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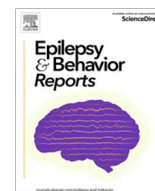
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Case Report

Infra-low frequency neurofeedback training in Dravet syndrome: A case study

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ABSTRACT

This case study examines how an intervention of infra-low frequency neurofeedback training (ILF-NFT) affects the symptomatology of an eight-year-old patient with Dravet syndrome (DS), a rare and highly disabling form of epilepsy. Our results demonstrate that ILF-NFT has improved the patient's sleep disturbance, has significantly reduced seizure frequency and severity, and has reversed neurodevelopmental decline, with positive development in intellectual and motor skills. No significant changes have been made to the patient's medication in the observed period of 2.5 years. Thus, we draw attention to ILF-NFT as a promising intervention in addressing DS symptomatology. Finally, we discuss the study's methodological limitations and warrant future studies to assess the effect of ILF-NFT in DS in more elaborate research designs.

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1. Introduction

Dravet syndrome (DS) is a rare and serious form of epilepsy (1 in 40,000) caused by a mutation in a gene that encodes sodium channels in the central nervous system, and which encompasses serious neurodevelopmental decline, causing severe impairments in multiple areas of brain functioning [1,2]. Epileptic seizures take different forms, including focal to bilateral tonic-clonic seizures, with increasing frequency throughout childhood and are largely treatment resistant. Further, sleep disorders are a major challenge with DS [3]. Additionally, DS is characterized by a high degree of electroencephalogram (EEG) heterogeneity, and thus, changes related to the EEG activity that cannot be used as either diagnostic or prognostic markers [4]. Here, infra-low frequency neurofeedback training (ILF-NFT) has shown promise in addressing sleep dysfunctions in several novel studies [5,6].

According to the international consensus on diagnosis and management of DS, treatment options are limited, and seizure remission rarely occurs, with consistent developmental decline and sleep problems [7]. The clinical treatment of DS is marked by different approaches to addressing core symptomatology as DS is one of the most difficult electroclinical syndromes. Here, primary management is often addressed with valproic acid, a potentiator of GABAergic functioning, as well as clobazam, a benzodiazepine

[8]. However, these treatments are associated with serious adverse effects such as hepatotoxicity, hyperammonemia, pancreatitis, and thrombocytopenia, along with changes in appetite, tremor, hair loss and sedation [8]. Taken together with the relatively modest responder rates and seizures reductions of 50% and 28% from few existing retrospective studies [9,10], these treatment options can be considered relatively ineffective. The ketogenic diet is a non-pharmacological treatment option where, with extensive dietary restrictions, seizure reduction can be achieved, although the treatment has its own reported side effects [11,12], with one study reporting a significant seizures reduction [13].

In this case study, we present an 8-year-old DS patient who has been using ILF-NFT for 2.5 years.

1.1. The history of neurofeedback

Since 1970, the effect of neurofeedback training (NFT) in treatment-resistant epilepsy has been described in many scientific publications. The evidence in these publications is limited by the fact that it has been difficult to conduct double-blind placebo-controlled studies. Several studies point to an effect following the end of training courses within basic research as well as within meta-analyses on the effects of NFT [14,15]. There exist more than 20 different methods of EEG NFT. This case study describes a DS patient who has been trained with the method of ILF-NFT, a widespread modality of NFT, targeted to address cognitive and affective psychological symptoms within a wide range of psychiatric

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disorders. The existing literature has been primarily focused on pilot and case studies demonstrating effects within a range of mental disorders such as attention deficit hyperactivity disorder (ADHD) [16,17], post-traumatic stress disorder (PTSD) [18–21], autism spectrum disorder (ASD) [22,23], depression [24], migraine [25], fibromyalgia [26], sclerosis [27], post-commotio syndrome [28,29], opioid and cocaine dependence [30], and in refractory disorders such as tinnitus [31–33]. Additionally, two existing case reports demonstrate ILF-NFT's effect on epilepsy [34,35].

1.2. Medical history of the clinical case

Despite the several medication options for DS, there is still not a sufficiently effective treatment for DS patients, to significantly reduce neurodevelopmental decline, sleep disorders, and seizures. In our study, a now 8-year-old girl presented with fever-induced seizures at 5 months of age, with increasing seizures frequency, up to three attacks per week and a duration of up to 30 min. In connection with prolonged seizures, she was admitted to the emergency department. The diagnosis of DS was given following detection of a specific gene mutation (SCN1A c.5752T > C; p. Ser1918Pro de novo)).

Seizures changed from being triggered only by fever to also being triggered by lower temperatures as well as physical activity and excessive sensory stimulation. Until July 2021, a body temperature above 37.8 degrees Celsius would trigger seizures for the DS patient. Until the start of ILF-NFT in December 2019, the DS patient experienced increasing sleep problems. The girl was awake two-four hours a night on five nights a week. This gradually decreased her cognitive and motor skills.

Neuropsychological assessment in January 2021 from the Danish epilepsy hospital, Filadelfia, showed marked impaired development with increased impulsivity and irritability, as well as decreased executive functioning. The girl's psychological development was assessed to be delayed by approximately one year. The girl tried several different types of anti-epilepsy medicine with various side effects, including serious effects on liver function due to Valproate. Additionally, treatment with Diazepam produced significant lethargy in the following days.

1.3. History of medical treatment during the 2.5 years covered by the case report

The DS patient received a combination of: Topiramate (Topimax), 25 mg tablet: 1 tablet, morning + 1 tablet, evening, against epilepsy; Stiripentol (Diacomit): 500 mg morning + 375 mg evening, against epilepsy; Clobazam (Frisium) 10 mg tablet: 0.5 tablet, morning + 0.5 tablet, evening; against epilepsy; and Melatonin: 1 mg sleep medicine. Additionally, if necessary, the DS patient received Paracetamol (Pamol Flash) 250 mg dispersible tablets, 1 tablet 4 times daily; antipyretic; and Diazepam (Stesolid) 5 mg/-dose rectal liquid solution, single-dose container for seizures.

2. Methods

In December 2019, the girl started using ILF-NFT with the equipment described below. The daughter's father was trained to administer ILF-NFT under the supervision of a psychiatrist and ILF-NFT specialist (co-author). Training sessions with the equipment were set up in the girl's home. During stays away from home, the family brought the equipment with them so that they could use ILF-NFT when away from home. The girl has, with few exceptions, been training daily ever since.

The training takes place as presented in Fig. 1. The method of ILT-NFT uses the hardware, NeuroAmp II EEG amplifier and the

software, Cygnet. Electrodes are mounted on the scalp at points defined in the training protocol defined from the 10/20 EEG system. Each training session last approximately 30 min.

The EEG signal is sent through the amplifier where the computer processes this. The signal is divided into two channels which are analyzed for feedback. The brain is trained corresponding to the neural activity of the underlying areas beneath the electrode sites. Feedback is given on two components of the EEG signal; (1) brain activity below 0.1 Hz is presented to the client by slow changes in the size and opacity of the image, and (2) brain activity between 4 Hz and 40 Hz is divided into nine frequency bands which are analyzed separately. With sudden changes of increased activity in one or more of these frequency bands, feedback is shown to the client as opaqueness over the images that hides the screen proportionally to how much the activity has increased. Feedback is given here with a 50 ms delay in relation to the measured EEG. Feedback can be conveyed with several applications. It is most common to create feedback on the basis of video material, through the use of the add-on software application, Advanced Media Player. Thus, neurofeedback occurs as the video changes in size and opacity in response to changes in brain activity. Additionally, part of the feedback is conveyed via sound changes during the sessions and optionally via a tactile vibration device. No conscious attention is required from the client to use ILF-NFT. It is sufficient that the eyes are directed towards the image, the ears towards the sound, and optionally, the skin towards the vibrations.

2.1. Training protocols

The protocol below is described in terminology with reference to the certification for ILF-NFT according to the Othmer method. From December 2019 to July 2021, we used combined calming and stabilizing ILF-NFT (Channel 1: T3 - P3, Channel 2: T4 - P4, Ground: Pz, Duration: 30 min). From July 2021, we used stabilizing ILF-NFT (Channel 1: T3 - Cz, Channel 2: T4 - Cz, Ground: Fz). Finally, from September 2021, we added additional calming training, and inhibition of prefrontal impulsivity (Channel 1: Fp1 - Cz, Channel 2: Fp2 - Cz + Channel 1: P3 - Cz, Channel 2: P4 - Cz, Ground: Fz). The training frequency was 0.0001 mHz. At each added training site, training time was divided so that the total duration was approximately 30 min. Feedback was conveyed using Cygnet's Advanced Media Player. Because of the software, it was not possible to extract brain variables and run correlational analyses between regulation success and behavioral outcomes [36,37].

3. Results

As this is the first study addressing DS using ILF-NFT, we had no *a priori* hypotheses in relation to the treatment response. As a function hereof, the results primarily consist of the parents' observations, including their recordings of seizures in the digital app they share with the Danish epilepsy hospital.

After the first three training sessions, there was a marked improvement in sleep. Before December 2019, the girl was awake two-four hours a night on five out of seven nights a week. Since then, sleep has been stable; awakenings in the night hours are now both rare and significantly shorter. The girl now sleeps steadily between 7 PM and 6 AM on six out of seven nights a week. The seizures stabilized until the summer of 2021, with seizures seven to ten days apart. These seizures became both shorter in duration and less severe. Since there was no need for pharmacologically administering Diazepam, she was not as lethargic in the days following seizures. Since July 2021, the girl has had a total of four seizures as seen in Fig. 2. The past 23 weeks have been seizure-free. In connection with a COVID-19 infection in January 2022, she had a

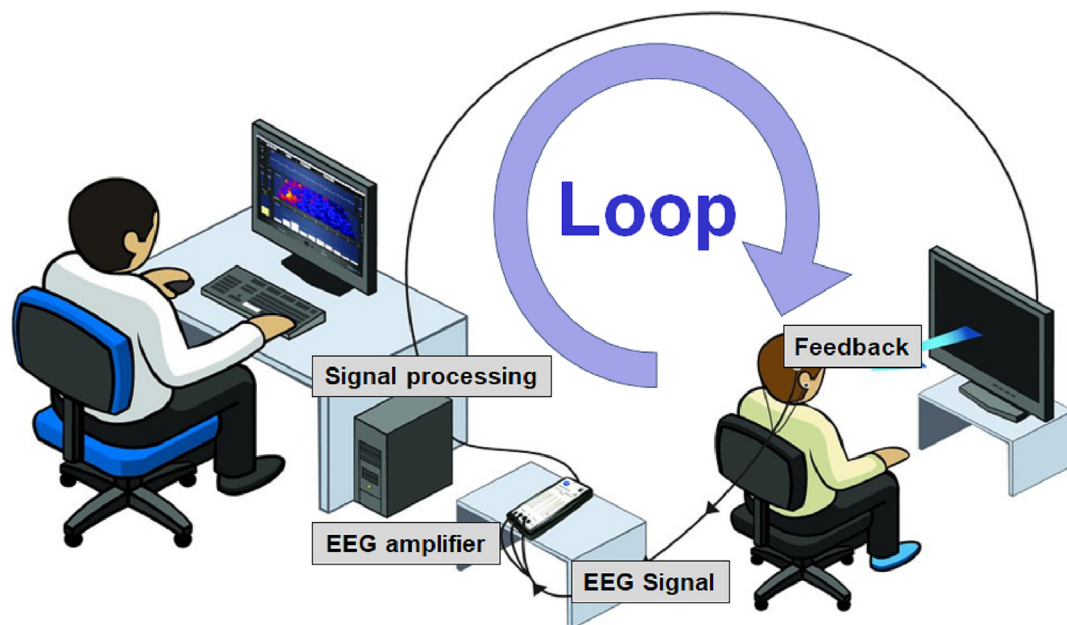


Fig. 1. The procedure of ILF-NFT. When administering ILF-NFT, small electrodes are first attached to the client's scalp using a conducting paste. Electrode placements for ILF-NFT sessions are usually determined from the client's self-report of symptom distress. During each session, the client sits with electrodes in front of a screen with headphones, watching a video. The electrodes are connected to the EEG amplifier (model: NeuroAmp II), which measures the brain activity from the specific electrode sites. The EEG amplifier is connected to a PC, where the software Cygnet creates an audio-visual representation of the brain activity on the screen that the client (in this case, the DS patient) sits and looks at for 30 min. Neurofeedback occurs as the video changes in size, opacity, and sound in response to changes in brain activity.

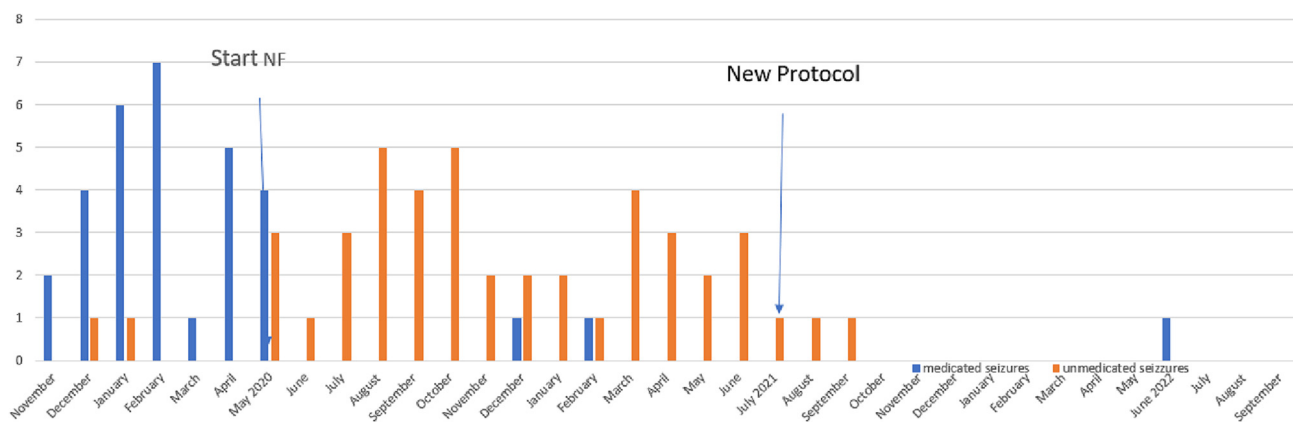


Fig. 2. Frequency of seizures in the patient before and following the onset of ILF-NFT intervention.

high fever of 39.5 degrees Celsius without having seizures. The girl now attends a special class at a regular school. Cognitively, she is developing positively, even though she is not age appropriate. Motor-wise, she is well-functioning, (e.g., she is able to jump on a trampoline for 15 min without having a seizure). She is happy and with a positive attitude towards life. When she does not use ILF-NFT for two or three days, the girl may feel unwell and will show restlessness and has trouble falling asleep. This disappears promptly after a single ILF-NFT session. No side effects have been associated with the ILF-NFT intervention.

4. Discussion

Over the past 50 years, NFT has demonstrated a promising effect in addressing various forms of epilepsy, in spite of noticeable study limitations such as double-blind research designs. Since it has not been possible to do double-blind randomized controlled

trials, the evidence is modest and the results, for example, are not recognized in neurology in Denmark. In the vast majority of studies, the original NFT training principle has been maintained with up-regulation of beta – somatosensory rhythm (SMR) EEG frequency band activity over the sensory-motor cortex. Since then, the intervention of ILF-NFT has targeted the training of the brain's slow cortical potentials with a frequency of <0.1 Hz, which are associated with functioning of the default mode network of the brain. Both hardware, software and training protocols have since been in continuous development, guided empirically by clinical judgements of arousal regulation indicators. Despite the lack of double-blind randomized controlled trials in examining the effects of ILF-NFT, the present results indicate marked positive effects of the intervention, judging by the positive changes observed in the seven-year-old DS patient. The girl's psychiatrist and neurofeedback specialist does not know what the future holds. Until now, it has provided marked treatment improvement in a highly severe and debilitating disease such as DS. We anticipate that the

application of ILF-NFT may be necessary in order to minimize her symptoms throughout her lifetime. Lastly, no changes have been made in the DS patient's medication dosage over the period.

5. Study limitations

There are several limitations to this study. First, we caution the extrapolation of the study's findings as they are reported from observations of the DS patient's family. Second, this study provides no longitudinal or objective measures of change as a function of the ILF-NFT intervention, either neural or performance-related. Here, we warrant future researchers to assess global neural change with the use of either resting state functional connectivity using the neuroimaging modality of magnetic resonance imaging (MRI) or using quantitative EEG. Second, the study would have benefitted from the use of neuropsychological and motor function testing. However, as this was an explorative approach to treating the case patient with ILF-NFT, we did not anticipate observing such marked improvements in sleep quality as well as in seizure frequency and severity. Retrospectively, the study would have greatly benefitted from a more systematic assessment protocol, both in relation to measuring and tracking neuropsychological and motor function change, as well as neural correlates of change through either MRI or quantitative EEG.

6. Conclusions

This case study demonstrates that the intervention of ILF-NFT in a patient with DS has shown marked positive effects on the syndrome. We highlight the beneficial effects on symptom reduction in seizure frequency and severity, as well as significantly improved sleep quality, including improvements in cognition, learning, and motor functioning, leading to an overall increased quality of life for the DS patient and her family. These results may be extrapolated onto other DS patients, and based on the study limitations, further research is warranted to examine the effect of ILF-NFT in DS in more controlled clinical contexts.

Ethical statement

We, the authors, Casper Schmidt & Henning Laugesen, declare that there are no violated ethical aspects of this study, and that the Dravet syndrome patient and her parent participated with full consent.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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