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Aim and Scope

NeuroRegulation is a peer-reviewed journal providing an integrated, multidisciplinary perspective on clinically relevant research, treatment, and public policy for neurofeedback, neuroregulation, and neurotherapy. The journal reviews important findings in clinical neurotherapy, biofeedback, and electroencephalography for use in assessing baselines and outcomes of various procedures. The journal draws from expertise inside and outside of the International Society for Neurofeedback and Research to deliver material which integrates the diverse aspects of the field. Instructions for submissions and Author Guidelines can be found on the journal website (http://www.neuroregulation.org).

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RESEARCH PAPERS

CLINICAL CORNER

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Comparing Live *Z*-Score Training and Theta/Beta Protocol to Reduce Theta-to-Beta Ratio: A Pilot Study

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Abstract

Objective/Background: Theta-to-Beta ratio is one of the most studied electroencephalography findings in ADHD in the neurotherapy field, alongside the neurofeedback (NF) protocols whose objective is reducing it. The NF field has developed to a great level in the last decade. One of the approaches that became of particular interest to the clinicians has been *Z*-score training (ZT). In general, there are still a few studies about the efficacy of ZT and even fewer that compare this technique with the classic protocols. This study aimed to check the efficacy of ZT in reducing Theta-to-Beta ratio. **Participants:** 15 patients diagnosed with combined type ADHD aged 7 to 18, recruited in retrospect. **Methods:** The participants were divided in two groups. One of the groups was provided with the ZT intervention and the other one, the Theta/Beta (T/B) protocol. Both groups went through ten 30-min NF sessions using videos selected by themselves as a reinforcement. The main outcomes of this study were the patients' Theta-to-Beta ratio metrics. **Results:** Both groups showed a decrease in Theta-to-Beta ratio; the ZT group showed a decrease of 1.02 points average and the T/B group showed a decrease of 0.15 points average, only being statistically significant for the ZT group.

Keywords: neurofeedback; *Z*-score training; Theta-to-Beta ratio

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Introduction

Biofeedback (BF) is an applied field within psychophysiology. Neurofeedback (NF), which is a subdivision of BF, is focused on controlling the electroencephalographic (EEG) activity (Carrobles, 2016). NF is based on the operant conditioning (i.e., behavior modification by rewards and punishments) application to the EEG activity (Monastra, Monastra, & George, 2002). The EEG activity is recorded by a device (amplifier) and processed with specialized software that allows it to break down the EEG into frequency bands (Delta, Theta, Alpha, Beta, etc.), and also to measure the average voltage or the amplitude of each band at a certain point (Carrobles, 2016; Demos, 2005).

In classical NF, also known as power training, it is possible to reinforce, inhibit, or ignore the different bands. For the bands that are being reinforced, an amplitude threshold is established that must be exceeded to obtain feedback. For the bands that are being inhibited, a threshold is established, and the amplitudes must remain under it in order to obtain reinforcement. When there is more than one frequency band being reinforced and/or inhibited, all set thresholds must be within the set range to receive feedback (Demos, 2005). This feedback—which can be visual (e.g., films), auditory (e.g., music), vibratory,

or mixed—is contingent on the fulfillment of the thresholds for each band present in the EEG.

Throughout the years, there have been a number of protocols within the context of the NF power training which are nowadays considered by the literature as classical protocols. Ever since the Monastra et al. (1999; Monastra, Lubar, & Linden, 2001) studies showed that the finding of a Theta-to-Beta ratio could be a possible indicator of attention-deficit/ hyperactivity disorder (ADHD), there began to emerge a great number of studies that used the Theta/Beta (T/B) protocol as a possible intervention in ADHD cases (Arns, de Ridder, Strehl, Breteler, & Coenen, 2009; Bakhshayesh, Hänsch, Wyschkon, Rezai, & Esser, 2011; Leins et al., 2007). Among those classical protocols, we find the T/B applied in general to Cz (one of the International 10/20 system locations) that inhibits Theta-to-Beta ratio, which essentially means inhibiting the Theta activity and enhancing the Beta activity at the sensorimotor cortex (Monastra et al., 2005; Rossiter, 2002). When the patient meets the criteria, he subsequently receives the reinforcement (Monastra et al., 2005; Rossiter & La Vaque, 1995).

Even though this protocol was first used to treat the ADHD, it has also been applied as a one-size-fits-all protocol for other conditions such as insomnia (Hammer, Colbert, Brown, & Ilioi, 2011; Schabus et al., 2014), cognitive performance (Doppelmayr & Weber, 2011), impulsivity (Bluschke, Broschwitz, Khol, Roessner, & Beste, 2016; Liu, Hou, Sourina, & Bazanova, 2016), and executive functions or autism (Kouijzer, de Moor, Gerrits, Congedo, & van Schie, 2009).

In recent years, technological advances have allowed new possibilities to be created in the field of NF (Hammer et al., 2011) through different paradigms: amplitude neurofeedback, *Z*-score-based neurofeedback, infralow frequency neurofeedback, infraslow fluctuation neurofeedback, or low resolution electromagnetic tomography analysis (LORETA)-based neurofeedback.

Since its inception at the beginning of the 2000s (Collura, 2008, 2014), *Z*-score training (ZT) has attracted interest among the NF scientific community resulting in several case (Collura, Guan, Tarrant, Bailey, & Starr, 2010; Koberda, Moses, Koberda, & Koberda, 2012; Pérez-Elvira, Carrobles, López Bote, & Oltra-Cucarella, 2019; Pérez-Elvira et al., 2018; Smith, 2008) and group studies (Groeneveld et al., 2019; Hammer et al., 2011; Krigbaum & Wigton, 2015; Wigton, 2014; Wigton & Krigbaum, 2015). In ZT all the patients' EEG *Z*-scores from all elements (absolute power, relative power, coherence, etc.) are computed and collected at all times, the percentage of *Z*-scores within a specific range (for instance, ±1 *SD*) is calculated, and the patient receives feedback every time the percentage of *Z*-scores within the normal range is equal to or higher than a requested percentage.

ZT has shown efficacy in different pathologies such as ADHD, epilepsy, migraine, depression, anxiety, insomnia, and learning disorders (Guan, 2016; Hammer et al., 2011; Pérez-Elvira et al., 2019; Walker, 2016). In fact, there are some authors, such as Lubar (2015), who indicate that NF based on *Z*-score promotes faster learning than classical NF. This has also been partly verified by the Wigton and Krigbaum studies (Krigbaum & Wigton, 2015; Wigton & Krigbaum, 2015) that presented a normalization of the EEG in approximately 10 sessions, against the average 40 necessary in the classical NF, (Krigbaum & Wigton, 2014; Thatcher, 2013; Wigton, 2013; Wigton & Krigbaum, 2015) or even more than 60 in some cases (Sürmeli & Ertem, 2011; Sürmeli, Erthem, Eralp, & Kos, 2012).

The aim of this investigation was to study ZT's capacity to reduce Theta-to-Beta ratio while comparing that intervention with an active control group who followed a T/B protocol.

Methods

Subjects

A total of 15 subjects, 12 boys and 3 girls from NEPSA Rehabilitación Neurológica (a Neurorehabilitation Clinic) who went looking for NF treatment, took part in this study, which has a gender ratio of 4:1 to represent the ratio of boys to girls usually found in ADHD. Their data were retrospectively analyzed. The inclusion criteria were:

1) being diagnosed with combined type ADHD by a school psychologist, a neurologist, and/or neuropediatrician,
2) being between the ages of 7 and 18 (*M* = 12, *SD* = 3.5, range = 7–18),
3) having a Theta-to-Beta ratio higher that what is to be expected for that age range (Demos, 2019),
4) not taking any medication, and
5) having completed 10 NF sessions between September and December 2018.

Moreover, all of the subjects took an intelligence test (Wechsler Intelligence Scale for Children – Fourth

Edition [WISC-IV] or Wechsler Abbreviated Scale of Intelligence – Second Edition [WASI-II]) and scored within the normal range.

The subjects or the subjects' parents signed an informed consent to apply the treatment on them and for the subsequent anonymized use of their data for researching purposes. The intervention took place at NEPSA Rehabilitación Neurológica, a neurological rehabilitation clinic authorized by the Health Department of the Autonomous Community of Castile-Leon (Spain). The Health Department granted approval for psychophysiological interventions of this kind within the context of psychological treatments.

Instruments and Procedure

Quantitative EEG Recording and Analysis

A quantitative EEG (qEEG) was recorded before starting the NF intervention and after 10 NF sessions. To record the EEG, the subjects were fitted with a 19-channel Free-cap (Institute for EEG-Neurofeedack [IFEN], Baldham, Germany) according to the International 10/20 system with Linked Ears montage (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2). For 3 min, the EEG signals were obtained and collected simultaneously over those 19 channels with a Discovery20 amplifier (BrainMaster Technologies, Inc., Bedford, OH). The EEG recordings were recorded in an eyes-open condition, using BrainAvatar 4.6.4 (BrainMaster Technologies, Bedford, OH).

The EEG signals were imported into the Analyzer of BrainAvatar 4.6.4, a software for computation and analysis, where artefacts (i.e., activity collected from the EEG that was not produced by the brain) were visually inspected and removed. The EEG was processed with Linked Ears Montage, and Theta-to-Beta ratio values were obtained for each participant. The Theta and Beta ranges were 4–8 Hz and 13–21 Hz, respectively (Demos, 2019).

It was explained to each participant or to their parents how the different treatments (T/B and ZT) worked according to the scientific data available at that moment, and they chose which one to follow. The final layout for the treatments was that nine subjects followed the T/B and six followed the ZT.

Neurofeedback

Theta/Beta Protocol Group

This group received a 30-min session twice a week in which the T/B protocol in Cz was applied with a total of 10 sessions. The sessions entailed inhibiting the Theta band, enhancing Beta, and inhibiting HiBeta. In our study, HiBeta range was 21–30 Hz. Short videos selected by the subjects were used to produce the feedback. A dimmer was placed in front of the video screen which brightened up when the patient met the criteria of the protocol (Theta and HiBeta below the selected threshold, and Beta above the selected threshold) or became opaque, preventing the video from being viewed, when the criteria were not met.

Z-scores Training Neurofeedback Group

This group followed the Brain Avatar's ZT PZOKUL protocol (BrainMaster Technologies, Inc., Bedford, OH) twice a week during a 30-min session with a total of 10 sessions. The locations F3, F4, P3, and P4 were selected since this combination of locations in ZT protocols has been suggested to regulate whole head EEG activity (Collura, 2008). This protocol has a training threshold that auto-adjusts based on the percentage of *Z*-scores within the upper and lower selected limits. We used a one standard deviation as the upper and lower thresholds following the indications of some authors (Thatcher & Lubar, 2015). Short videos selected by the subjects were used to produce the feedback. A dimmer was placed in front of the video screen which brightened up when the patient met the criteria or became opaque, preventing the video from being viewed, when the criteria were not met.

Statistical Analysis

The data were analyzed using version 25 SPSS software. Since our sample was small and heterogeneous, Mann-Whitney-U and Wilcoxon signed-rank test analyses were utilized. Statistical significance was set at $\alpha = 0.05$ for all analyses. Cohen's *d* effect size was also calculated to assess the magnitude of the observed changes.

Results

Our sample was composed of 15 subjects with ADHD, 12 boys and 3 girls, which corresponds to the common 4:1 ratio in this disorder. There were six subjects in the ZT group and nine subjects in the T/B group. Theta-to-Beta ratios were calculated for each subject and group at Cz location. Those results can be found in Table 1. Both groups showed no significant differences regarding age ($U = 19.50$, $p =$

.390), and there were no significant differences in the pretreatment Theta-to-Beta ratio between the groups (U = 24, p = .723).

Table 1

Age and pretreatment and posttreatment T/B ratios at Cz

	ZT Group		T/B Group	
	M	*SD*	*M*	*SD*
Age	11.17	3.97	12.56	3.28
Pre T/B ratio	2.63	0.11	2.62	0.21
Post T/B ratio	1.61	0.32	2.47	0.17

After 10 treatment sessions, both groups presented a decrease of Theta-to-Beta ratio (Figure 1). The ZT group showed an average difference of 1.02 points, which was statistically significant (W = −2.20, p = .02) and the T/B group showed an average difference of 0.15 points, which was not significant (W = −1.48, p = .110). Theta-to-Beta ratio's difference between both groups following the intervention was statistically significant (U = 5, p = .009). The Cohen's d analysis found a large effect of group type (d = 1.39).

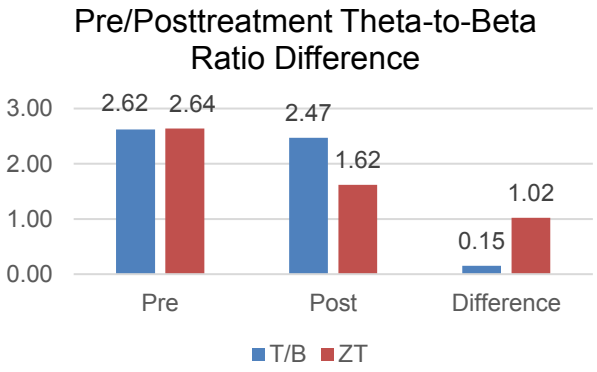

Figure 1. Theta-to-Beta Ratio, at Cz, for each group preneurofeedback (pre), postneurofeedback (post) and difference pre–post (difference). The Theta and Beta ranges were 4–8 Hz and 13–21 Hz, respectively.

Discussion

This retrospective study aimed to analyze the efficacy of a ZT intervention to regulate Theta-to-Beta ratio in a combined type ADHD sample. According to our findings, ZT is probably an effective way to regulate Theta-to-Beta ratio. Only 10 sessions created a large and statistically significant change in the desired direction. In addition, it had a bigger impact than the active control condition (T/B protocol) which did not produce a significant change after 10 sessions.

Even though the T/B has shown its efficacy in reducing Theta-to-Beta ratio (Janssen et al., 2017) and in our study it also created changes in the desired direction, they were not significant. One reason could be the fact that it usually takes the power classical protocols up to 40 sessions or more to produce a significant effect (Bell, Moss, & Kallmeyer, 2019; Krigbaum & Wigton, 2014; Sürmeli & Ertem, 2011; Sürmeli et al., 2012; Thatcher, 2013; Wigton, 2013; Wigton & Krigbaum, 2015).

On the other hand, our results are consistent with previous studies about ZT, in which there were relevant results in a few sessions (Bell et al., 2019; Pérez-Elvira et al., 2019; Wigton & Krigbaum, 2015). Wigton and Krigbaum (2015), and Krigbaum and Wigton (2015), developed a method to monitor the progression of the ZT treatment and observed a normalization of the patients' EEG in approximately 10 intervention sessions. In the same vein, Groeneveld et al. (2019), following Krigbaum and Wigton's monitoring method (2015), found a normalization of the EEG in an average 30 ZT sessions. Pérez-Elvira et al. (2019) reached the normalization of the EEG of a patient with insomnia in 30 ZT sessions.

A possible reason for the ZT´s superiority over the T/B protocol, at least regarding the number of sessions that are needed on each one, could be that amplitude NF allows to control a small number of factors at the same time (Soutar & Longo, 2011). However, ZT could simultaneously train up to 248 Z-scores (with 4 EEG channels) at the same time (Collura et al., 2010; Gracefire, 2016).

Even though there are enough studies that compare the use of NF, mostly its classical protocols, with other treatments, such as cognitive behavioral therapy (Moreno-García, Delgado-Pardo, Camacho-Vara de Rey, Meneres-Sancho, & Servera-Barceló, 2015; Moreno-García, Meneres-Sancho, Camacho-Vara de Rey, & Servera, 2019; Schönenberg et al., 2017), pharmacological (Bioulac et al., 2019; González-Castro, Cueli, Rodríguez, García, & Álvarez, 2016; Meisel, Servera, Garcia-Banda, Cardo, & Moreno, 2014; Moreno-García et al., 2015, 2019; Razoki, 2018; Rossiter & La Vaque, 1995; Yan, Zhang, Yuan, & Cortese, 2018), there was only one prior study

(Hammer et al., 2011) that had compared the efficacy of ZT with the one of a classical protocol. Hammer et al. (2011) found in their study improvements in sleep quality after 10 ZT sessions in people with insomnia. But, in contrast to Hammer et al. (2011) who used a classical sensorimotor modified protocol combined with ZT, we used as active control a group who followed the classical T/B protocol.

This study had several obvious limitations; the most important ones being the small size of the sample and the lack of follow-up. Another limitation was the fact that the study was aimed at both treatment methodologies (ZT and T/B) without explicitly considering the clinical variables, aside from the ADHD diagnosis, and thus there were no psychometric measures included. However, the study has provided certain evidence about the efficacy and the speed in reducing high Theta-to-Beta ratio, thus offering a foundation to study the same effect in future and more controlled investigations.

Moreover, the study has included effect size metrics, making it a candidate to be included in future meta-analysis. In conclusion, ZT seems to be a good and quick approach to reduce Theta-to-Beta ratio in ADHD patients.

Author Disclosure

The authors declare that they have no grants, financial interests, or conflicts of interest to disclose. This work is part of a doctoral thesis by Rubén Pérez-Elvira.

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NeuroRegulation

The Effect of Infraslow Frequency Neurofeedback on Autonomic Nervous System Function in Adults with Anxiety and Related Diseases

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Abstract

Peripheral body monitoring of autonomic nervous system (ANS) response has been routinely applied during infraslow fluctuation (ISF) neurofeedback training. This study hypothesized that ISF training has a distinct physiological effect on an individual that can be revealed by measuring autonomic function with peripheral biofeedback metrics that included heart rate variability (HRV), muscle tension, skin temperature, skin conductance, heart rate, respiration rate, and blood pressure. **Methods**. Thirty adults between the ages of 18 and 55, primarily with anxiety, were randomized into two groups: 20 in the experimental group and 9 in the control group. The experimental group completed 10 ISF neurofeedback training sessions while continuous monitoring of ANS changes was applied. The same process was completed for a control group that received one-channel sensorimotor rhythm (SMR) neurofeedback training. **Results.** Significant changes were seen in the skin conductance (p < .0001), electromyography (p = .01), very low frequency (p = .004), low frequency of HRV (p = .05) and blood pressure (systolic change p = .049) in the experimental group. No significant changes were seen in the control group. **Conclusion.** The study demonstrated that ISF neurofeedback training impacts the ANS as measured by peripheral biofeedback indicators.

Keywords: neurofeedback; infraslow frequency; electroencephalogram; autonomic; blood pressure; electromyogram; skin conductance; breathing; heart rate variability; inter beat interval; autonomic function

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Introduction

The body has a natural and sophisticated mechanism which ensures that there is as much physiological stability as possible while we navigate through life. The control center for this homeostatic mechanism is the autonomic nervous system (ANS) which unconsciously controls and manages heart rate (HR), breathing, blood pressure, and various other functions. It consists of the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) which complement each other and so regulate physiological processes in response to external or internal stimuli. When there is a stress reaction, the SNS will respond and shift the body from its normal state of equilibrium. Once the stimulus is over, the PNS will shift it back towards its point of equilibrium (Figure 1). If this process becomes less responsive and an individual remains in a state of increased or decreased arousal, it can lead to disease. Control of the ANS has largely been attributed to the midbrain structures and the hypothalamic pituitary adrenal axis. The contribution of behavioral networks in cortex to ANS regulation has only recently been understood (Beissner, Meissner, Bär, & Napadow, 2013; Thayer & Lane, 2000).

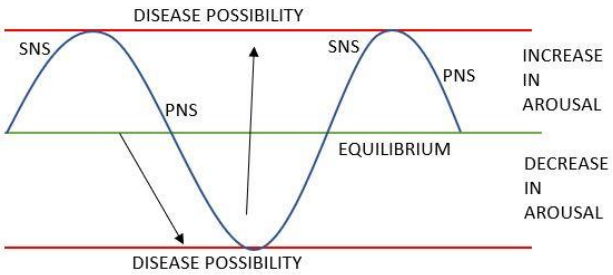

Figure 1. The autonomic nervous system and how it equilizes.

There is increasing evidence that mental and physical problems experienced by individuals are the result of flawed functional connectivity within resting state networks (Warren, Chou, & Steklis, 2020). Importantly, the underlying functional architecture of the brain is coordinated by infraslow frequencies. This superstructure of oscillations coordinate both the connections in and decoupling between active behavioral networks (Palva & Palva, 2012). These slow periodicities, described as less than 0.1 Hz, were first linked with behavior by Nina Aladjalova in the 1950s in the Soviet Union. With her crude chopper stabilized amplifiers, Aladjalova associated infraslow activity with parasympathetic, reparative response (Aladjalova, 1957). Recently, the development of commercially available direct current (DC) coupled amplifiers has led to an explosion of research of human behavior and the infraslow frequencies. In the last 20 years, studies of infraslow frequencies and attention-deficit/hyperactivity disorder (ADHD), hormone response, pain, memory, sleep, and seizure, to name just a few, have been published worldwide in journals and textbooks (Alshelh et al., 2016; Broyd, Helps, & Sonuga-Barke, 2011; Helfrich, Mander, Jagust, Knight, & Walker, 2018; Joshi et al., 2018; Lecci et al., 2017; Marshall, Mölle, Fehm, & Born, 2008). The centrality of the low regime in cortex is emphasized by recent evidence that suggests that these slow oscillations play a role in synchronizing faster activity and modulating cortical excitability (Hiltunen et al., 2014; Leong et al., 2018). The commercial availability of DC coupled amplifiers allowed clinicians to explore bandwidths outside of the traditionally defined analog limit of 0.5–50 Hz in clinical neurofeedback. Training these very low frequencies was dubbed infraslow fluctuation (ISF) training due to the interaction of frequency and DC potential shift (Smith, Collura, Ferrara, & de Vries, 2014).

The clinician's primary goal in ISF training is to find a client's optimum frequency (OF). Clinical experience has shown that this results in the best treatment response. Electrodes are placed at specific locations according to the internationally recognized 10/20 system (Silverman, 1963; Wei, Wu, & Tudor, 2017). To begin the optimization process, one of three potential bipolar montage sites are chosen depending on the results of the quantitative electroencephalogram (qEEG) and the client's chief complaint.

During ISF training the client experiences emergent state shifts that we refer to as symptoms of training. The symptoms that clients experience during and after the training session guide the clinician to the OF. Many clinicians use peripheral biofeedback measurements like skin temperature, skin conductance, or electromyography (EMG) as a guide to optimization as well. Once the optimum frequency is identified clients report improved sleep regulation, anxiety reduction, better appetite awareness and control, improved sexual function, and reduced reactivity to sound—all indications of improved sympathetic–parasympathetic response (Fink, Bronas, & Calik, 2018; McCorry, 2007).

The ANS has a central role in maintaining sympathetic–parasympathetic and cardiovascular homeostasis. It includes vagal cholinergic and sympathetic noradrenergic nerves supplying the heart and sympathetic noradrenergic nerves that enmesh arterioles. These nerves play a role in peripheral resistance to blood flow in the body, and therefore blood pressure. That is why clinicians and researchers have long sought valid, noninvasive, quantitative means to identify pathophysiologically relevant abnormalities of these systems (Goldstein, Bentho, Park, & Sharabi, 2011).

Heart rate variability (HRV) is one of the best-known means of physiological measurement and is defined as the beat to beat variability in the sinus rhythm over time. There is mounting evidence that points to the efficacy of HRV training in clinical practice due to its impact on sympathetic–parasympathetic function (Peper, Harvey, Lin, Tylova, & Moss, 2015). The monitoring of sympathetic–parasympathetic response during ISF neurofeedback training may aid in the identification of the client's optimum frequency (Camp, Remus, Kalburgi, Porterfield, & Johnson, 2012; Collura, 2013). Measurements of high frequency (HF) and low frequency (LF) power are good indicators of changes in HRV. It has been shown that HF mainly reflects respiratory sinus arrhythmia and HF HRV is understood to reflect the parasympathetic branch of the ANS (Akselrod et al., 1981; Stein, Bosner, Kleiger, & Conger, 1994). LF is

not as well understood, but it is believed that LF indicates baroreflex functionality and cardiac autonomic outflow (Goldstein et al., 2011). LF is often described in the literature as reflecting a combination of sympathetic and parasympathetic influences. HRV can be a valuable tool in the estimation of autonomic status especially when combined with other peripheral nervous system measures (Li, Rüdiger, & Ziemssen, 2019).

Studies propose that specific emotions may elicit distinct autonomic functions. Biofeedback measures may correlate with specific emotions; for example, temperature, HR, and skin conductance may correlate to fear, joy, sadness, and anger. This suggests that the correlation of emotional state with autonomic response may be possible through the implementation of biofeedback methods (Collet, Vernet-Maury, Delhomme, & Dittmar, 1997; Levenson, 1992).

Infraslow training is a recent addition to the relatively young field of neurofeedback. While the literature is growing rapidly (Leong et al., 2018; Mathew, Adhia, Smith, De Ridder, & Mani, 2020; Smith, 2013; Smith et al., 2014; Smith, Leiderman, & de Vries, 2017), the physiological systems involved and full impact on the body are not yet well understood. The aim of this research is threefold: (1) to contribute to the methods' scientific validity and eliminate speculation as to the physiological systems involved, (2) to identify the measurable responses that reveal the most sensitive and so the fastest path to optimization, and (3) to identify the best objective measure to help clients who lack subjective awareness of their physiological responses.

Methods

Participants and Setting

Sampling was randomized (Figure 1) and consisted of a population group that had already decided of their own volition to do neurofeedback training. These participants (Table 1) were randomly assigned to either the ISF or control group. All neurofeedback training was completed in a clinical setting.

Approval from the University of Pretoria Health Sciences Ethical Committee was obtained prior to the start of the study, and all participants completed an informed consent document.

Inclusion/Exclusion Criteria

Inclusion criteria.

- Reports of high anxiety.
- Reports of daily problems with concentration and memory.
- Complaints of sleep problems.
- Reports of emotional or anger control problems.
- Subjects that were able to participate in at least two training sessions per week.
- Subjects that completed a minimum of 10 sessions of neurofeedback training.

Exclusion criteria.

- Subjects using recreational drugs.
- Subjects using benzodiazepines.
- Subjects using any new form of medication during the study period that may influence the outcome.
- Subjects unable to complete a minimum of 10 training sessions.
- Subjects unable to attend two training sessions per week.

Screening Questionnaires

The subjects completed a clinical interview and an evaluation questionnaire to determine current function. The questionnaire was used by all ISF practitioners participating in the study to develop a broad range of information on their subjects.

From clinical interviews and the questionnaire, it was determined that the five main complaints shared by participants were:

- Anxiety/panic attacks (19 participants)
- Difficulty with either falling asleep or maintaining sleep (16 participants)
- Irritation/anger problems (7 participants)
- Executive function problems: concentration/ focus/memory complaints (20 participants)
- Constipation and or irritable bowls (6 participants)

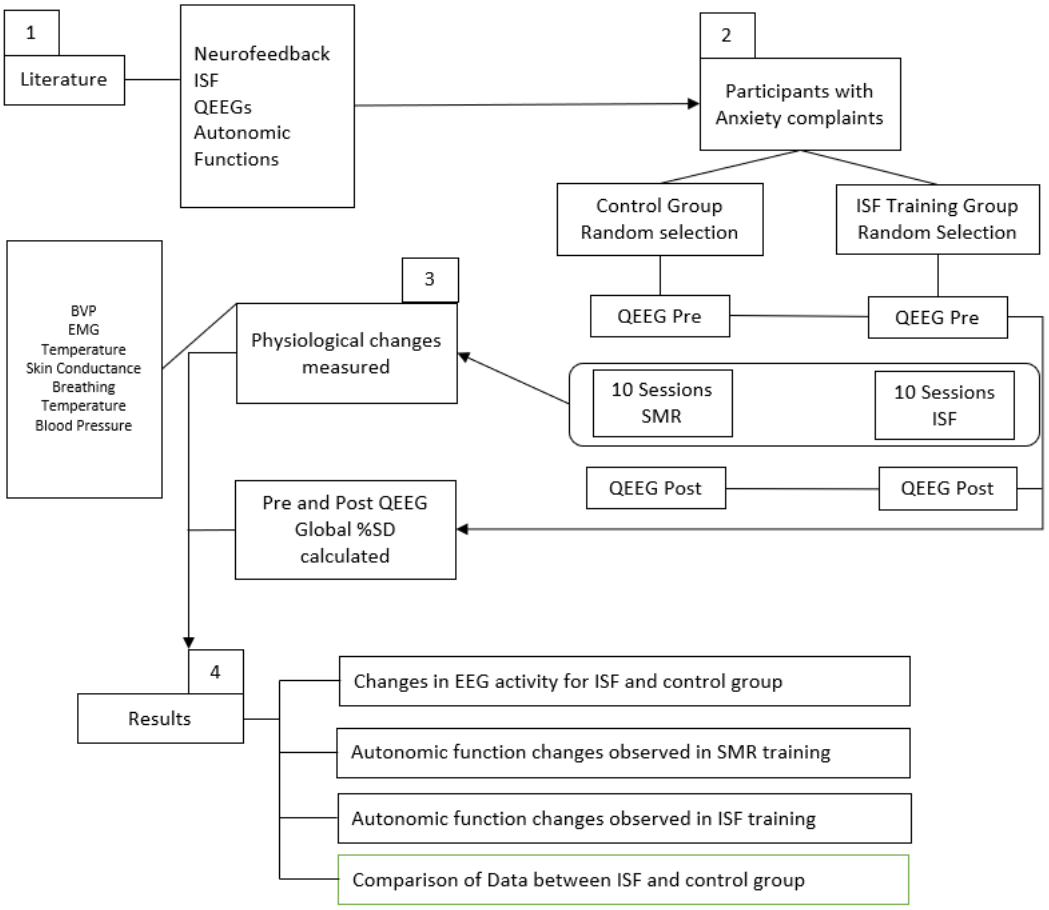

Figure 2. Consort flow chart.

Table 1
Participant demographics

Subject	Sex	Handedness	Age (Years)
C1	M	Left	36
C2	M	Right	39
C3	M	Right	26
C4	F	Right	36
C5	M	Left	19
C6	M	Right	55
C7	M	Right	18
C8	F	Right	55
C9	M	Left	26
S1	M	Right	35
S2	M	Right	22
S3	F	Right	23
S4	F	Right	24
S5	M	Right	49
S6	F	Left	36
S7	F	Right	23
S8	F	Right	23
S9	M	Right	37
S10	M	Right	24
S11	M	Right	48
S12	M	Right	49
S13	F	Right	38
S14	M	Right	22
S15	M	Right	55
S16	M	Right	38
S17	F	Right	49
S18	F	Right	34
S19	F	Right	27
S20	F	Right	18
Total Male	17	Mean Age	33.9
Total Female	12	– Control	34.4
		– Experimental	33.7

Physiological Data Monitoring

The ProComp Infiniti (Thought Technology Ltd., Montreal, Canada) was developed for the intended purpose of biofeedback, relaxation, and muscle re-education. It is an 8-channel multimodality device that provides real-time computerized biofeedback and data acquisition. The sampling rate is 2048 samples per second in two of the channels and 256 samples per second in the other six channels. The encoder can be used to render a wide range of physiological signs to be used in clinical observation as well as biofeedback.

The following measures were used in the study:

- Electromyography (EMG)
- Skin conductance
- Skin temperature
- Blood volume pulse (BVP), HR, and amplitude
- Breathing rate
- Blood pressure (Braun VitalScan 3 Wrist blood pressure monitor)

The BioGraph Infiniti software version 6.0 (Thought Technology Ltd., Montreal, Canada) allows simultaneous monitoring of the above mentioned physiological parameters (Huster, Mokom, Enriquez-Geppert, & Herrmann, 2014).

The EMG triode sensor was placed on the trapezius muscle on the right shoulder. The temperature sensor was fastened to the right thumb with a Velcro strap for all clients. The skin conductance sensor consists of two sensors that were placed on the second and third fingers. The BVP sensor was placed on the ring finger also with a Velcro strap. Breathing rate and amplitude was measured using a strap around the abdomen. The resting blood pressure was measured before and after each session while the participant remained in a seated position by making use of a wrist cuff and the values for systolic and diastolic blood pressure were recorded in millimeters of mercury (mmHg; Huster et al., 2014).

No biofeedback training was done, and the client never saw the physiological measurements so that they were never cognitively aware of any changes taking place. The measurements were recorded for 34 min, of which 30 min was the length of an ISF training session and 2 min pre- and postsession.

ISF Neurofeedback

The Discovery 24-channel EEG amplifier (BrainMaster Technologies, Inc., Bedford, OH) is a physiological monitoring and feedback system. It offers monitoring and feedback of brain signals that include the measurement of EEG, direct current, and slow cortical potentials (DC/SCP).

The BrainMaster Atlantis 4x4 (BrainMaster Technologies, Inc., Bedford, OH) 4-channel EEG amplifier is a physiological monitoring and feedback system. Just like the BrainMaster Discovery, it offers monitoring and feedback of EEG and DC/SCP. Each area on the scalp was cleaned using NuPrep skin preparation gel. Electrodes were then pressed onto the cleaned area using 10/20 conductive paste.

Training was done using a bipolar montage. A two-channel linked ear electrode array was implemented. This allowed for *Z*-score and amplitude monitoring at each site in a linked ear montage while bipolar training was simultaneously accomplished in a third virtual channel. Two active electrodes were placed at either T3-T4 or T4-P4. Two references were placed on the mastoid bone behind the ears. The ground was placed centrally at the Cz position according to the International 10/20 System. The duration of a session was 30 min.

Training was done via visual and auditory feedback. The subjects heard two reward sounds—a low tone when the amplitude decreased and a high tone when it increased. It is an instant reward and continues for the duration of the condition. There was no refractory period between rewards which allows for the rapid transmission of information to the subject concerning changes in the amplitude and phase of the ISF signal (Smith et al., 2014).

The objective in infraslow neurofeedback training is to find a frequency that produces a state of focus and relaxation within a client. Changes in frequency are guided by the changes in state that the subject experiences. These changes in state or “symptoms of training” reflect shifts along the autonomic spectrum. For instance, a subject may experience her eyes watering, a parasympathetic response, or her pupils becoming dilated, a sympathetic response. The therapist makes changes in frequency that reduce the targeted symptom of training and so moves a client closer to autonomic quiescence.

Recorded data was stored to later be statistically analyzed to track changes that occurred in session and from session to session.

Sensorimotor Rhythm (SMR)/Control Group

Each area on the scalp was cleaned using NuPrep skin preparation gel. Electrodes were then pressed onto the cleaned area using 10/20 conductive paste. Three electrodes were used. One active placed at the C4 site, one reference placed on the left mastoid, and a ground placed on the right mastoid. The duration of the training session was 30 min. The client watched a movie as did clients in the experimental group. In the background they could hear a tone which sounded when all parameters were met. To aid as visual feedback, the screen was dimmed when the client was not meeting the required thresholds and brightened when conditions were met. Neurofeedback for the control group consisted of a sensorimotor rhythm (SMR) protocol that enhanced 12–15 Hz activity and inhibited 3.5–7.0 Hz and 20–30 Hz activity. For some clients, an adjustment was made to reward 12–16 Hz as they reported feeling more focused with this frequency band.

The same set of physiological measurements as described for the ISF training group were gathered for the SMR training sessions. Like the experimental group, the control group's physiological monitoring was also recorded for the 30-min duration of the session with an additional 2 min pre- and post-session.

Statistical Analysis

The following measurements were taken and statistically analyzed to determine which changes show the most statistically relevant results:

BVP amplitude, BVP inter-beat-interval (IBI), BVP HR from IBI, BVP HR (smoothed), BVP IBI peak frequency, BVP very low frequency (VLF) % power, BVP LF % power, BVP HF % power, respiratory amplitude (abdominal), respiration rate, HR max – HR min, BVP amplitude mean, BVP HR mean (beats/min), BVP peak frequency mean (Hz), BVP IBI standard deviation of the RR interval (SDRR), BVP VLF % power mean, BVP LF % power mean, BVP HF % power mean, BVP VLF total power mean, BVP LF total power mean, BVP HF total power mean, BVP LF/HF (means), EMG mean (μV), skin conductance mean (μS), temperature mean (deg), respiratory rate mean (breaths/min), BVP IBI peak amplitude, BVP IBI peak amplitude trigger, BVP IBI NN intervals, BVP IBI percentage of NN intervals (pNN), BVP IBI pNN intervals (%).

All electronic data was stored on a laptop of the investigator, and daily backups were made to a cloud storage account.

All physiological data gathered in the BioGraph Infiniti software was scanned for any artefact. Identified artefact was removed before raw data was analyzed statistically.

The mean, median, standard deviation, and inter-quartile range were used to describe the statistical findings. To determine if there were trends in the ISF parameters over the 10 sessions, a linear mixed model was used where random intercept and slope effects as well as the difference between pre–post sessions were evaluated. The test was evaluated at a level of 5% significance, and all analysis was done with STATA 14.

Results

HRV Very Low Frequency (VLF) and Low Frequency (LF) Power

By making use of a fast Fourier transform (FFT) allorhythmia, the heart rhythm can be decomposed into different frequencies. This can be graphically represented and distinguishes HF, LF, and VLF. The amplitude of these frequencies is usually very different for an individual in a high stress state than for one who is relaxed (Figure 3).

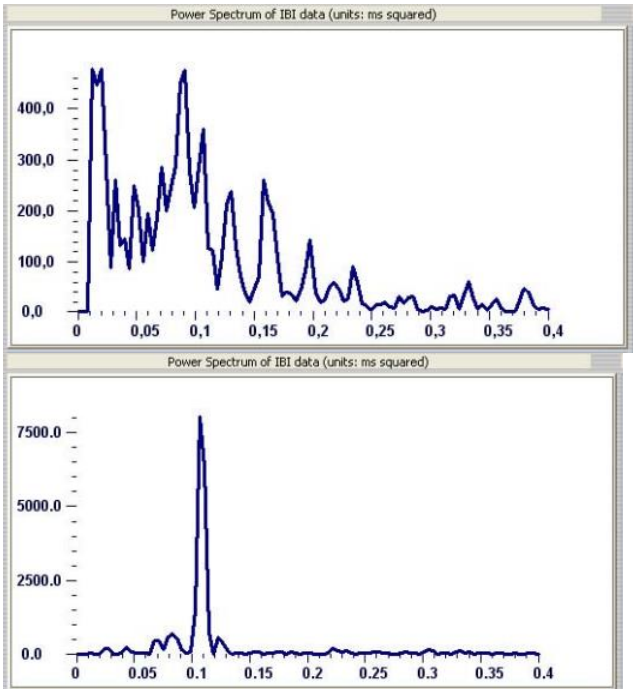

Figure 3. Comparison of HRV frequencies in a stress state (top) compared to a relaxed state (bottom; Thought Technology, 2014).

HRV depends on the activity of the ANS. The VLF has been found to be a major determinant of physical activity, and it has also been proposed as a marker of sympathetic activity. It is said to affect the vascular tone loop of the baroreflex system, thermal regulation, and activity of the renin-angiotensin system. A decrease in the VLF is hypothesized to be an indication of sympathetic blocking (Sztajzel, 2004).

The LF is an indication of both sympathetic and parasympathetic activity and is indicative of activity of the baroreflex function. The HF is indicative of parasympathetic activity (Sztajzel, 2004). A decrease in HF is theorized to reflect decreased vagal activity leading to decreased parasympathetic activation (Rodin, Bornfleth, & Johnson, 2017). There is controversy with respect to the ratio of LF to HF. Some consider it to be a measurement of balance between the sympathetic and parasympathetic nervous systems while others dispute that hypothesis (Eckberg, 1997; Malik, 1998).

When looking at the *t*-test results for the different components when comparing session 1 to session 10 the following values were obtained:

- VLF, $p = .05$. This indicates a significant decrease in the VLF % power. This may be an indication of decreased sympathetic activity as it is hypothesized that increased VLF represents sympathetic blocking (van der Kruijs et al., 2016).
- LF, $p = .004$. This indicates a significant increase in the LF % power. It reflects sympathetic and vagal influences on cardiac control via baroreceptor-mediated regulation of blood pressure according to some theories. Others suggest that it is a marker for sympathetic modulation (Prinsloo et al., 2011). The range for LF frequency is 0.04–0.15 Hz with PNS dominance believed to be from 0.04–0.70 Hz. When looking at the BVP peak mean frequency measured, the peak mean frequency measured at session 1 was 0.1 Hz and this decreased to 0.08 Hz at session 10. Due to it appearing insignificant the data was not further included in the larger results, but it does however indicate a possible shift towards being more parasympathetic dominant.

EMG Mean

Anxiety is often accompanied by muscle over-activity (Pluess, Conrad, & Wilhelm, 2009). The amplitude of action potentials recorded from the muscles of individuals with anxiety is higher than healthy controls. One would expect a decrease in muscle tension with relaxation and parasympathetic activation (Barrett, Barman, Boitano, & Brooks, 2012).

At rest there should be very low muscle activity as no muscle fibres are being recruited. Under chronic or repeated stress, certain muscles may not be able to return to a resting state. This is known as “residual” muscle tension and commonly causes back, shoulder, or neck pain. This can lead to increased fatigue (Sainsbury & Gibson, 1954). A high resting muscle tension also leads to an impedance of blood flow which slows down healing. Adaptive habits such as muscle guarding can also have a negative impact by reducing flexibility and decreasing muscular efficiency (Sainsbury & Gibson, 1954).

In the control group a change was seen in the positive direction when comparing session 1 to session 10. However, it was not statistically significant.

The *p*-value for EMG in the experimental group is $p = .01$ when comparing session 1 to session 10, which shows a significant decrease in muscle tension and more specifically the resting muscle tension.

Skin Conductance Mean

Skin conductance is generally accepted as one of the most sensitive measures of emotional arousal (Lin, Lin, Lin, & Huang, 2011). Skin conductance biofeedback is used to help an individual become aware of unconscious physiological responses to stress. A certain level of arousal is important, but if this increases too much it can lead to fatigue and anxiety as shown in Figure 4.

The *p*-value for skin conductance was $p < .0001$, which indicates a significant decrease in the experimental group when comparing session 1 to session 10. This is indicative of lower arousal levels, which is a positive change in a high anxiety population group where very high arousal levels are typically noted. There is also a decrease noted in the standard deviation of the group as well as a decrease of the median. This can be an indication of decreased anxiety as an increase in electrodermal activity is commonly reported in high anxiety individuals.

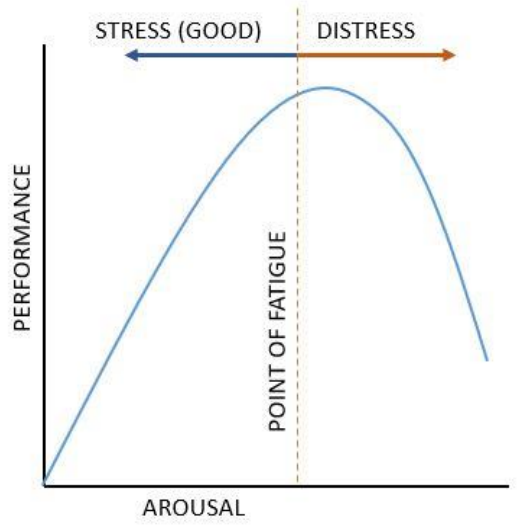

Figure 4. How stress and arousal influences performance.

Blood Pressure

The normal blood pressure in the brachial artery is approximately 120/70 mmHg in young adults (Figure 5). It is affected by cardiac output, peripheral resistance, and emotion. Individuals with hypertension were able to lower blood pressure by engaging in anxiety treatment (Grossman et al., 2005).

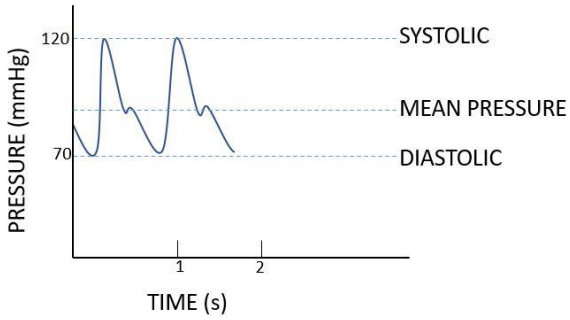

Figure 5. The Brachial artery pressure curve in a normal young adult indicating the relation of systolic and diastolic pressure to mean pressure.

There was a significant change noted in the post systolic comparison in the experimental group, *p*-value of .049. The diastolic value also approached a significant change, with a *p*-value of .083. Brachial artery pressure monitoring reveals a significant effect on the blood pressure of participants when doing ISF training when compared to the control group where no significant changes were noted.

As with the heart rate analysis there was also a very large change in the standard deviation of the group indicating that we are dealing with a nonlinear change. There appears to be a homeostatic change towards what is considered normal (Figure 6).

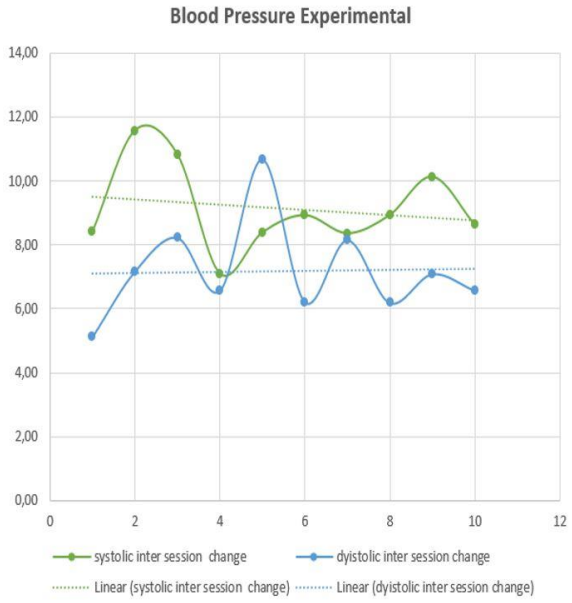

Figure 6a. In session change towards normal values for blood pressure experimental. x = session number, y = change towards normal.

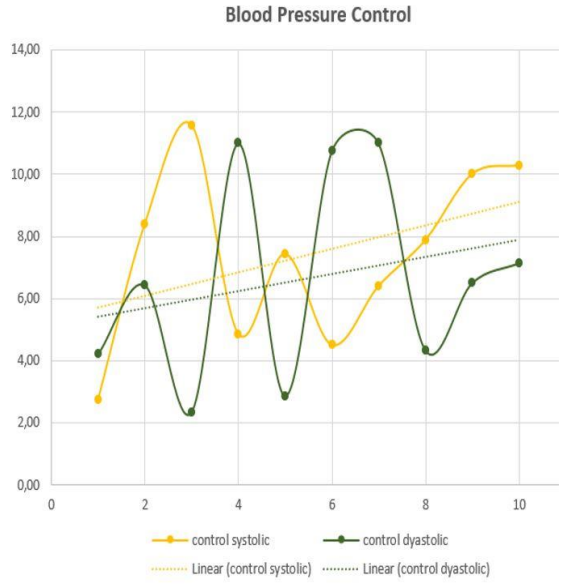

Figure 6b. In session change towards normal values for blood pressure control. x = session number, y = change towards normal.

Limitations of This Study and Recommendations for Future Research

The size of the experimental and control groups defines this research as a pilot study. A larger study is warranted with a larger group of both experimental and control participants. There was no blinding involved in this study. A future study may include blinding of the rater and the subject. That will give an even clearer indication of what variables are purely influenced by the ISF training.

Conclusion

In the evaluation of the changes in autonomic function, significant changes were noted in the experimental group for blood pressure (systolic), skin conductance, electromyogram, and, in the analysis of the frequency domain of HRV, for % power VLF and % power LF. Table 2 summarizes the most significant *p*-values that were measured during the study. Heart rate data showing significant decrease was not noted, but when looking at the change towards normal a definite trend was seen wherein the standard deviation of the experimental group decreased and their heart rates either increased or decreased towards what is known as an age- and sex-related norm. The same was noted in the blood pressure readings, where the standard deviation of the experimental group decreased, and more participants BP values increased or decreased towards more normal values. In other words, closer to the normal range of 120/70. No significant changes were observed in the control group.

Table 2
Summary of p-values obtained

Variable	*p*-value ISF	*p*-value Amplitude (SMR)
HRV VLF Power	.050	.30
HRV LF Power	.004	.98
EMG Mean	.010	.33
Skin Conductance Mean	< .0001	.39
Blood Pressure (Systolic)	.049	.74
Blood Pressure (Diastolic)	.083	.79

Physiological monitoring may be a useful tool in future studies to determine the ANS impact of neurofeedback training. In the present study, our data suggest that the mechanism of action of ISF neurofeedback training may involve the ANS. Our data also suggest that SMR training does not involve ANS function. While not unique in comparing one form of neurofeedback with another, the current study may be the first to provide data that differentiates the functional impact of one form of neurofeedback training from another. Finally, the results of this study suggest that peripheral biofeedback measures of electromyogram, skin conductance, the frequency bands of HRV, and blood pressure may help in the frequency optimization process of infraslow neurofeedback training. These peripheral measures help to clarify the physiological impact on clients who may lack the subjective awareness to report accurately.

Author Declaration

Mark Smith is the owner of Neurofeedback Therapy Services of New York. NTSNY produces neurofeedback workshops that include teaching infraslow fluctuation neurofeedback training. He provided neurofeedback protocols for this research and participated in editing of the final version of the manuscript. He did not participate in the research design, implementation, or evaluation of the data. All other authors declare no competing interests.

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NeuroRegulation

Effect of EEG Neurofeedback Training in Patients with Moderate–Severe Traumatic Brain Injury: A Clinical and Electrophysiological Outcome Study

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Abstract

Traumatic brain injury (TBI) is a leading cause of death, and its survivors with a disability are considered to be an important global health priority. In view of a diverse range of disability and its impact on TBI survivors, the need for effective rehabilitation modalities is on a high rise. Therefore, the present study was aimed to investigate the efficacy of EEG neurofeedback training (EEG-NFT) in moderate–severe TBI patients on their clinical and electrophysiological outcomes. The study was an experimental longitudinal design with a pre-post comparison. A total of 14 TBI patients in a postinjury period between 3 months to 2 years were recruited. All participants received twenty sessions of EEG-NFT. Baseline and post-NFT comparisons were made on postconcussion symptoms (PCS) and electrophysiological variables. The result indicates a significant reduction in the severity of PCS following EEG-NFT. A consistent pattern of reduced slow waves and fast waves amplitude ratios was also noted at post-NFT, although it was not significant across all the brain regions. The present study suggests EEG-NFT as a contributing factor in improving PCS and normalization of qEEG in TBI patients, which holds an implication for clinical decision-making of EEG-NFT as a viable alternative to be offered to TBI patients.

Keywords: neurofeedback; traumatic brain injury; EEG; postconcussion symptoms; electrophysiology

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Introduction

Traumatic brain injury (TBI) disrupts the normal functioning of the brain caused by a bump, blow, or jolt to the head (Marr & Coronado, 2004). It is a major concern worldwide, also referred to as *"The Silent Epidemic"* (Rusnak, 2013; Vaishnavi, Rao, & Fann, 2009). The global incidence of TBI is estimated to be 69 million individuals per year (Dewan et al., 2018). In India, it is estimated that annually approximately 1.6 million individuals sustain a TBI (Gururaj, 2002). The prevalence of TBI increased by 8.4% from 1990 to 2016 and accounts for a considerable portion of the global injury burden (GBD 2016 TBI and SCI Collaborators, 2019). The major etiological factors of TBI are road traffic accidents (60%), falls (20–25%), and violence (10%; Gururaj, 2002). From 2003 to 2013, in India road accidents have increased by 5% per year while the population increased by 1.4% per year, suggesting a high prevalence of TBI (Singh, 2017).

TBI results in a large number of deaths or survivors with impairments in a wide array of cognitive domains such as executive functions (Azouvi et al., 2016), processing speed (Fong, Chan, Ng, & Ng, 2009), response inhibition (Dimoska-Di Marco, McDonald, Kelly, Tate, & Johnstone, 2011), memory

(West, Curtis, Greve, & Bianchini, 2011; Wright, Schmitter-Edgecombe, & Woo, 2010), and social cognition (Spikman, Timmerman, Milders, Veenstra, & van der Naalt, 2012). These impairments ascend to the behavioral, cognitive, emotional, and physical changes that affect a person's quality of life (QOL; Langlois, Rutland-Brown, & Wald, 2006). The cognitive functioning was found impaired in moderate–severe TBI patients even after two years postinjury (Schretlen & Shapiro, 2003). Postconcussion symptoms (PCS) are the most commonly reported sequelae of TBI, which include headache, dizziness, fatigue, temper, sleep disturbance, memory problems, blurred vision, poor concentration, anxiety, and irritability (Dikmen, Machamer, Fann, & Temkin, 2010; McLean, Dikmen, Temkin, Wyler, & Gale, 1984; Stålnacke, 2012). A significant range of psychiatric disorders such as depression, generalized anxiety disorder, posttraumatic stress disorder, and agoraphobia are found to be associated with posttraumatic injury (Bryant et al., 2010). Population-based studies report that patients with post-head-injury are more liable to develop epilepsy and a binge pattern of alcohol use (Christensen, 2012; Ferguson et al., 2010; Horner et al., 2005).

The consequences of TBI are not only circumscribed to these overt changes and dysfunctions but also lead to the disruptions and alterations of brain function, including changes in electrophysiological patterns. These alterations have been found to be associated with poor functional outcomes. EEG abnormalities can be focal, multifocal, or widespread depending upon the severity and location of the injury (Brigo & Mecarelli, 2019; Galovic, Schmitz, & Tettenborn, 2018). A considerable amount of studies has been shown to correspond to quantitative EEG (qEEG) changes after the concussion. The most common qEEG findings of persons with mild TBI (mTBI) are attenuated alpha frequency in the posterior region and increased theta activity (Arciniegas, 2011; Lewine et al., 2019; Nuwer, Hovda, Schrader, & Vespa, 2005; Tebano et al., 1988; Thatcher, Walker, Gerson, & Geisler, 1989). Acute disruption of cortical-thalamic networks led to an increase in delta and theta band and a decrease in beta band in TBI (Moeller, Tu, & Bazil, 2011). A consequential higher theta-alpha, theta-beta, and delta-alpha amplitude ratio and minimized EEG coherence were also noted in mTBI (Chen, Tao, & Chen, 2006; Modarres, Kuzma, Kretzmer, Pack, & Lim, 2016; Moeller et al., 2011; Watson et al., 1995). An epileptiform activity has been observed immediately followed by a diffuse slowing of the EEG after head injury (Walker, Kollros, & Case, 1945).

With a diverse range of disability and its impact on TBI survivors, new intervention modalities are being attempted to address the TBI-related issues. One of such modalities is EEG neurofeedback training (EEG-NFT) that uses electrophysiological measures of an individual to self-regulate their psychophysiological state (Ali, Viczko, & Smart, 2020). It is a noninvasive and nonpharmacological intervention based on the principles of operant conditioning. EEG-NFT has shown promising effects for ameliorating cognitive, behavioral, emotional, and physical dysfunctions among patients with TBI (Bennett et al., 2018; Keller, 2001; Munivenkatappa, Rajeswaran, Indira Devi, Bennet, & Upadhyay, 2014; Reddy, Rajeswaran, Devi, & Kandavel, 2013; Schoenberger, Shiflett, Esty, Ochs, & Matheis, 2001).

There are very limited to no studies being attempted of investigating clinical and electrophysiological changes in the moderate–severe TBI following EEG-NFT. Therefore, the present study uses the alpha reinforcement and theta inhibition training with the aim to reduce theta-alpha amplitude ratio to explore the electrophysiological alterations and the subsequent consequences on PCS among patients with moderate–severe TBI.

Methods and Materials

Participants

The sample comprised of 19 individuals (15 males and 4 females) diagnosed with TBI with normal or corrected hearing and vision in the age range of 18–50 years (mean age = 32.47 years; *SD* = 7.52). All participants with TBI had a Glasgow Coma Scale (GCS) score 12 or less with a postinjury period between 3 months to 2 years.

Participants with a diagnosis of mTBI (GCS: 13–15), with extracranial injuries, having a previous history of any comorbid neurological, psychiatric, or neurosurgical conditions, substance dependence, or mental retardation, and those who underwent any form of structured psychological intervention in the last year were excluded.

Procedure

After obtaining ethical clearance from the Institute Ethics Committee, a written informed consent form was sought from each participant who met inclusion criteria. Sociodemographic and clinical details were obtained, and baseline assessments were

conducted using the Rivermead Postconcussion Symptoms Questionnaire (RPQ) and a resting-state eyes-opened EEG recording. Following the baseline, all the participants received 20 sessions of EEG-NFT (those who completed 80% of sessions were also considered as completers). To examine the posttraining effect, the same baseline assessments were readministered immediately after the completion of EEG-NFT.

Rivermead Postconcussion Symptoms Questionnaire. It was used to assess the severity of the symptoms reporting in the postinjury period. It consists of 16 items assessing the most commonly reported PCS. The scores ranged from 0–4 where 0 indicates *the symptoms were not experienced*, 1 as *the symptom was no more a problem*, 2 as a *mild problem*, 3 as a *moderate problem*, and 4 as a *severe problem*. The participants were asked to rate the degree to which they experienced the symptoms. The total score represented the overall severity of PCS.

EEG recording. The EEG was conducted in a dimly lit, sound-attenuated room while the patient was seated comfortably. The recording was performed using SynAmps amplifiers (Compumedics Neuroscan, Charlotte, NC) with 32 Ag/AgCl, passive electrodes, fitted in the lycra stretch cap. Sampling frequency was kept at 1 kHz with a notch filter at 50 Hz. For eye movement, horizontal and vertical electrooculograms (EOG) were used bipolarly. One electrode on each mastoid was used as a reference. Electrodes impedance was ascertained less than 10 kΩ.

Intervention. The participants received 20 sessions of EEG-NFT conducted three times a week spanning the whole intervention program over a period of 2 months. It was carried out in a quiet, dimly lit room using a dedicated NFT system (Atlantis system, BrainMaster Technologies, Inc., Bedford, OH). Each participant received alpha-theta training (reinforcing alpha and inhibiting theta) activity with the aim of reducing the theta-alpha amplitude ratio. The active sites were fixed at O1 and O2 locations as per the 10–20 International system, each reference electrode on mastoid, and the ground electrode on the forehead. An abrasive gel was used to clean and prepare the scalp/skin followed by mounting the electrode using a conductive paste. Before the procedure, the goal and nature of the task were explained thoroughly to the participant. The display screen was selected as per the participants' choice. The participants were instructed to relax and focus on the screen. The reward was given through visual feedback (i.e., an increase in the score), which is displayed on the screen. Each NFT session lasted for 40-min duration. The training was done under the supervision of a trained clinical neuropsychologist (as per the norms of the rehabilitation council of India).

Data analysis. EEG data were analyzed using Neuroscan v4.5 (Compumedics Neuroscan, Charlotte, NC). Finite impulse response (FIR) bandpass filter from 0.1 to 30 Hz with a zero-phase shift at 12 dB/octave was applied to retain all relevant frequencies. For eye movement and other artifacts corrections, EEG data were marked manually, and spatial filter transformation was performed through principal component analysis (PCA) using singular value decomposition (SVD). Spectral analysis was performed on artifact-free data using 1024 data points. The signals from all the electrode positions underwent the fast Fourier transformation (FFT) on 500 ms epochs with a Hanning window of 1024 Hz. The resulting frequency spectra were divided into frequency band of interest: delta (0.1–3.0 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–30 Hz).

Further statistical analyses were carried out on SPSS v20.0. To check the normality for all values of interest Shapiro-Wilk test was performed (Shapiro & Wilk, 1965). The data group that was normally distributed a paired *t*-test was performed, while for the data that violated the normality assumption, a similar nonparametric Wilcoxon signed-rank test was used. A statistical significance threshold was set at $p < .05$.

Results

From the 19 participants with TBI who were recruited for EEG-NFT, two participants dropped out (did not turn up for sessions after baseline assessment or did not complete up to 80% of the sessions). From the remaining 17 participants, three patients could not complete baseline and/or post-NFT assessments.

Rivermead Postconcussion Symptoms Questionnaire (RPQ)

The RPQ-total score which forms the severity of TBI symptoms significantly reduced ($p = .018$) in post-NFT compared to the baseline. The effect size within-subjects also showed a medium effect (0.725) on RPQ-T scores (Table 1; Figure 1).

Table 1
Rivermead Postconcussion Symptoms Questionnaire total (RPQ-T) score (n = 14).

S. No.	Variable	Baseline (Mean ± *SD*)	Post-NFT (Mean ± *SD*)	*p* Value	Effect Size Cohen's *d*
1	RPQ-T	16.57 ± 10.523	10.29 ± 9.587	.018*	0.725

Note. * Significance at 0.05 level.

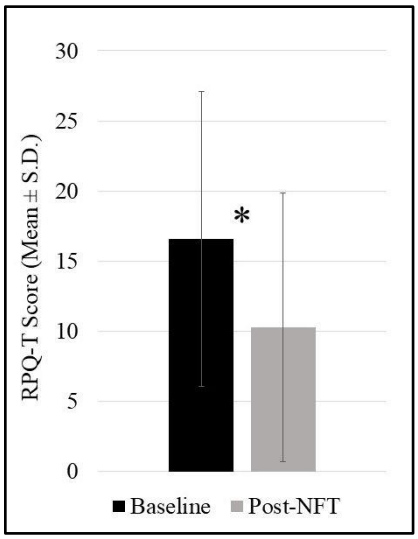

Figure 1. Rivermead Postconcussion Symptoms Questionnaire total (RPQ-T) score at baseline and post-NFT (*n* = 14).

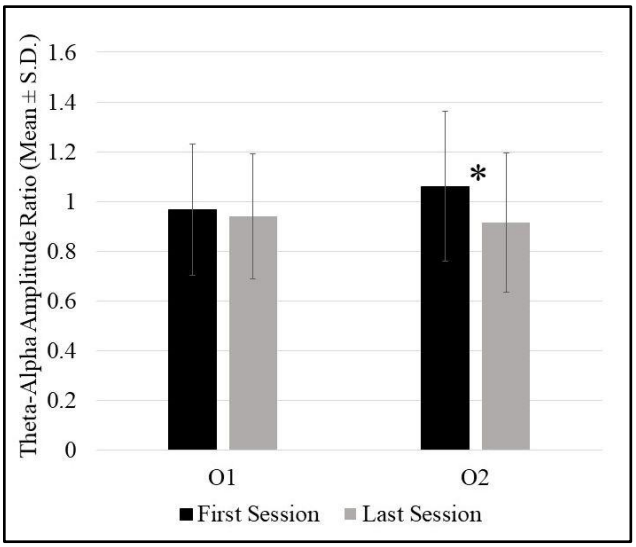

Figure 2. The average amplitude of theta-alpha ratio at O1 and O2 locations in the first and last session (*n* = 14).

EEG Neurofeedback Training (EEG-NFT)

For the EEG-NFT sessions, a ratio of an average amplitude of theta and alpha frequency bands was calculated at O1 and O2 locations in the first and last session. The result indicates that the theta-alpha ratio has reduced at both O1 (*p* = .665) and O2 (*p* = .011) locations, although this was not statistically significant at O1 (Table 2; Figure 2).

Table 2
Average amplitude of theta-alpha ratio at O1 and O2 locations in the first and last session (n = 14).

S. No.	Location	First Session (Mean ± *SD*)	Last Session (Mean ± *SD*)	*p* Value
1	O1	0.967 ± 0.265	0.94 ± 0.252	.665
2	O2	1.06 ± 0.302	0.914 ± 0.28	.011*

Note. * Significance at 0.05 level.

EEG Analysis

For each electrode, EEG amplitude values were averaged across the participants. Further, these electrodes were grouped into five different brain regions to examine the regional differences in EEG amplitude. An average score of the individual electrode in that region formed the score for each region (Figure 3).

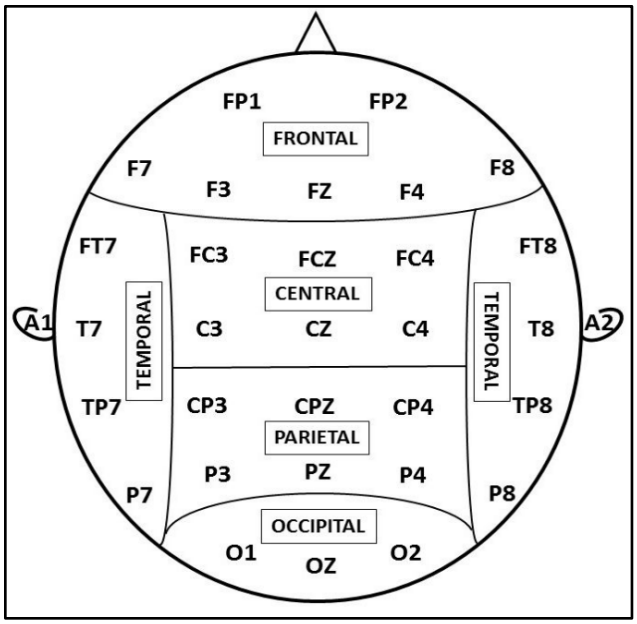

Figure 3. 32-electrodes were grouped into five brain regions (frontal, central, temporal, parietal, and occipital) as per 10–20 system.

A consistent pattern of a reduced delta-alpha, theta-alpha, and theta-beta ratios ratio was observed across all the brain regions in post-NFT compared to the baseline. Although this was statistically significant only in the temporal (p = .041) and central (p = .038) regions for delta-alpha and in the occipital (p = .033) for theta-alpha (Table 3; Figure 4).

Table 3

Average EEG amplitude of delta-alpha, theta-alpha, and theta-beta ratio at baseline and post-NFT (n = 14).

S. No.	Variable	Baseline (Mean ± *SD*)	Post-NFT (Mean ± *SD*)	*p* Value
1	Occipital delta-alpha	0.283 ± 0.059	0.275 ± 0.064	.599
2	Parietal delta-alpha	0.267 ± 0.075	0.247 ± 0.069	.122
3	Temporal delta-alpha	0.313 ± 0.065	0.284 ± 0.073	.041*
4	Central delta-alpha	0.291 ± 0.086	0.27 ± 0.078	.038*
5	Frontal delta-alpha	0.363 ± 0.074	0.331 ± 0.08	.054
6	Occipital theta-alpha	1.319 ± 0.399	1.184 ± 0.377	.033*
7	Parietal theta-alpha	1.186 ± 0.281	1.17 ± 0.319	.826
8	Temporal theta-alpha	1.088 ± 0.452	0.97 ± 0.346	.113
9	Central theta-alpha	1.201 ± 0.449	1.118 ± 0.406	.136
10	Frontal theta-alpha	1.537 ± 0.371	1.432 ± 0.409	.111
11	Occipital theta-beta	2.357 ± 1.067	2.244 ± 0.665	.603
12	Parietal theta-beta	2.712 ± 1.265	2.597 ± 1.356	.440
13	Temporal theta-beta	3.005 ± 1.287	2.699 ± 1.359	.062
14	Central theta-beta	2.831 ± 1.388	2.726 ± 1.445	.430
15	Frontal theta-beta	3.141 ± 1.38	2.953 ± 1.523	.302

Note. * Significance at 0.05 level.

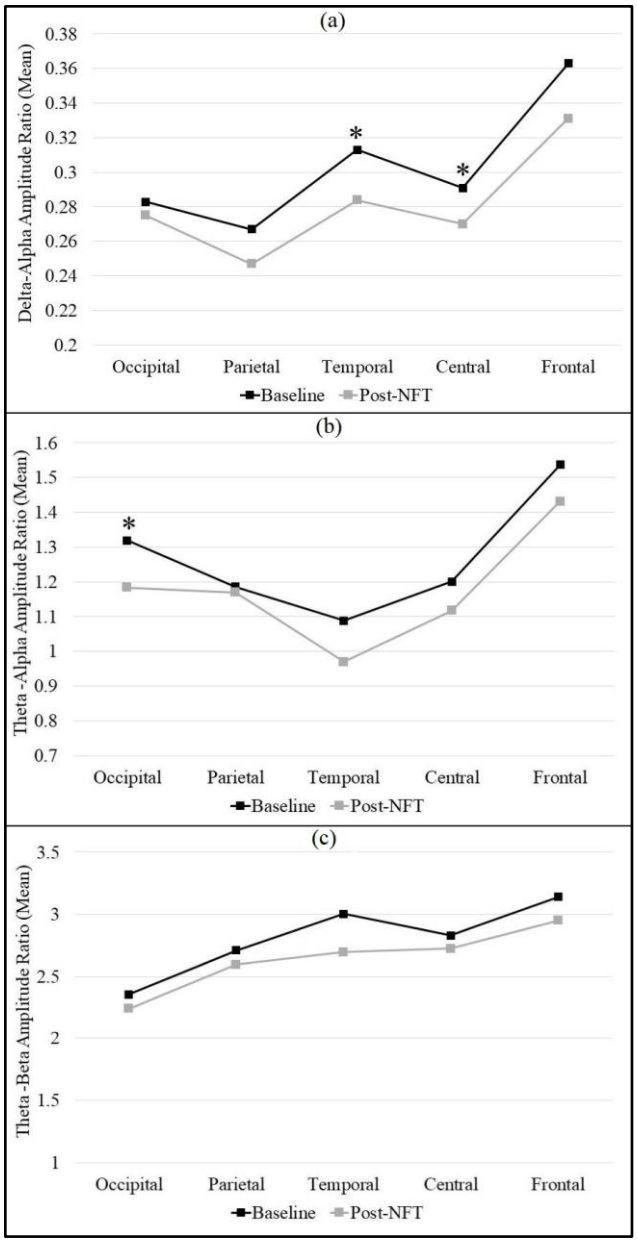

Figure 4. The average EEG amplitude of (a) delta-alpha, (b) theta-alpha, and (c) theta-beta ratios at baseline and post-NFT (n = 14).

Discussion

The current study investigated the efficacy of EEG-NFT in patients with moderate–severe TBI on their clinical and electrophysiological outcomes. Participants were assessed at baseline and post-NFT using Rivermead Postconcussion Symptoms Questionaire total (RPQ-T) score and EEG amplitude.

Effectiveness of EEG-NFT on Clinical Outcome

The findings from the study indicate a significant reduction in the severity of PCS on the RPQ-T score. These findings are in line with previous studies showing that EEG-NFT leads to a significant decrease in PCS (Rajeswaran, Bennett, Thomas, & Rajakumari, 2013; Reddy et al., 2013). A study by Reddy et al. suggested a negative correlation of RPQ with QOL and neuropsychological functioning (Reddy, Rajeswaran, Devi, & Kandavel, 2017). Therefore, the reduction of PCS on RPQ-T might contribute to improving QOL and cognitive functioning in patients with TBI, which is corroborated by earlier studies (Bennett, Sampath, Christopher, Thennarasu, & Rajeswaran, 2017; Hoffman, Stockdale, & van Egren, 1996; Munivenkatappa et al., 2014; Reddy, Rajeswaran, Bhagavatula, & Kandavel, 2014).

Effectiveness of EEG-NFT on the Electrophysiological Outcome

EEG amplitude ratio is potentially an important indicator of cognitive ability (Trammell, MacRae, Davis, Bergstedt, & Anderson, 2017) and constitutes a more reliable index to monitor electrophysiological alterations over time in TBI (Álvarez et al., 2008). The qEEG data reported herein suggest a consistent pattern of reduced slow waves and fast waves (SW/FW) amplitude ratios at post-NFT. Although significant changes were observed only for delta-alpha in the temporal and central regions and for theta-alpha in the occipital region.

A positive association of cognitive deterioration has been found with an increased SW/FW ratio in patients with moderate–severe TBI (Álvarez et al., 2008). A study by Leon-Carrion et al. indicates a negative correlation between delta-alpha ratio and functional outcome in patients with head injury (Leon-Carrion, Martin-Rodriguez, Damas-Lopez, Barroso y Martin, & Dominguez-Morales, 2009). An increased theta-beta ratio has been related to higher impulsive behavior (van Dongen-Boomsma et al., 2010) and lower response inhibition (Putman, van Peer, Maimari, & van der Werff, 2010). Therefore, a reduction in the SW/FW amplitude ratio might be related to better cognitive functioning (Álvarez et al., 2008) and could be attributed to significantly reduced PCS observed in our study.

These qEEG changes can be suggested by modulation in thalamo-cortical networks that refines the intrinsic neural network, led to the normalization of qEEG pattern in TBI following EEG-NFT (Munivenkatappa et al., 2014). Since, SW/FW amplitude values negatively correlate with cerebral

blood flow and brain metabolism functioning (Coles et al., 2004; Nagata, Tagawa, Hiroi, Shishido, & Uemura, 1989), a reduction in SW/FW values might be associated with a recovery of the brain metabolism in TBI (Álvarez et al., 2008).

The findings from the EEG-NFT sessions indicate that qEEG changes were not due to chance, as there were progressive changes in qEEG across NFT sessions. It is also worthwhile noticing that electrophysiological changes in the present study were marked 3 months to 2 years of postinjury, suggesting that these changes were not concomitant by the time.

To conclude, the findings suggest EEG-NFT as a contributing factor in improving postconcussion symptoms and normalization of qEEG in patients with moderate–severe TBI. The present study also holds an implication for clinical decision-making of EEG-NFT as a viable alternative to be offered to patients with moderate-severe TBI. The limitations of the present study are the small sample size, limited variables, and lack of control group. Accounting together these limitations affect the generalizability of the study. Therefore, future research would require structural, functional, biochemical, and cognitive correlates on a larger cohort following the intervention.

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NeuroRegulation

An Artistic Approach to Neurofeedback for Emotion Regulation

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Abstract

While literature has suggested that neurofeedback performance improves when sensory feedback is related to the pathology under consideration, it is still difficult to represent a proper feedback representative of our emotional state. In this study, we have initiated a collaboration between neuroscientists and artists to develop a visual representation of emotions. Emotions were represented as particles moving in a white sphere according to valence and arousal levels. Several possibilities for particle control were explored: direction of particles, their concentration in a specific place, or their gravity. Participants were asked to evaluate these possibilities on scales ranging from *0* to *5* on how artistic the different representations were and could be used as a clinical activity, whether they thought they had successfully controlled the particles during the neurofeedback exercise, and whether they had appreciated the experience. We found that controlling the direction and concentration of particles was considered the most artistic, with an average score around 3 out of 5, and that 47% of the 107 participants considered the concentration of particles as artistic. In addition, we found that participants could significantly control the direction of particles during this session. Our approach constitutes a first step before evaluating the effectiveness of our emotional neurofeedback over several sessions.

Keywords: neurofeedback; emotion; art

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Introduction

Neurofeedback is a technique that consists of measuring in real time a neurophysiological activity in order to extract a parameter of interest and present it to the participant, typically via visual or auditory feedback. The purpose is to teach the participant to modify this parameter. Neurofeedback can be used to improve cognitive performance, such as memory, attention, or emotions (Gaume, Vialatte, Mora-Sánchez, Ramdani, & Vialatte, 2016; Gruzelier, 2014). It can be used in healthy people (Gruzelier, 2018), but it is mainly perceived as a therapeutic tool for the treatment of mental disorders (e.g., epilepsy, attention disorders, addiction, depression). There are at least two ways in which regulating brain activity by neurofeedback can be beneficial for the treatment of mental disorders. Self-regulatory training can focus on an abnormal process, such as hyper- or hypoactivation of specific brain areas or networks. But neuromodulation can also act in another way, by activating or suppressing circuits that do not function

abnormally, but whose neuromodulation can nevertheless produce clinical benefits (Linden, 2013). This implies that clinical benefits can be achieved through self-regulatory training that activates compensatory circuits or inhibits circuits that appear normal when viewed in isolation but contribute to pathology-related dysfunction (Linden, 2014).

The important parameters to consider when conducting a neurofeedback experiment are the method of measuring neurophysiological activity, the brain areas to be targeted, and the type of feedback to be presented to participants. All these parameters obviously depend on the phenomenon we want to study. The two main techniques for measuring neurophysiological activity in neurofeedback are electroencephalography (EEG) and functional magnetic resonance imaging (fMRI). EEG neurofeedback consists of measuring the power of cerebral electrical activity at frequency bands of interest on a few electrodes placed on the surface of the scalp, with a time accuracy of the order of a millisecond. EEG neurofeedback has the advantage of being easy to use and can be performed ambulatory. Neurofeedback by fMRI is a relatively recent development of neurofeedback based on blood oxygenation contrasts from the blood-oxygen-level-dependent (BOLD) signal (for reviews, see deCharms, 2008; Sulzer et al., 2013; Weiskopf, 2012). Neurofeedback training by fMRI can overcome some of the limitations of traditional forms of neurofeedback in EEG, thanks to its higher spatial resolution and the integration of the entire brain. This approach is noninvasive, spatially accurate, and capable of targeting deep brain structures such as the amygdala. Unlike EEG neurofeedback, the fMRI technique does not really provide real-time feedback because of the hemodynamic delay of about 5 seconds between current neural activity and the vascular response that creates the fMRI signal. However, this delay is not an obstacle to neurofeedback when participants receive this information prior to the experiment (Linden, 2014; Weiskopf et al., 2004).

The cerebral area to measure and to be controlled by the participant is a parameter that depends on the phenomenon to be studied and is defined from the existing literature in the field. In the case of using neurofeedback to learn how to regulate emotions, most EEG neurofeedback studies focus on the activity of the prefrontal cortex, which acts as a modulator of primary emotional responses, through its connections with deep brain structures (Spielberg et al., 2012). Dominant activity in right versus left prefrontal areas is associated with withdrawal behavior and negative emotions, while opposite representation (i.e., higher activity on the left vs. right) accompanies approach behaviors and positive emotions (Davidson, 1988, 1998; Papousek et al., 2014). Thus, the alpha frontal asymmetry recorded in the EEG reflects functional differences between approach and avoidance motivation systems (see as reviews Coan & Allen, 2004; Davidson, 1992, 1998; Harmon-Jones & Gable, 2018; Sutton & Davidson, 1997). Since alpha power is assumed to reflect a decrease in metabolic activity (Cook, O'Hara, Uijtdehaage, Mandelkern, & Leuchter, 1998; Davidson, Ekman, Saron, Senulis, & Friesen, 1990), reduced alpha activity in right prefrontal electrodes is associated with negative emotions; for example, after viewing unpleasant films (Papousek et al., 2014; Wheeler, Davidson, & Tomarken, 1993). On the other hand, reduced alpha activity on the left is related to positive emotions; for example, after viewing happy movies or listening to pleasant music (Arjmand, Hohagen, Paton, & Rickard, 2017; Wheeler et al., 1993). Several case studies have shown the effectiveness of training to control alpha asymmetry to reduce depressive symptoms (Baehr & Baehr, 1997; Baehr, Rosenfeld, & Baehr, 1997; Choi et al., 2011; Peeters, Oehlen, Ronner, van Os, & Lousberg, 2014). Frontal asymmetries associated with emotions and motivation have also been observed at the theta band level (Aftanas & Golocheikine, 2001; Ertl, Hildebrandt, Ourina, Leicht, & Mulert, 2013) and at the upper beta band level (Paquette, Beauregard, & Beaulieu-Prévost, 2009; Pizzagalli et al., 2002). In addition to the measurement of emotional valence, Ramirez and Vamvakousis (2012) added an additional parameter in calculating the emotional arousal, in order to conform to Russell's emotional representation model. Arousal is calculated as the ratio between beta and alpha bands at the prefrontal cortex. When associated with valence, it offers the possibility to have a bidimensional representation of emotions. In fMRI, neurofeedback techniques target deep brain structures that cannot be recorded in the EEG, such as the amygdala or the insula, which play a major role in motivational approach and avoidance systems (Cunningham, Arbuckle, Jahn, Mowrer, & Abduljalil, 2010; Cunningham, Raye, & Johnson, 2005; Schlund & Cataldo, 2010; Spielberg et al., 2012). Several pilot studies have explored the feasibility of training to regulate emotions with fMRI neurofeedback in patients with neuropsychiatric disorders. These studies focused on the self-regulation of the anterior insula (Caria, Sitaram, Veit, Begliomini, & Birbaumer, 2010; Caria et al., 2007) in schizophrenic patients (Ruiz et al., 2013), and the self-regulation of the left amygdala (Zotev et al., 2011; Zotev, Phillips, Young, Drevets, & Bodurka, 2013) in

patients with bipolar or depressive disorders (Young et al., 2014). While training to overregulate amygdala activity had a potentially positive effect on depressed patients (Young et al., 2014; Yuan et al., 2014), training to underregulate may help reduce amygdala hyperactivation and improve emotional regulation in patients with bipolar disorder. The combination of simultaneous recordings in EEG and fMRI in the self-regulation of emotions has also been explored (Cavazza et al., 2014; Kinreich, Podlipsky, Jamshy, Intrator, & Hendler, 2014; Meir-Hasson, Kinreich, Podlipsky, Hendler, & Intrator, 2014; Shtark et al., 2015; Zich et al., 2015). Cavazza and colleagues (2014) found an increase in BOLD activity in the prefrontal cortex while subjects regulated their frontal asymmetry in neurofeedback. Similarly, a correlation between the laterality of the BOLD signal at the amygdala and the level of alpha-frontal asymmetry has been observed (Zotev et al., 2016). Research on MRI neurofeedback is expanding rapidly, and there is no doubt that new methods of functional exploration will emerge in the coming years (Linhartová et al., 2019; Lubianiker et al., 2019; Paret et al., 2019).

The last parameter to be taken into account, namely the sensory feedback presented to the participants, is still little explored. Remarkably, psychosociological factors, particularly motivational factors, which also have a major influence on the potential clinical effectiveness of neurofeedback, have been poorly evaluated. Thus, whatever the pathology considered, the majority of neurofeedback tasks are tedious, with brain activity frequently represented in the form of histograms whose level rises or falls in real time. Recently, less abstract methods of representing feedback have been used; for example, through the use of immersive environments (Lubianiker et al., 2019). Playful neurofeedback applications, such as video games, have also been developed but are not related to the pathology to treat, which raises questions about their effectiveness. It has already been pointed out that traditional approaches to brain studies do not take into account the specificities of each individual (Bagdasaryan & Quyen, 2013). Thus, it is likely that a neurofeedback approach will have to adapt to the pathology of interest. Exploratory approaches to representing feedback in relation to the activity you want to improve have been put in place (Lubianiker et al., 2019). For example, using neurofeedback to optimize the performance of actors, participants saw themselves on stage thanks to 3D glasses and the control of their brain activity made possible to vary the brightness of the scene and to reduce the noise of the audience (Gruzelier, 2014). In the context of emotions and the management of emotional disorders, representing feedback related to the pathology is much more complex because it raises the question about the possibility to represent visually or auditorily an emotion. Since emotion is a central part of people's dealings with artworks, first approaches have been tested in this direction; for example, with color schemes that vary when one must feel tenderness or anxiety (Lorenzetti et al., 2018). Ramirez and colleagues performed a musical neurofeedback task for treating depression in elderly people (Ramirez, Palencia-Lefler, Giraldo, & Vamvakousis, 2015). In that study, participants could manipulate musical parameters in real time by increasing the volume of music with a high arousal state and increasing the tempo when the valence level also increased (Ramirez et al., 2015).

As part of this project, we have initiated a collaboration between scientists and digital artists to develop a visual representation of emotions that can be used in neurofeedback experiments. For this purpose, it was necessary that, in addition to being artistic, the feedback provided to participants be controllable, and therefore usable in a clinical activity. To establish a visual representation of emotions, the artists involved in the project started from the very definition of the word *emotion*. The term *emotion* has an active connotation since it derives from the Latin word *emovere*, to set in motion (which gives the terms movement, motivation). Thus, emotions were represented as moving particles slightly tinged according to their location within a white sphere. Several possibilities for particle control have been proposed to determine which would be most effective in a neurofeedback exercise. This study evaluated these different control options at several public events to determine which artistic representation would be most appropriate for neurofeedback. To do this, we not only evaluated the artistic aspect of the exercise but also the sensation of particle control and the pleasure of performing the task, which are major motivational parameters to be taken into account in neurofeedback.

Methods

Population

This study included 107 participants, 51 men and 56 women aged 27.6 (±17.1) years on average. Prior to the experiment, oral informed consent was obtained from all participants. The study took place either in laboratory conditions or at various scientific and artistic events in 2018, namely Brain Week, European Researchers' Night, the VIVO exhibition "Entrez en nature!" and the Hacking Health Besancon. According to French law, this study was classified as a psychology observational study outside of the Jardé

law and did not require submission to an ethics committee. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Course of the Experiment

At the beginning of the experiment, participants were comfortably seated in a chair, informed of the experimental procedure, and instructed to remain as calm as possible and to not move for the duration of the experiment of about 15 minutes. An EEG headset was then installed with an impedance check lasting about 5 minutes. A 2-min rest recording was then made to establish a baseline of valence and arousal values. Then, subjects were instructed to try to reach a specific emotional state. Four types of emotional states could be asked of participants, according to Russell's model (Russell, 1980): either a positive valence and a high arousal (emotion of joy or excitement), a positive valence and a low arousal (emotion of calm, relaxation), a negative valence and a high arousal (emotion of irritation, anger), or a negative valence and low arousal (emotion of sadness, fatigue).

Brain Data Acquisition

The EEG data were acquired from an EEG Emotiv EPOC+ system (EMOTIV Inc., San Francisco, CA). This system consists of 16 saline-based electrodes and a wireless amplifier. The electrodes are located at positions AF3, F7, F3, FC5, T7, P7, O1, O2, P8, T8, FC6, F4, F8, AF4, according to the International 10–20 system. Two electrodes located just above the ears (P3, P4) are used as a reference. The data is collected at a sampling rate of 128 Hz and transmitted to the computer via Bluetooth.

Although EEG Emotiv systems, which are relatively inexpensive, provide a lower quality signal than when the signal is obtained on more expensive EEG devices (but see Dikker et al., 2017), the choice of this material was based on the pragmatic advantages of such a device. The installation time of each Emotiv EPOC+ system is considerably shorter, about 5 minutes, than for gel-based systems, where the gel application for each electrode can ultimately last up to one hour, which considerably extends the duration of the experiments. In addition, since the focus of this study was on evaluating the graphical interface, signal quality was not the main measurement criterion.

Processing of EEG Data

EEG processing of valence and arousal is based on methods already used in previous studies (Ramirez et al., 2015; Ramirez & Vamvakousis, 2012) using a two-dimensional arousal-valence design (Russell, 1980). Data were collected every 2 s. To determine the valence level, the activation levels of the cortical hemispheres were compared. The F3 and F4 electrodes were used to compare alpha activity on the right and left hemispheres because they are located above the prefrontal lobe. Valence was thus calculated by comparing the alpha power at the electrodes F3 and F4 (i.e., by applying the following formula: AlphaF4 − AlphaF3). The arousal level was determined by calculating the ratio of beta (12–28 Hz) and alpha (8–12 Hz) oscillations, which may be a reasonable indicator of an individual's arousal level (Ramirez et al., 2015). The EEG signal was measured on the four electrodes AF3, AF4, F3, and F4, which are located above the prefrontal cortex, and arousal was calculated as follows: (BetaF3 + BetaF4 + BetaAF3 + BetaAF4) / (AlphaF3 + AlphaF4 + AlphaAF3 + AlphaAF4).

No method of correcting or removing artifacts was applied to the EEG signal. To minimize eye movements, participants were asked to fix the center of the screen during each experiment. To minimize muscle artifacts, participants were asked not to move. If signal quality was not central to this study, in the next steps of performance measurement these parameters will have to be monitored.

Artistic Representation of Participants' Emotional State

Three types of visual representations were evaluated by participants (Figure 1). All were based on the same principle, namely a representation of emotions in the form of particles tinted according to their location and moving in a white sphere. These particles appeared gradually throughout the experiment.

From this common basis, each representation had its own specificities. Each interface played with these particles by modulating the forces applied to them. In the first representation, group of particles moved up or down according to the arousal level, and to the right or left according to the valence level. Thus, for a negative emotion with low arousal, the particles moved to the lower left level of the sphere. Depending on the emotion they were requested to reach, the participants tried to move the particles to a specific part of the sphere. Participants visualized in real time the moving particles in order to give them the feeling of absolute control over their brain activity

(see https://youtu.be/c_6IfurxzLc for a video of Representation 1). In the second representation, the objective was to gather the particles in the center of the screen. If the subject was able to modulate his brain activity to the right emotional state, the particles moved towards the center and remained in this position. If the brain activity did not correspond to the requested emotional state then the particles would move back to the periphery (see https://youtu.be/ZeXl43Z7DRU for a video of Representation 2). For the third representation, the objective was to achieve the fastest particle drop from the top to the bottom of the screen until it stuck to the bottom. The more the subject was able to reach the correct emotional state, the faster the particles fell from the top to the bottom of the screen. The more the brain activity moved away from the requested state, the more the particles fell slowly (see https://youtu.be/fuxBEpWwpFA for a video of Representation 3).

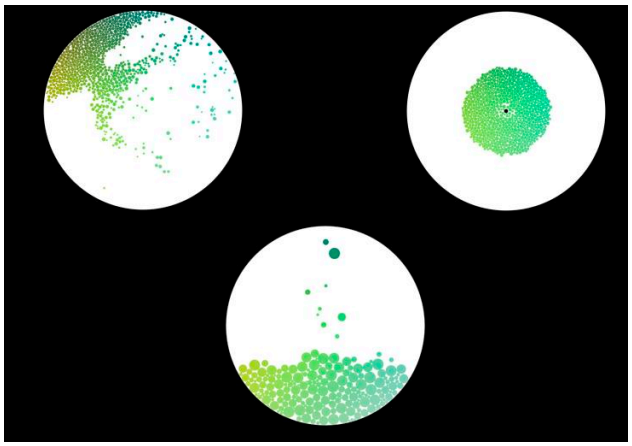

Figure 1. The different types of artistic representation used. In Representation 1 at the top left, participants had to move the particles to a specific part of the screen. In the Representation 2 at the top right, the participants had to be able to concentrate the particles in the center of the screen. In Representation 3 at the bottom, the objective was to drop the particles as quickly as possible from the top to the bottom of the screen.

The programming of this software is based on the Processing language and intensively uses the physical simulation library adapted for the language by Daniel Shiffman Box2D. The communication between this program and the software that receives and processes the EEG information is done via the OSC protocol, with values ranging between 0 and 100 for valence and arousal. Each visual representation was projected on a circular screen via a video projector. The duration of each exercise was 3 min. 89% of the subjects did the same exercise twice, each time with different emotional states to achieve.

Data Collection

EEG data collected in real time were automatically processed to indicate whether the subject had achieved the right emotion during the experiment. For each experiment, the percentage of times a subject had reached the correct level of valence and the correct level of arousal was reported.

In addition, at the end of the experiment, questionnaires were distributed to participants who were asked to indicate on scales between *0* and *5* how the task was artistic, could be used as a clinical activity, whether they felt they had succeeded in controlling particles during the neurofeedback exercise, and whether they had enjoyed the experience.

Results

Evaluation of Each Visual Representation

Of the 107 participants, 45 subjects were tested with Representation 1, 34 with Representation 2, and 28 with Representation 3. For one of the users of Representation 3, the questionnaire was not completed. The average scores given for each experiment are presented in Figure 2.

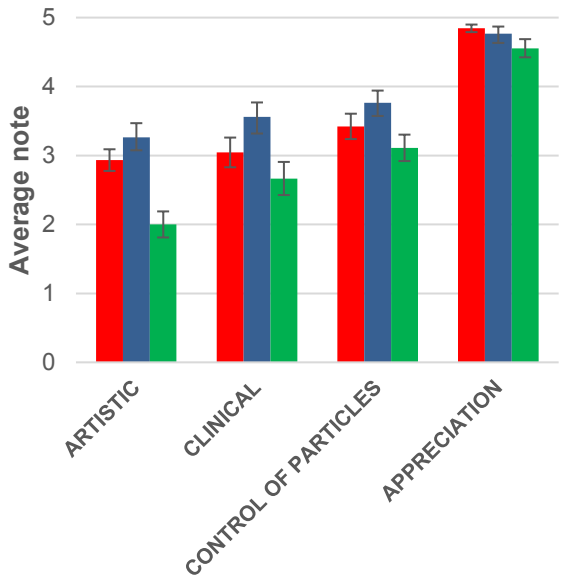

Figure 2. Ratings given by the participants during the end-of-experiment questionnaire for each of the questions asked (red: Representation 1, blue: Representation 2, green: Representation 3). Error bars represent standard error.

To determine the perception of the audience for the three visual representations, we used nonparametric statistical analyses. With regard to the artistic aspect of the neurofeedback experience, large differences in assessment were observed (Kruskal-Wallis, p = .0002), the artistic assessment of Representation 3 being significantly lower than the other two representations (Mann-Whitney, p = .004 compared to Representation 1 and p = .0002 compared to Representation 2). For the evaluation of the clinical aspect of each representation, a significant difference was also observed (Kruskal-Wallis, p = .03). The clinical evaluation of Representation 3 was lower than that of Representation 2 (Mann-Whitney; p = .03). To assess whether subjects felt they were in control of the task, only a tendency was observed (Kruskal-Wallis; p = .06). Finally, with regard to the assessment of the task, very high scores were reported for the three tasks, with no significant differences between them (Kruskal-Wallis; p = .12).

To further explore the difference of artistic perception between the three types of representation, we reported an experience as artistic when participants gave a note of *4* or *5*, and nonartistic when participants gave a note of *0* or *1*, a method already used before (Zhang, Jadavji, Zewdie, & Kirton, 2019). We found that in Representation 2, 47% of participants reported having an artistic experience (and 26% a nonartistic experience), whereas there were only 29% of participants in Representation 1 (33% nonartistic), and 11% in Representation 3 (75% nonartistic), as shown in Figure 3.

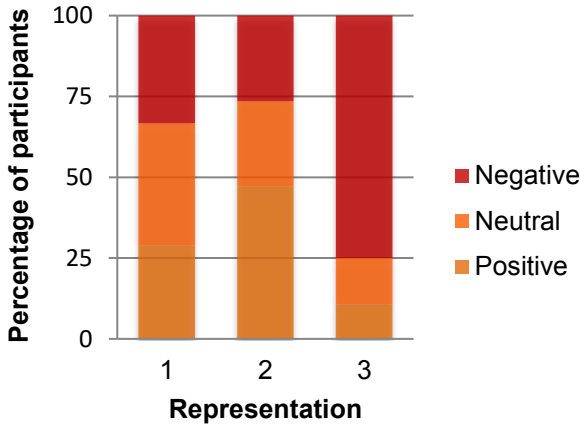

Figure 3. Artistic evaluation of the three types of representation. An experience was considered artistic (Positive) when participants gave a score of *4* or *5*, a partially artistic (Neutral) experience with a score of *3*, and a nonartistic (Negative) experience with a score of *1* or *2*. In Representation 2, almost half of the participants reported performing an artistic neurofeedback task.

Neurofeedback Evaluation

Although the main purpose of this study was to evaluate the artistic aspect of the device, we did evaluate the participants' ability to correctly modulate their brain activity during their first session. We compared the percentage of subjects who managed to move the particles according to instruction requested by the experimenter (e.g., positive valence and positive arousal), and compared the results to the chance level set at 25% (one in four chance of being in the right area). For none of the three representations were the subjects able to significantly reach the correct region (t-test, p > .1 for all representations).

In the absence of an overall effect, we measured whether subjects were able to control one of the two components (valence or arousal). To study if the subjects had managed to go more easily in one of the components, the chance level was then set at 50%. For valence alone, no representation gave significant results (t-test, p > .1 for Representations 1 and 2; p > .5 for Representation 3). For arousal alone, only the performances of Representation 1 were significantly higher than random ($t(44)$ = 2.92, p

< .01). A description of the performance of the subjects for each representation is given in Table 1.

Table 1
Percentage of participants who were able to place their emotions in the correct area.

	Valence + Arousal	Valence Alone	Arousal Alone
Representation 1	28.89	51.11	66.67*
Representation 2	35.29	50.00	64.71
Representation 3	21.43	28.57	67.86

Note. For the valence and arousal together, the chance level was set at 25%. For the valence alone and for the arousal alone, the chance level was set at 50%. A star (*) means that performance is significantly different from chance at the threshold p < .05.

Finally, we compared whether performance improved in subjects who performed the experiment twice (40 subjects for Representation 1, 29 for Representation 2, and 26 for Representation 3). For each of the representations separately as well as overall, no improvement was observed (paired *t*-test, $p > .1$ for all).

Discussion

The objective of this pilot study was to evaluate whether neurofeedback experiments used in therapeutics could also be artistic. The need for an artistic neurofeedback interface is emerging as the scientific community's opinion about the effectiveness of neurofeedback is very widely divided (Arns, Heinrich, & Strehl, 2014; Micoulaud-Franchi & Fovet, 2016; Micoulaud-Franchi et al., 2015), with an optimistic part thinking that neurofeedback can be effective and a skeptical part for whom neurofeedback training has no scientific or therapeutic value. Thus, it was important that the proposed activity not be seen as just a game and that it really helps to regulate emotions. During the realization of the interface, artists were requested to create a representation, concrete or abstract, of emotions and not only a game unrelated to the final goal of the project (treatment of emotional disorders). Studies have shown that the more playful an application of neurofeedback is, the better the performance (Bayliss, Inverso, & Tentler, 2004; Oude Bos & Reuderink, 2008), provided that the playful aspect is related to the pathology considered (Arns et al., 2017). According to Bandura (1999), people live in a psychological environment that they have largely created themselves. Many people are in distress because they are ruminating and cannot control disturbing thoughts. Controlling mental processes is thus a key factor in the self-regulation of emotional states. If neurofeedback is intended to be beneficial to patients by helping them control their own mental processes and therefore their emotional states, having a visual representation of these states can be particularly useful (Linden, 2014).

Our goal was to evaluate the most appropriate type of visual feedback to represent emotions. The choice to represent emotions under the form of particles was dictated by the dynamism of this representation. The different forces at play in the organization of particles make them constantly in motion. It is this permanent movement that induces the most interesting aspect; it is the nonpunitive response to the objective. The result of the patient's attempt is not right or wrong, it tends towards or away from the objective, in a natural movement, which can be reminiscent of a lens on a body of water. Particles react with each other to collision, friction, rebound, and sometimes gravity. Of the three representations that were tested, the first two obtained a similar clinical and artistic evaluation, with higher scores for Representation 2. In future experiments, the choice of the artistic representation will depend on the purpose of the neurofeedback task: Representation 1 allows visualizing precisely where the subject's emotional state is located, while Representation 2 mainly gives a binary response (particles are in the center for good emotional state and in the periphery otherwise). Representation 1 requires the integration of the two parameters but has the advantage of being superimposable with the Russell circumplex, which is interesting from a didactic point of view. However, despite similar scores with Representation 1, almost 50% of participants perceived Representation 2 as artistic, compared to 30% of participants in Representation 1. Representation 2 may better meet the objective of the study, thanks to a visual representation that is less punitive than in other tasks in the event of an error. Therefore, this task may be considered as the entry point in this set of three experiments in a therapy framework. Representation 3 resulted in poorer artistic and clinical evaluations, possibly because participants felt a competitive aspect in having to drop the balls quickly. In addition, in this representation, it is more difficult to know if brain activity is well controlled since the participant does not have a particle fall rate reference on which to refer. It is interesting to note how the modification of a single parameter, in this case the gravitational force, can

have major implications on the artistic and clinical perception of the task. In terms of the pleasure of completing the task, the results of the three representations are encouraging since the subjects greatly appreciated participating in the experiment and had the impression that they were controlling the particles. These parameters are important to motivate a subject to repeat a neurofeedback experiment, because in some cases, more than 30 sessions are required to demonstrate neurofeedback effectiveness (Marzbani, Marateb, & Mansourian, 2016).

Artistic scores may not be considered as very high, with the average score in Representations 1 and 2 being around 3 out of 5, but it is important to note that the aim was not to obtain the highest possible artistic score, but to achieve a task that is perceived as artistic and applicable in clinical practice. With the development of portable and relatively inexpensive EEG systems, there are now a number of projects that have associated art with sensory feedback, with no real possibility of clinical application. For example, the GlobalMind project sought to combine art and EEG activity to generate audiovisual effects. This has led to the production of "Spectacle of the Mind" shows presented to the general public. Another example is the Ascent project (https://www.nytimes.com/2012/06/24/fashion/the-ascent-levitating-in-brooklyn.html) where an installation allows individuals to levitate by modulating their ability to concentrate around an auditory and luminous show. It is by controlling this activity that participants can climb more or less high in the air. In addition to these exclusively artistic uses of real time feedback in EEG, other approaches have been used with both an artistic and pedagogical focus. For example, the project "My Virtual Dream" was presented in Toronto in 2013 at the Nuits Blanches art festival and measured EEG activities of 523 participants in a single night (Kovacevic, Ritter, Tays, Moreno, & McIntosh, 2015). Participants practiced simple EEG tasks targeting either a state of relaxation or a state of concentration. During the evening, an improvement in performance was observed, observable after only 1 minute of training. A dome that allows spatialization of the individual's brain activities and has also been developed to improve the individual's immersive appearance compared to a simple screen (Grandchamp & Delorme, 2016). This tool is intended to illustrate scientific knowledge about the brain. The authors also believe that this type of artistic and immersive environment would increase patients' motivation while reducing their training time and fatigue. Of course, such a dome remains difficult to use in common clinical practice.

In this study it is important to dissociate the emotion measurement device from the representation interface. As the main purpose of this neurofeedback pilot was to evaluate the artistic aspect of the interface, data processing, signal filtering, real-time rejection of flashes, and eye or muscle movements were not optimally exploited, although they can have a major influence on the quality of EEG plots. Similarly, it is possible to improve the quality of the EEG signal by using gel-based electrodes. Here we measured emotions with the material and parameters already described in the literature to calculate valence and arousal (Ramirez et al., 2015). However, it is important to note that this interface could be used with different methods of measuring emotions and on different populations. For example, there are other methods for detecting emotions in EEGs; for example, with connectivity analysis (Koush et al., 2017). In this case, subjects must regulate the top-down activity of the prefrontal cortex to the amygdala. This artistic interface could also be applied to fMRI, the other major neuroimaging method for measuring emotions. Although the fMRI technique provides only indirect measurements of neural activity and has a much lower temporal resolution than the EEG, its spatial resolution and access to deeper structures make it an attractive tool for network mapping and neurofeedback. Depending on the method chosen and the brain region targeted, this emotional measurement interface could potentially be applied for the treatment of mental disorders such as depression, schizophrenia, or bipolar disorders.

This study is the first step, and several points remain to be clarified to test the effectiveness of this type of artistic representation. First, it is not known how well the subjects were trying to achieve the requested emotional state. We did not control the extent to which subjects used different strategies among themselves and over time, which can strongly influence neurofeedback performance. Moreover, from a methodological point of view, it will be necessary to establish a control condition, a critical point in any neurofeedback study, to verify whether the effect comes from the experience itself or from other factors such as the attention given to the patient (Micoulaud-Franchi & Fovet, 2018; Thibault & Raz, 2017). In addition, it is well known that the placebo effect can have a significant influence on the outcome. However, if the result is present, the use of such a method may be acceptable, even as a placebo (Thibault & Raz, 2016). Finally, future evaluations will have to assess whether the artistic interface manages to keep the level of motivation of participants at a high level during repeated experiences. Although all subjects strongly appreciated performing the

experiment and felt that they were controlling the particles, it is likely that this motivation will gradually decrease and will need to be assessed in comparison to other types of visual feedback.

Conclusion

In this first approach involving the collaboration between neuroscientists and digital artists, we were able to set up a neurofeedback interface for emotion regulation that is perceived as both an artistic and clinical activity. It will remain to be explored whether the therapeutic effect of neurofeedback can make clinical sense and how to carry out a neurofeedback examination in an optimal way. For this reason, the design of appropriate control conditions for clinical trials is a real challenge. It will also be necessary to identify precisely the patient populations for which neurofeedback can work. The cognitive and motivational factors underlying effective neurofeedback training are largely unknown. For example, if this interface is to be applied to patients suffering from anhedonia, the subcomponents causing the anhedonic disorder should be well separated because they may originate in different brain regions (Thomsen, 2015).

Author Disclosure

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NeuroRegulation

Don't Disregard Deep Brain Stimulation in Patients with Concomitant Gaucher and Parkinson Disease

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Abstract

Gaucher disease and Parkinson's disease can co-occur, and mutations in the glucocerebrosidase (GBA) gene are considered the most common genetic association with Parkinson´s disease. Response to pharmacological and surgical therapies is poorly studied. We present the case of a patient diagnosed with Gaucher disease at 18 years old. At 59 years old right foot dystonia was first noticed. Levodopa was initiated and two years later motor dyskinesias were incapacitating. Although neuropsychological testing showed frontal dysfunction, as the deficit was stable, subthalamic nucleus deep brain stimulation was tried in October 2017. More than one year later the patient remains active and autonomous.

Keywords: Parkinson's disease; neuropsychology; Gaucher disease; GBA gene mutation

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Introduction

Gaucher disease (GD) is the most common lysosomal storage disorder, and it is due to homozygous or compound heterozygous mutations in the glucocerebrosidase (GBA) gene (O'Regan, deSouza, Balestrino, & Schapira, 2017), coding the enzyme β-glucocerebrosidase (Rodriguez-Porcel, Espay, & Carecchio, 2017). It is a multisystem disease, traditionally classified into three clinical subtypes. Concomitant Gaucher and Parkinson's disease (PD) is rare, and literature on PD-related phenotype, response to pharmacological therapy, and deep brain stimulation (DBS) is scarce. Despite the rarity of the association, mutations in the GBA gene have been coined as one of the most common genetic associations with PD (Balestrino & Schapira, 2018), although the underlying mechanism is still poorly understood (O'Regan et al., 2017). Furthermore, it was found that even heterozygous carrier status is associated with PD, and is, at present, the most frequent known risk factor for PD (Goker-Alpan et al., 2004). It is estimated that up to 30% of GBA mutation carriers will progress to develop PD by the age of 80 (Anheim et al., 2012). There seems to be a "dose response," dependent on GBA burden (Thaler et al., 2018).

GD usually precedes the onset of PD (Collins et al., 2018). A clinical series of 19 patients with concomitant Gaucher and PD found an earlier mean age of onset of PD, shorter disease duration, and poorer response to levodopa (Lopez et al., 2016). Collins et al. (2018) found that motor symptoms were typical and indistinguishable from idiopathic PD. There are conflicting data regarding the rate of

cognitive decline and neuropsychiatric features, and a recent study did not find significant differences between patients with idiopathic PD and those with GD plus PD (Thaler et al., 2018). Evidence on motor response to DBS in PD patients with Gaucher disease is scarce, and long-term studies evaluating cognitive changes after DBS are lacking.

Case Report/Case Presentation

We present the case of a 63-year-old female diagnosed with GD at 18 years of age, under enzyme replacement therapy with imiglucerase. She had a splenectomy at 24 years of age and had no further systemic complications. Her family history was relevant for 2 of 11 siblings with GD.

In 2012, at 59 years of age, a rest tremor of the right hand was first noticed along with right foot dystonia. Levodopa was tried with a favorable response. After 2014, motor fluctuations and peak dose dyskinesias rapidly became incapacitating. Amantadine and rotigotine were tried, but side effects were intolerable. The patient was referred to our clinic in 2016 to assess the eligibility for DBS. She was under levodopa/carbidopa 25/100 every 3 hours.

The patient was extensively investigated, including with brain CT scan and MRI, both unrevealing. *DaTscan* (with Ioflupane I 123 Injection) showed a markedly reduced uptake in the striatum (left more than right).

At our center, we performed an acute levodopa challenge test. Motor assessment, using the motor (Part III) of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), before (59) and 1 hour after drug administration (35), was documented. Psychiatric evaluation deemed the patient a suitable candidate for surgery. On the other hand, neuropsychological tests at first showed a frontal/subcortical dysfunction associated with a probable comprise of other cortical regions and the patient was found unfit for subthalamic nucleus (STN) DBS by the neuropsychologists. Six months later, a repeated evaluation showed a slight improvement, attributable to a less noticeable emotional lability, and the patient underwent surgery (STN DBS) on October 2017.

At present, 1.5 years after DBS, the patient remains without levodopa, managed solely with the stimulation (ranges of stimulation: Frequency: 150–170 Hz, because tremor was the predominant symptom; Pulse width: 60–90 µs; Voltage; 1.5–3.0 V). At last follow-up, in the motor assessment in best ON (Stimulation ON), using Part III of the UPDRS, the patient scored 19. Nonmotor assessment was not performed. Neuropsychological testing one year after surgery showed stable deficits. Disturbing visual hallucinations were reported and are being managed with clozapine, sertraline, and rivastigmine. The patient remains active, partially autonomous, and the major complaint now is language dysfunction, namely aphasia, not attributable to side effects of DBS.

Discussion/Conclusion

There are two approved therapies for patients with GD: enzyme replacement therapy and substrate reduction therapy. Neither is an effective treatment for neurological symptoms, since they don´t cross the blood brain barrier (Balestrino & Schapira, 2018). There is no evidence that any of the used treatments reduces the risk of Parkinsonism (Chetrit et al., 2013; Elstein, Alcalay, & Zimran, 2015), and these patients should be treated similarly to those with PD without GD (Elstein et al., 2015).

We report a patient with GD and PD who underwent DBS. We found two other cases amongst a large Israeli cohort (Chetrit et al., 2013). They were considered candidates owing to levodopa-induced dyskinesias. Both patients reported dramatic and sustainable symptomatic improvement. On the other hand, Lythe et al. (2017) reported that patients with GD who had DBS had more severe cognitive impairment compared to PD patients with GBA mutations.

Our aim was to shed light on a group of patients that may benefit from DBS. The problem found by the functional disorders group rested on the cognitive dysfunction found in this patient. At the moment, there is some debate about the acceptable degree of cognitive impairment previous to DBS. The fact that cognitive decline is a known adverse effect of STN DBS further increased our uncertainties. We opted to repeat the neurophysiological evaluation, and there the deficits were stable. Ergo, we decided to follow through with the surgical treatment achieving a positive result (using the MDS UPDRS scale), and according to the patient and her family members. The target used was the STN; however, the GPi could have been a good option, because it may have fewer cumbersome effects in cognition. Our case illustrates a good motor and stable cognitive outcome in patients with concomitant PD and GD submitted to STN DBS.

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