediatric Ivorian population, aged between 3 and 10 years, with SMR - promotion Neurofeedback training - protocols for the enhancement of sensory-motor rhythms. 87 children (45 female, 42 male) have been recruited at the Don Orione Hospital, Bonoua. A large portion of patients has a diagnosis of epilepsy following neonatal cerebral palsy; in these cases, epilepsy was treated as a clinical condition with possible remission, unlike the other non-reversible clinical dimensions. The entire population shows on average a long-lasting statistically significant reduction in the number of weekly seizure episodes (-17.0 [-6.0, -31.7] at T_1, 10 days after the treatment, -10.3 [-22.7, -1.0] at T_2, 30 days after the treatment and -4.4 [-12.0, 2.0] at T_3, 90 days after the treatment) along with an increase of the relative power of SMR band (12-15 Hz) by 11.4% [6.2%, 19.7%] between the first and the last neurofeedback session. By presenting the physiological rationale underlying the functioning of neurofeedback in epilepsy, our study aims to contribute to the neuroscientific understanding of the sensory-motor cortical rhythm mechanisms in this pathology and to enrich one of the possible research directions that seem promising. Aware of the limited scientific literature on the subject, the factors underlying the effectiveness of the protocols are presented and discussed in terms of crisis reduction, improvement of patients' behavioral symptoms and quality of life, results that seem to provide elements for thought for a rigorous scientific investigation.

Keywords: *Neurofeedback; Electroencephalography; Cerebral Palsy; Sensory-Motor Cortical Rhythm*

Abbreviations

NFB: Neurofeedback; SMR: Sensory-Motor Cortical Rhythm; CP: Cerebral Palsy; EEG: Electroencephalography; PWE: People with Epilepsy; LMICs: Living in Low-and Middle-Income Countries; AAN: American Academy of Neurology; SA: South Africa; WHA: World Health Assembly; WHO: World Health Organization; AED: Antiepileptic Drug; DRE: Drug Resistant Epilepsy; BCI: Brain-Computer Interface; fMRI: Functional Magnetic Resonance Imaging; ADHD: Attention Deficit Hyperactivity Disorder; HRV: Heart Rate Variability; DMNs: Default-Mode Networks; FC; Functional Connectivity

Introduction

Etiology or risk factors

The prevalence of epilepsy is particularly high in several African countries [1]. Parasitic infections, particularly neurocysticercosis, are important etiological factors [1]. Other reasons for the high prevalence include intracranial infections of bacterial or viral origin, perinatal brain damage, head injuries, toxic agents, and hereditary factors [1]. Malaria is endemic in tropical Africa [1], epilepsy has long been recognized as one of its late sequelae [1]. There are >40 million people with epilepsy (PWE) living in low and middle-income countries (LMICs). The incidence of active epilepsy in sub-Saharan Africa is particularly high, especially in children. EEG can help classify an epilepsy syndrome and guide medication choice and is one of the basic care metrics set out in the American Academy of Neurology (AAN) epilepsy guidelines.

African Region recorded the highest prevalence of CP (1.6%) [2]. In rural South Africa (SA), the prevalence of CP has been estimated to be as high as 10/1000 live births [3]. The pathophysiological processes are often juxtaposed on antenatal factors, genetics, toxins, fetal priming, failure of neuroscientific autoregulatory mechanisms, abnormal biochemistry and abnormal metabolic pathways. Placing this primed compromised compensated brain through the stresses of an intrapartum process could be the final straw in the pathway to brain injury and later CP [4].

Background

In November 2020, the Seventy-third World Health Assembly adopted resolution WHA73.10 requesting the Director General of World Health Organization WHO, inter alia, to develop a 10-year intersectoral global action plan on epilepsy and other neurological disorders [5]. Every year, neurological disorders such as stroke, epilepsy and dementia kill nine million people [5]. Marginalized population and those living in communities with poor health systems are particularly vulnerable [5]. The strategic objectives of the global action plan address issues such as timely and responsive diagnosis treatment and care, promotion and prevention, research, innovation, leverage epilepsy diagnostics such as the Electroencephalography (EEG), neuroimaging technology [5]. Promote and facilitate the exchange of best practices at international, regional and national levels in order to inform the implementation of integrated care models [5].

Pediatric epilepsy is particularly challenging due to neurodevelopmental comorbidities associated with the underlying pathology which are then compounded by antiepileptic drug (AED) side effects [6].

Neurosurgical treatment can be offered only in a minority of patients with drug resistant epilepsy (DRE) (around 20%), and is effective in about 50% (ranging from 36 to 93% according to the localization and the etiology of the epilepsy) of cases. Therefore, a large population is either not eligible or presents a pathology that is insufficiently improved by neurosurgery [7].

Electroencephalographic neurofeedback (EEG-NFB) is a biofeedback procedure measuring an electrophysiological activity using a brain-computer interface (BCI) in order to extract a neurophysiological signal of interest that is presented in real-time to the participant. As such, it may be considered to be a unique therapy involving both neural and behavioral modulation at the same time [7].

Sensorimotor Rhythm (SMR) reduces the frequency and severity of seizure activity [8]. SMR, a specific arciform rhythm of the sensorimotor cortex (corresponding to C3-Cz-C4) in awake participants which is suppressed by thinking about or performing movement in the contralateral hand, has a frequency of 12- 20Hz with a spectral peak of 12-15Hz. SMR seems to originate from inhibitory thalamocortical circuits, hence its potential to regulate hyperexcitability [6].

Clinical findings with SMR EEG-NFB

Functional magnetic resonance imaging (fMRI) studies in human subjects have shown that the SMR EEG pattern is clearly associated with an increase in metabolic activity in the striatum of the 3 basal ganglia nuclear complex [9]. Further, examining fMRI changes in children with attention deficit hyperactivity disorder (ADHD) who improved significantly in cognitive tests after SMR Neurofeedback training.

Lavesque and Beauregard [9] have observed a specific and significant increase in metabolic activity in the striatum. This convergence of findings suggests that facilitation and/or regulation of the SMR substrate alters motor output, and sets the stage for reduced proprioceptive afferent input to thalamus [9]. In initial studies involving relatively small sample sizes and pre-treatment baseline measures as a control condition, on average 80% of patients trained at enhancing SMR amplitudes were shown to display significant clinical improvements [9]. For instance, clinicians reported that 3 months of SMR training was associated with significantly reduced seizure incident in 5 out of 7 patients who had previously suffered from very poorly controlled seizures [9]. A single implicit EEG neurofeedback session to a single session of infra-low frequency neurofeedback or sham neurofeedback, with electrodes over the right middle temporal gyrus and the right inferior parietal lobule randomly assigned can result in significant modulation of the brain's intrinsic connectivity [10]. Immediately before and after the session, the participants underwent a resting state fMRI [10]. They observed a moving rocket, the speed of which was modulated by the waveform derived from a band-limited infra-low frequency filter [10]. First, a brain circuit related to the implicit neurofeedback process itself is described, consisting of the lateral occipital cortex, right dorsolateral prefrontal cortex, left orbitofrontal cortex, right ventral striatum, and bilateral dorsal striatum [10].

Clinical findings. Evidence of the effectiveness of a single session of SMR EEG-NFB

As a multidimensional construct, attention cannot be reduced to a single measure of cognitive performance but rather emerges from a dynamic structuring of neural interactions. According to the concept of neurovisceral integration [11], those interactions cohere through nonlinear interdependencies to form a complex system comprising cortical, subcortical, and cardiac autonomic regulation [11]. A single session of SMR-NFB, is reliably reflected in the multiscale multifractality of heart rate variability (HRV) dynamics because of the particular structuring of brain-heart interplay resulting from SMR-NFB [11]. A single SMRNFB session improves brain modulation, as reflected in both self-reported feelings and neurophysiological correlates [11].

It has been shown that a single session of NFB-training targeting sensorimotor brain areas led to strengthening of both sensorimotor and default-mode networks (DMNs). Increased functional connectivity (FC) of the empathy networks has also been described after modulation of anterior insula. In patients with major depressive disorder, amygdala-targeted NFB training led to amygdala FC changes during resting state [12].

Limits of the Study

For ethical reasons, we could not enroll a control group, because it was clearly not possible to suspend pharmacotherapy (lamotrigine and sodium valproate). A second limitation of our study is the relatively small sample of subjects. Realizing that, to date, we have little literature regarding the therapy using the SMR protocol with EEG-NFB on a pediatric population diagnosed with epilepsy, we hope that the evidence of our pilot study can enrich and encourage a research path that promises good results.

Materials and Methods

The present research work was conducted from 2022 to 2024 at the Don Orione Hospital in Bonoua, Ivory Coast, under the joint coordination of the local health management and the NGO World Medical Aid. The Don Orione Hospital is one of the main and best-equipped healthcare facilities in the area and is mainly dedicated to the treatment of psychomotor and sensory disabilities in adults and children. The pediatric wards provide long-term hospitalization, welcoming children and their companions (usually mothers or grandmothers) for several weeks in order to deliver comprehensive healthcare treatments such as surgical interventions, physiotherapy, internal medicine, neuropsychology, and rehabilitation.

The patients who participated in the study were hospitalized at the healthcare facility for about 1 month.

87 children aged between 3 and 10 years (42 males, 45 females) with a diagnosis of epilepsy poorly responsive to medication were recruited. The pharmacological molecules administered to the study patients were lamotrigine 3 mg/kg or sodium valproate 30 mg/kg. In addition to pharmacological therapy, a training with clinical EEG Neurofeedback was performed using validated pediatric SMR protocols for the treatment of epilepsy.

36 children underwent 5 sessions of NFB SMR; 51 children underwent 3 sessions of NFB SMR. Although the literature highlights that good treatment efficacy also depends on the number of sessions [8,13], it is necessary to explain that it was not possible to guarantee all patients a cycle of 5 sessions due to organizational reasons, meaning some children completed their hospitalization period before the full therapeutic cycle was completed. It was assessed to include all patients in the study who, due to diagnosis and progression of the disease, could somehow benefit from it; this choice was not motivated only by ethical and deontological reasons, but also by some promising evidence in the literature that seems to suggest a change in SMR cortical rhythms originate even after a small number of NFB sessions [6,8,9,11,13,14].

Regardless of the number of sessions performed on each subject, the patients were included in a single group to better analyze the efficacy of the NFB treatment itself with no difference between the number of sessions. This approach better applies to day-to-day clinical practice, especially in such a difficult context, where ideal conditions are difficult to be met and sticking to the ideal protocol is rarely possible, thus making the results more realistic and replicable in a similar context.

For each treated patient, the number of weekly seizure episodes was evaluated respectively at T_0 (i.e. at the time of enrollment); at T_1 (i.e. after 10 days from the end of the treatment cycle); at T_2 (i.e. after 30 days from the end of the treatment cycle); and at T_3 (i.e. after 90 days from the end of the treatment cycle).

Furthermore, the maximum relative amplitude of the SMR band Cz-A1 was measured at T_0 (that is, at the time of enrollment) and at T_{LS} (that is, the day of the last NFB session). It should be clarified that the measurements of cortical rhythm values and seizure episodes at T_0, T_{IS} and T_1 were carried out by healthcare personnel at the pediatric neurorehabilitation unit, while the measurements of seizure events at T_2 and T_3 were conducted by the patients' caregivers at their homes and reported by phone to the hospital staff.

SMR neurofeedback training increase

The study of brain rhythms is fundamental in determining the mental state of a subject. EEG signal is divided into so called "frequency bands", where lower frequencies mark for more relaxed mental conditions. In particular, the following protocol (called SMR training) is meant to help the subject learn how to force its own brain to move towards more calm brain activity, characterized by prevalence of SMR rhythms [15]. For EEG acquisition, a setup of two Ag or Ag-Cl electrodes was used to obtain two derivations: Cz-A1, following the 10-20 international system. A ground electrode was placed on the back of the non-dominant hand. The placement of the electrodes is crucial for the success of the procedure: it is necessary to achieve a low impedance between the electrodes (a suggested maximum of 10 kΩ) because the EEG signal has a much-limited amplitude (in the order of μV) and is therefore highly susceptible to external noise. The electrodes must, therefore, ensure adequate quality of electrode-skin contact.

The SMR rhythm gets suppressed both with active movements of the subject and with the mental representation of the movement; an SMR increase is therefore linked with a decrease in muscle tone and readiness for action, resulting in an overall working but calm mental state.

For this study the chosen protocol aimed at reinforcing the skill of attention with simultaneous muscle relaxation by increasing the SMR rhythm.

During the training, the patient faces a monitor where playful and cartoonish scenarios are presented, along with sounds with no words so that the language barrier can be removed. The goal of the training is to increase the SMR relative power from session to session and the ideal achievement would be a higher final value of SMR relative power compared to the initial one. T_0 obtain such a result, the scenario varies according to the SMR rhythm of the patient, who gets rewarded when the SMR rhythm increases, both with visual and audio feedback (i.e. a rabbit in a labyrinth finding the correct path and collecting carrots when SMR criteria are met). Each session is divided into 3 rounds of 5 minutes each. During the first of these rounds, the relative amplitude of the SMR band power is computed to keep track of the progresses and is later compared between the first and last session (See results and discussion).

Results and Discussion

As explained in materials and methods section, the entire population was included in a single group regardless of the number of NFB sessions received to better replicate the day-to-day clinical practice. The boxplots presented in figure 1 show the comparison between the number of weekly seizure episodes pre-treatment (T_0) and post-treatment (T_1, T_2, T_3).

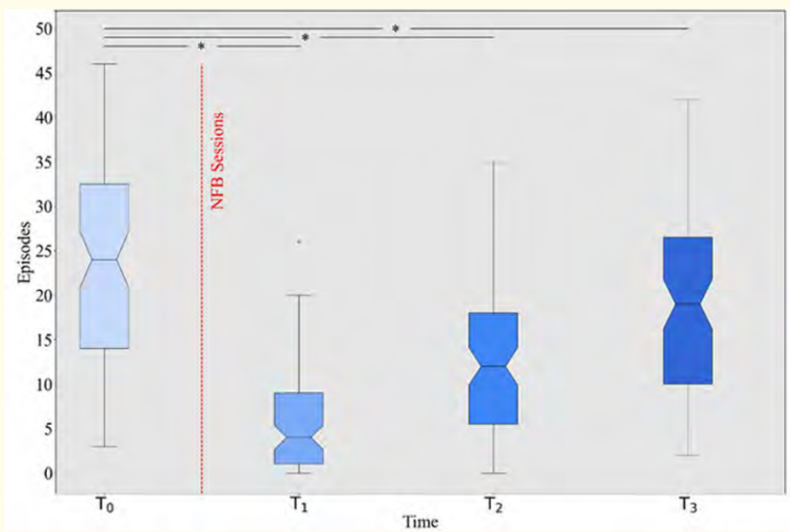

Figure 1: *Number of weekly seizure episodes over time.*

**The difference between the populations is statistically relevant with p<<0.001.*

The numerical results are presented in table 1, which shows a clear reduction in the number of weekly seizure episodes. A Shapiro-Wilk normality test was performed on each distribution to assess their normality, but since neither of them turned out to be normal, instead of the standard deviation, the 5-95 percentile range is presented to provide further information about the entire population.

		Number of weekly episodes [adim]	
Time	T_0	22.9	Mean difference [P0.05, P0.95]**
	$T_1 - T_0$	-17.0 [-6.0, -31.7]	
	$T_2 - T_0$	-10.3 [-22.7, -1.0]	
	$T_3 - T_0$	-4.4 [-12.0, 2.0]	

Table 1: *Comparison between weekly episodes at each time point and at T_0.*

***P_{xx} indicates the xx-th percentile.*

The most important reduction, as expected, is at T_1 (10 days after the end of the treatment cycle), where the number of episodes on average is reduced by 17.0 [-6.0, -31.7]. It is important to notice that such a result is not limited to T_1 but is still present at T_2 and T_3 even if to a smaller extent. Specifically, at T_2 (30 days after the end of the treatment) the reported number of episodes is still relevantly lower than the one at T_0, with an average reduction of 10.3 [-22.7, -1.0] weekly episodes, while at T_3 (90 days after the end of the treatment) the remaining effect of the treatment is still visible with an average reduction of 4.4 [-12.0, 2.0] weekly episodes.

Since no normality was detected by the Shapiro-Wilk tests, a non-parametric Wilcoxon test was performed to check the statistical relevance of the differences between T_1, T_2, T_3 and T_0, all resulting in a p-value<<0.001.

A clear pattern can be inferred from the data in figure 1 and table 1, showing that the NFB treatment provides a strong effect right after the protocol, which slowly becomes more mitigated with time. This behavior indicates that more NFB sessions could be more effective to grant a more robust and stable outcome; however, it is relevant to notice that even after 90 days from the end of the protocol, a statistically relevant difference is still present, thus highlighting the positive effect of the treatment itself even with a limited number of sessions.

Since the NFB protocol aimed at increasing the SMR band, great attention was given to the amplitude of this rhythm to verify if the patients developed an increase in the associated band power. T_0 do so, the maximum relative power of the SMR band (12-15 Hz) was computed at T_0 and at T_{LS} (last NFB session) and its change is shown in figure 2. On average, the patients increased their relative power of the SMR band 11.4% [6.2%, 19.7%], thus showing that the NFB cycle provoked a change in the oscillatory rhythms of the patients' brain, increasing the relative power of the band which was promoted during the protocol.

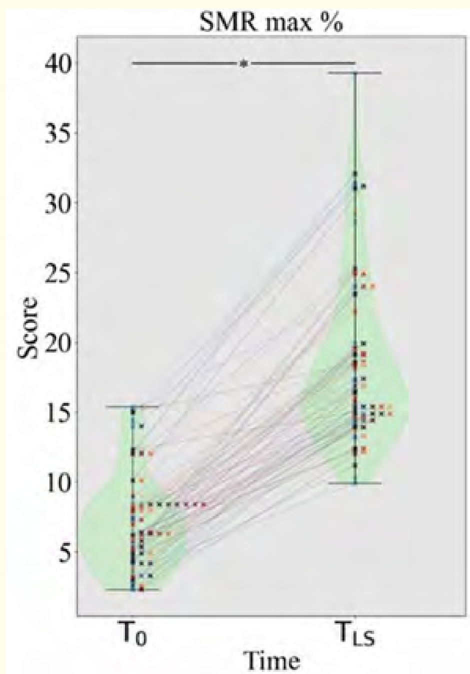

Figure 2: *SMR% comparison between first session and last session.*

**The difference between the populations is statistically relevant with p<<0.001.*

Conclusion

This research work - a pilot study - aims to investigate new non-invasive therapeutic possibilities in a very specific population and context characterized by little or no previous clinical research. There are > 40 million people with epilepsy (PWE) living in low-and middle-income countries (LMICs).

As discussed in background section, it appears necessary to identify and promote effective therapeutic strategies that are complementary or alternative to pharmacotherapy and neurosurgery [5-7].

The literature has shown promising results in the treatment of epilepsy with NFB [8,9] with no side effects and a favorable cost-benefit ratio. The present study, in line with previous research conducted on Western population, seems promising despite some evident limitation: for ethical reasons, we could not enroll a control group, because it was clearly not possible to suspend pharmacotherapy (lamotrigine and sodium valproate). A second limitation of our study is the relatively small sample of subjects. Realizing that, to date, there is little literature regarding the therapy using the SMR protocol with EEG-NFB on a pediatric population diagnosed with epilepsy. The numerical results are presented in table 1, which shows a clear reduction in the number of weekly seizure episodes. The data presented in results and discussion section seem to highlight a time-dependent efficacy of the treatment, that is, it is greater in the period immediately following the treatment and then tends, over course of a few weeks, to return to the initial pathological condition. These observations would seem to suggest the opportunity to treat these patients continuously to maximize and stabilize the therapeutic effects of the NFB treatment.

Although the possibility of conducting double-blind studies is an ethical obstacle, future clinical trials on larger population samples and over longer periods will certainly be necessary.

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