# NeuroRegulation

The Official Journal of ISNR
INTERNATIONAL SOCIETY FOR NEUROREGULATION & RESEARCH

Volume 8, Number 3, 2021

# NeuroRegulation



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*NeuroRegulation* (ISSN: 2373-0587) is published quarterly by the International Society for Neuroregulation and Research (ISNR), 13876 SW 56th Street, PMB 311, Miami, FL 33175-6021, USA.




## 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 Neuroregulation 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).

NeuroRegulation

ISNR INTERNATIONAL SOCIETY FOR NEUROREGULATION & RESEARCH

Volume 8, Number 3

2021

Contents

**RESEARCH PAPERS**



**CLINICAL CORNER**

NeuroRegulation

ISNR INTERNATIONAL SOCIETY FOR NEUROREGULATION & RESEARCH

# Neurofeedback Rehabilitation Reduces Anxiety in Methamphetamine Abusers

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**Abstract**

Addictive disorders are characterized by cognitive, behavioral, and neurological impairments caused by dysregulations of brain structure that can extend well beyond early withdrawal in the months and years of recovery. The present study aimed to examine the efficacy of neurofeedback rehabilitation on anxiety in methamphetamine abusers. The sample consisted of 14 male methamphetamine drug addicts who were randomly assigned to an experimental group ($n$ = 7) and a control group ($n$ = 7). Participants were assessed for Axis I disorders (SCID) and the Beck Anxiety Inventory (BAI). Mixed repeated ANOVA, independent $t$-tests, and chi-square were used for data analysis. The experimental group received 18 sessions of neurofeedback rehabilitation and standard psychological interventions treatment as usual, while the control group received only standard interventions. Results showed that neurofeedback significantly reduced anxiety in methamphetamine abusers at posttreatment and during a one-month follow-up. Along with other psychological interventions, neurofeedback rehabilitation is recommended for methamphetamine abusers.

***Keywords***: anxiety; methamphetamine abuse; neurofeedback; rehabilitation

**Citation**: Nooripour, R., Sikström, S., Ghanbari, N., Hosseinian, S., Hassani-Abharian, P., & Ilanloo, H. (2021). Neurofeedback rehabilitation reduces anxiety in methamphetamine abusers. *NeuroRegulation*, *8*(3), 128–136. https://doi.org/10.15540/nr.8.3.128

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## Introduction

Addictive disorders are characterized by cognitive, behavioral, and neurological impairments caused by dysregulations in brain structure that can persist well beyond early withdrawal through the months and years of recovery (Doostian et al., 2019). Research on psychological and neurophysiological dimensions of substance use disorders has recently attracted considerable attention (Mallorquí-Bagué et al., 2020; Richter et al., 2020). Patients suffering from substance use have been found to have a higher incidence of co-occurring Axis I and Axis II disorders, especially when stimulants are methamphetamine. Anxiety is the most common comorbid Axis I disorder in substance users. Anxiety disorder in young adults doubles the risk of later substance use (Albini et al., 2020). Emotional response levels at diagnosis of substance abuse are often lower with clinical comorbidity (Doostian et al., 2019). Self-medication in the form of amphetamine use occurs in patients with anxiety disorder, which is a risk for subsequent substance use. Psychological distress increases dropout rates during substance abuse treatment (Elkington et al., 2010; Roche et al., 2020).

The early onset of mental illness, particularly anxiety, increases the likelihood of substance abuse. However, evidence suggests that pharmacotherapy in ADHD patients does not increase the risk of substance use disorder (Albini et al., 2020). Co-occurring anxiety disorders should be considered when treating substance abuse. Symptoms of methamphetamine dependence, such as craving, impulsivity, and psychological abnormalities, are associated with pathological neurophysiology (Fitzpatrick et al., 2020). Eugene Peniston first proposed treating addictive disorders with neurofeedback in 1991 (Imperatori et al., 2017). Research has shown that this method effectively reduces the psychological symptoms and effects of substance abuse (Askovic et al., 2020; Gruzelier et al., 2014; Kelley, 1997; Rostami & Dehghani-Arani, 2015).

Neurofeedback based on electroencephalography (EEG) has recently been shown to be an efficient rehabilitation for substance abuse disorders (Nooripour et al., 2018). Feedback allows patients to change their rhythm and frequency of brain waves. Neurophysiological studies suggest that EEG provides information about the relationship between basic cortical brain mechanisms and psychological states in the field (Kosmyna & Maes, 2019). Neurofeedback rehabilitation is a method that has recently been studied for its efficacy in psychopathological disorders such as stress and anxiety (Askovic et al., 2020; Harris et al., 2021; Hou et al., 2021). The method aims to help people change brainwave patterns without using invasive methods (Niv, 2013).

Neurofeedback rehabilitation is a way to condition the brain's electrical system, rewarding patterns that work well and inhibiting undesirable activities. It is also believed to stimulate growth and alter the efficiency of brain cells, improving brain function and cognitive-behavioral function (Davelaar, 2018). During neurofeedback rehabilitation, individuals learn to change the patterns of their brain waves through conditioning (Luctkar-Flude et al., 2017). Neurofeedback rehabilitation has been shown to promote relaxation, reduce stress, and alleviate psychological abnormalities in patients who are addicted to drugs and alcohol (Gray, 2017).

One method of neurofeedback rehabilitation is alpha/theta wave conditioning. Alpha brainwaves of frequency 8–12 Hz are associated with feelings of well-being (Gruzelier et al., 2014; Imperatori et al., 2017). Theta brainwaves of frequency 4–7 Hz have been associated with presleep state or daydreaming, including traumatic anxiety-provoking events with spontaneous hypnagogic imagery and/or abreaction (Gregory et al., 2020; Ticci et al., 2019). Alpha-theta rehabilitation is primarily designed to increase alpha and theta waves. Increasing the frequency of these waves enhances relaxation and the effects of conscious awareness (Imperatori et al., 2017). This relaxed state is referred to as the twilight state, in which the offender creates hypnagogic images or mental perceptions of repressed feelings and memories. These perceptions play a central role in the healing process. Few studies have examined neurofeedback rehabilitation for anxiety in substance abuse disorders (Chen & Lin, 2020; Hammond, 2005; Simkin et al., 2014).

Hanslmayr et al. (2005) reported better performance in a cube rotation task after rehabilitation with upper alpha neurofeedback. Participants who were able to increase upper alpha amplitude (10–12 Hz) through neurofeedback rehabilitation showed better results in this task than participants who were unable to do so. Similarly, Vernon et al., (2003) reported that healthy participants were able to increase sensorimotor rhythm (SMR) activity after only eight neurofeedback rehabilitation sessions, and that this increase was associated with improvements in a cued recall task. Finally, Egner et al. (2004) trained participants to increase either SMR (12–15 Hz) or low beta rhythm (15–18 Hz). Previous studies recommended the SMR protocol as a training program through which participants could increase SMR and beta and downregulate theta (Avirame et al., 2016; Karageorghis et al., 2018). Increasing SMR to C4 (based on the international 10–20 system) is associated with a decrease in impulsivity symptoms and a facilitation of thalamic inhibitory mechanisms. In addition, increasing beta waves and decreasing excessive left hemisphere theta waves to C3 is recommended to improve responding. Although SMR training resulted in increased perceptual sensitivity, low beta training resulted in faster reaction times (Gruzelier, 2014).

Imaging techniques, such as SMR, functional magnetic resonance imaging (fMRI), and EEG, offer a window into the functioning brain, providing a unique opportunity to examine the neurobiological effects of these interventions in addiction. Imaging studies can be used to describe the brain systems involved in select interventions, clarify which mechanisms are dysfunctional, offering the opportunity to explore differences and commonalities between different interventions. Imaging-based neurobiological indicators entail information that goes beyond self-report or behavior

alone and have been shown to be good predictors of relapse following treatment (Brewer et al., 2008; Janes et al., 2010; Moeller & Goldstein, 2014). In SMR training protocol on the Cz area, the active electrode was placed at Cz with a left-ear reference (A1). The right earlobe was connected to circuit ground. In this program the reinforcement band was SMR (12–15 Hz) frequency band, and the suppressed frequency were delta (2–5 Hz), theta (5–8 Hz) and high beta (18–30 Hz) frequency bands. Thresholds were adjusted in a way that if the participant maintained the reinforcement band above the threshold for 80% of the time during at least 0.5 s, and the suppressed band under the threshold for 20% of the time, feedback was received. Whenever participants could maintain the reinforcement bands above the threshold for 90% of the time during two continuous trials, the threshold was changed automatically so that it was closer to the optimal threshold (Scott et al., 2005).

Due to the lack of sufficient research, neurofeedback rehabilitation is not yet recognized as a treatment for substance abuse problems; it is of interest to provide additional evidence of the efficacy of neurofeedback rehabilitation on anxiety in methamphetamine addicts.

## Method

### Participants

The population studied included a group of methamphetamine addicts in Tehran. Twenty-five participants who met the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; DSM-5; American Psychiatric Association [APA], 2013) criteria for methamphetamine use disorder were selected. They were selected from Tehran drug rehabilitation centers between March 2019 and December 2019. Subjects were selected based on the following inclusion criteria:

1. They met DSM-V criteria for methamphetamine use disorder.
2. They showed interest in participating in the intervention.
3. They were between 20 and 50 years old.
4. They had at least a 12-month history of methamphetamine use.
5. They had no other substance-related disorders except smoking.
6. They could speak and write fluent Farsi.

The exclusion criteria were: Any history of psychiatric (bipolar disorder or major depression, psychosis) or neurological disorders.

Participants were randomly assigned to the neurofeedback rehabilitation group or the control group. Three subjects from the neurofeedback rehabilitation group and four from the control group dropped out before the study was completed. Therefore, the final analysis was performed on seven participants in the neurofeedback rehabilitation group ($n$ = 7) and seven participants in the control group ($n$ = 7; see Figure 1).

### Procedure

All participants were asked to complete the instruments (Structured Clinical Interview for DSM-IV [SCID] and Beck Anxiety Inventory [BAI]) before, at the midpoint, and after the intervention, and at a 4-week follow-up period. The neurofeedback rehabilitation group received the treatment protocol for 2.5 months. The protocol consisted of 18 sessions and two sessions per week, with each session lasting 25–30 minutes. The neurofeedback rehabilitation protocols in each session were based on SMR, Cz area (central cortex) rehabilitation (Scott et al., 2005), and Pz area (parietal cortex) alpha-theta (Gregory et al., 2020), performed in 20 min using the ProComp2 system (Thought Technology Ltd, Montreal, Canada; Scott et al., 2005).

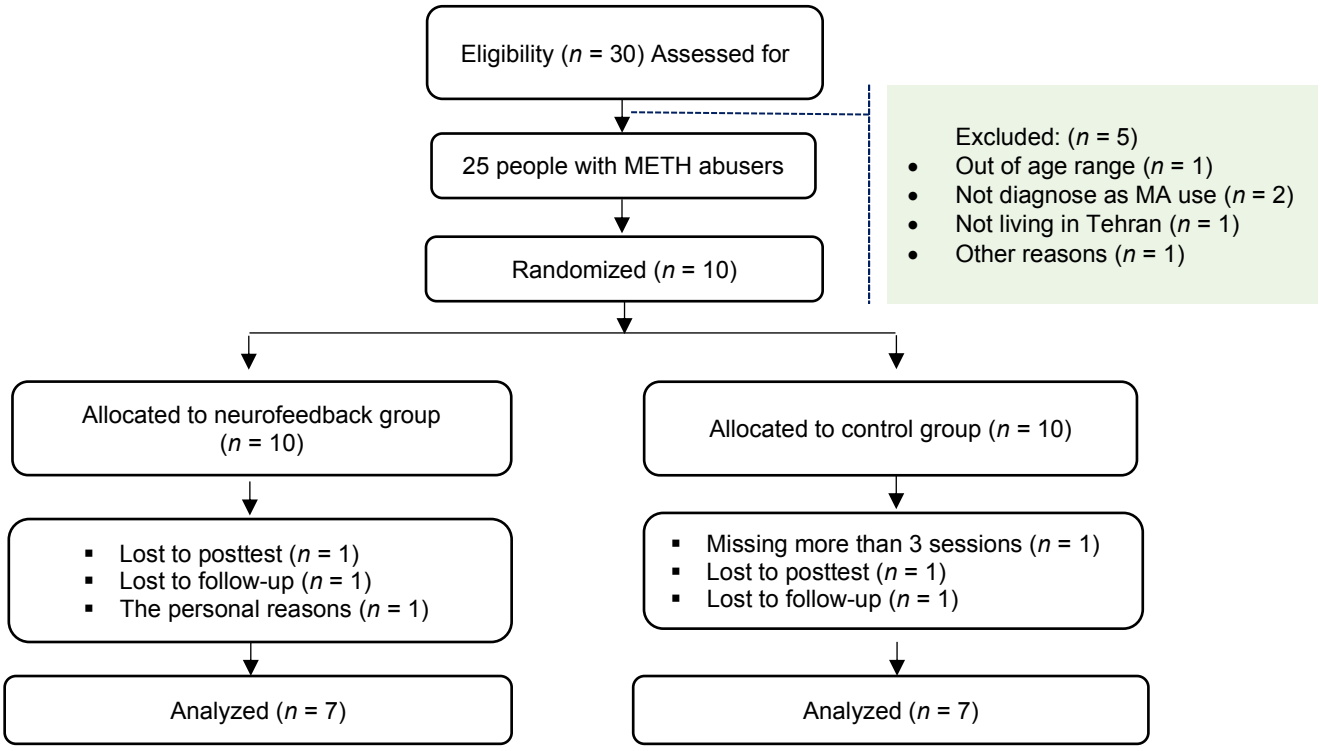
### Measures

***Structured Clinical Interview for DSM-IV (SCID)***. The interview assessed the first Axis I Disorders in SCID-I. This included seven groups characterized by mood disorders as psychiatric issues, substance dependence, anxiety, eating complications, and compatibility problems. This instrument's reliability and validity are 0.81 to 0.84, respectively (Sharifi et al., 2009).

***Beck Anxiety Inventory (BAI)***. Beck Anxiety Inventory was used for rapid detection and differentiation from other disorders, particularly depression and anxiety (REF1988). This inventory assesses individuals' anxiety status during the last week on a 21-question multiple-choice self-report, where each answer is scored on a scale of 0 (*not at all*) to 3 (*severely*). Osman et al. (1997) reported a test–retest validity of 0.75. Studies have indicated that this inventory's psychometric properties are desirable in Iran (Khesht-Masjedi et al., 2015).

***Data Analysis***. Data were analyzed by the mixed repeated ANOVA, independent $t$-test, and chi-square, using the statistical software SPSS-26.

**Figure 1.** *Summary of Patient's Flow Diagram.*




***Ethical Consideration***. The applied method is consistent with the National Research Committee's ethical standards, the Helsinki Declaration of 1964, subsequent revisions, or equivalent ethical norms. All participants in the study embraced informed consent to participate in the study.

## Results

As for demographic variables, including age, marital status, job status, and substance use characteristics, there were no significant differences between the two groups (Table 1).

**Table 1**

*Comparisons of Demographic Characteristics Across Groups*

| | Neurofeedback (*n* = 7) | Control (*n* = 7) | Statistical Analyses |
|---|---|---|---|
| Job status (unemployed/part time/employed) | (1/4/2) | (2/4/1) | $\chi^2(2) = 0.66$, n.s. |
| Marital status (single/married/divorced) | (2/4/1) | (2/3/2) | $\chi^2(2) = 0.47$, n.s. |
| Age (*SD*) | 37.14(4.56) | 37.57(5.06) | $t(12) = 0.16$, n.s. |
| Age of unset of substance use (years) | 18.82(4.06) | 19.35(4.47) | $t(12) = 0.23$, n.s. |
| Methamphetamine abuse duration (years) | 3.23(1.43) | 4.11(1.67) | $t(12) = 1.04$, n.s. |

**Note**. Values represent mean scores (*SD* between brackets); n.s. = no significant differences between groups.

Repeated measures ANOVA was performed to test differences between the neurofeedback and control groups in anxiety. The group (neurofeedback vs. control) as between-subjects and the measurement time point (preintervention, midintervention 1–3, postintervention, and follow-up) as within-subjects were tested. There were no differences between the two groups on the pretest. There was a significant main effect between the neurofeedback and control groups, $F(1, 12) = 5.85$, $p \leq .05$, $\eta 2 = .33$; a main effect of time (within-subject), $F(5, 60) = 25.8$, $p \leq .001$, $\eta 2 = .68$ (Table 2 and Figure 2); and an interaction effect of time (within-subject) with group (between-subjects) TIME x GROUP, $F(5, 60) = 19.69$, $p \leq .001$, $\eta 2 = .62$.

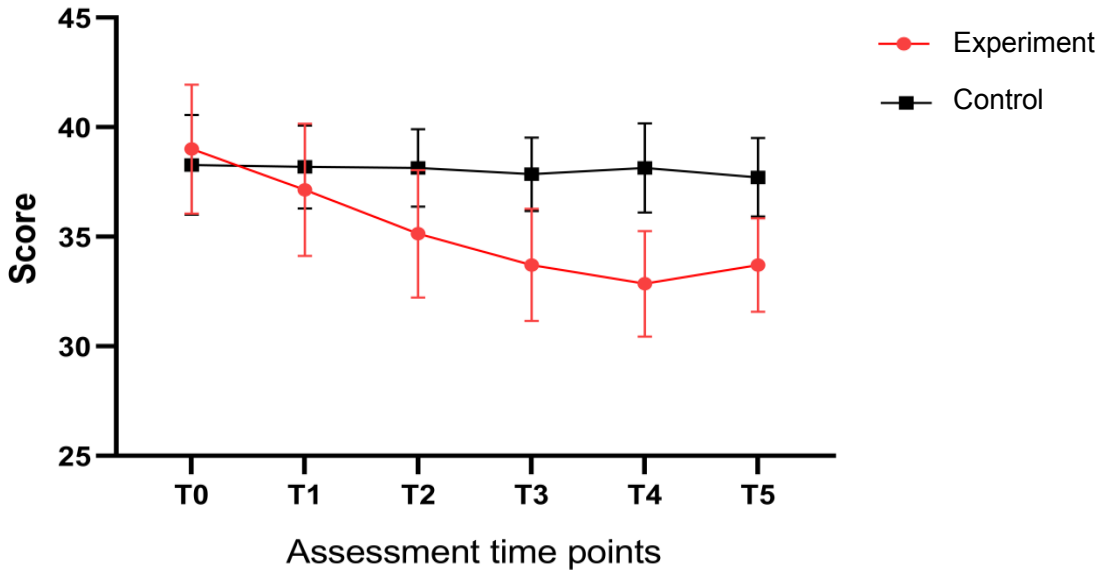
**Table 2**

*Summary of Beck Anxiety Inventory (BDI) Score in Pre-, Mid-, Postintervention, and 1-month Follow-up Measures and Mixed Repeated ANOVA*

| Group | | T0 | T1 | T2 | T3 | T4 | T5 | Intervention | Time | Intervention*Time |
|---|---|---|---|---|---|---|---|---|---|---|
| Experiment | *M* | 39.00 | 37.14 | 35.14 | 33.71 | 32.85 | 33.71 | $F = 5.85$ | $F = 25.80$ | $F = 19.69$ |
| (*n* = 7) | *SD* | 2.94 | 3.02 | 2.91 | 2.56 | 2.41 | 2.13 | $p \leq .05$ | $p \leq .001$ | $p \leq .001$ |
| Control | *M* | 38.28 | 38.28 | 38.14 | 37.85 | 38.14 | 37.71 | | | |
| (*n* = 7) | *SD* | 2.28 | 1.88 | 1.77 | 1.67 | 2.03 | 1.79 | | | |

**Note**. T0 = preintervention (week 0); T1 = midterm (week 2); T2 = midterm (week 4); T3 = midterm (week 6); T4 = postintervention (week 8); T5 = 1-month follow-up (week 12).

**Figure 2.** *Comparison of the Levels of Anxiety in Experimental (Neurofeedback) and Control Groups at Different Time Slots.*




**Note.** T0 = preintervention (week 0); T1 = midterm (week 2); T2 = midterm (week 4); T3 = midterm (week 6); T4 = postintervention (week 8); T5 = 1-month follow-up (week 12).

## Discussion

The current research examined the effectiveness of neurofeedback rehabilitation on anxiety in methamphetamine abusers. The results showed that neurofeedback rehabilitation significantly reduced anxiety among methamphetamine abusers during the posttreatment period. The same finding was also collected during a 1-month follow-up.

Neurofeedback rehabilitation is based on the idea that the mind can regenerate, change, and learn to heal itself. The mechanism associated with neurofeedback rehabilitation can be linked to a neurophysiological level. For example, a relationship between electroencephalograms and the thalamocortical mechanisms is responsible for the rhythms and frequencies of the electroencephalogram. Disrupted rhythms and frequencies of electroencephalograms can be normalized by neurofeedback rehabilitation, and these clinical effects are sustained (Niv, 2013). Our results on reduced anxiety are consistent with some studies, such as (Khajehpour et al., 2019; Liu et al., 2020).

Aliño Costa et al. (2017) found that EEG alpha had an anxiety-reducing effect on the experimental group. The use of an alpha-theta protocol in patients with anxiety disorder depends on the extent of the alpha area in the brain, especially in the parietal and occipital lobes. When the alpha range (8–12) is low, alpha enhancement may reduce anxiety symptoms. When the alpha range is high, a decrease in alpha can lead to anxiety-related symptoms. In the present study, the alpha enhancement protocol was used. According to Raymond et al. (2005), the alpha-theta protocol left the patient in theta mode.

Several studies, such as Gregory et al. (2020) have suggested that the most active and transformative properties of neurofeedback protocols teach substance abuse patients to intentionally intensify the amplitude and coherent interaction of their alpha and theta brainwave frequencies. The alpha-theta neurofeedback mechanism may allow participants to better tolerate stress, anxiety, and anxiety-provoking situations, especially during initial recovery periods.

Increased SMR amplitudes are associated with enhanced control of somatosensory and sensorimotor pathways, which could explain more accurate and even faster processing in reaction time paradigms. The basic idea is that individuals learn to self-regulate bioelectrical brain processes through operant conditioning, as measured by neurofeedback. Electrodes are placed on the scalp and specific parameters such as slow cortical potentials, alpha rhythm, SMR are extracted from the signal in real time. The participant is presented with easy to understand displays with simple shapes or video games. He is instructed to change the feedback display (e.g., increase or decrease the parameters of a bar or circle), which changes the associated brain activity. It would be interesting to conduct an SMR-NFT study that includes recording of neurofeedback during reaction time paradigms (Reichert et al., 2015). This would allow an analysis of SMR changes in relation to fast and slow responses, both within a session and across the entire experiment.

Schönenberg et al. (2017) also found no superiority of a theta/beta neurofeedback training over a meta-cognitive therapy or even a sham neurofeedback condition. Both (Bink et al., 2015; Schönenberg et al., 2017) applied the training in subjects with a single, well-defined disorder without any comorbidities. It is better the mechanism of SMR could be explored more. This pattern of results generally confirms that chronically hypoactive regions implicated in prefrontal control in drug addiction (Goldstein & Volkow, 2011) can be normalized through cognitive and motivational/emotional interventions. Results also demonstrate that different cognitive interventions act, at least partly, through a common mechanism, supporting a previous meta-analysis that posited the recruitment of the inhibitory control network as a shared therapeutic mechanism between cognitive and pharmacological interventions (Konova et al., 2013).

Spectral amplitude estimates were calculated for the active site (Cz) on raw 1-s EEG segments. A bandpass filter was used to extract the reward neurofeedback frequency band for SMR (12–15 Hz), and feedback was provided when the participant increased their SMR (12–15 Hz) by 10% for each baseline measured. Visual feedback was provided in the form of a graphic image animation. There was also a respiratory pacemaker with six cycles per minute, and the wave of heart rate and respiratory rate was measured to obtain physiological data from heart rate variability (HRV). This was done because the training of resonant frequency breathing affected the action of the somatic system (Vaschillo et al., 2006) and influenced the bottom-up circuit that produced SMR (Reid et al., 2013).

Drugs disrupted cognitive processes involving and affecting the hippocampal region and frontal cortex

structures. Drugs have been shown to increase the process of apoptosis (planned cell death) and may exacerbate inhibition of neurogenesis (formation of neural tissue). One possibility is that neurofeedback reduces the cognitive deficits caused by substances by counteracting the apoptosis process and promoting neurogenesis. Limitations of the present study are using a self-report survey and the lack of a Sham or placebo group (fictitious stimulation). The SMR neurofeedback training can be considered as a training protocol to reduce anxiety in methamphetamine abusers. However, applying a cross-sectional design was a limitation to our study. Future studies are recommended to examine the obtained results through longitudinal designs. The results obtained suggest that therapists could use neurofeedback as an intervention method to treat methamphetamine addicts. Incorporating biological and neurological levels into future studies may be another step toward improving substance abuse treatment. Additionally, the specific significant changes during this neurofeedback protocol on neurological pathways can be studied with fMRI and PT scans in future studies.

## Author Contributions

All authors contributed to the designing, conducting, and writing all parts of the research.

## Author Acknowledgment

The authors extend their gratitude to all the clinics and participants for their cooperation with the project.

## Author Disclosure

With an equal share of contribution to the project, the authors have no grants, financial interests, or conflicts to disclose.

## References

Albini, M., Morano, A., Fattouch, J., Fanella, M., Avorio, F., Basili, L. M., Irelli, E. C., Manfredi, M., Giallonardo, A. T., & Di Bonaventura, C. (2020). Anxiety as the only manifestation of focal non-convulsive status epilepticus: Case report and review of the literature. *Neurocase, 26*(2), 98–102. https://doi.org/10.1080/13554794.2020.1741647

Aliño Costa, M., Gadea, M., Hidalgo, V., Pérez, V., & Sanjuán, J. (2017). An effective neurofeedback training, with cortisol correlates, in a clinical case of anxiety. *Universitas Psychologica, 15*(5). https://doi.org/10.11144/Javeriana.upsy15-5.entc

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

Askovic, M., Watters, A. J., Coello, M., Aroche, J., Harris, A. W. F., & Kropotov, J. (2020). Evaluation of neurofeedback for posttraumatic stress disorder related to refugee experiences using self-report and cognitive ERP measures. *Clinical EEG and Neuroscience, 51*(2), 79–86. https://doi.org/10.1177/1550059419849170

Avirame, K., Nuss, L., & Todder, D. (2016). Safety and feasibility of neurofeedback training (NFB) during sleep in uncooperative child with autism: Case report. *NeuroRegulation, 3*(3), 135–139. https://doi.org/10.15540/nr.3.3.135

Bink, M., van Nieuwenhuizen, C., Popma, A., Bongers, I. L., & van Boxtel, G. J. M. (2015). Behavioral effects of neurofeedback in adolescents with ADHD: A randomized controlled trial. *European Child & Adolescent Psychiatry, 24*(9), 1035–1048. https://doi.org/10.1007/s00787-014-0655-3

Brewer, J. A., Worhunsky, P. D., Carroll, K. M., Rounsaville, B. J., & Potenza, M. N. (2008). Pretreatment brain activation during Stroop task is associated with outcomes in cocaine-dependent patients. *Biological Psychiatry, 64*(11), 998–1004. https://doi.org/10.1016/j.biopsych.2008.05.024

Chen, T.-C., & Lin, I.-M. (2020). The learning effects and curves during high beta down-training neurofeedback for patients with major depressive disorder. *Journal of Affective Disorders, 266*, 235–242. https://doi.org/10.1016/j.jad.2020.01.175

Davelaar, E. J. (2018). Mechanisms of neurofeedback: A computation-theoretic approach. *Neuroscience, 378*, 175–188. https://doi.org/10.1016/j.neuroscience.2017.05.052

Doostian, Y., Bahmani, B., Farhoudian, A., Azkhosh, M., & Khanjani, M. S. (2019). Vocational rehabilitation for individuals with substance-related disorders. *Iranian Rehabilitation Journal, 17*(2), 105–112. https://doi.org/10.32598/irj.17.2.105

Egner, T., Zech, T. F., & Gruzelier, J. H. (2004). The effects of neurofeedback training on the spectral topography of the electroencephalogram. *Clinical Neurophysiology, 115*(11), 2452–2460. https://doi.org/10.1016/j.clinph.2004.05.033

Elkington, K. S., Bauermeister, J. A., & Zimmerman, M. A. (2010). Psychological distress, substance use, and HIV/STI risk behaviors among youth. *Journal of Youth and Adolescence, 39*(5), 514–527. https://doi.org/10.1007/s10964-010-9524-7

Fitzpatrick, R. E., Rubenis, A. J., Lubman, D. I., & Verdejo-Garcia, A. (2020). Cognitive deficits in methamphetamine addiction: Independent contributions of dependence and intelligence. *Drug and Alcohol Dependence, 209*, 107891. https://doi.org/10.1016/j.drugalcdep.2020.107891

Goldstein, R. Z., & Volkow, N. D. (2011). Dysfunction of the prefrontal cortex in addiction: Neuroimaging findings and clinical implications. *Nature Reviews Neuroscience, 12*(11), 652–669. https://doi.org/10.1038/nrn3119

Gray, S. N. (2017). An overview of the use of neurofeedback biofeedback for the treatment of symptoms of traumatic brain injury in military and civilian populations. *Medical Acupuncture, 29*(4), 215–219. https://doi.org/10.1089/acu.2017.1220

Gregory, J. C., Romero, D., & Jones, M. S. (2020). Predictors of neurofeedback outcomes following qEEG individualized protocols for anxiety. *NeuroRegulation, 7*(1), 18–25. https://doi.org/10.15540/nr.7.1.18

Gruzelier, J. H. (2014). Differential effects on mood of 12–15 (SMR) and 15–18 (beta1) Hz neurofeedback. *International Journal of Psychophysiology, 93*(1), 112–115. https://doi.org/10.1016/j.ijpsycho.2012.11.007

Gruzelier, J. H., Foks, M., Steffert, T., Chen, M. J.-L., & Ros, T. (2014). Beneficial outcome from EEG-neurofeedback on creative music performance, attention and well-being in school children. *Biological Psychology, 95*, 86–95. https://doi.org/10.1016/j.biopsycho.2013.04.005

Hammond, D. C. (2005). Neurofeedback with anxiety and affective disorders. *Child and Adolescent Psychiatric Clinics of North America, 14*(1), 105–123. https://doi.org/10.1016/j.chc.2004.07.008

Hanslmayr, S., Sauseng, P., Doppelmayr, M., Schabus, M., & Klimesch, W. (2005). Increasing individual upper alpha power by neurofeedback improves cognitive performance in human subjects. *Applied Psychophysiology and Biofeedback, 30*(1), 1–10. https://doi.org/10.1007/s10484-005-2169-8

Harris, S., Hundley, G., & Lambie, G. (2021). The effects of neurofeedback on depression, anxiety, and academic self-efficacy. *Journal of College Student Psychotherapy, 35*(1), 15–29. https://doi.org/10.1080/87568225.2019.1606689

Hou, Y., Zhang, S., Li, N., Huang, Z., Wang, L., & Wang, Y. (2021). Neurofeedback training improves anxiety trait and depressive symptom in GAD. *Brain and Behavior, 11*(3), e02024. https://doi.org/10.1002/brb3.2024

Imperatori, C., Valenti, E. M., Della Marca, G., Amoroso, N., Massullo, C., Carbone, G. A., Maestoso, G., Quintiliani, M. I., Contardi, A., & Farina, B. (2017). Coping food craving with neurofeedback. Evaluation of the usefulness of alpha/theta training in a non-clinical sample. *International Journal of Psychophysiology, 112*, 89–97. https://doi.org/10.1016/j.ijpsycho.2016.11.010

Janes, A. C., Pizzagalli, D. A., Richardt, S., Frederick, B. deB., Chuzi, S., Pachas, G., Culhane, M. A., Holmes, A. J., Fava, M., Evins, A. E., & Kaufman, M. J. (2010). Brain reactivity to smoking cues prior to smoking cessation predicts ability to maintain tobacco abstinence. *Biological Psychiatry, 67*(8), 722–729. https://doi.org/10.1016 /j.biopsych.2009.12.034

Karageorghis, C. I., Bigliassi, M., Guérin, S. M. R., & Delevoye-Turrell, Y. (2018). Brain mechanisms that underlie music interventions in the exercise domain. In S. Marcora & M. Sarkar (Eds.), *Progress in Brain Research* (vol. 240, pp. 109–125). Elsevier. https://doi.org/10.1016/bs.pbr.2018.09.004

Kelley, M. J. (1997). "Native Americans, neurofeedback, and substance abuse theory". Three year outcome of alpha/theta neurofeedback training in the treatment of problem drinking among Dine' (Navajo) people. *Journal of Neurotherapy, 2*(3), 24–60. https://doi.org/10.1300/J184v02n03_03

Khajehpour, H., Mohagheghian, F., Ekhtiari, H., Makkiabadi, B., Jafari, A. H., Eqlimi, E., & Harirchian, M. H. (2019). Computer-aided classifying and characterizing of methamphetamine use disorder using resting-state EEG. *Cognitive Neurodynamics, 13*(6), 519–530. https://doi.org/10.1007/s11571-019-09550-z

Khesht-Masjedi, M. F., Omar, Z., & Kafi Masoleh, S. M. (2015). Psychometrics properties of the Persian version of Beck Anxiety Inventory in North of Iranian adolescents. *International Journal of Educational and Psychological Researches, 1*(2), 145–153. https://doi.org/10.4103/2395-2296.152233

Konova, A. B., Moeller, S. J., & Goldstein, R. Z. (2013). Common and distinct neural targets of treatment: Changing brain function in substance addiction. *Neuroscience & Biobehavioral Reviews, 37*(10 Part 2), 2806–2817. https://doi.org/10.1016/j.neubiorev.2013.10.002

Kosmyna, N., & Maes, P. (2019). AttentivU: An EEG-based closed-loop biofeedback system for real-time monitoring and improvement of engagement for personalized learning. *Sensors, 19*(23), 5200. https://doi.org/10.3390/s19235200

Liu, W., Chen, X.-J., Wen, Y.-T., Winkler, M. H., Paul, P., He, Y.-L., Wang, L., Chen, H.-X., & Li, Y.-H. (2020). Memory retrieval-extinction combined with virtual reality reducing drug craving for methamphetamine: Study protocol for a randomized controlled trial. *Frontiers in Psychiatry, 11*, 322. https://doi.org/10.3389/fpsyt.2020.00322

Luctkar-Flude, M., Groll, D., & Tyerman, J. (2017). Using neurofeedback to manage long-term symptoms in cancer survivors: Results of a survey of neurofeedback providers. *European Journal of Integrative Medicine, 12*, 172–176. https://doi.org/10.1016/j.eujim.2017.06.003

Mallorquí-Bagué, N., Lozano-Madrid, M., Testa, G., Vintró-Alcaraz, C., Sánchez, I., Riesco, N., Perales, J. C., Navas, J. F., Martínez-Zalacaín, I., Megías, A., Granero, R., Veciana de las Heras, M., Chami, R., Jiménez-Murcia, S., Fernández-Formoso, J. A., Treasure, J., & Fernández-Aranda, F. (2020). Clinical and Neurophysiological Correlates of Emotion and Food Craving Regulation in Patients with Anorexia Nervosa. *Journal of Clinical Medicine, 9*(4), 960. https://doi.org/10.3390/jcm9040960

Moeller, S. J., & Goldstein, R. Z. (2014). Impaired self-awareness in human addiction: Deficient attribution of personal relevance. *Trends in Cognitive Sciences, 18*(12), 635–641. https://doi.org/10.1016/j.tics.2014.09.003

Niv, S. (2013). Clinical efficacy and potential mechanisms of neurofeedback. *Personality and Individual Differences, 54*(6), 676–686. https://doi.org/10.1016/j.paid.2012.11.037

Nooripour, R., Hosseinian, S., Afrouz, G. A., & Bakhshani, N.-M. (2018). Effectiveness of neurofeedback on executive functions and tendency toward high-risk behaviors in adolescents with attention deficit hyperactivity disorder. *International Journal of High Risk Behaviors and Addiction, 7*(4), e82012. https://doi.org/10.5812/ijhrba.82012

Osman, A., Kopper, B. A., Barrios, F. X., Osman, J. R., & Wade, T. (1997). The Beck Anxiety Inventory: Reexamination of factor structure and psychometric properties. *Journal of Clinical Psychology, 53*(1), 7–14. https://doi.org/10.1002/(SICI)1097-4679(199701)53:1<7::AID-JCLP2>3.0.CO;2-S

Raymond, J., Varney, C., Parkinson, L. A., & Gruzelier, J. H. (2005). The effects of alpha/theta neurofeedback on personality and mood. *Cognitive Brain Research, 23*(2–3), 287–292. https://doi.org/10.1016/j.cogbrainres.2004.10.023

Reichert, J. L., Kober, S. E., Neuper, C., & Wood, G. (2015). Resting-state sensorimotor rhythm (SMR) power predicts the ability to up-regulate SMR in an EEG-instrumental conditioning paradigm. *Clinical Neurophysiology, 126*(11), 2068–2077. https://doi.org/10.1016/j.clinph.2014.09.032

Reid, A., Nihon, S., Thompson, L., & Thompson, M. (2013). The effects of heart rate variability training on sensorimotor rhythm: A pilot study. *Journal of Neurotherapy, 17*(1), 43–48. https://doi.org/10.1080/10874208.2013.759020

Richter, F., García, A. M., Rodriguez Arriagada, N., Yoris, A., Birba, A., Huepe, D., Zimmer, H., Ibáñez, A., & Sedeño, L. (2020). Behavioral and neurophysiological signatures of interoceptive enhancements following vagus nerve stimulation. *Human Brain Mapping, 42*(5) 1227–1242. https://doi.org/10.1002/hbm.25288

Roche, K., Moss, S., Baxendale, E., & Stephens, S. (2020). Are psychological distress, substance misuse, and sexual sensation seeking associated with autoerotic asphyxiation-related distress? *The Canadian Journal of Human Sexuality, 29*(2), 221–227. https://doi.org/10.3138/cjhs.2020-0004

Rostami, R., & Dehghani-Arani, F. (2015). Neurofeedback training as a new method in treatment of crystal methamphetamine dependent patients: A preliminary study. *Applied Psychophysiology and Biofeedback, 40*(3), 151–161. https://doi.org/10.1007/s10484-015-9281-1

Schönenberg, M., Wiedemann, E., Schneidt, A., Scheeff, J., Logemann, A., Keune, P. M., & Hautzinger, M. (2017). Neurofeedback, sham neurofeedback, and cognitive-behavioural group therapy in adults with attention-deficit hyperactivity disorder: A triple-blind, randomised, controlled trial. *The Lancet Psychiatry, 4*(9), 673–684. https://doi.org/10.1016/S2215-0366(17)30291-2

Scott, W. C., Kaiser, D., Othmer, S., & Sideroff, S. I. (2005). Effects of an EEG biofeedback protocol on a mixed substance abusing population. *The American Journal of Drug and Alcohol Abuse, 31*(3), 455–469. https://doi.org/10.1081/ADA-200056807

Sharifi, V., Assadi, S. M., Mohammadi, M. R., Amini, H., Kaviani, H., Semnani, Y., Shabani, A., Shahrivar, Z., Davari-Ashtiani, R., Shooshtari, M. H., Seddigh, A., & Jalali, M. (2009). A Persian translation of the Structured Clinical Interview for

*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*: Psychometric properties. *Comprehensive Psychiatry, 50*(1), 86–91. https://doi.org/10.1016/j.comppsych.2008.04.004

Simkin, D. R., Thatcher, R. W., & Lubar, J. (2014). Quantitative EEG and neurofeedback in children and adolescents: Anxiety disorders, depressive disorders, comorbid addition and attention-deficit/hyperactivity disorder, and brain injury. *Child and Adolescent Psychiatric Clinics of North America, 23*(3), 427–464. https://doi.org/10.1016/j.chc.2014.03.001

Ticci, C., Luongo, T., Valvo, G., Ferrari, A. R., Brovedani, P., Masi, G., Pellacani, S., & Sicca, F. (2019). Clinical and electroencephalographic correlates of psychiatric features in children with frontal lobe epilepsy. *Epilepsy & Behavior, 92*, 283–289. https://doi.org/10.1016/j.yebeh.2019.01.008

Vaschillo, E. G., Vaschillo, B., & Lehrer, P. M. (2006). Characteristics of resonance in heart rate variability stimulated by biofeedback. *Applied Psychophysiology and Biofeedback, 31*(2), 129–142. https://doi.org/10.1007/s10484-006-9009-3

Vernon, D., Egner, T., Cooper, N., Compton, T., Neilands, C., Sheri, A., & Gruzelier, J. (2003). The effect of training distinct neurofeedback protocols on aspects of cognitive performance. *International Journal of Psychophysiology, 47*(1), 75–85. https://doi.org/10.1016/S0167-8760(02)00091-0

**Received:** May 10, 2021
**Accepted:** July 26, 2021
**Published:** September 30, 2021

NeuroRegulation

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# The Effect of Infra-Slow Fluctuation Neurofeedback Training on a Cohort of Insomnia Participants

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**Abstract**

Neurofeedback has gained great interest as a noninvasive treatment for various disorders. However, there is still a lack in literature regarding the effects of infra-slow fluctuation (ISF) neurofeedback training. ISF neurofeedback training is aimed at the lowest brainwave oscillations and attempts to balance dysregulated brainwave activity by inducing shifts in the parasympathetic and sympathetic response. The aim of this study was to determine whether ISF neurofeedback training has a significant effect in participants with insomnia by using quantitative electroencephalography (qEEG), Central Nervous System Vital Signs (CNS VS), and by measuring the changes of physiological vitals. The intervention consisted of 10 sessions for 40 participants separated equally into two groups. Significant results were achieved with improved core temperature ($p$ = .002), finger temperature ($p$ < .001), lower heart rate ($p$ = .002), systolic ($p$ = .003) and diastolic blood pressure ($p$ = .001). The qEEG components significantly improved within standard ranges. An improved neurocognitive state was achieved in terms of CNS VS, with a decrease in depression ($p$ = .003), anxiety ($p$ < .001), and stress ($p$ < .001). This study demonstrated that ISF neurofeedback training should be considered as a viable alternative that can be used concurrently with other insomnia treatment methods.

***Keywords***: insomnia, ISF, neurofeedback, qEEG, CNS Vital Signs, ANS vitals

**Citation**: Bekker, M., Balt, K., Bipath, P., Jordaan, J., & du Toit, P. (2021). The effect of infra-slow fluctuation neurofeedback training on a cohort of insomnia participants. *NeuroRegulation*, *8*(3), 137–148. https://doi.org/10.15540/nr.8.3.137

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## Introduction

Sleep is associated with distinct and important physiological changes; however, it is often thought of as a nonactive phase during which individuals become rested. On the contrary, sleep is essential for general health and well-being and is a highly regulated, active process which involves various metabolic pathways (Carley & Farabi, 2016).

Insomnia typically occurs when a metabolic pathway becomes dysregulated. Insomnia is categorized as a sleep disorder by the International Classification of Sleep Disorders (ICSD-3; Judd & Sateia, 2019), as well as the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; American Psychiatric Association [APA], 2013). Insomnia is characterized by the inability to fall asleep or to stay asleep despite having the opportunity for sleep, which results in daytime dysfunction. Due to inadequate quantity and quality of sleep, individuals present with fatigue, varying levels of irritability, poor work performance and daytime functional impairments (Devi et al., 2018). There are numerous models that describe the pathophysiology of insomnia, and include physiological hyperarousal; genetic, molecular, and cellular mechanisms; dysregulated electrophysiology; and behavioral and cognitive factors (Ban et al., 2011).

The management and treatment of insomnia is divided into nonpharmacological treatments and pharmacological therapies. A nonpharmacological treatment that is often utilized is cognitive behavioral therapy (CBT-I; Krystal et al., 2019). Pharmacological therapies include the use of medications from different classes such as benzodiazepines (Sieghart & Sperk, 2002), z-drugs (Krystal et al., 2019), melatonin receptor agonists (Mayer et al., 2009; Ng et al., 2017; Wing et al., 2012), selective H1 antagonists (Krystal et al., 2013), orexin receptor antagonists (Michelson et al., 2014), antidepressants (Krystal, 2009), antipsychotics (Krystal, 2009), nonselective antihistamines (Morin et al., 2005), and anticonvulsants (Gajraj, 2007; Krystal et al., 2019; Rose & Kam, 2002). Unfortunately, pharmacological therapies have associated risks and side effects which may result in drug dependency.

In an attempt to reduce pharmacological dependence, researchers have started to investigate alternative treatment methods such as neurofeedback. Neurofeedback is a modality of biofeedback that is focused on the brain and is based on scientific concepts developed in the 1950s to elicit conscious control over the autonomic nervous system (Demos, 2005). It is a noninvasive, nonpharmacological method that is used to alter underlying cognitions and behaviors based on brainwave abnormalities by using self-regulation (Enriquez-Geppert et al., 2017). Self-regulation of the brain's wave patterns is learned through operant conditioning (Asher & Wierbowski, 2017).

Neurofeedback encourages operant conditioning by pairing desirable and undesirable brainwave activity with a feedback signal such as visual and auditory feedback (Marzbani et al., 2016). Feedback is based on electrophysiological components, and rewards or punishments are awarded accordingly. Rewards are provided when the desired brain activity is achieved and is in the form of an auditory tone and continuation of visual video content. Punishments are provided when undesired brain activity occurs and is in the form of high or low auditory tones and dimming of visual video content (Marzbani et al., 2016).

The type of neurofeedback that was used in this research study is infra-slow fluctuation (ISF) neurofeedback training. ISF neurofeedback training is directed at the lowest frequencies that the brain produces, known as < 0.1 Hz (Smith, 2018b). The purpose of ISF training is to find the optimal frequency at which the subjects' brainwaves are most balanced. This state of homeostasis refers to a state in which dysregulated brainwave characteristics such as amplitude, coherence, and deviancy of brainwave activity are improved within standard ranges and represent a balanced model of the brain as seen in a quantitative electroencephalography (qEEG) report.

ISF training relies on cortical activation and induces shifts between the sympathetic and parasympathetic response (Peché, 2015). Previous research has demonstrated that ISFs originate from mechanisms at a local cellular level, mainly from neurons, glia, and blood components (Palva & Palva, 2012). Together, these ISF potentials reflect the working of underlying physiological networks by forming a superstructure of ISFs that regulate, integrate, and initiate decoupling between neuronal networks that are active. Therefore, during an ISF neurofeedback session this superstructure of neuronal networks is addressed and targeted by modification of the shared information associated between cortical areas (Smith, 2013).

Each ISF neurofeedback session results in slow signal reinforcement within the brain which further produces behavioral changes and physiological improvements (Smith, 2013). By training the lowest energy levels of the brain, ISF neurofeedback can potentially coordinate the processes of the autonomic nervous system such as heart rate, blood pressure, blood flow, and digestion, and achieve a mental balance between calmness and being alert (Smith, 2018a). The reinforcement of regulated brain states promotes the readjustment of brainwave activity in various regions of the brain, and more towards the standardized baseline of activity levels (Smith, 2018a). After readjustment, the brain becomes more flexible to change to ensure appropriate responses to situations and the environment that can induce a fight-or-flight or rest-and-digest activation (Smith, 2018a).

However, ISF neurofeedback has only recently gained significant research interest; therefore, scientific publications and evidence of the mechanisms thereof are still scarce. Published ISF neurofeedback research areas include the effects thereof in ADHD, obesity, food addictions, anxiety, autism, and chronic pain (Balt et al., 2020; Collura & Frederick, 2016; Leong et al., 2018; Pigott & Cannon, 2014). Therefore, ISF neurofeedback was identified as the intervention method during this study, to demonstrate whether its effects can be applied to sleep disorders due to growing demands for alternative treatments.

## Methods

This research study was approved by the Faculty of Health Sciences, Masters and Ethics Committee (63/2020) of the University of Pretoria. Informed consent was obtained from all of the participants that were recruited. Participants were provided with a review session during which their results were discussed.

### Aim

The aim of this study was to determine whether ISF neurofeedback training had a significant effect on qualitative electroencephalogram activity, CNS Vital Signs, and physiological vitals in participants with insomnia.

### Participant Criteria and Selection

The research study was designed as a quasi-experimental study with a control group. A total sample size of 40 participants was recruited. Participants were assigned to an experimental group ($n$ = 20) or a control group ($n$ = 20). Participants recruited for the experimental group were based on reports and diagnosis of insomnia by a clinical neurophysiologist or medical professional; whereas, the control group had to meet the criteria of being between the ages of 18 and 75, as well as agree out of their own volition to do neurofeedback training as required for the study. Participants were excluded if they had epilepsy, changed medication whilst doing ISF training, reported use of recreational drugs, or if participants were pregnant at the time of recruitment.

### Pre and Post Measurements

***Electrophysiological Properties***. Participants of both the experimental and control group underwent a comprehensive 21-channel qEEG, pre and post of the 10 ISF neurofeedback sessions. The qEEG was completed with the BrainMaster Discovery 24 Series (BrainMaster Technologies, Inc., Bedford, OH), using sintered AgCl/Cl electrodes together with Ten20 conductive paste and Nuprep scrub to ensure the adhesiveness of the electrodes to the scalp. The international 10–20 system was followed for accurate electrode placement. The software that was utilized included Brain Avatar version 4.6.4. and qEEG-Pro, which provided an in-depth analysis of EEG components of interest such as: $z$-scores, deviant voxels, amplitude, and coherence (qEE-Pro, Netherlands).

***Neurocognitive Function***. A Central Nervous System Vital Signs (CNS VS) assessment was completed online pre and post of the 10 ISF neurofeedback sessions to determine and evaluate the neurocognitive states of all participants (CNS Vital Signs, 2019). The assessment consisted of 12 standardized tests assigned to the sleep protocol. The tests and questionnaires included the verbal memory test, visual memory test, finger tapping test, symbol digit coding, Stroop test, shifting attention test, continuous performance test, pain scale test (PST), Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), Medical Outcomes Survey (MOS) and the Depression, Anxiety and Stress scale (DASS; CNS Vital Signs, 2019).

***Physiological Parameters***. To determine the effect of ISF neurofeedback training within a single session, physiological vitals such as blood pressure, heart rate, core and finger temperature measurements were obtained pre and post each ISF neurofeedback session, for all participants.

To improve the accuracy of the reading, blood pressure and heart rate measurements were obtained from the left arm twice, pre and post each ISF neurofeedback session. Measurements were obtained using a Clicks Extra-large Blood Pressure Monitor (Clicks, Cape Town, South Africa).

Pre and post of each ISF neurofeedback session, participants were instructed to hold the sensor of the Stress Thermometer SC911 between their thumb and index finger for 30 s to obtain a finger temperature measurement (Bio-Medical Instruments, Inc., Clinton Township, MI). Core temperature measurements were made by the placement of the sensor underneath the arm in the armpit for 30 seconds.

### ISF Neurofeedback

For the purposes of this research study, ISF neurofeedback training required the use of 5 sintered Ag/AgCl electrodes (Peché, 2018). The electrodes were connected to the BrainMaster Atlantis I (4 x 4) amplifier via a 2-channel input cable (BrainMaster Technologies, Inc., Bedford OH). The software that was used to set the training frequency was Brain Avatar version 4.6.4. A screen/monitor and a sound system were used to display video and audio, respectively. The audio of the movie together with the different reward and punishment tones were used for the ISF training. The active electrodes were placed at the T3/T4 sites on the scalp and are commonly used as the starting point for ISF neurofeedback training, which allows for training across the hemispheres. Furthermore, there were two reference electrodes placed behind each ear on

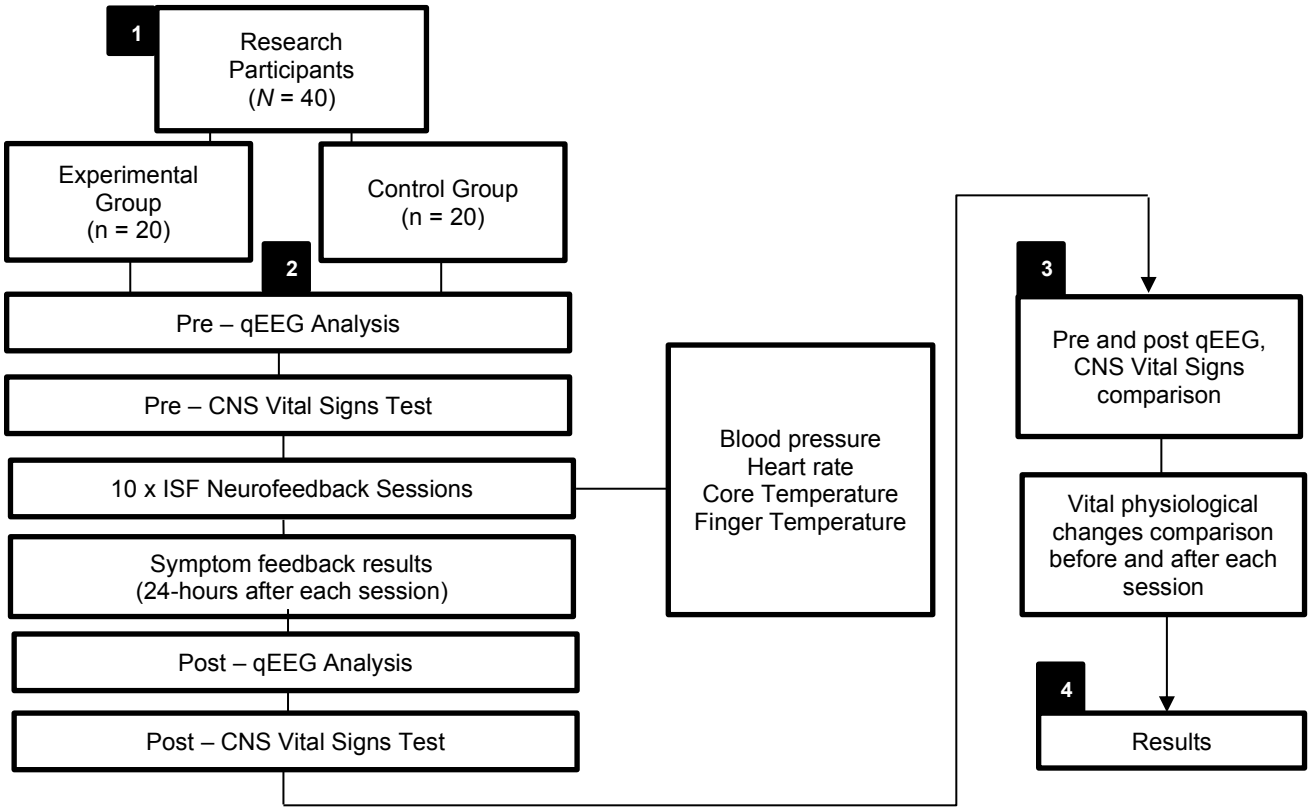
the mastoid bone and one ground electrode placed in the centre of the scalp, known as Cz.

The training was initiated at a frequency of 0.0030 Hz and if participants demonstrated or reported any physiological changes the frequency was changed to either a higher or lower frequency depending on whether the symptom reflected activation of the sympathetic nervous system or the parasympathetic nervous system, in increments of 0.0005 Hz.

The auditory feedback was specific to each participant as it guided their brain toward the set frequency to achieve an overall balance of the brainwaves. The visual feedback was provided with a "Dimmer Window." This dimmer screen dimmed the screen during neurofeedback training to provide a secondary feedback. The screen dimmed if the brainwaves fluctuated away from the desired baseline and encouraged the waves towards a balanced and regulated state.

The ISF training session duration was 30 min in total, thereafter the participant had to report whether they experienced any symptoms after the training, within the first 24 hours. During every subsequent training session, shifts in frequency were made until a constant state of positive symptoms had been achieved at their determined optimum frequency and if the brainwaves were demonstrating improvement and stabilization in terms of EEG components.

**Figure 1.** *Research and experimental design*.




## Statistical Analysis

IBM SPSS Statistics version 26 was utilized to conduct the statistical analysis. The data obtained were analyzed by conducting descriptive statistical analysis together with nonparametric tests such as the Related-Samples Wilcoxon Signed Rank test. A comparison was completed between the groups for each measured component by an Independent-Samples Mann-Whitney U test to determine if the groups responded in the same or different manner in response to the ISF neurofeedback training and to eliminate potential placebo effects.

## Results

The experimental group ($n$ = 20) consisted of 11 females and 9 males, with a mean age of 34 years.

The control group ($n$ = 20) consisted of 12 females and 8 males, with a mean age of 27 years.

## Physiological Vitals

Table 1 represents the Related-Samples Wilcoxon Signed Rank test summaries and the significance level for the control and experimental groups by calculating the median difference of the measured vitals. Figure 2 (Graphs A–E) illustrates the mean differences achieved in both groups that are measured pre and post from the ISF neurofeedback training sessions.

**Table 1**

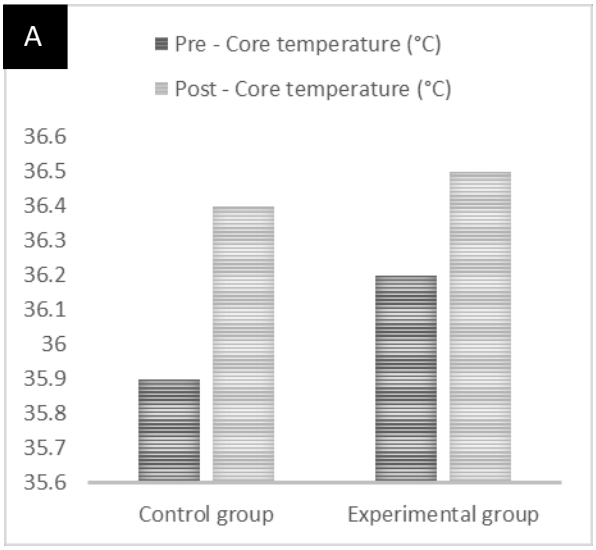
*Vital Test Summaries*

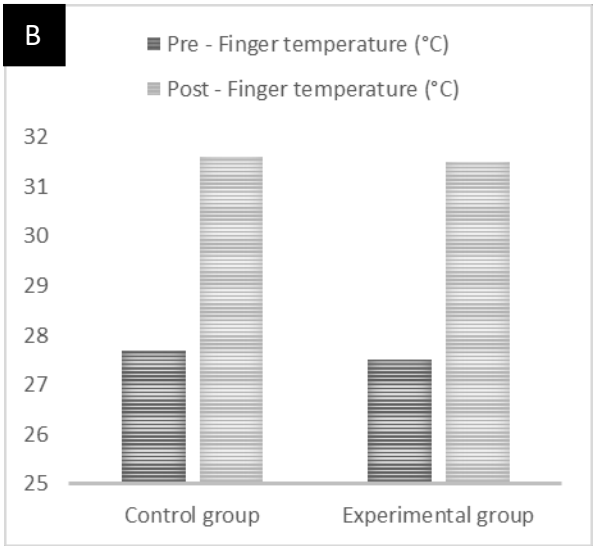
| Related-Samples Wilcoxon Signed Rank Test Summary | | | | |
|---|---|---|---|---|
| | Vitals | Test Statistic | Standard Error | Significance ($p$-value) |
| CONTROL GROUP | Core Temperature | 4.000 | 26.786 | < 0.001 |
| | Finger Temperature | 0.000 | 26.786 | < 0.001 |
| | Heart rate | 180.500 | 26.782 | 0.005 |
| | Systolic blood pressure | 170.000 | 26.782 | 0.015 |
| | Diastolic blood pressure | 145.500 | 28.847 | 0.042 |
| EXPERIMENTAL GROUP | Core Temperature | 20.000 | 26.786 | 0.002 |
| | Finger Temperature | 1.000 | 26.786 | < 0.001 |
| | Heart rate | 186.000 | 26.786 | 0.002 |
| | Systolic blood pressure | 185.000 | 26.786 | 0.003 |
| | Diastolic blood pressure | 198.000 | 26.784 | 0.001 |

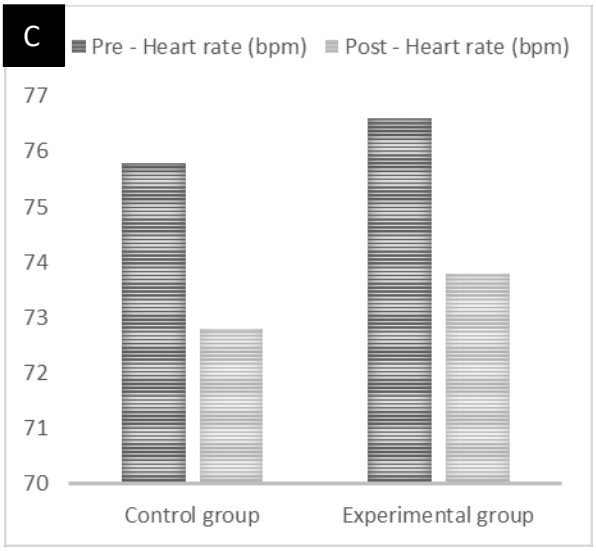
Both groups achieved significant $p$-values for all measured vitals that represent the change that occurred in the autonomic physiological vital functioning. The change in core and finger temperature demonstrate an increase in temperature after ISF neurofeedback training. This result illustrates a change in blood circulation based on stress levels. When a participant is stressed or tensed, blood circulation is directed to major organs and muscles due to vasoconstriction of blood vessels beneath the skin. Therefore, hands and feet are often cold when a participant is in a stressed state and a drop in temperature can be noted when measured at the extremities. When a participant is more relaxed, peripheral blood circulation is increased due to vasodilation of blood vessels and hands and feet become warmer. Therefore, an increase in the measured temperatures from the extremities can be expected (Bio-Medical Instruments, Inc., Clinton Township, MI).

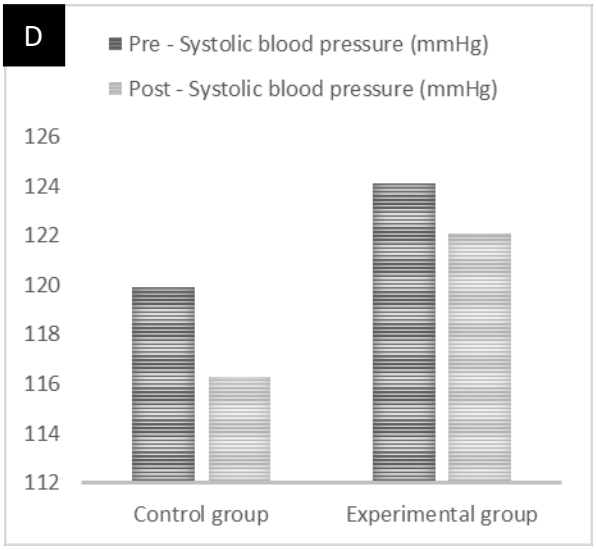
A significant change was achieved for heart rate in both groups. This difference represents an overall decline in heart rate from pre–post measurements. Therefore, participants demonstrated a lower heart rate after ISF neurofeedback training.

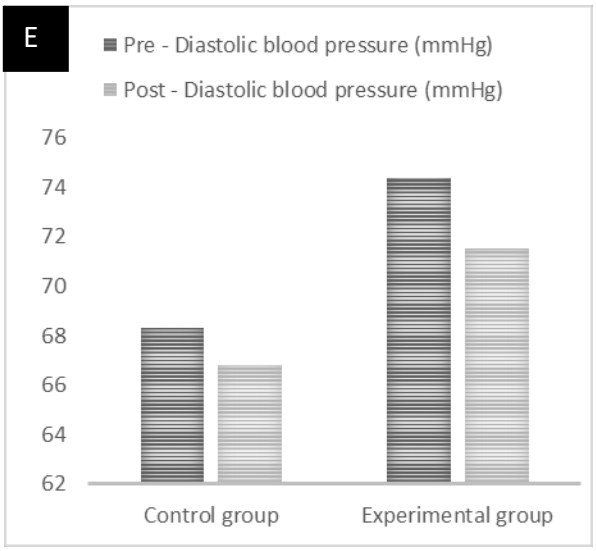
**Figure 2.** *Mean pre and post values obtained for core temperature, finger temperature, heart rate, systolic blood pressure and diastolic blood pressure from the control and experimental group during the course of 10 ISF neurofeedback sessions.*






An overall decrease in systolic blood pressure was achieved from pre–post for both groups. A significant decrease in the diastolic blood pressure was also achieved. However, participants from the experimental group demonstrated higher prediastolic blood pressure in comparison to the control group. This difference in prediastolic blood pressure supports the insomnia pathophysiology model regarding altered blood pressure measurements which can result in an increased arousal state and ultimately insomnia symptoms (Zhang et al., 2014).

## The qEEG Components

The qEEG components were analyzed pre–post in both eyes-open and eyes-closed states for each component separately, namely *z*-scores, deviant voxels, amplitude, and coherence. Previous EEG research studies concluded that eyes-open and eyes-closed conditions should be used as separate baseline resting states due to fluctuating dominancy of brainwaves in each state. During the eyes-open state, alpha brainwave activity is suppressed due to visual stimulation within the posterior cortical regions, whereas suppression in the delta and theta brainwave activity has been noted during eyes-open states in frontal and lateral regions of the brain (Kan et al., 2017).

***Z-Scores***. A *z*-score represents a standardized value that corresponds with normal or abnormal brainwave activity and is categorized within standard deviations. For this *z*-score analysis, the aim was to determine whether *z*-scores for each brainwave significantly increased or decreased. The Independent-Samples Wilcoxon Signed Rank Test was utilized to determine the significance of the change measured pre–post from the ISF neurofeedback intervention.

**Table 2**
*Z-Score Eyes-Open (EO) and Eyes-Closed (EC) p-values*

| | Control Group | | Experimental Group | |
|---|---|---|---|---|
| Brainwave | *p* (EO) | *p* (EC) | *p* (EO) | *p* (EC) |
| Delta | 0.001 | 0.881 | < 0.001 | 0.331 |
| Theta | < 0.001 | 0.232 | < 0.001 | 0.219 |
| Alpha | 0.011 | 0.499 | 0.005 | 0.103 |
| Lo-Beta | 0.001 | 0.191 | 0.003 | 0.600 |
| Beta | < 0.001 | 0.017 | 0.005 | 0.121 |
| Hi-Beta | 0.004 | 0.040 | 0.012 | 0.251 |
| Gamma | 0.012 | 0.029 | 0.011 | 0.067 |
| Alpha1 | 0.012 | 0.469 | 0.011 | 0.192 |
| Alpha2 | 0.011 | 0.385 | 0.027 | 0.571 |

Significant results were achieved for all brainwave *z*-scores in both groups in the eyes-open state. This finding is indicative of *z*-scores decreasing within normal standard deviations. Significant findings in the eyes-closed state were only achieved for the control group's z-scores of beta ($p$ = 0.017), hi-beta ($p$ = 0.040) and gamma ($p$ = 0.029). Overall, the *z*-scores in the eyes-closed state demonstrated little change, and more investigation is required to determine the full extent of ISF neurofeedback effects in both eye states.

## Deviant Voxels

A deviant voxel represents the deviant percentage of a specific voxel within an array. In this study the brain was modelled as a three-dimensional array by qEEG-Pro and corresponded with 10–20 electrode placements. These placements further provided reference points from which deviant voxels can be measured. The deviant voxels for each brainwave were calculated cumulatively across the brain and the percentage measurement was utilized for analysis. The Independent-Samples Wilcoxon Signed Rank Test was utilized in both eye states to determine the significance of the measured changes in deviant voxels.

As seen in Table 3, significantly improved results were achieved overall and for each brainwave in an eyes-open state in the control group.

**Table 3**
*Deviant Voxels Eyes-Open (EO) and Eyes-Closed (EC) p-values*

| Related-Samples Wilcoxon Signed Rank Test Summary | | | | |
|---|---|---|---|---|
| | Control Group | | Experimental Group | |
| Brainwave | *p* (EO) | *p* (EC) | *p* (EO) | *p* (EC) |
| Overall | < 0.001 | 0.140 | < 0.001 | 0.023 |
| Delta | 0.001 | 0.161 | < 0.001 | 0.100 |
| Theta | 0.001 | 1.000 | < 0.001 | 0.011 |
| Alpha | 0.003 | 0.546 | 0.005 | 0.779 |
| Lo-Beta | < 0.001 | 0.390 | 0.001 | 0.019 |
| Beta | 0.002 | 0.104 | 0.001 | 0.007 |
| Hi-Beta | 0.001 | 0.062 | < 0.001 | 0.007 |
| Gamma | 0.012 | 0.070 | 0.104 | 0.023 |
| Alpha1 | 0.003 | 0.456 | 0.015 | 0.793 |
| Alpha2 | 0.005 | 0.926 | 0.042 | 0.985 |

These significant findings are indicative of a decrease in deviant voxel percentages. The experimental group displayed a similar trend with significant findings measured overall and in each brainwave except for the deviant voxel measurements of the gamma brainwave.

There were no significant changes in the deviant voxel measurements obtained in an eyes-closed state from the control group. Significant eyes-closed results were achieved in the experimental group for the global overall ($p$ = 0.023), theta ($p$ = 0.011), lo-beta ($p$ = 0.019), beta ($p$ = 0.007), hi-beta ($p$ = 0.007) and gamma ($p$ = 0.023) deviant voxel measurements.

## Amplitude and Coherence

Amplitude refers to the size of the peak of the signal from each brainwave, measured in microvolts. Coherence refers to the similarity of the frequency of two signals and reflects how interconnected two sites in the brain are in terms of the information being shared between the sites (Warner, 2013).

Amplitude and coherence measurements can be standardized into two categories of standard deviations namely, positive (+1, +2) and negative (−1, −2) deviations. The aim of the analysis was to determine if amplitude and coherence measurements shifted in standard deviations and moved towards the norm (0) by either demonstrating an increase in the first (+/−) standard deviation or a decrease in the second (+/−) standard deviation.

The Related-Samples Wilcoxon Signed Rank Test was used in the analysis to determine the median differences for both (+/−) standard deviations of the amplitude and coherence measurements. As seen in Table 4, significant findings were achieved in the eyes-open state for the control and experimental group in all amplitude and coherence groups except for the category of: Amplitude %Z < −1 and Amplitude %Z < −2. Similar results were achieved in the eyes-closed state with the control and experimental group reporting significant findings for all amplitude and coherence groups except for the category of: Amplitude %Z < −1 and Amplitude %Z < -2. This result is due to an overall pre- and post-distribution within the positive (+1, +2) standard deviation categories, demonstrating that participants generally have high amplitude peaks instead of low amplitude peaks that are distributed across the brain.

Coherence was measured to determine if ISF neurofeedback training is effective in improving coherence across all measured 10-20 sites and if there is any correlation with an improvement in insomnia symptoms. As stipulated, significant *p*-

values were achieved for both groups in positive and negative standard deviation categories. This result indicates that coherence measurements became more distributed within the standard deviation categories.

**Table 4**
*Amplitude and Coherence p-values*

| Related-Samples Wilcoxon Signed Rank Test Summary | | | | |
|---|---|---|---|---|
| | Control Group | | Experimental Group | |
| Amplitude (A) & Coherence (C) %Z | *p* (EO) | *p* (EC) | *p* (EO) | *p* (EC) |
| A %Z > 1 | < 0.001 | < 0.001 | 0.002 | < 0.001 |
| A %Z > 2 | < 0.001 | < 0.001 | 0.001 | < 0.001 |
| A %Z < −1 | 0.465 | 1.000 | 1.000 | 0.258 |
| A %Z < −2 | 1.000 | 1.000 | 0.180 | 1.000 |
| C %Z > 1 | < 0.001 | < 0.001 | 0.019 | 0.010 |
| C %Z > 2 | 0.000 | < 0.001 | 0.012 | 0.009 |
| C %Z < −1 | < 0.001 | < 0.001 | 0.019 | 0.002 |
| C %Z < −2 | < 0.001 | < 0.001 | 0.013 | 0.001 |

## CNS Vital Signs

CNS Vital Signs were utilised to determine neurocognitive function pre and post of the ISF neurofeedback intervention. As seen demonstrated in Table 5, CNS VS component results were reported as standardized values and represent a level of neurocognitive function. The significance of the change measured from the standardized score was correlated with a *p*-value.

## Neurofeedback Symptoms

The statistical analysis of the neurofeedback symptoms involved the analysis of the symptoms reported by the participants on the neurofeedback symptom report. Symptoms measured included emotional reactivity, emotional sensitivity, difficulty falling asleep, lack of deep sleep, agitation, sedation, physical tension, dizziness, nightmares, sugar cravings, appetite, headaches, nausea, diarrhea, and constipation.

This analysis consisted of a cross-tabulation of the total count of reported cases for each symptom, the percentage thereof, together with the standardized residual value. The degree of the symptom was ranked in a range of 1–3, with 1 = *no symptom*, 2 = *mild symptom* , and 3 = *severe symptom*.

**Table 5**
*CNS Vital Signs p-values*

| Related-Samples Wilcoxon Signed Rank Test Summary | | |
|---|---|---|
| CNS Vital Signs Component | Control Group *p* | Experimental Group *p* |
| Neurocognition Index (NI) | 0.002 | 0.005 |
| Composite Memory | 0.197 | 0.670 |
| Verbal Memory | 0.289 | 0.687 |
| Visual Memory | 0.214 | 0.777 |
| Psychomotor speed | 0.016 | 0.409 |
| Reaction Time | 0.141 | 0.030 |
| Complex Attention | 0.115 | 0.028 |
| Cognitive Flexibility | 0.031 | 0.002 |
| Processing Speed | 0.026 | 0.153 |
| Executive Function | 0.021 | 0.002 |
| Simple Attention | 0.054 | 0.598 |
| Motor Speed | 0.765 | 0.708 |
| Pain Scale | 0.014 | 0.010 |
| Epworth Sleepiness Scale (ESS) | 0.182 | 0.214 |
| Duration of Sleep | 0.102 | 0.011 |
| Sleep Latency | 0.007 | 0.005 |
| Sleep Efficiency | 0.131 | 0.022 |
| Need Meds to Sleep | 0.317 | 0.039 |
| Sleep Disturbance | 1.000 | 0.008 |
| Day Disfunction Due to Sleepiness | 0.194 | 0.004 |
| Overall Sleep Quality | 0.166 | <0.001 |
| PSQI Total Score | 0.032 | <0.001 |
| Physical Functioning | 0.453 | 0.440 |
| Role Functioning – Physical | 0.167 | 0.836 |
| Role Functioning – Emotional | 0.088 | 0.016 |
| Energy/Fatigue | 0.073 | 0.017 |
| Emotional Well-being | 0.070 | 0.014 |
| Social Functioning | 0.005 | 0.107 |
| Pain | 0.289 | 0.716 |
| General Health | 0.137 | 0.265 |
| Health Change | 0.928 | 0.175 |
| Depression | 0.007 | 0.003 |
| Anxiety | 0.005 | <0.001 |
| Stress | 0.027 | <0.001 |

Most of the symptoms that were reported were within the first degree of the scale. Therefore, the severity of the symptoms experienced after ISF neurofeedback training were low with only certain symptoms being reported as severe, namely emotional reactivity (10%), difficulty falling asleep (30%), lack of deep sleep (30%), sugar cravings (10%), and diarrhea (10%) across both groups.

## Discussion

Participants achieved improved regulation of ANS vitals as seen with the measurement results. Core temperature post measurements became distributed between 36.5˚C and 37˚C for both groups and demonstrated improved regulation in comparison to pre-measurements which were scattered between 34˚C and 37.5˚C. Finger temperature measurements demonstrated both groups becoming more relaxed and improved regulation with shifts towards the parasympathetic response with post measurements ranging between 30˚C and 34˚C. Pre measurements achieved lower peaks in temperature between 25˚C and 30˚C and demonstrated that participants were likely to be more tense before the ISF neurofeedback training.

Heart rate post measurements decreased within ranges of 60–80 beats per minute for both groups, whereas pre measurements ranged between 70–90 beats per minute. Therefore, heart rate became more regulated after ISF neurofeedback training with healthier ranges which further demonstrated improved relaxation of participants. Post measurements of systolic blood pressure demonstrated ranges between 115–130 mmHg for both groups, in comparison to higher pre measurement ranges of 120–140 mmHg. Furthermore, diastolic blood pressure post measurements reached a peak at 70 mmHg for both groups, whereas pre measurements were scattered between 60–80 mmHg. Therefore, improved cardiovascular activity was achieved in terms of heart rate and blood pressure measurements for both groups. This outcome further demonstrated that ISF neurofeedback training can elicit a calming effect and improve vital function regulation in participants.

The significant results achieved for core and finger temperature, heart rate, systolic and diastolic blood pressure are substantial as this confirms that ISF neurofeedback training impacts the regulation of autonomic functions of the ANS. Furthermore, these significant results support the findings of previous neurofeedback research in which researchers demonstrated that ISF neurofeedback training can regulate ANS functions by using peripheral biofeedback indicators (Balt et al., 2020).

These ANS vital findings are of great significance as they provide a pathway for ISF neurofeedback training as a potential cotreatment for insomnia, as some models of pathophysiology suggest that individuals can develop insomnia due to a comorbidity such as elevated blood pressure or abnormal temperature regulation.

Within the qEEG analysis, *z*-scores measured after the ISF neurofeedback intervention were significantly lower in both groups. This decrease in *z*-score values demonstrate that ISF neurofeedback training has the ability to train *z*-scores within standardized brainwave activity ranges and establishes a balanced overall state across all brainwaves.

Significant findings were achieved for the deviant voxels for all brainwaves in the eyes-open state in the control and experimental group. No significant findings were achieved in the eyes-closed state for the control group. Significant results were achieved for only specific brainwaves in the experimental group, namely global overall, theta, lo-beta, beta, hi-beta and gamma. A plausible reason for a significant change in deviant voxel activity in the previously mentioned brainwaves for the experimental group is that these brainwaves are mainly responsible for initiating slow wave activity (theta) that induces sleep and faster brainwave activity (lo-beta, beta, hi-beta, gamma) that is required for day-to-day functioning. In the experimental group these brainwaves may be initially dysregulated as described in the pathophysiology model of dysregulated electrophysiology and creates symptoms of insomnia (Ban et al., 2011; Perlis et al, 2001).

Other qEEG components that play an important role with regards to the balance achieved between the various brainwaves is amplitude and coherence. Amplitude can be trained across brainwave bandwidths to improve asymmetries during ISF neurofeedback training. The measured amplitude results support the theory of hyperarousal and dysregulated electrophysiological properties associated with insomnia (Ban et al., 2011; Riemann et al., 2010). The analysis further demonstrated that amplitudes decreased from pre to post measurements. Amplitudes decreased within standard deviations and moved towards standardized norms for each participant's age.

Therefore, amplitude measurements were distributed across the brain within standardized ranges after the ISF neurofeedback training intervention.

Coherence refers to the interconnectivity and synchronization of the frequency of two signals between two sites in the brain (Warner, 2013). This measurement can be used to determine if regions in the brain are in a state of hypo- or hypercoherence. Hypocoherence is a state of poor intersite interaction and can result in poor efficiency of cognitive processes due to cortical regions being unable to connect and share information between sites; whereas hypercoherence refers to a rigid state where patterns of intersite connections become locked together. This results in the brain becoming dependant on the intersite patterns and ultimately only activating certain cortical structures and centers. The brain then becomes unable to process information efficiently and obstructs the formation of new neural connections (Warner, 2013).

As stipulated, significant *p*-values were achieved for both groups in positive and negative standard deviation categories. This result indicates that coherence measurements became more distributed within the standard deviation categories. Thus, coherence measurements improved after the ISF neurofeedback intervention in both eye states with the control group reporting more instances of hypercoherence and the experimental group both hyper- and hypocoherence.

CNS Vital Signs provided in-depth neurocognitive function reports of all participants pre and post of the ISF neurofeedback intervention. Significant p-values were achieved for various neurocognitive components as listed, but most importantly significant results were achieved for both groups in the Pittsburgh Sleep Quality Index (PSQI). Thus, both groups reported improved quality of sleep after 10 sessions of ISF neurofeedback training. Furthermore, significant results were achieved for both groups in the Depression, Anxiety and Stress Score (DASS) test. Demonstrating improvements in depression, anxiety, and stress. The DASS results support previous research findings suggesting that ISF neurofeedback has the potential to be utilized as long-term treatment plans for depression, anxiety, and stress (Smith et al., 2014).

To further improve the quality of scientific reporting, placebo effects were determined between the experimental and control group. All measured components were compared between the groups to determine if participants displayed similar trends in the effects of the ISF neurofeedback training. The Independent-Samples Mann-Whitney U test was used to statistically analyze the trends between both groups. No significant differences were achieved between the groups after the ISF neurofeedback training intervention took place. Therefore, no placebo effects were reported in this study, as both groups statistically displayed the same responses in effects after ISF neurofeedback training.

In summary, the aim together with all objectives set out in the research protocol were achieved. Importantly, participants demonstrated improved qEEG and CNS Vital Signs outcomes with an overall improvement in the quality of sleep, ANS vital regulation such as heart rate, body temperature and blood pressure, as well as improved neurocognitive functions and a decrease in depression, anxiety, and stress. Therefore, ISF neurofeedback training has demonstrated its efficacy in improving qEEG activity together with neurocognitive factors which can aid in the improvement of insomnia symptoms in an insomnia cohort.

## Conclusion

This study demonstrated that by using ISF neurofeedback training to improve vitals, neurocognitive functions and dysregulated electrophysiological brain activity, insomnia symptoms can be improved. Therefore, ISF neurofeedback training should be considered as a viable supplementary insomnia treatment that can be used concurrently with other treatment methods, which can reduce the dependence of pharmacological treatments. ISF neurofeedback training has demonstrated remarkable results in various areas of research and future research studies should continue to aim to include a variety of scientific principles to ensure that the validity of ISF neurofeedback training is upheld.

## Acknowledgements

Karlien Balt, for providing access to the KB Neurofeedback cc practice, facilities, and apparatus. CNS Vital Signs, for providing discounted research rates for the online assessments.

### Author Declarations

A bursary was provided by the postgraduate funding department of the University of Pretoria, for the tuition fees associated with the research study. The authors declare that there is no conflict of interests involved in this research study.

## References


American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

Asher, T., & Wierbowski, B. (2017). *Brain training: The future of psychiatric treatment?* Harvard University. https://sitn.hms.harvard.edu/flash/2017/brain-training-future-psychiatric-treatment/

Atlantis I 4x4 series system [Apparatus]. (2020). Bedford, OH: BrainMaster Technologies, Inc. https://brainmaster.com/product/atlantis/

Balt, K., Du Toit, P., Smith, M. L., & van Rensburg, C. J. (2020). The effect of infraslow frequency neurofeedback on autonomic nervous system function in adults with anxiety and related diseases. *NeuroRegulation, 7*(2), 64–74. https://doi.org/10.15540/nr.7.2.64

Ban, H-J., Kim, S. C., Seo, J., Kang, H-B., & Choi, J. K. (2011). Genetic and metabolic characterization of insomnia. *PLoS ONE, 6*(4), e18455. https://doi.org/10.1371/journal.pone.0018455

BrainAvatar 4.0 Discovery Acquisition (Version 4.6.4) [Computer software]. (2019). Bedford, OH: BrainMaster Technologies Inc. https://www.brainmaster.com/product/brainavatar-4-0-discovery-acquisition/

BrainMaster Discovery 24 Series [Computer software and hardware]. (2019). Bedford, OH: BrainMaster Technologies, Inc.

Carley, D. W., & Farabi, S. S. (2016). Physiology of sleep. *Diabetes Spectrum, 29*(1), 5–9. https://doi.org/10.2337/diaspect.29.1.5

CNS Vital Signs. (2019). *CNS Vital Signs Interpretation Guide*. Morrisville, NC: CNS Vital Signs, LLC. https://www.cnsvs.com/WhitePapers/CNS_VS_BriefInterpretation_Guide.pdf

Collura, T. F., & Frederick, J. A. (2016). *Handbook of clinical QEEG and neurotherapy*. New York, NY: Routledge/Taylor & Francis Group.

Demos, J. N. (2005). Getting started with neurofeedback. W. W. Norton & Company.

Devi, C. B. P., Samreen, S., Kumari, N. K., & Sharma, J. (2018). A review on insomnia: The sleep disorder. *The Pharma Innovation Journal, 7*(12), 227–230. https://www.thepharmajournal.com/archives/2018/vol7issue12/PartE/7-11-125-807.pdf

Enriquez-Geppert, S., Huster, R. J., & Hermann, C. S. (2017). EEG-neurofeedback as a tool to modulate cognition and behavior: A review tutorial. *Frontiers in Human Neuroscience, 11*, 51. https://doi.org/10.3389/fnhum.2017.00051

Gajraj, N. M. (2007). Pregabalin: Its pharmacology and use in pain management. *Anesthesia & Analgesia, 105*(6), 1805–1815. https://doi.org/10.1213/01.ane.0000287643.13410.5e

Judd, B. G., & Sateia, M. J. (2019). Classification of sleep disorders. https://www.uptodate.com/contents/classification-of-sleep-disorders#H4

Kan, D. P. X., Croarkin, P. E., Phang, C. K., & Lee, P. F. (2017). EEG differences between eyes-closed and eyes-open conditions at the resting stage for euthymic participants. *Neurophysiology, 49*(6), 432–440. https://doi.org/10.1007/s11062-018-9706-6

Krystal, A. D. (2009). A compendium of placebo-controlled trials of the risks/benefits of pharmacological treatments for insomnia: The empirical basis for U.S. clinical practice. *Sleep Medicine Reviews, 13*(4), 265–274. https://doi.org/10.1016/j.smrv.2008.08.001

Krystal, A. D., Prather, A. A., & Ashbrook, L. H. (2019). The assessment and management of insomnia: An update. *World Psychiatry, 18*(3), 337–352. https://doi.org/10.1002/wps.20674

Krystal, A. D., Richelson, E., & Roth, T. (2013). Review of the histamine system and the clinical effects of $H_1$ antagonists: Basis for a new model for understanding the effects of insomnia medications. *Sleep Medicine Reviews, 17*(4), 263–272. https://doi.org/10.1016/j.smrv.2012.08.001

Large screen arm blood pressure monitor [Apparatus]. (2020). Capetown, South Africa: Clicks. https://clicks.co.za/clicks_large-screen-arm-bloodpressuremonitor/p/300191?gclid=CjwKCAiA2O39BRBjEiwApB2Ikq98ieHRx5YYmuehv4UIvaaD3GA9J-ZZ35VbjHMPxDeXg5CWSPI8NBoCgc8QAvD_BwE&gclsrc=aw.ds

Leong, S. L., Vanneste, S., Lim, J., Smith, M., Manning, P., & De Ridder, D. (2018). A randomised, double-blind, placebo-controlled parallel trial of closed-loop infraslow brain training in food addiction. *Scientific Reports, 8*, 11659. https://doi.org/10.1038/s41598-018-30181-7

Marzbani, H., Marateb, H. R., & Mansourian, M. (2016). Neurofeedback: A comprehensive review on system design, methodology and clinical applications. *Basic and Clinical Neuroscience, 7*(2), 143–158. https://doi.org/10.15412/J.BCN.03070208

Mayer, G., Wang-Weigand, S., Roth-Schechter, B., Lehmann, R., Staner, C., & Partinen, M. (2009). Efficacy and safety of 6-month nightly ramelteon administration in adults with chronic primary insomnia. *Sleep, 32*(3), 351–360. https://doi.org/10.1093/sleep/32.3.351

Michelson, D., Snyder, E., Paradis, E., Chengan-Liu, M., Snavely, D. B., Hutzelmann, J., Walsh, J. K., Krystal, A. D., Benca, R. M., Cohn, M., Lines, C., Roth, T., & Herring, W. J. (2014). Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: A phase 3 randomised, double-blind, placebo-controlled trial. *The Lancet Neurology, 13*(5), 461–471. https://doi.org/10.1016/S1474-4422(14)70053-5

Morin, C. M., Koetter, U., Bastein, C., Ware, J. C., & Wooten, V. (2005). Valerian-hops combination and diphenhydramine for treating insomnia: A randomized placebo-controlled clinical trial. *Sleep, 28*(11), 1465–1471. https://doi.org/10.1093/sleep/28.11.1465

Ng, K. Y., Leong, M. K, Liang, H., & Paxinos, G. (2017). Melatonin receptors: Distribution in mammalian brain and their respective putative functions. *Brain Structure and Function, 222*(7), 2921–2939. https://doi.org/10.1007/s00429-017-1439-6

Palva, J. M., & Palva, S. (2012). Infra-slow fluctuations in electrophysiological recordings, blood-oxygenation-level-dependent signals, and psychophysical time series. *NeuroImage, 62*(4), 2201–2211. https://doi.org/10.1016/j.neuroimage.2012.02.060

Peché, D. (2015). *ISF or Infra Slow Fluctuation Training*. Neurofeedback Therapy. http://www.neurofeedback-therapy.co.za/Wordpress/2015/02/26/isf-or-infra-slow-frequency-training/

Perlis, M. L., Smith, M. T., Andrews, P. J., Orff, H., & Giles, D. E. (2001). Beta/gamma EEG activity in patients with primary and secondary insomnia and good sleeper controls. *Sleep, 24*(1), 110–117. https://doi.org/10.1093/sleep/24.1.110

Pigott, H. E., & Cannon, R. (2014). Neurofeedback is the best available first-line treatment for ADHD: What is the evidence for this claim? *NeuroRegulation, 1*(1), 4–23. https://doi.org/10.15540/nr.1.1.4

qEEG-Pro [Database]. (2019). Netherlands: qEEG-Pro B. V. https://qeegpro.eegprofessionals.nl/database/

Riemann, D., Spiegelhalder, K., Feige, B., Voderholzer, U., Berger, M., Perlis, M., & Nissen, C. (2010). The hyperarousal model of insomnia: A review of the concept and its evidence. *Sleep Medicine Reviews, 14*(1), 19–31. https://doi.org/10.1016/j.smrv.2009.04.002

Rose, M. A., & Kam, P. C. A. (2002). Gabapentin: Pharmacology and its use in pain management. *Anaesthesia, 57*(5), 451–462. https://doi.org/10.1046/j.0003-2409.2001.02399.x

Sieghart, W., & Sperk, G. (2002). Subunit composition, distribution and function of GABA(a) receptor subtypes. *Current Topics in Medicinal Chemistry, 2*(8), 795–816. https://doi.org/10.2174/1568026023393507

Sintered Silver/Silver Chloride Electrodes. (2019). https://www.eeginfoeurope.com/fileadmin/images/produkte/elektroden/sintered-electrodes.pdf

Smith, M. L. (2013). Infra-slow fluctuation training; On the down-low in neuromodulation. *NeuroConnections*, *Fall 2013*, 38–46.

Smith, M. (2018a). *The benefits of infraslow neurofeedback training*. Neurofeedback Services of New York. https://neurofeedbackservicesny.com/the-benefits-of-infraslow-neurofeedback-training/

Smith, M. (2018b). *Types of neurofeedback*. Neurofeedback Services of New York. https://neurofeedbackservicesny.com/types-of-neurofeedback/

Smith, M. L., Collura, T. F., Ferrera, J., de Vries, J. (2014). Infra-slow fluctuation training in clinical practice: A technical history. *NeuroRegulation, 1*(2), 187–207. https://doi.org/10.15540.nr.1.2.187

Stress Thermometer SC911 [Apparatus]. (2020). Clinton Township, MI: Bio-Medical Instruments, Inc. https://bio-medical.com/stress-thermometer-sc911.html

Warner, S. (2013). *Cheat Sheet for Neurofeedback*. Stress Therapy Solutions. http://www.stresstherapysolutions.com/uploads//STSCheatSheetoftheBrain.pdf

Wing, Y. K., Zhang, J., Lam, S. P., Li, S. X., Tang, N. L., Lai, K. Y., & Li, A. M. (2012). Familial aggregation and heritability of insomnia in a community-based study. *Sleep Medicine, 13*(8), 985–990. https://doi.org/10.1016/j.sleep.2012.04.013

Zhang, J., Lam, S.-P., Li, S. X., Ma, R. C. W., Kong, A. P. S., Chan, M. H. M., Ho, C-S., Li, A. M., & Wing, Y.-K. (2014). A community-based study on the association between insomnia and hypothalamic-pituitary-adrenal axis: Sex and pubertal influences. *The Journal of Clinical Endocrinology & Metabolism, 99*(6), 2277–2287. https://doi.org/10.1210/jc.2013-3728

**Received:** August 30, 2021
**Accepted:** September 2, 2021
**Published:** September 30, 2021

NeuroRegulation

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# Intensive Neurofeedback-based Training to Improve Impaired Attention and Executive Functions Secondary to Resection of Tuberculum Sellae Meningioma: A Case Study

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**Abstract**

**Introduction.** The present study aimed to evaluate the effectiveness of neurofeedback (NFB) for the treatment of acquired cognitive impairment after brain tumor surgery. **Methods.** The patient was a 49-year-old bilingual African woman who underwent surgical craniotomy after a tuberculum sellae meningioma was diagnosed. Cognitive deficits were evident following post-surgical recovery, and therefore intensive NFB training consisting of 15 sessions was carried out over a period of three weeks. Full neuropsychological testing and quantitative EEG analysis were performed before and after the training for outcome measurements. **Results.** The treatment resulted in improved attention and executive functions; specifically sustained, focused, and divided attentional abilities; cognitive flexibility, access to the lexical vocabulary, and a better processing speed. Analysis of the qEEG revealed an increased alpha peak frequency value and reduced delta/alpha ratio in frontal areas. The EEG examination revealed interhemispheric asymmetry after treatment. **Conclusion.** These findings suggest that a delta/alpha decrease might account for some clinical effects on cognitive abilities seen in a brain tumor resection survivor, reducing cognitive symptoms that can have a significant impact on daily life functions. Future studies on larger patients' samples should clarify the feasibility of NFB protocols for patients with brain tumors.

***Keywords***: EEG biofeedback; qEEG; neurorehabilitation; brain tumor; cognitive functions

**Citation**: Lagravinese, G., Sardone, R., De Trane, S., Montenegro, F., Losavio, E., Fiore, P., & Battista, P. (2021). An intensive neurofeedback-based training to improve attention and executive functions secondary to meningioma of tuberculum sellae resection: A case study. *NeuroRegulation*, *8*(3), 149–161. https://doi.org/10.15540/nr.8.3.149

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## Introduction

Tuberculum sellae meningiomas (TSMs) are relatively common, accounting for 5 to 10% of all intracranial meningiomas (Goel et al., 2002; Nakamura et al., 2006). Located above the tuberculum sellae, suprasellar meningiomas occupy the posterior medial zone of the anterior cranial fissure and originate from the superior surface of the sphenoidal body, tuberculum or, possibly, the jugum. Due to their origin location, the prognosis of TSMs poses a special challenge because of their proximity to major arteries, visual pathways, and the hypothalamus (Ehresman et al., 2019). TSMs are frequently associated with changes in cognition, personality, and behavior before surgery (Abel et al., 2016). Among others, the main clinical and cognitive features described in literature consist of sight deterioration or even blindness due to the compression of the optic nerve and chiasm,

impaired attention and executive functions (e.g., loss of concentration and generalized slowing of thought processes), as well as poor regulation of emotions and ensuing apathy, depression, and poor psychomotor speed secondary to frontal lobe compression (Abel et al., 2016; Bitter et al., 2013; Simoca et al., 1994; Tucha et al., 2000). Frontal lobes play an important role in the regulation of higher cognitive functions such as attention that can be classified as selective, divided, shifting; and executive functions encompassing a set of abilities serving to plan and evaluate effective strategies for problem solving (Battista et al., 2020, 2021). Attentional deficits can be completely or partially responsible for the observed impairment in working memory, learning, retention, perception, and problem solving; most of the cognitive disorders described in the TSM patients seem to be related to an increased reaction time. These cognitive symptoms can be present even after the surgical removal of the TSM and are one of the most vexing problems for survivors. If not addressed, they can evolve over time into cognitive phenotypes such as mild cognitive impairment (Cramer et al., 2019).

The above-described clinical manifestations experienced by TSM survivors are reflected in electroencephalographic (EEG) changes. Electrical brain activity may be depicted by quantified electroencephalography (qEEG) as different frequency bands, associated with different mental states (Sanei & Chambers, 2013). Five main EEG frequency bands are described according to different frequency ranges and associated with distinct levels of activity: Delta waves (0.1–3.0 Hz), related to deep sleep; theta waves (4–7 Hz) related to drowsiness and meditation; alpha waves (8–12 Hz) related to vigilance and relaxed wakefulness; sensorimotor rhythm (SMR; 12.5–15.5 Hz) which is active when sensory or motor areas are idle; beta waves (13–30 Hz) which range from focal attention and deep focus at low frequencies to emotional arousal and motor functions; and gamma waves (> 30 Hz) related to learning and higher cognitive processing (Sanei & Chambers, 2013). Variations of frequency rhythms such as increased focal slowing, a lower frequency, higher amplitude, greater persistence, wider distribution, beta asymmetry and epileptiform discharges can ensue after surgical TSM removal (Bartolomei et al., 2006; Beaumont & Whittle, 2000; Cobb et al., 1979; Derks et al., 2014; van Dellen et al., 2013). In particular, it has been shown that following a TSM resection, dramatic changes may occur in the EEG that can stabilize overall, leaving deficits that are difficult to define but usually consist of excessive theta/lower alpha waves (Rothoerl et al., 2003; Telera et al., 2012).

After surgical meningioma resection, a regression of cognition and visual impairments can ensue (Di Cristofori et al., 2018; Zweckberger et al., 2017). According to Zweckberger et al. (2017), subjects with a diagnosis of TSM can spontaneously undergo a recovery from the cognitive deficits after 6–12 months from surgery. However, this scenario is infrequent and, in most patients, cognitive deficits may persist up to four years after surgery if not properly treated (Barrash et al., 2020; Di Cristofori et al., 2018; Rijnen et al., 2019) and in some cases become irreversible, with an impact on levels of functionality (Krupp et al., 2009).

Neurofeedback (NFB), or EEG-biofeedback, is a noninvasive intervention based on the principles of operant conditioning. It considers behavioral, cognitive, and subjective aspects as well as brain activity. In order to modulate the electrical activity of the brain, it provides real-time visual and auditory feedback to the patient, displaying moment-to-moment information on the state of an individual's physiological functioning. The goal of this technique is to encourage the subject to learn to operate self-regulation of the putative neural substrates underlying specific behaviors. It addresses several issues of brain dysregulation, involving training to reduce the excessive theta/lower alpha waves during attentional tasks that are responsible for reduced processing speeds, while enhancing beta activities (Hammond, 2011). Based on this feedback, various learning principles, and therapist guidance, changes in brain patterns can occur which are associated with positive changes in physical, emotional, and cognitive states. The patient is often not consciously aware of the mechanisms through which such changes are accomplished, although people routinely acquire the ability to sense these positive changes and are often able to access these states outside the feedback session. When provided with appropriate training by a professional, patients do not generally experience negative side effects. The studies conducted to date have promoted a better understanding of not only the efficacy of NFB but also of the underlying neural circuits related to the process of cerebral self-regulation. Reinforcing beta frequencies can increase attention and arousal in healthy subjects (Egner & Gruzelier, 2004). Research studies have demonstrated promising results of NFB intervention for epilepsy, psychogenic nonepileptic seizures, migraine, attention-deficit/hyperactivity disorder (ADHD), traumatic brain injury, and affective disorders (i.e., Shakibaei et al.,

2021; Sitaram et al., 2017). Few studies have yet investigated the effectiveness of NFB training in patients with cancer surgery sequelae (Hetkamp et al., 2019). The available records found improvements of cancer-related symptoms such as pain, fatigue, depression/anxiety, and sleep, ameliorating the quality of life (Benioudakis et al., 2016; Gorini et al., 2015; Luctkar-Flude & Groll, 2015; Patel et al., 2020; Prinsloo et al., 2017).

NFB has not yet been studied in depth in adults with acquired cognitive impairment after brain tumor resection. To the best of our knowledge, only one randomized clinical trial has been conducted on brain tumor patients to investigate the effects on NFB training on cognitive impairments. No specific NFB treatment effects were found, but the patients were pediatric brain tumor survivors and were treated with radiotherapy and chemotherapy that may have influenced the results (de Ruiter et al., 2016). Against this background of paucity of data about the application of NFB for cognitive impairment in adult brain tumor survivors, here we describe a case of an adult person with TSM postsurgery-acquired cognitive impairment, referred to our clinic for rehabilitation. We hypothesized that NFB training would improve objective measures of neurocognitive functioning as measured by neuropsychological testing.

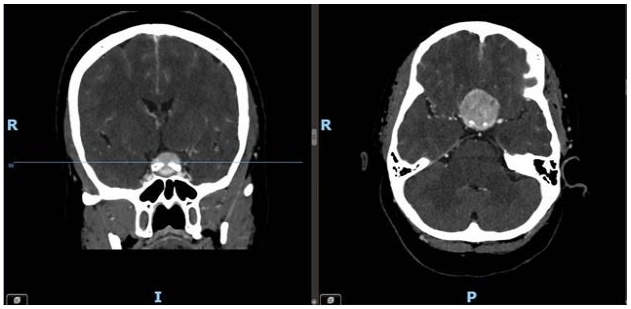
## Material and Methods

### Clinical Case Presentation

The patient was a 49-year-old bilingual (French and Italian) African woman, with 13 years of formal education and right-handed (Oldfield, 1971), who worked as a supermarket cashier and had lived in Italy since she was 20 years old. The woman presented a history of 4 days of headache, resistant to common painkillers, and progressive visual loss in the lower right eye. Due to these symptoms, she attended the Accident and Emergency department on November 8, 2020, where she underwent computerized tomography (CT) scans showing the presence of a TSM in the right fronto-parietal areas (Figure 1). Laboratory tests were also performed, and she was diagnosed with hypothyroidism, hypogonadotropic hypogonadism, and hyperprolactinemia likely due to TSM compression of the peduncle.

The patient was hospitalized on November 11, 2020, at the Neurosurgery Unit of the Azienda Ospedaliera Policlinico of Bari with a diagnosis of hydrocephalus after the operation for meningotheliomatous meningioma of the tuberculum sellae, hypopituitarism, and a recent state of nonconvulsive disease from viral encephalitis. On the following day, after the preoperative examinations were completed, the patient underwent neurosurgical intervention of the left peritoneal ventricle derivation with a Hakin-Cordis valve, calibrated at 170 mmH2O.

**Figure 1.** *CT scan of the patient showing a large tuberculum sellae brain tumor*.




The subject underwent craniotomy and resection of the TSM performed with a neuronavigation system and intraoperative neurophysiological monitoring. The awakening and postoperative course were unremarkable. On December 11, 2020, she was transferred to the intensive care unit of the Azienda Ospedaliera Policlinico of Bari, where she was monitored and underwent a percutaneous tracheostomy. When she woke up, she presented tetra hyposthenia. During this period, she suffered a critical episode followed by a comatose state and right cephalus-oculoversion. EEG was performed, suggestive of right focal nonconvulsive illness. She was then treated pharmacologically.

During the postintensive care hospital stay, she underwent a brain CT scan showing a progressive reduction of the valve opening pressure, at that time set at 130 mmH2O. On January 7, 2021, the woman was admitted to our neurorehabilitation unit of the Maugeri Institute in Bari for intensive postacute inpatient rehabilitation treatment. On admission, the patient was alert and cooperative. She had poor autobiographical memory and was disoriented in time and space. She presented with flaccid tetra-paresis, more severe on the right side; upper and lower limb osteotendinous reflexes were absent; and central palsy of the facial nerve was also present. Pupils were anisocoric for OD > OS with mydriasis in nonreactive OD.

## Procedure

### The Neurofeedback Training

The patient was treated in accordance with the ethical standards of the 1964 Helsinki declaration and its further amendments. At the beginning of the training protocol, the patient gave informed consent to the treatement after the nature and the goal of the NFB training had been explained.

Besides the physical therapy (1 hour, twice a day) and the pharmacological treatment (Cortisone 25 mg, Sodium Phenytoin 100 mg, and Escitalopram 10 mg), the patient underwent a qEEG recording in resting condition and at pretraining and posttraining neuropsychological testing.

A total of 15 sessions of NFB training were administered, each lasting 35 min, over a period of 3 weeks at five sessions per week (early afternoon at the same hour). The participant was seated in a comfortable armchair, eyes open, and electrodes were applied. A Gold electrode applied with gel on Cz localization on the scalp was used as an active guide (according to the international reference 10–20 system), grounded at the left and right earlobes. Impedance control for all channels was kept below 5 kΩ.

The NFB training consisted of the "beta/theta ratio" protocol, rewarding and encouraging 13–18 Hz brainwaves (low beta), while simultaneously discouraging 4–8 Hz brainwaves (theta) and 19–28 Hz brainwaves (high beta) in Cz for 15 half-hour NFB sessions. The protocol employed visual–auditory feedback to guide the patient to achieve an autonomous reduction of inattention and hypoarousal by inhibiting the theta (4–8 Hz) and high beta (19–28 Hz) frequencies and promoting (reward frequency) of low beta waves (13–18 Hz) as a feedback parameter, according to the existing protocol by Fuchs and colleagues (Fuchs et al., 2003). To this purpose, the "boat race game" available on the BioGraph Infiniti software (Thought Technology, Montreal, Canada) was adopted. In this task, the participant is shown three boats; each corresponds and moves forward according to the theta, high beta, and low beta wave activity threshold, respectively. Feedback thresholds were set automatically for all three amplitudes in order to maximize rewards, thereby encouraging training while at the same time making real-time adjustments as the level of difficulty was gradually increased.

The subject was instructed to make the low beta-associated boat move forward while preventing the theta and high beta-associated boats from moving forward. Pleasant sounds and a green light rewarded the subject when the low beta boat reached the finish line, whereas an unpleasant sound and red light ensued when the associated theta and high beta boats reached the end. For the baseline EEG recording, as well as the NFB sessions, ProComp2 hardware and the Biograph Infiniti Suite 360 software (Thought Technology, Montreal, Canada) were used.

## Outcome Measures

### Neuropsychological Testing

A neuropsychological evaluation was performed at the time of arrival (before the NFB training) and at the time of discharge (after the NFB training). Well-validated, reliable, and widely used neuropsychological tests were selected to provide a comprehensive assessment of neurocognitive functioning (see Supplementary Material, Neuropsychological Testing and Table S1 for a full description of the protocol). When available, we used their parallel forms for the posttraining assessment in order to decrease practice effects without losing the gestalt of the measures administered. The following cognitive domains were evaluated: global cognitive functioning, verbal and visual memory, attention and executive functions, visuo-constructive abilities, language, functional assessment. Specifically, the Trail Making Test (TMT A-B; Giovagnoli et al., 1996) and the Attentional Matrices (Spinnler & Tognoni, 1987) were applied to measure attentional abilities such as sustained, divided attention and shifting processes; and the Stroop Color and Word Test (Caffarra et al., 2002) and the Phonemic and Semantic fluency tests (Carlesimo et al., 1996) to measure cognitive flexibility, access to the lexical vocabulary, speed of processing, and inhibition components of executive functions.

### EEG Recording

The pre- and posttraining EEG recordings were performed using a BE Plus PRO Standard (EB Neuro, Florence, Italy) device and EB Neuro Galileo software. A longitudinal 21 electrodes montage with bipolar derivation was used, in accordance with the international 10–20 system. Precabled EB Neuro headset channels of common reference EEG channels were recorded (Reference: Fz; Ground: Fz–Cz). Gold EEG electrodes fitted with 10 kΩ, 1-W current-limiting safety resistors were applied to Fp1, F7, T3, T5, O1, and the contralateral homologous channels. The sample rate of the signal was 256 Hz. The continuous EEG was processed with fast

Fourier transform (FFT). High frequency and notch filters were set at 50 Hz, while low frequencies were set at 1.6 Hz (TC: 0.1 sec). Trial conditions responses were tested with eyes open, eyes closed, and intermittent flashing light (SLI protocol 3–30 Hz).

### Quantitative Electroencephalography (qEEG) Measures

Using a customized version of the method flt_clean_windows (BCIlab) to compute a moving windowed signal power, abnormal data with extreme magnitude from the continuous dataset were deleted to compute a moving windowed signal power. EEG 1s windows segments were removed if their power exceeded the 90% distribution quantile. Synchronous increases in signal amplitude were detected using the difference between the superior and inferior envelopes following the shape-preserving piecewise cubic interpolation (Butt & Brodlie, 1993), and EEG portions producing values greater than two standard deviations (in amplitude distribution) were removed.

Power spectral density was computed for each channel by averaging periodograms of windowed signal sections, using the pwelch function in MATLAB (The Math Works, Natick, MA). The window length was 2 s (512 time points), and 8 min of artifact-free EEG data of the patient were used for power analyses. The power spectral density was analyzed before and after the treatment using EEG records with the same temporal and quality features. The average power spectrum density (PSD) across all scalp electrodes was defined as the overall scalp power spectrum. We computed the average PSD for the following frequency bands: delta (1–4 Hz) and alpha (8.1–14 Hz). The “area’s power spectrum” was defined as the mean PSD over adjacent electrodes within the following areas: frontal area (left side: Fp1, AF3, AF7, F1, F3, F5, F7; right side: Fp2, AF4, AF8, F2, F4, F6, F8), central area (left side: FC1, FC3, FC5, FT7, C1, C3, C5, T3, CP1, CP3, CP5; right side: FC2, FC4, FC6, FT8, C2, C4, C6, T4, CP2, CP4, CP6) and posterior area (left side: P1, P3, P5, T5, PO7, P03, O1; right side: P2, P4, P6, T6, PO8, P04, O2).

Signal processing and analyses were performed offline using MATLAB with custom scripts based on the EEGLAB toolbox (Delorme & Makeig, 2004). The average power values were subdivided into the four bands (alpha, beta, delta, and theta) qEEG metrics. Only alpha and delta showed a sufficient numerical consistency to compute the spectral power. In addition, the delta/theta ratio (DAR), i.e., the ratio of mean scalp delta to alpha power, was calculated. Higher DAR scores indicate a higher EEG low-frequency activity (Finnigan et al., 2007). To assess specific cognitive functions, we separated, using digital postprocessing filters, the low beta waves or beta 1 (12.5–16 Hz, "beta 1 power") from the middle-high beta power or beta 2 (16.5–28 Hz). In addition, the power ratio index (PRI), consisting of the following equation PRI = (alpha + beta) / (delta + theta) was calculated to assess the shelving of the entire spectrum power. The total power was considered for each band as the arithmetic mean for the whole scalp.

### Signals Elaboration and Statistical Analysis

The following formula was used to calculate the percentage of improvement during the neuropsychological tests: [(posttreatment − pretreatment) / pretreatment] * 100 (Benvenuti et al. 2011; Shakibaei et al., 2021). According to this formula, an improvement by 50% or more, without any increased medication, is considered a clinically significant improvement (Blanchard & Schwarz, 1988).

Mean amplitudes (μV) were calculated for each band: alpha, beta, delta, theta, and beta/theta ratio. To assess the differences of mean amplitude of each waveband, we subdivided the biofeedback treatments into three groups of lengths, per 5 days of treatment (group 1 = days 0–5; group 2 = days 6–10; group 3 = days 11–15). Normality of data was assessed and confirmed by Shapiro–Wilk test for the total distribution of alpha, beta, delta, theta, and theta/beta values for each day/treatment and across the lengths groups. Then we performed ANOVA analysis to assess any significant difference in amplitude trends across the three lengths groups and the 95% confidence intervals (CI). In addition, we built linear regression models to analyze whether the increase by day of treatment could predict the mean changes for every brainwave band, with 95% CI. All statistical analyses were performed using R software (Core Team 2013; R Foundation for Statistical Computing, Vienna, Austria). In addition, alpha, theta, delta, high/low beta DAR and PRI spectral power values (expressed as eigenvectors) were computed for the pretraining and posttraining EEG, to assess probable permanent quantitative permanent changes in the brainwaves before and after training, as described in the specific paragraph.

## Results

### EEG Measures

Eye and head movements or muscle artifacts were removed after a visual inspection of EEG data, for

artifact exclusion. The spectral power scores resulting from the pre- and posttreatment qEEG power analysis are reported in Table 1. Only alpha and delta bands showed sufficient numerical consistency to compute the spectral power using absolute numerical eigenvectors for magnitude. We report the results considering also the ratios of the different bands. We found an increase of frontal alpha power and reduced DAR power in the frontal and posterior areas. No significant changes were found in theta and beta bands in resting state EEG examinations, as these remained stable across the assessments.

**Table 1**

*EEG Power Analysis and Quantitative Electroencephalography (qEEG) Measures Pre- and Posttreatment*

| | Frontal | | Central | | Posterior | | Total | |
|---|---|---|---|---|---|---|---|---|
| Band | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
| Delta | 24.17 | 28.6 | 23.46 | 23.17 | 26.49 | 26.31 | 24.7 | 26.02 |
| Theta | 1.42 | 1.49 | 1.65 | 1.78 | 1.14 | 1.42 | 1.40 | 1.56 |
| Alpha | 4.92 | 6.21 | 5.47 | 5.47 | 5.01 | 6.92 | 5.13 | 6.21 |
| Beta | 1.80 | 1.91 | 1.28 | 1.26 | 1.90 | 1.81 | 1.66 | 1.66 |
| Beta 1 | 1.99 | 2.61 | 1.32 | 1.39 | 1.81 | 1.91 | 1.70 | 1.97 |
| Beta 2 | 1.75 | 1.78 | 1.45 | 1.21 | 1.96 | 1.89 | 1.72 | 1.62 |
| Delta/Alpha Ratio | 4.91 | 4.60 | 4.28 | 4.23 | 5.28 | 3.80 | 4.82 | 4.21 |
| Power Ratio Index | 3.80 | 3.70 | 3.72 | 3.70 | 3.99 | 3.80 | 3.83 | 3.73 |

Table 2 shows the comparison of average amplitude (μV) for each band, among the three treatment length groups (group 1 = days 0–5; group 2 = days 6–10; group 3 = days 11–15). Beta amplitudes show a significantly increased trend across the lengths groups ($p < .01$), as in the linear model, for every day of treatment the beta amplitude increased on average by 0.46 μV (95% CI [0.41, 0.52]; Table 3).

**Table 2**

*Description of the Whole Sample According to Treatment Length Groups*

| | Treatment Length | | | |
|---|---|---|---|---|
| | Days 1–5 | Days 6–10 | Days 11–15 | *p* value |
| Alpha | 8.55 ± 0.44 | 9.06 ± 0.87 | 9.00 ± 0.97 | .38 |
| Beta | 3.03 ± 0.77 | 5.86 ± 1.06 | 7.75 ± 0.24 | < .01 |
| Delta | 15.14 ± 2.31 | 11.98 ± 1.75 | 9.18 ± 0.58 | < .01 |
| Theta | 16.24 ± 0.78 | 12.68 ± 1.68 | 9.83 ± 1.55 | < .01 |
| Theta/Beta | 5.72 ± 1.75 | 2.27 ± 0.7 | 1.27 ± 0.22 | < .01 |

*One-way ANOVA*

**Table 3**

*Linear Regression Model on Collected Variables as Dependent Variable and Days of Treatment as Regressor*

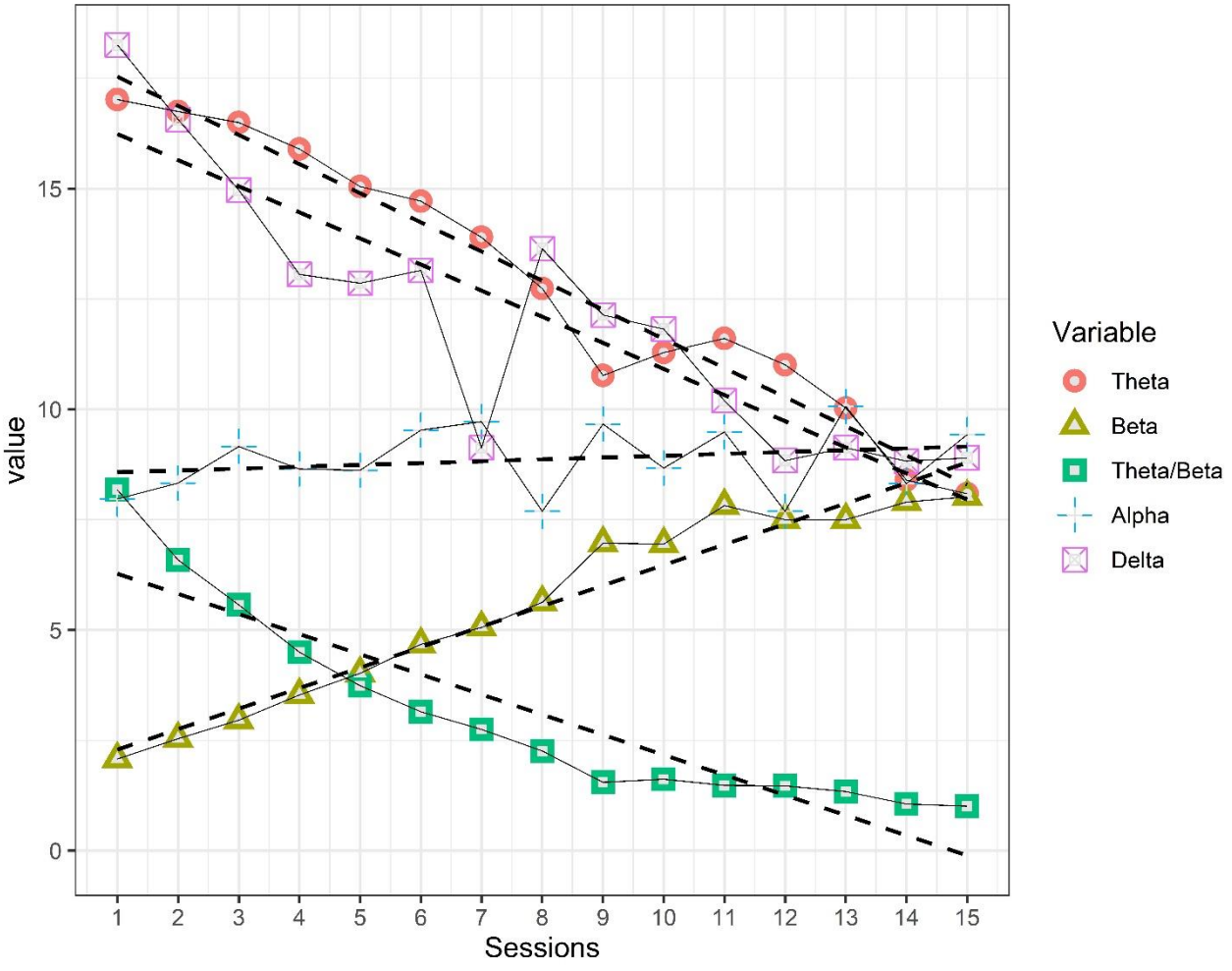
| | Coefficient | Std Err | 95% CI | *p* value |
|---|---|---|---|---|
| | Dependent Variable: Alpha | | | |
| Days of Treatment | 0.04 | 0.05 | [−0.05, 0.13] | .37 |
| | Dependent Variable: Beta | | | |
| Days of Treatment | 0.46 | 0.03 | [−0.41, 0.52] | < .01 |
| | Dependent Variable: Delta | | | |
| Days of Treatment | −0.59 | 0.08 | [−0.76, 0.43] | < .01 |
| | Dependent Variable: Theta | | | |
| Days of Treatment | −0.66 | 0.04 | [−0.73, −0.59] | < .01 |
| | Dependent Variable: Theta/Beta | | | |
| Days of Treatment | −0.46 | 0.05 | [−0.56, −0.35] | < .01 |

Delta, theta, and theta over beta ratio (TBR) bands showed a marked decreased trend in amplitudes among ordinal treatments lengths groups, all values being statistically significant ($p < .01$). The results were confirmed by linear regression models that

showed respectively that, for every day of treatment increase: delta had a predicted decrease by -0.59 (95% CI [−0.76, −0.43]), theta by −0.66 (95% CI [−0.73, −0.59]), theta/beta by −0.46 (95% CI [−0.56, −0.35]) and SMR by −0.09 (95% CI [−0.11, −0.08]; Table 3).

At the pretraining EEG examination, we found an asymmetrical plot on the temporal regions. Throughout the right hemisphere, we also found an inconsistent representation of slow waves, of the theta or delta band. In the temporo-parieto-occipital regions, the appearance of synchronous epileptiform graph elements (especially sharp-waves followed by slow waves) was observed. The representation of alpha sequences on the posterior regions was inconsistent. The posttraining EEG recording showed a basically symmetrical base path, with representations of alpha sequences on posterior regions. A scatter plot between days of treatment and collected variables displays the electrical activity changes in our patient over the 15 sessions (Figure 2), featuring widespread representation of rapid rhythms, a subcontinuous persisting presence on the right temporal regions of slow waves of theta band, with the constant and more widespread appearance, on the same hemisphere, of theta waves (4–7 Hz) sequences, showing little tendency to a contralateral diffusion.

**Figure 2.** *Scatter plot between days of treatment and collected variables*.




**Note.** Whole sessions mean (μV) of theta (4–7 Hz), beta std. (13–21 Hz) and theta/beta ratio during NFB training obtained from BioGraph software trend report after artifacts rejection over the 15 sessions.

The qEEG power analysis highlighted an increased delta activity in frontal regions (delta band pretreatment: 24.17 vs. posttreatment: 28.6), alpha activity in frontal regions (alpha band pretreatment: 4.92 vs. posttreatment: 6.21) and in posterior regions (alpha band pretreatment: 5.01 vs. posttreatment: 6.92), while theta and beta bands remained stable. DAR appeared significantly reduced in posterior regions (DAR pretreatment: 5.28 vs. posttreatment: 3.80) with a trend toward reduction in frontal areas but remained unchanged in central areas.

### Neuropsychological Profile Pre- and Post-NFB Training

During the first neuropsychological examination, the patient appeared poorly oriented in regards to time, space, and autobiographical parameters. Her mood was apathetic and flat. On performance at the first-level battery, her general cognitive efficiency was impaired (MMSE = 22/30; Cut-off < 23.8). A poor performance emerged from the screening evaluation of global executive function (FAB = 10/18; Cut-off < 12.03), with a worse performance in the conceptualization and inhibitory control tests. The patient showed impairments in short-term and long-term visuospatial memory, due to her compromised spatial exploration ability and the presence of constructional apraxia. Spontaneous speech was characterized by fluent language characterized by short but well-structured sentences; she presented several anomia and semantic paraphasias to the confrontation naming task. No difficulties were recorded at episodic memory tests, nor learning and recognition of new verbal information. Attentional abilities were limited, with amplified reaction times and long latency in answering questions. Difficulties in attentional-executive function appeared to be severe and critical. The speed of information processing, selective attention in the focused and divided component, sensitivity to interference, inhibition of automatic responses, and conceptualization of time were all compromised. She also showed a lack of cognitive flexibility based on external feedback and choice of strategies in verbal fluency tasks, with several episodes of perseverations, and difficulties in learning functional strategies. The scores resulting from the first neuropsychological evaluation are reported in Supplementary Material, Table S1.

After 15 sessions of NFB training, the patient showed a reduction of the poor cognitive symptoms, with a qualitative improvement in the reaction times and attentional abilities. The posttraining neuropsychological assessment was administered after 3 weeks of NFB (Supplementary Material, Table S1). Compared to the performance at the pretraining assessment, her general cognitive efficiency had improved (MMSE = 26.89/30, Cut-off < 23.8), as well as global executive functionality (FAB = 14.20/18; Cut-off < 12.03), with worse performances registered in the conceptualization tests and mental flexibility. In addition, the results of pretreatment and posttreatment scores showed that the TMT A-B score decreased from 202 s to 88 s to complete the trial-A, decreased from 496 s to 212 s to complete the trial-B, and increased from 20.5 to 40.75 for the Attentional Matrices Test. These results indicate an increase of 56.43%, 57.25%, and 98.76%, respectively, in the attentional abilities after the training (Table 4). Moreover, we registered an improvement of her semantic fluency ability (the score increased from 10 to 25) and time to perform the Stroop Color and Word Test (the score decreased from 37.70 s to 20.72 s). These results indicate an increase by 81.22% and 98.9%, respectively, in two of the main components of the executive functions (access to the lexical vocabulary and speed of information processing) after the training (Table 4). At the behavioral level, perseverations appeared to a lesser extent and the patient showed much faster flexibility and reaction times. A latency in tasks that required more space exploration persisted. Concerning the other noncognitive areas, at the end of the rehabilitation cycle, the patient had successfully regained mobility, balance, and motor autonomy.

**Table 4**

*Attention and Executive Functions Tests, Scores, and Percentage of Improvement of the Patient Pre- and Post-NFB Training*

| Neuropsychological Test | Pre-NFB | Post-NFB | % Improvement |
|---|---|---|---|
| Trail Making Test A | 202 | 88 | 56.43 |
| Trail Making Test B | 496 | 212 | 57.25 |
| Attentional Matrices | 20.50 | 40.75 | −98.78 |
| Stroop Color and Word Test – Time | 37.70 | 20.72 | 97.70 |
| Semantic Fluency | 10 | 25 | 60.00 |

## Discussion

NFB is known to act through thalamocortical regulatory systems and increase cortical excitation thresholds (Mayer & Arns, 2016). The neurobiological underpinnings of NFB are based on the promotion of "long-term potentiation" (LTP; Sitaram et al., 2017), which constitutes a central element for associative learning, involving glutamate NMDA receptors and other neurotransmitters such as dopamine (event-dependent). Learning is the result of the concomitant occurrence of a strong presynaptic and postsynaptic activity conveyed by the release of dopamine. Based on contingent feedback, dopaminergic projections to the striatum can modify behavior in response to salient stimuli. In our patient, NFB contributed to systemically enhance LTP in the disrupted frontal and parietal areas involved in the fulfillment of attentional and executive tasks (Alvarez & Emory, 2006; Ball et al., 2011; Murray & Wojciulik, 2004), through their connections with the thalamus to regulate cortical arousal. Evidence regarding the positive effects on cognitive performance of NFB training is gradually emerging (Enriquez-Geppert et al., 2017). Recent studies testing NFB as a neurorehabilitation technique highlighted its efficacy on performance enhancement of several cognitive functions such as executive functions (Viviani & Vallesi, 2021), attention and memory (Yeh et al., 2020) in healthy individuals. Similarly, NFB seems to be effective in improving quality of life and as a nonpharmacological treatment for the relief of cognitive symptoms of many clinical conditions such as mild cognitive impairment (Trambaiolli et al., 2021), poststroke (Renton et al., 2017), and traumatic brain injury (Ali et al., 2020).

In the present case, the patient underwent a NFB training over 15 sessions. The results of this training, applied in a patient who had undergone right fronto-parietal craniotomy, were analyzed to investigate the efficacy of NFB in a brain tumor survivor. They reveal an improvement of attentional functions, selective, sustained, and divided attention and speed information processing, and improvements of executive functioning, specifically of cognitive flexibility and access to the lexical vocabulary, speed of information processing. These improvements were also mirrored in the functional autonomy of daily life, as the patient recovered her instrumental activities. Along with the clinical and neuropsychological outcomes, the neurophysiological brain activity changed across the sessions, as well as in comparison between before and after NFB training. In agreement with previous studies, the patient successfully learned to efficiently self-regulate her brain activity efficiently. In fact, statistical analyses revealed significant changes such as the augmented amplitude and percentage of beta bands across the sessions. On the contrary, slow wave activity, which was dominant in the first phase, as delta and theta bands, decreased significantly. No relevant differences in alpha activity were detected among the training sessions. The above-described neurophysiological changes support previous works which used the same protocol such as ADHD and demonstrated an improvement in attentional abilities (Van Doren et al., 2017). Importantly, the TBR amplitude dropped significantly over the weeks. The TBR was found to be negatively related to the executive control network but directly related to mind wandering and the default mode network (van Son et al., 2019).

After the training sessions, analyses revealed consistent changes in task accomplishment, and the qualitative pre–post resting state qEEG showed different but not contradictory results. The qualitative qEEG comparison between the pre- and posttraining showed an increase in alpha waves and particularly in the frontal alpha band activity post-NFB training. Similar results have been reported in the literature, associated with positive cognitive outcomes (e.g., inhibitory control and shifting, attention, executive functions, abstract reasoning, nonverbal intelligence). Alpha activity is linked to vigilance, information and cognitive processing such as attentional and executive functions, as well as maintaining an optimal cerebral arousal state (Klimesch, 2012; Schleiger et al., 2014). In our patient, we also observed a reduced DAR in the posterior cortices. Such a result is coherent with the negative correlation between the posterior DAR and cognitive outcomes found by Schleiger and colleagues (Schleiger et al., 2014). High DAR values indicate excess in delta power and lower alpha waves associated with poorer functional and cognitive outcomes (Aminov et al., 2017; Finnigan et al., 2007; Finnigan et al., 2016; Schleiger et al., 2014). No relevant changes were found in theta and beta bands in resting-state EEG examinations, as they remained stable across the assessments.

Notably, the qEEG signals elaborations of beta waves revealed a trend toward change. In particular, low beta waves, associated with thinking, focusing, sustained attention, alertness, and excitement showed a slight increase in frontal areas (beta 1 band pretreatment: 1.99 vs. posttreatment: 2.61) and a positive trend on global activity. On the contrary, high beta waves, linked to intensity,

hyperalertness and anxiety (Marzbani et al., 2016), showed a negative trend in global EEG measures. The limited increment of low beta waves could be explained by the fact that the waves appear when the subject is actively involved in a cognitive task and remains focused. For that reason, it is less likely to be detected during an EEG resting state. Moreover, as previously described by de Munck and colleagues, EEG wave bands are actively interdependent (de Munck et al., 2009). Consequently, the active training on low beta (13–18 Hz) produced an increase of lower hertz such as alpha bands (8–12 Hz) in resting state. Similar results were described in a study on healthy subjects conducted by Jurewicz and colleagues. The authors demonstrated that beta band upregulation resulted in alpha and beta increases, but the amplitude increment was greater for the alpha than the beta band (Jurewicz et al., 2018). As suggested by the authors, the alpha band activity could exercise a cortical inhibitory effect to balance global activity when beta oscillations rise in amplitude (Jurewicz et al., 2018).

To our knowledge, this is the first case report describing the efficacy of an intensive NFB training in a patient post-TSM resection. The data available on NFB training for cancer patients are scanty and mainly focused on pain, mood, and quality of life (Hetkamp et al., 2019). Few studies investigated the effects of NFB training on cognition in cancer patients, and most of these were survey self-reports (Alvarez et al., 2013; Luctkar-Flude & Groll, 2015; Sarvghadi et al., 2019). Above all, the high heterogeneity of clinical conditions and treatments, and the use of different outcome measurement tools, constitute a relevant limitation hampering the possibility of comparing the efficacy of protocols and approaches and making it difficult to compare the overall positive results. Furthermore, since cognitive impairment secondary to meningioma resections is the main clinical sequela (Cobb et al., 1979; Ehresman et al., 2019; Rothoerl et al., 2003; Zweckberger et al., 2017), further studies investigating NFB as a rehabilitation training of cognitive functions are warranted.

## Limitations and Future Perspectives

Our study presents several limitations. Firstly, the concurrent antiepileptics medication might have played a role in the EEG wave symmetry; nevertheless, it is unlikely that pharmacological effects would be effective in such a short time, and they do not exert a role in hemispheric symmetry. In addition, the patient underwent motor rehabilitation to regain mobility, balance, and motor autonomy. As strongly documented in existing literature, physical activity exerts a central role in regaining bodily and cognitive functions, so we hypothesize that physiotherapy could have facilitated neural plasticity and played a role together with the NFB training (Ali et al., 2018). The reduced treatment time before discharge is an important limitation since it precluded the investigation of whether the patient would have continued to improve more or would remain stable.

Uncertainty regarding the long-term effects of NFB training is an open issue. Regarding long-term effects, there is some evidence regarding the presence of a "homeostatic rebound" (or "homeostatic plasticity"; Marder & Goaillard, 2006), or the ability of neurons to regulate their own excitability relative to the activity of the circuit, after NFB training. It is unclear to what extent homeostatic plasticity impairs long-term changes in brain activity and behavior, as there is evidence that these changes can occur days, months, or even many years after training (Gevensleben et al., 2010; Harmelech et al., 2013; Megumi et al., 2015). In the case described, it would have been interesting to evaluate whether homeostatic plasticity appeared or not after one year from the treatment. It has yet to be discovered whether the cognitive improvements remain stable over time.

To conclude, NFB training requiring the active participation of the subject can offer the possibility of endogenously manipulating brain activity. There are still several open questions regarding NFB. Future studies should focus on the development of standardized protocols, as well as the understanding of interindividual differences in the achievement of self-regulation, learning abilities, and the possibility of generalizing the gain obtained during NFB training to everyday life. Given the paucity of studies in the literature on this topic, the present case illustrates the potential usefulness of NFB to improve cognitive impairment in TSM patients in the subsequent postoperative period. It is mandatory in the future to rule out any confounding of results by nonspecific training effects.

### Acknowledgements

We respectfully thank the patient for agreeing to participate in our research project. We particularly thank Dr. Fabio Castellana for his help in statistical outputs.

## Compliance with Ethical Standards

***Conflict of Interest.*** The authors declare that they have no conflicts of interest.

***Ethical Approval.*** Consent to participate: written informed consent was obtained from the patient for publication of this case report and accompanying images. The institutional ethics committee approved this case study.

## Author Disclosure

This work was supported by the Ricerca Corrente funding scheme of the Ministry of Health, Italy. PB is a former Atlantic Fellow for Equity in Brain Health at the Global Brain Health Institute (GBHI) University of California San Francisco (UCSF) and was supported with funding from GBHI.

## Author Contributions

GL, RS, and PB contributed substantially to the conception and design of the work, drafting and revising the manuscript for important intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work. GL, RS, FM, and PB performed the analyses. SDT, EL, and PF drafted corresponding sections of the manuscript. All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

## References

Abel, T. J., Manzel, K., Bruss, J., Belfi, A. M., Howard, M. A., III., & Tranel, D. (2016). The cognitive and behavioral effects of meningioma lesions involving the ventromedial prefrontal cortex. *Journal of Neurosurgery, 124*(6), 1568–1577. https://doi.org/10.3171/2015.5.JNS142788

Ali, F. S., Hussain, M. R., Gutiérrez, C., Demireva, P., Ballester, L. Y., Zhu, J.-J., Blanco, A., & Esquenazi, Y. (2018). Cognitive disability in adult patients with brain tumors. *Cancer Treatment Reviews, 65*, 33–40. https://doi.org/10.1016/j.ctrv.2018.02.007

Ali, J. I., Viczko, J., & Smart, C. M. (2020). Efficacy of neurofeedback interventions for cognitive rehabilitation following brain injury: Systematic review and recommendations for future research. *Journal of the International Neuropsychological Society, 26*(1), 31–46. https://doi.org/10.1017/S1355617719001061

Alvarez, J. A., & Emory, E. (2006). Executive function and the frontal lobes: A meta-analytic review. *Neuropsychology Review, 16*(1), 17–42. https://doi.org/10.1007/s11065-006-9002-x

Alvarez, J., Meyer, F. L., Granoff, D. L., & Lundy, A. (2013). The effect of EEG biofeedback on reducing postcancer cognitive impairment. *Integrative Cancer Therapies, 12*(6), 475–487. https://doi.org/10.1177/1534735413477192

Aminov, A., Rogers, J. M., Johnstone, S. J., Middleton, S., & Wilson, P. H. (2017). Acute single channel EEG predictors of cognitive function after stroke. *PLoS ONE, 12*(10), e0185841. https://doi.org/10.1371/journal.pone.0185841

Ball, G., Stokes, P. R., Rhodes, R. A., Bose, S. K., Rezek, I., Wink, A.-M., Lord, L.-D., Mehta, M. A., Grasby, P. M., & Turkheimer, F. E. (2011). Executive functions and prefrontal cortex: A matter of persistence? *Frontiers in Systems Neuroscience, 5*, 3. https://doi.org/10.3389/fnsys.2011.00003

Barrash, J., Abel, T. J., Okerstrom-Jezewski, K. L., Zanaty, M., Bruss, J. E., Manzel, K., Howard, M., III., & Tranel, D. (2020). Acquired personality disturbances after meningioma resection are strongly associated with impaired quality of life. *Neurosurgery, 87*(2), 276–284. https://doi.org/10.1093/neuros/nyz440

Bartolomei, F., Bosma, I., Klein, M., Baayen, J. C., Reijneveld, J. C., Postma, T. J., Heimans, J. J., van Dijk, B. W., de Munck, J. C., de Jongh, A., Cover, K. S., & Stam, C. J. (2006). Disturbed functional connectivity in brain tumour patients: Evaluation by graph analysis of synchronization matrices. *Clinical Neurophysiology, 117*(9), 2039–2049. https://doi.org/10.1016/j.clinph.2006.05.018

Battista, P., Griseta, C., Capozzo, R., Lozupone, M., Sardone, R., Panza, F., & Logroscino, G. (2020). Frontal lobe syndrome and dementias. In C. R. Martin, & V. R. Preedy (Eds.), *Genetics, Neurology, Behavior, and Diet in Dementia* (pp. 617–632). Academic Press. https://doi.org/10.1016 /B978-0-12-815868-5.00039-6

Battista, P., Griseta, C., Tortelli, R., Guida, P., Castellana, F., Rivolta, D., & Logroscino, G. (2021). The Modified Five-Point Test (MFPT): Normative data for a sample of Italian elderly. *Neurological Sciences, 42*(6), 2431–2440. https://doi.org/10.1007/s10072-020-04818-3

BE Plus PRO Standard [Hardware]. (n.d.). Florence, Italy: EB Neuro S.p.A.

Beaumont, A., & Whittle, I. R. (2000). The pathogenesis of tumour associated epilepsy. *Acta Neurochirurgica, 142*(1), 1–15. https://doi.org/10.1007/s007010050001

Benioudakis, E. S., Kountzaki, S., Batzou, K., Markogiannaki, K., Seliniotaki, T., Darakis, E., Saridaki, M., Vergoti, A., & Nestoros, J. N. (2016). Can neurofeedback decrease anxiety and fear in cancer patients? A case study. *Postępy Psychiatrii i Neurologii, 25*(1), 59–65. https://doi.org/10.1016/j.pin.2015.12.001

Benvenuti, S. M., Buodo, G., Leone, V., & Palomba, D. (2011). Neurofeedback training for Tourette syndrome: An uncontrolled single case study. *Applied Psychophysiology and Biofeedback, 36*(4), 281–288. https://doi.org/10.1007/s10484-011-9169-7

BioGraph Infiniti Suite 360 [Software]. (n.d.). Montreal, Canada: Thought Technology Ltd.

Bitter, A. D., Stavrinou, L. C., Ntoulias, G., Petridis, A. K., Dukagjin, M., Scholz, M., & Hassler, W. (2013). The role of the pterional approach in the surgical treatment of olfactory groove meningiomas: A 20-year experience. *Journal of Neurological Surgery Part B, Skull Base, 74*(2), 97. https://doi.org/10.1055/s-0033-1333618

Blanchard, E. B., & Schwarz, S. P. (1988). Clinically significant changes in behavioral medicine. *Behavioral Assessment, 10*(2), 171–188.

Butt, S., & Brodlie, K. W. (1993). Preserving positivity using piecewise cubic interpolation. *Computers & Graphics, 17*(1), 55–64. https://doi.org/10.1016/0097-8493(93)90051-A

Caffarra, P., Vezzadini, G., Dieci, F., Zonato, F., & Venneri, A. (2002). A short version of the Stroop test: Normative data in an Italian population sample = Una versione abbreviata del test di Stroop: Dati normativi nella popolazione italiana. *Nuova Rivista di Neurologia, 12*(4), 111–115.

Carlesimo, G. A., Caltagirone, C., Gainotti, G., Fadda, L., Gallassi, R., Lorusso, S., Marfia, G., Marra, C., Nocentini, U., & Parnetti, L. (1996). The mental deterioration battery: Normative data, diagnostic reliability and qualitative analyses of cognitive impairment. *European Neurology, 36*(6), 378–384. https://doi.org/10.1159/000117297

Cobb, W. A., Guiloff, R. J., & Cast, J. (1979). Breach rhythm: The EEG related to skull defects = Rythme de brèche: EEG en relation avec des pertes d'os crânien. *Electroencephalography and Clinical Neurophysiology, 47*(3), 251–271. https://doi.org/10.1016/0013-4694(79)90278-5

Core Team, R language and environment for statistical computing [Software]. (2013). Vienna, Austria: R Foundation for Statistical Computing. http://www.r-project.org

Cramer, C. K., McKee, N., Case, L. D., Chan, M. D., Cummings, T. L., Lesser, G. J., Shaw, E. G., & Rapp, S. R. (2019). Mild cognitive impairment in long-term brain tumor survivors following brain irradiation. Journal of Neuro-Oncology, 141(1), 235–244. https://doi.org/10.1007/s11060-018-03032-8

Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods, 134*(1), 9–21. https://doi.org/10.1016/j.jneumeth.2003.10.009

de Munck, J. C., Gonçalves, S. I., Mammoliti, R., Heethaar, R. M., & Lopes da Silva, F. H. (2009). Interactions between different EEG frequency bands and their effect on alpha–fMRI correlations. *NeuroImage, 47*(1), 69–76. https://doi.org/10.1016/j.neuroimage.2009.04.029

Derks, J., Reijneveld, J. C., & Douw, L. (2014). Neural network alterations underlie cognitive deficits in brain tumor patients. *Current Opinion in Oncology, 26*(6), 627–633. https://doi.org/10.1097/CCO.0000000000000126

de Ruiter, M. A., Oosterlaan, J., Schouten-van Meeteren, A. Y. N., Maurice-Stam, H., van Vuurden, D. G., Gidding, C., Beek, L. R., Granzen, B., Caron, H. N., & Grootenhuis, M. A. (2016). Neurofeedback ineffective in paediatric brain tumour survivors: Results of a double-blind randomised placebo-controlled trial. *European Journal of Cancer, 64*, 62–73. https://doi.org/10.1016/j.ejca.2016.04.020

Di Cristofori, A., Zarino, B., Bertani, G., Locatelli, M., Rampini, P., Carrabba, G., & Caroli, M. (2018). Surgery in elderly patients with intracranial meningioma: Neuropsychological functioning during a long term follow-up. *Journal of Neuro-Oncology, 137*(3), 611–619. https://doi.org/10.1007/s11060-018-2754-3

EB Neuro Galileo Suite [Software]. (n.d.). Florence, Italy: EB Neuro S.p.A.

Egner, T., & Gruzelier, J. H. (2004). EEG biofeedback of low beta band components: Frequency-specific effects on variables of attention and event-related brain potentials. *Clinical Neurophysiology, 115*(1), 131–139. https://doi.org/10.1016/s1388-2457(03)00353-5

Ehresman, J. S., Garzon-Muvdi, T., Rogers, D., Lim, M., Gallia, G. L., Weingart, J., Brem, H, Bettegowda, C., & Chaichana, K. L. (2019). Risk of developing postoperative deficits based on tumor location after surgical resection of an intracranial meningioma. *Journal of Neurological Surgery Part B, Skull Base, 80*(1), 59–66. https://doi.org/10.1055/s-0038-1667066

Enriquez-Geppert, S., Huster, R. J., & Herrmann, C. S. (2017). EEG-neurofeedback as a tool to modulate cognition and behavior: A review tutorial. *Frontiers in Human Neuroscience, 11*, 51. https://doi.org/10.3389/fnhum.2017.00051

Finnigan, S. P., Walsh, M., Rose, S. E., & Chalk, J. B. (2007). Quantitative EEG indices of sub-acute ischaemic stroke correlate with clinical outcomes. *Clinical Neurophysiology, 118*(11), 2525–2532. https://doi.org/10.1016/j.clinph.2007.07.021

Finnigan, S., Wong, A., & Read, S. (2016). Defining abnormal slow EEG activity in acute ischaemic stroke: Delta/alpha ratio as an optimal QEEG index. *Clinical Neurophysiology, 127*(2), 1452–1459. https://doi.org/10.1016/j.clinph.2015.07.014

Fuchs, T., Birbaumer, N., Lutzenberger, W., Gruzelier, J. H., & Kaiser, J. (2003). Neurofeedback treatment for attention-deficit/hyperactivity disorder in children: A comparison with methylphenidate. *Applied Psychophysiology and Biofeedback, 28*(1), 1–12. https://doi.org/10.1023/a:1022353731579

Gevensleben, H., Holl, B., Albrecht, B., Schlamp, D., Kratz, O., Studer, P., Rothenberger, A., Moll, G. H., & Heinrich, H. (2010). Neurofeedback training in children with ADHD: 6-month follow-up of a randomised controlled trial. *European Child & Adolescent Psychiatry, 19*(9), 715–724. https://doi.org/10.1007/s00787-010-0109-5

Giovagnoli, A. R., Del Pesce, M., Mascheroni, S., Simoncelli, M., Laiacona, M., & Capitani, E. (1996). Trail making test: Normative values from 287 normal adult controls. *The Italian Journal of Neurological Sciences, 17*, 305–309. https://doi.org/10.1007/bf01997792

Goel, A., Muzumdar, D., & Desai, K. I. (2002). Tuberculum sellae meningioma: A report on management on the basis of a surgical experience with 70 patients. *Neurosurgery, 51*(6), 1358–1364. http://doi.org/10.1227/01.NEU.0000309111.78968.BC

Gorini, A., Marzorati, C., Casiraghi, M., Spaggiari, L., & Pravettoni, G. (2015). A neurofeedback-based intervention to reduce post-operative pain in lung cancer patients: Study protocol for a randomized controlled trial. *JMIR Research Protocols, 4*(2), e52. https://doi.org/10.2196/resprot.4251

Hammond, D. C. (2011). What is neurofeedback: An update. *Journal of Neurotherapy, 15*(4), 305–336. https://doi.org/10.1080/10874208.2011.623090

Harmelech, T., Preminger, S., Wertman, E., & Malach, R. (2013). The day-after effect: Long term, Hebbian-like restructuring of resting-state fMRI patterns induced by a single epoch of cortical activation. *The Journal of Neuroscience, 33*(22), 9488–9497. https://doi.org/10.1523/JNEUROSCI.5911-12.2013

Hetkamp, M., Bender, J., Rheindorf, N., Kowalski, A., Lindner, M., Knispel, S., Beckmann, M., Tagay, S., & Teufel, M. (2019). A systematic review of the effect of neurofeedback in cancer patients. *Integrative Cancer Therapies, 18*, 1534735419832361. https://doi.org/10.1177/1534735419832361

Jurewicz, K., Paluch, K., Kublik, E., Rogala, J., Mikicin, M., & Wróbel, A. (2018). EEG-neurofeedback training of beta band (12–22 Hz) affects alpha and beta frequencies–A controlled study of a healthy population. *Neuropsychologia, 108*, 13–24. https://doi.org/10.1016/j.neuropsychologia.2017.11.021

Klimesch, W. (2012). Alpha-band oscillations, attention, and controlled access to stored information. *Trends in Cognitive Sciences, 16*(12), 606–617. https://doi.org/10.1016/j.tics.2012.10.007

Krupp, W., Klein, C., Koschny, R., Holland, H., Seifert, V., & Meixensberger, J. (2009). Assessment of neuropsychological parameters and quality of life to evaluate outcome in patients with surgically treated supratentorial meningiomas. *Neurosurgery, 64*(1), 40–47. https://doi.org/10.1227/01.NEU.0000336330.75381.39

Luctkar-Flude, M., & Groll, D. (2015). A systematic review of the safety and effect of neurofeedback on fatigue and cognition. *Integrative Cancer Therapies, 14*(4), 318–340. https://doi.org/10.1177/1534735415572886

Marder, E., & Goaillard, J.-M. (2006). Variability, compensation and homeostasis in neuron and network function. *Nature Reviews Neuroscience, 7*(7), 563–574. https://doi.org/10.1038/nrn1949

Marzbani, H., Marateb, H. R., & Mansourian, M. (2016). Neurofeedback: A comprehensive review on system design, methodology and clinical applications. *Basic and Clinical Neuroscience, 7*(2), 143–158. https://doi.org/10.15412/J.BCN.03070208

MATLAB [Computer software]. (n.d.). Natick, MA: The Math Works, Inc.

Mayer, K., & Arns, M. (2016). Electroencephalogram neurofeedback: Application in ADHD and epilepsy.

*Psychiatric Annals, 46*(10), 594–600. https://doi.org/10.3928/00485713-20160906-01

Megumi, F., Yamashita, A., Kawato, M., & Imamizu, H. (2015). Functional MRI neurofeedback training on connectivity between two regions induces long-lasting changes in intrinsic functional network. *Frontiers in Human Neuroscience, 9*, 160. https://doi.org/10.3389/fnhum.2015.00160

Murray, S. O., & Wojciulik, E. (2004). Attention increases neural selectivity in the human lateral occipital complex. *Nature Neuroscience, 7*(1), 70–74. https://doi.org/10.1038/nn1161

Nakamura, M., Roser, F., Struck, M., Vorkapic, P., & Samii, M. (2006). Tuberculum sellae meningiomas: Clinical outcome considering different surgical approaches. *Neurosurgery, 59*(5), 1019–1029. https://doi.org/10.1227/01.NEU.0000245600.92322.06

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia, 9*(1), 97–113. https://doi.org/10.1016/0028-3932(71)90067-4

Patel, K., Sutherland, H., Henshaw, J., Taylor, J. R., Brown, C. A., Casson, A. J., Trujillo-Barreton, N. J., Jones, A. K. P., & Sivan, M. (2020). Effects of neurofeedback in the management of chronic pain: A systematic review and meta-analysis of clinical trials. *European Journal of Pain, 24(*8), 1440–1457. https://doi.org/10.1002/ejp.1612

Prinsloo, S., Novy, D., Driver, L., Lyle, R., Ramondetta, L., Eng, C., McQuade, J., Lopez, G., & Cohen, L. (2017). Randomized controlled trial of neurofeedback on chemotherapy-induced peripheral neuropathy: A pilot study. *Cancer, 123*(11), 1989–1997. https://doi.org/10.1002/cncr.30649

ProComp2 2-channel Biofeedback & Neurofeedback System [Hardware]. (n.d.). Montreal, Canada: Thought Technology, Ltd.

Renton, T., Tibbles, A., & Topolovec-Vranic, J. (2017). Neurofeedback as a form of cognitive rehabilitation therapy following stroke: A systematic review. *PloS ONE, 12*(5), e0177290. https://doi.org/10.1371/journal.pone.0177290

Rijnen, S. J. M., Meskal, I., Bakker, M., De Baene, W., Rutten, G.-J. M., Gehring, K., & Sitskoorn, M. M. (2019). Cognitive outcomes in meningioma patients undergoing surgery: Individual changes over time and predictors of late cognitive functioning. *Neuro-Oncology, 21*(7), 911–922. https://doi.org/10.1093/neuonc/noz039

Rothoerl, R. D., Bernreuther, D., Woertgen, C., & Brawanski, A. (2003). The value of routine electroencephalographic recordings in predicting postoperative seizures associated with meningioma surgery. *Neurosurgical Review, 26*(2), 108–112. https://doi.org/10.1007/s10143-002-0240-y

Sanei, S., & Chambers, J. A. (2013). *EEG signal processing*. John Wiley & Sons.

Sarvghadi, P., Ghaffari, A., & Rostami, H. R. (2019). The effects of neurofeedback training on short-term memory and quality of life in women with breast cancer. *International Journal of Therapy and Rehabilitation, 26*(11), 1–8. https://doi.org/10.12968/ijtr.2018.0088

Schleiger, E., Sheikh, N., Rowland, T., Wong, A., Read, S., & Finnigan, S. (2014). Frontal EEG delta/alpha ratio and screening for post-stroke cognitive deficits: The power of four electrodes. *International Journal of Psychophysiology, 94*(1), 19–24. https://doi.org/10.1016/j.ijpsycho.2014.06.012

Shakibaei, F., Sabaghypour, S., Isfahani, F. F., & Jazi, N. D. (2021). EEG biofeedback for treatment of psychogenic non-epileptic seizures (PNES) in multiple sclerosis: A case report. *Applied Psychophysiology and Biofeedback, 46*(2), 175–181. https://doi.org/10.1007/s10484-020-09496-7

Simoca, I., Olărescu, A. A., Jipescu, I., & Lisievici, M. (1994). Postoperative outcome of intracranial meningiomas; long-term prognosis. *Romanian Journal of Neurology and Psychiatry = Revue Roumaine de Neurologie et Psychiatrie, 32*(4), 237–251.

Sitaram, R., Ros, T., Stoeckel, L., Haller, S., Scharnowski, F., Lewis-Peacock, J., Weiskopf, N., Blefari, M. L., Rana, M., Oblak, E., Birbaumer, N., Sulzer, J. (2017). Closed-loop brain training: The science of neurofeedback. *Nature Reviews Neuroscience, 18*(2), 86–100. https://doi.org/10.1038/nrn.2016.164

Spinnler, H., & Tognoni, G. (1987). Italian group on the neuropsychological study of ageing: Italian standardization and classification of neuropsychological tests. *The Italian Journal of Neurological Sciences, 6*, 1–120.

Telera, S., Carapella, C. M., Caroli, F., Crispo, F., Cristalli, G., Raus, L., Sperduti, I., & Pompili, A. (2012). Supraorbital keyhole approach for removal of midline anterior cranial fossa meningiomas: A series of 20 consecutive cases. *Neurosurgical Review, 35*(1), 67–83. https://doi.org/10.1007/s10143-011-0340-7

Trambaiolli, L. R., Cassani, R., Mehler, D. M. A., & Falk, T. H. (2021). Neurofeedback and the aging brain: A systematic review of training protocols for dementia and mild cognitive impairment. *Frontiers in Aging Neuroscience, 13*, 682683. https://doi.org/10.3389/fnagi.2021.682683

Tucha, O., Smely, C., Preier, M., & Lange, K. W. (2000). Cognitive deficits before treatment among patients with brain tumors. *Neurosurgery, 47*(2), 324–334. https://doi.org/10.1097/00006123-200008000-00011

van Dellen, E., Hillebrand, A., Douw, L., Heimans, J. J., Reijneveld, J. C., & Stam, C. J. (2013). Local polymorphic delta activity in cortical lesions causes global decreases in functional connectivity. *NeuroImage, 83*, 524–532. https://doi.org/10.1016/j.neuroimage.2013.06.009

Van Doren, J., Heinrich, H., Bezold, M., Reuter, N., Kratz, O., Horndasch, S., Berking, M., Ros, T., Gevensleben, H., Moll, G. H., & Studer, P. (2017). Theta/beta neurofeedback in children with ADHD: Feasibility of a short-term setting and plasticity effects. *International Journal of Psychophysiology, 112*, 80–88. https://doi.org/10.1016/j.ijpsycho.2016.11.004

van Son, D., de Rover, M., De Blasio, F. M., van der Does, W., Barry, R. J., & Putman, P. (2019). Electroencephalography theta/beta ratio covaries with mind wandering and functional connectivity in the executive control network. *Annals of the New York Academy of Sciences, 1452*(1), 52–64. https://doi.org/10.1111/nyas.14180

Viviani, G., & Vallesi, A. (2021). EEG-neurofeedback and executive function enhancement in healthy adults: A systematic review. *Psychophysiology, 58*(9), e13874. https://doi.org/10.1111/psyp.13874

Yeh, W.-H., Hsueh, J.-J., & Shaw, F.-Z. (2020). Neurofeedback of alpha activity on memory in healthy participants: A systematic review and meta-analysis. *Frontiers in Human Neuroscience, 14*, 562360. https://doi.org/10.3389/fnhum.2020.562360

Zweckberger, K., Hallek, E., Vogt, L., Giese, H., Schick, U., & Unterberg, A. W. (2017). Prospective analysis of neuropsychological deficits following resection of benign skull base meningiomas. *Journal of Neurosurgery, 127*(6), 1242–1248. https://doi.org/10.3171/2016.10.JNS161936

**Received:** September 21, 2021
**Accepted:** September 24, 2021
**Published:** September 30, 2021

NeuroRegulation

ISNR INTERNATIONAL SOCIETY FOR NEUROREGULATION & RESEARCH

# fMRI-EEG Fingerprint Regression Model for Motor Cortex

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**Abstract**

The combination of modern machine learning and traditional statistical methods allows the construction of individual regression models for predicting the blood oxygenation level dependent (BOLD) signal of a selected region-of-interest within the brain using EEG signal. Among the many different models for motor cortex, we chose the EEG Fingerprint one-electrode approach, based on rigid regression model with Stockwell EEG signal transformation, used before only for the amygdala. In this study we demonstrate the way of finding suitable model parameters for the cases of BOLD signal reconstruction for five individuals: three of them were healthy, and two were after a hemorrhagic stroke with varying degrees of damage according to Medical Research Council (MRC) Weakness Scale. The principal possibility of BOLD restoring using regressor model was demonstrated for all the cases considered above. The results of direct and indirect comparisons of BOLD signal reconstruction at the motor region for healthy participants and for patients who suffered from a stroke are presented.

***Keywords***: EEG; fMRI BOLD; regression model; motor cortex; stroke

**Citation**: Rudnev, V., Melnikov, M., Savelov, A., Shtark, M., & Sokhadze, E. (2021). fMRI-EEG fingerprint regression model for motor cortex. *NeuroRegulation*, *8*(3), 162–172. https://doi.org/10.15540/nr.8.3.162

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## Introduction

There are certain advantages of combining functional magnetic resonance imaging (fMRI) and electroencephalographic (EEG) modalities. The EEG data has an excellent submillisecond resolution which allows for an adequate representation of rich temporal dynamics of the neural ensembles' activity recorded from the scalp surface. The issues arising from the limited number of electrodes used to record 2D signals and facial skin and muscles' conductivity result in a limited spatial resolution of the signal and inadequate signal-to-noise ratio. This is also known as an ill-posed inverse problem of reconstruction of the source of EEG activity (Custo et al., 2014). FMRI allows to improve the spatial resolution to a submillimeter level, while temporal dynamics of the blood oxygenation level dependent (BOLD) signal is generally recorded with few seconds repetition time (Ogawa et al., 1990). It should be noted that the BOLD signal does not directly represent a neural activity, but rather is a currently poorly understood combination of hemodynamic response and metabolic processes characterized by a relatively slow temporal dynamic (Logothetis, 2002).

In addition, the analysis of BOLD signals reveals spatial patterns that are correlated by time and may represent functional connectivity (Beckmann et al., 2005; Smith et al., 2009). Lastly, it is a known fact that the parameters of the hemodynamic response function (HRF) differ depending on a certain brain area and varies from subject to subject (Handwerker et al., 2012). Thus, perspectives of studying dynamics of brain metabolic response on the smaller time scale will result in a better understanding of various basic brain processes.

Traditional methods of EEG signal reconstruction using EEG band power-based regressors convoluted with the HRF do not fully reflect the whole picture of nuances and complexities of the

EEG phenomena (Laufs et al., 2003; Murta et al., 2017; Yin et al., 2016). Due to limitations of the time scale and the number of available electrodes, as well as predetermined frequency ranges (e.g., alpha, beta, gamma, etc.), the resulting structure of the EEG becomes oversimplified (Marecek et al., 2016). The authors consider a model presented in the study by Meir-Hasson et al. (2016) to be one of the most promising models. A group of subjects underwent scanning during the so-called "emotional regulation," and the resulting data showed the efficacy of the authors' method of reconstruction of BOLD signal from the region of interest (ROI) based on EEG data recorded during the biofeedback (Keynan et al., 2016, 2019). In the described approach, there were no limitations to HRF shape, and respective time delays were factored into the model. The authors used the Stockwell transformation (ST) of EEG signal followed by a down sampling of frequency in the time-frequency domain (Stockwell, 2007). The increase of the temporal resolution of reconstructed BOLD signal was discussed as a part of the model which created the possibility of better understanding its temporal dynamics. This method was claimed as a universal one that could be applied for various functional brain networks and, more importantly, allowed for the simulation of signal of intracerebral ROIs and not just cortical structures.

However, to the best of our knowledge, the model was tested only for the amygdala; therefore, its versatility and applicability to other brain structures and predictive power in that case require further investigation. Several methodical issues such as specific frequency ranges, bands, electrodes, or other model hyperparameters are subject to further research and adjustment. The aim of the current study based on the aforementioned Meir-Hasson model (2016) was to investigate possibility and accuracy of the sensorimotor (SMR) BOLD signal reconstruction that reflects hand motion from EEG recordings. Relative homogeneity and simplicity of motor action should lead to effective prediction with adequate determination coefficients. We expect that in a case of motor area activity the predicted impact of specific EEG bands such as mu- and SMR-bands will be the greatest one.

## Methods

### Equipment, Materials, and Subjects

The study was performed at the tomography center using an Ingenia magnetic resonance machine (Philips, Amsterdam, Netherlands) with a magnetic field induction of 3.0T equipped with iViewBold software for real-time fMRI results. A head coil with a slanting mirror based on dStream technology and a mobile pixels-compatible monitor (NordicNeuroLab, Bergen, Norway) were used. Reference anatomical images were obtained using the T1 Mapping 3D turbo field echo (TFE) method, TR (repetition time) / TE (echo time) = 7.5 / 3.7 ms with a field of view of 250 x 250 x 180 $mm^3$ and a reconstructed voxel size (3D image element) of 1 x 1 x 1 $mm^3$. The reconstruction included the creation of three packs of slices oriented along the main orthogonal planes (Multiplanar Reformation Procedure [MPR], i.e., multiplanar reconstruction). The main working T2 weighted images (T2WI) were obtained by the secure shell (SSH) protocol, Standard Portable Intermediate Representation (SPIR) echo planar imaging (EPI) method, TR / TE = 2500 / 35 ms with a sagittal orientation of a packet of 25 slices 5 mm thick and a field of view of 220 x 220 $mm^2$, with a resolution on a 2 x 2 $mm^2$ plane. The uniform distribution of the slices in the TR interval provided a constant recording rate of 100 ms per slice, and their nonstandard sagittal arrangement simplified the identification of target zones. The relatively large thickness of the slices made it possible to limit their number and achieve optimal sensitivity at a time of TE = 35 ms. BrainVision (Brain Products GmbH, Gilching, Germany) encephalograph and a BrainCap MR-compatible helmet for EEG BrainCap MR (EASYCAP GmbH, Wörthsee, Germany), 32-channel/128-channel Ag/AgCl electrodes including the reference one, using an extended 10-20 system, were synchronously monitored for electrical activity of the brain. An electrode for recording ECG was placed under the shoulder blade of the subject. Before placing the participants in the tomograph, the level of electrode impedance < 20 kOhm was achieved.

In total, five right-handed subjects took part in the experiment, see Table 1. Three of five subjects were healthy individuals (S1, S2, S3 in Table 1), two subjects had left-sided poststroke paresis (I1 and I2). Subject I1 had a mild motor impairment (4 points on the Medical Research Council Weakness Scale [MRC] for muscle strength assessment), subject I2 had a severe motor impairment (2 points on the same scale). All study participants signed informed consent form approved by the local institutional ethics committee.

The experiment included two phases. During the first phase, simultaneous EEG and fMRI signals were recorded at the tomography center. Each subject participated in a similar session: the EEG signal was recorded using BrainVision 32-channel system with a 5000 Hz sampling rate and 250 Hz bandwidth. The

experiment had a block design: each subject used his hand in response to the stimulus on the monitor screen (the task was to squeeze a ball for the entire duration of stimulus). During the session, time of stimulus presentation was equivalent to 25 s, followed by a rest period of the same duration, and the total number of scan recordings was 240 s; i.e., 600 s per session, in total 24 blocks per session. This paradigm was repeated for the left hand only. The data obtained in each experiment (first phase) was subsequently used to build the EEG–fMRI regression model.

**Table 1**
*Subjects' Characteristics*

| | Age | MRC score* | Sex |
|---|---|---|---|
| S1 | 21 | 5 | m |
| S2 | 20 | 5 | m |
| S3 | 29 | 5 | m |
| I1 | 38 | 4 | f |
| I2 | 42 | 2 | m |

The second phase of the experiment was conducted outside of the MRI scanner. Same subjects participated, and the second session of the first phase was executed with the same stimuli along with the recording of EEG data using Neuron-Spectr-5 commercial electroencephalograph (Neurosoft, Ivanovo, Russia). In the experiment the MCScap textile cap (Medical Computer Systems, MCS, Moscow, Russia) with 30 removable passive Ag/AgCl electrodes was placed according to the 10-20 system. Montage was referenced to Cz electrode.

## Signal Refinement EEG

Recording EEG signal in the MR scanner is affected by gradient exposure due to the fast magnetic field alternations. The amplitudes of physiological component of the signal decline on a logarithmic scale, while prominence of the gradient (MR) component does not fade as fast. Thus, during the signal processing phase it is necessary to closely monitor the process of EEG signal refinement from MR gradient, so that the physiological component of the spectrum does not degrade. We used an EEGLab Software Package for that purpose (Delorme & Makeig, 2004). During the refinement process, Bergen plugin (Moosmann et al., 2009) was used for subtraction of the gradient artifacts, as well as Functional Magnetic Resonance Imaging of the Brain (FMRIB) plugin was applied for pulse artifacts removal (Iannetti et al., 2005; Niazy et al., 2005) using standard settings. For the signal free of magnetic artifact, our cleaning procedure was close to the Makoto's preprocessing pipeline steps (Swartz Center for Computational Neuroscience, n.d.). To remove occasional large amplitude noise/artifact subspace reconstruction (ASR), clean raw data plugin was chosen (Chang et al., 2018). For the constant fixed source noise/artifact signals independent component analyses (ICA) was used, where an automatic classification label for independent components (IClabel) EEGLab plugin was run to classify which of the independent components had to be subtracted (Pion-Tonachini et al., 2019). All algorithms used have their inner parameters as the number of principal component analysis (PCA) components (FMRIB plugin) or level of probability (IClabel plugin); therefore, the cleaning procedure was done always under visual inspection of signal and its spectral characteristic.

## Analysis of fMRI Data

Data in international DICOM imaging standard format were converted to Neuroimaging Informatics Technology Initiative (NIFTI) format using the MRIConvert utility (University of Oregon, Lewis Center for Neuroimaging, n.d.). To obtain BOLD signal the statistical parametric mapping (SPM) fMRI data analysis were used. Statistical analysis was performed in the SPM package (UCL Queen Square Institute of Neurology, n.d.). Standard settings were applied unless otherwise stated. The following processing steps were also performed: correction of mutual frame positions (Reslice) to eliminate the consequences of subjects' head movements and time differences in obtaining individual slices (Slice Timing), coregistration of structural and mean functional images (Coregister), division into gray and white matter and areas of cerebrospinal fluid with simultaneous transformation to the standard MNI (Montreal Neurological Institute) coordinate space with an isotropic distribution of 2 mm (Segment, Normalize: Write) and smoothing (Smooth) of functional tomograms using a spatial filter with a Gaussian nucleus of half-height width 6 mm. At the individual level, tasks were modeled by conversion of the standard function of the hemodynamic response and the rectangular function corresponding to the work and rest blocks. The design also included additional regressors: head movement correction parameters (three axes of displacement and three planes of rotation) to eliminate corresponding noise. This stage also employed a high-frequency filter with a cutoff period

of 128 s. Final analysis based on *t*-statistic $p < .05$ (fwe = 1e-5) were used to determine motor activation volume under block design consideration. The BOLD signal as the sum of those vowels were extracted for all participants in experiment.

## Model Description

Availability of the signals with high spatial resolution (fMRI) and high temporal resolution (EEG) made it possible to build the model for BOLD signal reconstruction. It was shown by Meir-Hasson et al. (2014, 2016) that combining these two signals recorded from the amygdala, defining a connection mathematically, and then computing a regression model that predicts BOLD signal based on EEG data was possible. The certain steps to build such a model are shown in Figure 1. In the case of BOLD signal, the transformation procedure is rather trivial; the BOLD signal is normalized with a subsequent increase of the sampling rate to 4 Hz.

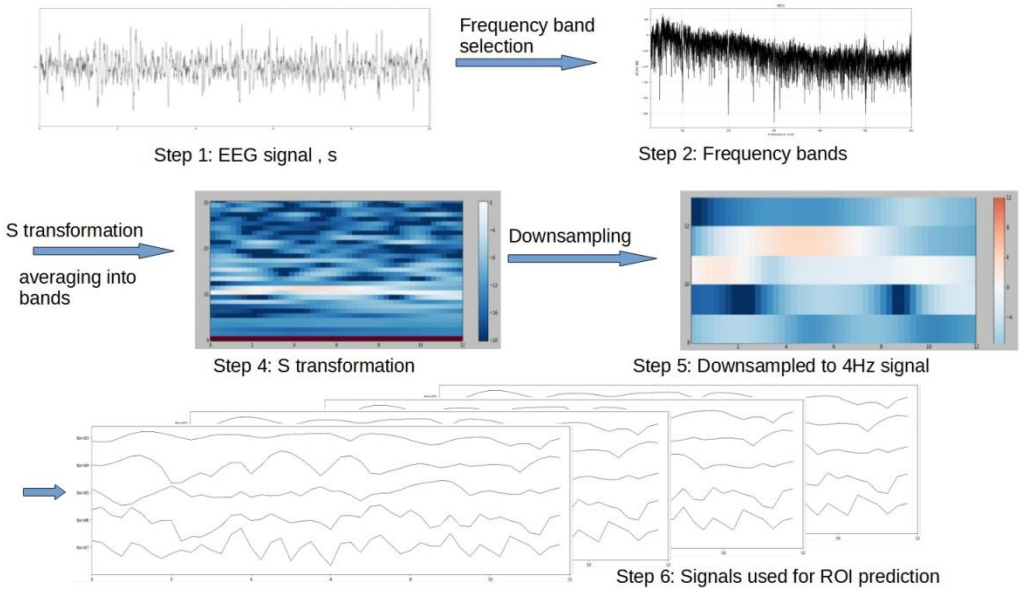
Transformation of EEG signal should be performed keeping in mind temporal dynamics of the BOLD signal. Hemodynamic response value reaches its peak to 5- to 6-seconds point from the stimulus onset, the whole response is somewhat about 10 seconds, and, strictly speaking, this function is heterogeneous with respect to a certain brain area. Thus, for the further EEG signal processing a 12-s time frame was selected for one of the electrodes for EEG signal with 80 Hz sampling frequency. For a better identification of the relevant EEG signal characteristics for a subsequent regression analysis, the 12-s frame was transformed into a time-frequency region using Stockwell transformation (ST) procedures implemented in the MNE-Python package (Gramfort et al., 2013).

To reduce number of the signal characteristics, the frequency band was limited to 30 Hz, and then divided into three frequency unknown subbands (to be found). In the time region the sampling rate was reduced from 80 Hz to 4 Hz, while the BOLD signal had the same frequency. After all transformations (five steps), one time frame of EEG signal resulted into a total of 144 parameters (12 s x 4 Hz x 3 bands) that could be used as a vector of independent values for the ridge regression (Figure 1); i.e., to one value of the BOLD signal. Moving the whole 12-s time frame by 0.25 s, other 144 parameters (regressors) of transformed EEG signal can be used with the next value of the BOLD signal. The BOLD signal in this case is a dependent variable.

## Optimizing Model Hyperparameters

At the beginning of the construction of the model, it was decided to limit the frequency band of the EEG signal to 6–30 Hz and consider only three subband frequency intervals. Thus, the model is characterized by nine unknown hyperparameters including: width – ST transformation coefficient; alpha – ridge regression coefficient; electrode; and six frequency parameters that define three subfrequency intervals.

**Figure 1.** *Steps Required for the EEG Signal Transformation.*



## Results

### Building Individual Models

The subjects performed the motor task "squeeze the ball" with a simultaneous recording of the fMRI and EEG signals. During the first phase, after removal of tomographic and miscellaneous artifacts from the data, a regression model for each subject was created for two halves of experimental data. Prior to BOLD signal reconstruction with a commercial electroencephalograph, we estimated the accuracy of the model using the $r^2$ metric for all subjects.

### Electrode Selection, Alpha and ST Width

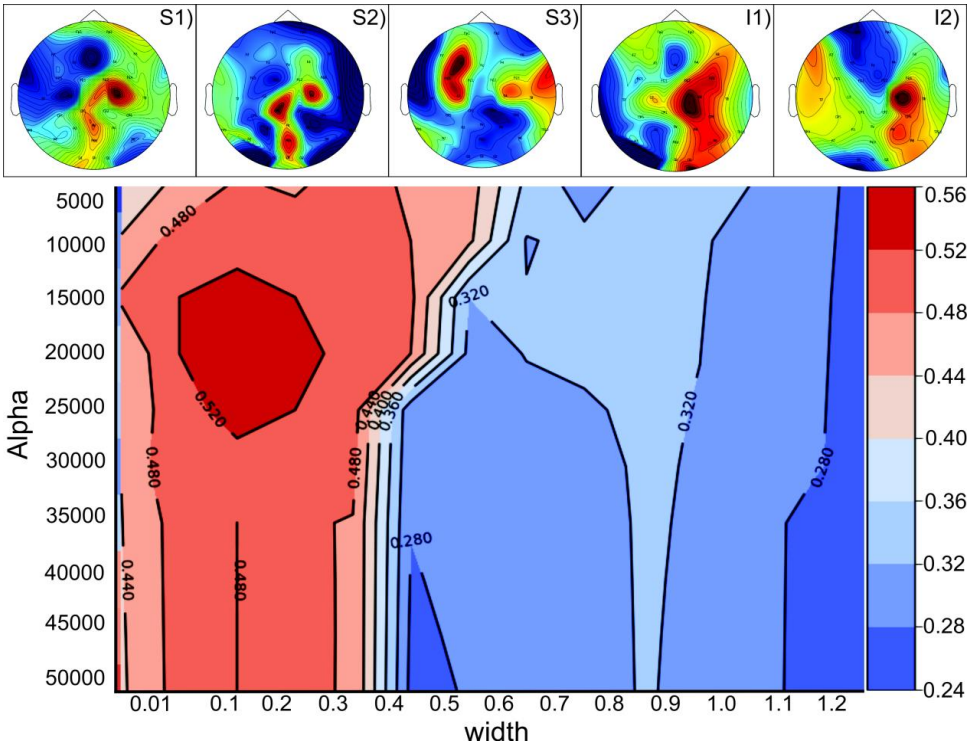
The procedure for determining the required values of hyperparameters was as follows. At the first stage, a restriction was introduced on the number of subfrequency intervals, namely, one frequency interval of 9–25 Hz was selected related to SMR activity, including classical mu-rhythm and upper beta rhythm (Emmert et al., 2016). The values of the ST width parameter and the alpha parameter of the ridge regressor were sorted out for each electrode. The model building process went through the cross-validation procedure with k-fold = 10. Data set was split into k = 10 consecutive folds (without shuffling). Then each fold was used as a validation set once while the k − 1 remaining fold formed the training set. The overall model was optimized as the mean of five subjects. The following task was set: for each value of alpha, ST width and electrode to find such values of the coefficient regression models that gives the maximum values of the correlations of the summary model:

$$MaximizeG(f1, f2) = Corr(\sum_{i=1}^{5} Rigid^{i}(f1, f2)) \forall alpha, electrode, width$$

where $Rigid^{i}(f1, f2)$ is the individual ridge regressor model.

As expected, the best electrode for constructing a model for left-hand movement was C4 contralateral electrode located closest to the motor region of the right brain hemisphere; 0.1 width ST; and alpha 20.000 (see Figure 2).

**Figure 2.** *The upper part represents the classifier work for each of 30 electrodes for each subject; the lower part is a contrast map for the C4 electrode of the summary model depending on ST width and alpha.*



### Frequency Sub-Bands Selection

At the second stage for the further optimization of previously found hyperparameters C4 electrode, 0.1 width ST, and alpha 20000 with three subfrequency intervals were used, giving six unknown variables. To search for a set of hyperparameters that would produce the best results the Hyperopt optimization library was chosen (Bergstra et al., 2013), that is faster than a simple grid search.

The optimization procedure was applied simultaneously to five subjects. The number of iterations was 5000. The BOLD signal obtained directly from fMRI data by extraction of the voxel intensities described earlier is highlighted orange. The BOLD signal obtained as a result of reconstruction is shown in blue; the resulting model from the first half of the experimental data was applied to the EEG signal of the second half of the experimental data. This procedure for constructing a model with its subsequent verification with a real BOLD signal was applied for the model obtained from the data of the second half of the experiment.

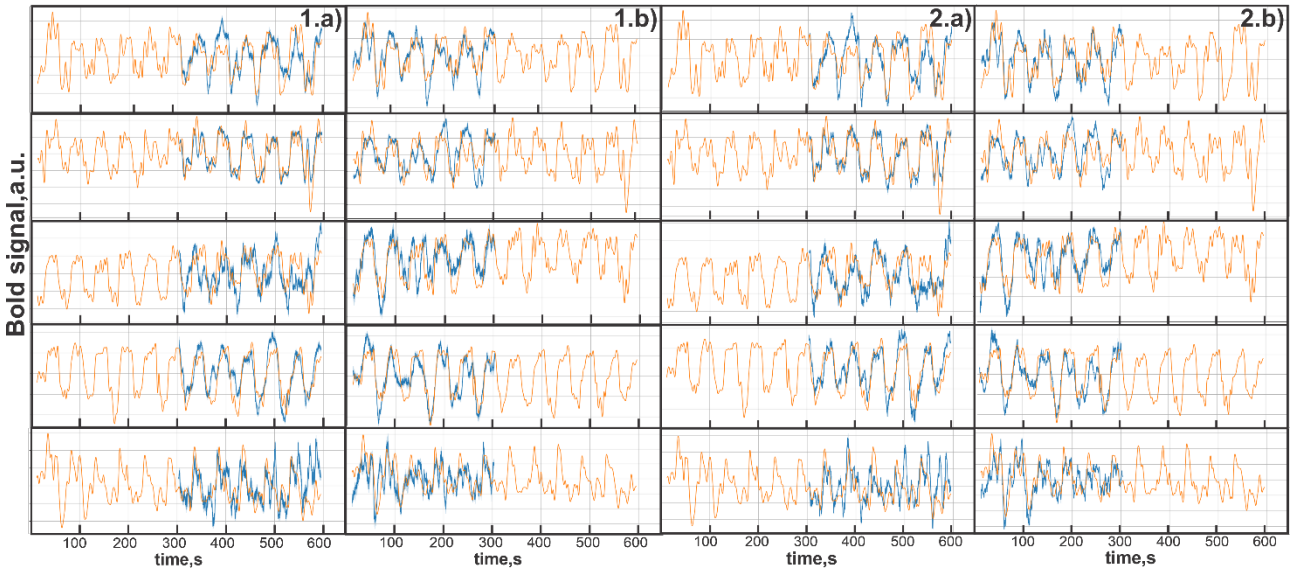
Frequency bands for the best result were found to be, consequently, 8–12, 12–14, and 16–22 Hz. Thus, a complete set of nine hyperparameters was found, which made it possible to start building individual models. The result of applying individual model to the selected frequency band (8–12, 12–14, 16–22 Hz) is shown at Figure 3. The correlation values are shown in Table 2.

**Table 2**

*Statistically Significant Values of the Correlation Coefficients for 10 Randomly Constructed Models for the Subjects (Train / Test Split). Part I – The Model was Built from the First Half of Data, Part II – From the Second Part of Data.*

| | Part I | | | | | Part II | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | S1 | S2 | S3 | I1 | I2 | S1 | S2 | S3 | I1 | I2 |
| 1 | 0.74 | 0.81 | 0.52 | 0.85 | 0.45 | 0.79 | 0.61 | 0.69 | 0.85 | 0.73 |
| 2 | 0.63 | 0.81 | 0.64 | 0.83 | 0.47 | 0.78 | 0.62 | 0.73 | 0.81 | 0.70 |
| 3 | 0.69 | 0.87 | 0.59 | 0.78 | 0.43 | 0.75 | 0.66 | 0.75 | 0.87 | 0.71 |
| 4 | 0.70 | 0.86 | 0.65 | 0.86 | 0.46 | 0.74 | 0.69 | 0.80 | 0.78 | 0.61 |
| 5 | 0.76 | 0.85 | 0.60 | 0.82 | 0.55 | 0.79 | 0.68 | 0.72 | 0.79 | 0.66 |
| 6 | 0.71 | 0.82 | 0.53 | 0.83 | 0.47 | 0.74 | 0.67 | 0.79 | 0.82 | 0.66 |
| 7 | 0.58 | 0.82 | 0.57 | 0.79 | 0.52 | 0.73 | 0.65 | 0.75 | 0.84 | 0.71 |
| 8 | 0.76 | 0.83 | 0.63 | 0.78 | 0.38 | 0.78 | 0.67 | 0.75 | 0.87 | 0.75 |
| 9 | 0.65 | 0.83 | 0.51 | 0.77 | 0.50 | 0.80 | 0.56 | 0.80 | 0.78 | 0.71 |
| 10 | 0.72 | 0.84 | 0.68 | 0.80 | 0.39 | 0.76 | 0.60 | 0.72 | 0.86 | 0.67 |
| mean | 0.69 | 0.83 | 0.59 | 0.81 | 0.46 | 0.77 | 0.64 | 0.75 | 0.83 | 0.69 |

**Figure 3.** *Results of Direct Comparison of Reconstructed BOLD Signal (Blue) with the Real One (Orange) for Five Subjects S1, S2, S3, I1, I2 from Top to Bottom.*



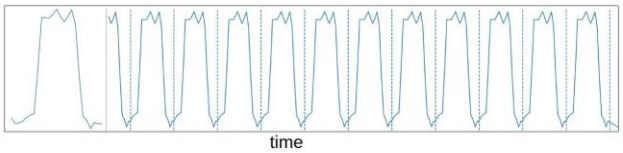

**Note.** On the left 1.a) the model was built according to the first half of experimental data, on the right 1.b) according to the second half of data. 2.a), the individuals' models with three selected frequency bands were built according to the first half of experimental data, 2.b) according to the second part of data.

## Reconstruction of BOLD-Dependent EEG Signal Building Pseudo-BOLD Signal

The same subjects further underwent a second session outside the scanner with not MR-compatible electroencephalograph Neuron-Spectr-5 used for the signal recording and for implementing a previously created model.

Due to the absence of the BOLD signal, it was not possible to directly compare the predicted BOLD signal with the real one. An averaged BOLD signal curve based on the analysis of actual BOLD signals was introduced, the middle point of which matched the label of the end of hand motor task (Figure 4). Correlation coefficient between this pseudo-BOLD signal and the reconstructed BOLD signal was accepted as an estimated metric of likelihood.

**Figure 4.** *Model of the BOLD signal and its BOLD reconstruction.*

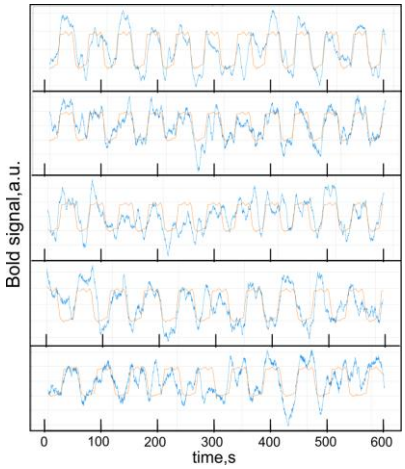



**Note.** By labels, i.e., the moment when block associated with movement starts (dash lines). Left: the real BOLD signal; right: the signal reconstruction based on labels.

## Reconstruction

Previously constructed individual regression models were applied to the EEG signals recorded with a commercial electroencephalograph. The result is presented in Figure 5, where reconstructions of BOLD signals built according to individual models of subjects according to data obtained with a commercial electroencephalograph are shown.

**Figure 5.** *Reconstruction of the BOLD Signal by the EEG pattern*.




**Note.** Only reconstruction marked by asterisks from Table 3 are shown.

Orange color shows the model BOLD signal reconstructed by event labels. They cannot be compared directly; however, the shape time points of the signal values that increase and decrease in five experiments appear to be very similar to the normal dynamics of the BOLD signal registered in the MR scanner.

More information on reconstruction is presented in Table 3. Left column indicates patients depending on I or II part of data. Columns M(I2), M(I1), M(S1), M(S2), M(S3) show individual regression models for patients S1, S2, S3, I1, I2, where letter M is reserved for model. Channel columns (CH) represent EEG recording channels used for BOLD reconstruction for patients S1, S2, S3, I1, I2.

**Table 3**

*Correlation Coefficients Between the Reconstructed Signal and the Corresponding Pseudo BOLD Signal.*

| Model/ Patient | M(I2) | CH | M(I1) | CH | M(S3) | CH | M(S2) | CH | M(S1) | CH | ∑ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| S1(1) | 0.29 | C4 | 0.68 | C4 | 0.35 | C4 | 0.80 | C4 | 0.80* | C4 | 3 |
| S1(2) | 0.26 | C4 | 0.69 | C4 | 0.32 | C4 | 0.78 | C4 | 0.78 | C4 | 3 |
| I1(1) | 0.57 | C4 | 0.72* | C4 | 0.57 | C4 | 0.68 | C4 | 0.68 | C4 | 5 |
| I1(2) | 0.61 | C4 | 0.60 | C4 | 0.52 | C4 | 0.65 | C4 | 0.65 | C4 | 5 |
| S2(1) | 0.35 | C4 | 0.66 | C4 | 0.37 | C4 | 0.73* | C4 | 0.73 | C4 | 3 |
| S2(2) | 0.29 | C4 | 0.63 | C4 | 0.31 | C4 | 0.81 | C4 | 0.82 | C4 | 3 |
| I2(1) | 0.57* | CP2 | 0.72 | CP2 | 0.57 | CP2 | 0.68 | CP2 | 0.68 | CP2 | 5 |
| I2(2) | 0.61 | CP2 | 0.60 | CP2 | 0.52 | CP2 | 0.65 | CP2 | 0.65 | CP2 | 5 |
| S3(1) | 0.52 | C4 | 0.66 | C4 | 0.47* | C4 | 0.75 | C4 | 0.75 | C4 | 4 |
| S3(2) | 0.40 | C4 | 0.67 | C4 | 0.42 | C4 | 0.69 | C4 | 0.69 | C4 | 3 |
| ∑ | 5 | | 10 | | 4 | | 10 | | 10 | | |

**Note.** *p < .001 according to the correlation coefficients with n = 958.*

## Analysis of Results

From Table 3 it can be concluded that there are universal models that can be used for different subjects. Specifically, application of the I2 model (1) in brackets is indicated for which half of the data the model was built and allowed obtaining the BOLD reconstruction signal for all five subjects with a correlation coefficient greater than 0.5. At this stage it is not clear to what extent this model can be used to the greater area due to the lack of the data (subjects) to make statistically significant conclusions.

Subject I2 demonstrated good reconstruction signal at the CP2 electrode, but not at C4 as was expected. As this electrode is close to the motor

area, it can be assumed that the EEG cap was applied incorrectly so the electrode may have shifted. To avoid such problems in the future, we plan to record the coordinates of the electrodes.

## Discussion

The new tendencies in the neurological research originate from the desire to preserve the benefits of the fMRI-EEG data without using MR scanner. This research task is labeled as a problem of the BOLD-dependent EEG. Some research studies involving simultaneous records of fMRI and EEG signals utilize EEG spectral features that may be useful in predicting specific BOLD dynamics (de Munck et al., 2009; Goense & Logothetis, 2008; Goldman et al., 2002; Kilner et al., 2005; Mantini et al., 2007; Murta et al., 2015; Rosa et al., 2010; Wan et al., 2006). Such innovation necessity is motivated by the immobility and the cost of bimodal platform. Current studies attempt to retain its advantages outside the scanner and produce a "shadow" copy of fMRI using the BOLD-dependent EEG. The key idea is to use the obtained data on fMRI-EEG interdependencies with a modern commercial electroencephalograph.

Our study of SMR cortex BOLD signal prediction using EEG signal was based on the EEG-channel-specific BOLD prediction technique described in the articles by Meir-Hasson et al. (2014, 2016). Unlike the original study, the motor region of the cortex responsible for the real movements was chosen. To the best of our knowledge, there were not published any similar studies targeted to any cortical region of the brain except of amygdala. Despite the fact that this approach suits to different brain structures, it is necessary to adjust unique model hyperparameters; namely, certain electrodes, division of the EEG spectrum into frequency bands, providing the best reconstruction of the BOLD signal, ST width parameter, and, finally, rigid regressor alpha parameter. Indeed, the results of our study confirm the effectiveness of this approach and demonstrate that BOLD signal reconstructions by EEG have statistically significant levels of correlation coefficients with "ground truth" real and pseudo-BOLD signals. This means that the technique allows to avoid or significantly limit the usage of MR scanner without dramatic loss of quality of the reconstructed BOLD signal and to maintain its spatial precision in certain tasks.

In this study the individual EEG-fMRI models were built for each participant. A total of five subjects took part in the experiment. Three of them were healthy, one had a mild motor impairment, and one was with a severe poststroke motor impairment.

This article describes the procedure for obtaining hyperparameters needed for building a regression model for reconstruction of BOLD-dependent signal by EEG pattern that is valid for all five subjects. A direct comparison of the BOLD reconstruction with a real statistically significant correlation coefficient was carried out (9 of 10 comparisons have correlation coefficients more than 0.59, including a patient with severe paresis). An indirect comparison of data obtained on a commercial electroencephalograph showed correlation coefficients greater than 0.5 for all subjects. For patient I2, according to indirect comparison, the best electrode was found to be not C4, but CP2. A possible reason is different sizes of the cap used at the tomographic center where data in bimodal EEG + fMRI mode were obtained, and the cap used at the clinical electroencephalograph. To avoid this problem, it is planned to record coordinates of the electrodes in the future.

The next step is moving away from individual models to a small number of universal ones (or even to one model fitting all) and thus limiting the use of the fMRI. According to data from Table 3, we may assume that this is possible. At this stage, the number of subjects was not sufficient to provide a statistically significant answer. Differences in individual physiological characteristics of participants make the construction of such models a complicated task. There are already proposed techniques such as hierarchical cluster analysis to overcome these difficulties (Meir-Hasson et al., 2014, 2016; Wei et al., 2018).

As there are no methods of direct comparison of the reconstructed BOLD signal with a real one when only one electroencephalograph is used, it is planned to include objective monitoring tools (EMG sensors) in our future experiments. However, some open questions remain: the applicability of the model for different temporal designs, the relationship of hand's pressing force and ball manipulation, and model's adequacy in case of motor imaging.

The long-term goal is a usage of the BOLD-dependent EEG in the rehabilitation of people who suffer from a stroke that resulted in damage of the motor area. There is a need to improve the existing ineffective paradigm of neurorehabilitation which results in up to 44% of disability after stroke (Katan & Luft, 2018). We hope that the technologies for reconstructing the BOLD using one or only a few EEG electrodes will potentially make it possible to

significantly simplify and reduce the cost of rehabilitation of this category of patients using BOLD-dependent EEG as a competitive recovery monitoring tool.

## Conclusion

Demonstration of the possibility of restoring the BOLD-dependent signal, not only in healthy subjects but also in the patients with stroke, shows that this approach can be applicable to people with damage to the motor regions of the brain. The question of how static the obtained models are and whether they can be applied at the entire stage of rehabilitation of poststroke patients remains open, as well as the question of building universal models.

Our findings demonstrated that the model proposed by Meir-Hasson et al. (2016) and the hypothesis of its universality with respect to different brain structures are generally correct and may be used at least for the SMR cortex, although some additional tuning of frequencies and subband selection procedure, as well as different electrode should be used in this case.

### Author Acknowledgement

Sponsored by Russian Science Foundation grant N 21-15-00209.

### Compliance with Ethical Standards

***Conflict of Interest.*** None of the authors have potential conflicts of interest to be disclosed.

***Ethical Approval.*** All procedures in this research study were performed in accordance with the ethical standards compliant with the 1964 Helsinki declaration. Signed informed consent approved by the Federal Research Center of Fundamental and Translational Medicine Ethics Committee was obtained from all individuals who participated in the study.

## References

Beckmann, C. F., DeLuca, M., Devlin, J. T., & Smith, S. M. (2005). Investigations into resting-state connectivity using independent component analysis. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 360*(1457), 1001–1013. https://doi.org/10.1098/rstb.2005.1634

Bergstra, J., Yamins, D., & Cox, D. D. (2013). Making a science of model search: Hyperparameter optimization in hundreds of dimensions for vision architectures. *Proceedings of the 30th International Conference on Machine Learning (ICML 2013), 28*, 115–123.

Chang, C.-Y., Hsu, S.-H., Pion-Tonachini, L., & Jung, T.-P. (2018). Evaluation of artifact subspace reconstruction for automatic EEG artifact removal. *2018 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, 1242–1245. https://doi.org/10.1109/EMBC.2018.8512547

Custo, A., Vulliemoz, S., Grouiller, F., Van De Ville, D., & Michel, C. (2014). EEG source imaging of brain states using spatiotemporal regression. *NeuroImage*, *96*, 106–116. https://doi.org/10.1016/j.neuroimage.2014.04.002

de Munck, J. C., Gonçalves, S. I., Mammoliti, R., Heethaar, R. M., & Lopes da Silva, F. H. (2009). Interactions between different EEG frequency bands and their effect on alpha-fMRI correlations. *NeuroImage*, *47*(1), 69–76. https://doi.org/10.1016/j.neuroimage.2009.04.029

Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*, *134*(1), 9–21. https://doi.org/10.1016/j.jneumeth.2003.10.009

Emmert, K., Kopel, R., Sulzer, J., Brühl, A. B., Berman, B. D., Linden, D., Horovitz, S. G., Breimhorst, M., Caria, A., Frank, S., Johnston, S., Long, Z., Paret, C., Robineau, F., Veit, R., Bartsch, A., Beckmann, C. F., Van De Ville, D., & Haller, S. (2016). Meta-analysis of real-time fMRI neurofeedback studies using individual participant data: How is brain regulation mediated? *NeuroImage*, *124*(Part A), 806–812. https://doi.org/10.1016/j.neuroimage.2015.09.042

Goense, J. B. M., & Logothetis, N. K. (2008). Neurophysiology of the BOLD fMRI signal in awake monkeys. *Current Biology*, *18*(9), 631–640. https://doi.org/10.1016/j.cub.2008.03.054

Goldman, R. I., Stern, J. M., Engel, J., Jr., & Cohen, M. S. (2002). Simultaneous EEG and fMRI of the alpha rhythm. *NeuroReport*, *13*(18), 2487–2492. https://doi.org/10.1097/01.wnr.0000047685.08940.d0

Gramfort, A., Luessi, M., Larson, E., Engemann, D. A., Strohmeier, D., Brodbeck, C., Goj, R., Jas, M., Brooks, T., Parkkonen, L., & Hämäläinen, M. (2013). MEG and EEG data analysis with MNE-Python. *Frontiers in Neuroscience*, *7*, 267. https://doi.org/10.3389/fnins.2013.00267

Handwerker, D. A., Gonzalez-Castillo, J., D'Esposito, M., & Bandettini, P. A. (2012). The continuing challenge of understanding and modeling hemodynamic variation in fMRI. *NeuroImage*, *62*(2), 1017–1023. https://doi.org/10.1016/j.neuroimage.2012.02.015

Iannetti, G. D., Niazy, R. K., Wise, R. G., Jezzard, P., Brooks, J. C. W., Zambreanu, L., Vennart, W., Matthews, P. M., & Tracey, I. (2005). Simultaneous recording of laser-evoked brain potentials and continuous, high-field functional magnetic resonance imaging in humans. *NeuroImage*, *28*(3), 708–719. https://doi.org/10.1016/j.neuroimage.2005.06.060

Katan, M., & Luft, A. (2018). Global burden of stroke. *Seminars in Neurology*, *38*(2), 208–211. https://doi.org/10.1055/s-0038-1649503

Keynan, J. N., Cohen, A., Jackont, G., Green, N., Goldway, N., Davidov, A., Meir-Hasson, Y., Raz, G., Intrator, N., Fruchter, E., Ginat, K., Laska, E., Cavazza, M., & Hendler, T. (2019). Author correction: Electrical fingerprint of the amygdala guides neurofeedback training for stress resilience. *Nature Human Behaviour*, *3*(2), 194. https://doi.org/10.1038/s41562-019-0534-5

Keynan, J. N., Meir-Hasson, Y., Gilam, G., Cohen, A., Jackont, G., Kinreich, S., Ikar, L., Or-Borichev, A., Etkin, A., Gyurak, A., Klovatch, I., Intrator, N., & Hendler, T. (2016). Limbic activity modulation guided by functional magnetic resonance imaging-inspired electroencephalography improves implicit emotion regulation. *Biological Psychiatry*, *80*(6), 490–496. https://doi.org/10.1016/j.biopsych.2015.12.024

Kilner, J. M., Mattout, J., Henson, R., & Friston, K. J. (2005). Hemodynamic correlates of EEG: A heuristic. *NeuroImage*, *28*(1), 280–286. https://doi.org/10.1016/j.neuroimage.2005.06.008

Laufs, H., Krakow, K., Sterzer, P., Eger, E., Beyerle, A., Salek-Haddadi, A., & Kleinschmidt, A. (2003). Electroencephalographic signatures of attentional and cognitive default modes in spontaneous brain activity fluctuations at rest. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(19), 11053–11058. https://doi.org/10.1073/pnas.1831638100

Logothetis, N. K. (2002). The neural basis of the blood-oxygen-level-dependent functional magnetic resonance imaging signal. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *357*(1424), 1003–1037. https://doi.org/10.1098/rstb.2002.1114

Mantini, D., Perrucci, M. G., Del Gratta, C., Romani, G. L., & Corbetta, M. (2007). Electrophysiological signatures of resting state networks in the human brain. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(32), 13170–13175. https://doi.org/10.1073/pnas.0700668104

Marecek, R., Lamos, M., Mikl, M., Barton, M., Fajkus, J., Rektor, I., & Brazdil, M. (2016). What can be found in scalp EEG spectrum beyond common frequency bands. EEG-fMRI study. *Journal of Neural Engineering*, *13*(4), 046026. https://doi.org/10.1088/1741-2560/13/4/046026

Meir-Hasson, Y., Kinreich, S., Podlipsky, I., Hendler, T., & Intrator, N. (2014). An EEG Finger-Print of fMRI deep regional activation. *NeuroImage*, *102*(Part 1), 128–141. https://doi.org/10.1016/j.neuroimage.2013.11.004

Meir-Hasson, Y., Keynan, J. N., Kinreich, S., Jackont, G., Cohen, A., Podlipsky-Klovatch, I., Hendler, T., & Intrator, N. (2016). One-class FMRI-inspired EEG model for self-regulation training. *PLoS ONE*, *11*(5), e0154968. https://doi.org/10.1371/journal.pone.0154968

Moosmann, M., Schönfelder, V. H., Specht, K., Scheeringa, R., Nordby, H., & Hugdahl, K. (2009). Realignment parameter-informed artefact correction for simultaneous EEG–fMRI recordings. *NeuroImage*, *45*(4), 1144–1150. https://doi.org/10.1016/j.neuroimage.2009.01.024

Murta, T., Chaudhary, U. J., Tierney, T. M., Dias, A., Leite, M., Carmichael, D. W., Figueiredo, P., & Lemieux, L. (2017). Phase-amplitude coupling and the BOLD signal: A simultaneous intracranial EEG (icEEG) - fMRI study in humans performing a finger-tapping task. *NeuroImage*, *146*, 438–451. https://doi.org/10.1016/j.neuroimage.2016.08.036

Murta, T., Leite, M., Carmichael, D. W., Figueiredo, P., & Lemieux, L. (2015). Electrophysiological correlates of the BOLD signal for EEG-informed fMRI. *Human Brain Mapping*, *36*(1), 391–414. https://doi.org/10.1002/hbm.22623

Niazy, R. K., Beckmann, C. F., Iannetti, G. D., Brady, J. M., & Smith, S. M. (2005). Removal of FMRI environment artifacts from EEG data using optimal basis sets. *NeuroImage*, *28*(3), 720–737. https://doi.org/10.1016/j.neuroimage.2005.06.067

Ogawa, S., Lee, T. M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences of the United States of America*, *87*(24), 9868–9872. https://doi.org/10.1073/pnas.87.24.9868

Pion-Tonachini, L., Kreutz-Delgado, K., & Makeig, S. (2019). ICLabel: An automated electroencephalographic independent component classifier, dataset, and website. *NeuroImage*, *198*, 181–197. https://doi.org/10.1016/j.neuroimage.2019.05.026

Rosa, M. J., Daunizeau, J., & Friston, K. J. (2010). EEG-fMRI integration: A critical review of biophysical modeling and data analysis approaches. *Journal of Integrative Neuroscience*, *9*(4), 453–476. https://doi.org/10.1142/s0219635210002512

Swartz Center for Computational Neuroscience. (n.d.). *Makoto's preprocessing pipeline*. https://sccn.ucsd.edu/wiki/Makoto%27s_preprocessing_pipeline

Smith, S. M., Fox, P. T., Miller, K. L., Glahn, D. C., Fox, P. M., Mackay, C. E., Filippini, N., Watkins, K. E., Toro, R., Laird, A. R., & Beckmann, C. F. (2009). Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(31), 13040–13045. https://doi.org/10.1073/pnas.0905267106

Stockwell, G. (2007). Why use the S-Transform? In L. Rodino, B.-W. Schulze, & M. W. Wong (Eds.), *Pseudo-differential operators: Partial differential equations and time-frequency analysis* (pp. 279–309). Providence, RI: American Mathematical Society.

UCL Queen Square Institute of Neurology. (n.d.). *Statistical Parametric Mapping. Software*. The Wellcome Centre for Human Neuroimaging. https://www.fil.ion.ucl.ac.uk/spm/software/

University of Oregon. (n.d.). *MRIConvert files*. Lewis Center for Neuroimaging. https://lcni.uoregon.edu/downloads/mriconvert

Wan, X., Riera, J., Iwata, K., Takahashi, M., Wakabayashi, T., & Kawashima, R. (2006). The neural basis of the hemodynamic response nonlinearity in human primary visual cortex: Implications for neurovascular coupling mechanism. *NeuroImage*, *32*(2), 616–625. https://doi.org/10.1016/j.neuroimage.2006.03.040

Wei, C.-S., Lin, Y.-P., Wang, Y.-T., Lin, C.-T., & Jung, T.-P. (2018). A subject-transfer framework for obviating inter- and intra-subject variability in EEG-based drowsiness detection. *NeuroImage*, *174*, 407–419. https://doi.org/10.1016/j.neuroimage.2018.03.032

Yin, S., Liu, Y., & Ding, M. (2016). Amplitude of sensorimotor Mu rhythm is correlated with BOLD from multiple brain regions: A simultaneous EEG-fMRI study. *Frontiers in Human Neuroscience*, *10*, 364. https://doi.org/10.3389/fnhum.2016.00364

**Received:** July 19, 2021
**Accepted:** August 16, 2021
**Published:** September 30, 2021

NeuroRegulation

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# Vagally Mediated Heart Rate Variability: A Risk Factor for Hypertension

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**Abstract**

Hypertension is among the leading causes of mortality and an important contributor toward disability-adjusted life years worldwide. Several factors contribute toward individuals' risk to develop hypertension. Stress is considered an important pathogenic component affecting blood pressure regulation. However, systematic reviews examining the effect of psychosocial stressors and anxiety on hypertension produced spurious results. The observed heterogeneity in the operationalization of stress and subsequent reactivity hindered the characterization of the evidence for the association between exposure, physiological reactivity, and risk for hypertension. This is of paramount importance as physiological reactivity constitutes a biological interface mechanism through which stressors affect blood pressure regulation. The neural substrates of vagally mediated heart rate variability (VM-HRV) indicate that it is able to assimilate such an interfacing mechanism. Large-scale epidemiological studies provided substantial evidence linking decreases in VM-HRV with the development and progression of hypertension, indicating that individuals' reactivity to stressors, as measured via VM-HRV, increases individuals' risk for the development and progression of hypertension. As such, VM-HRV can reinforce current screening initiatives and support treatment-related prognosis. Self-regulation techniques, like heart rate variability biofeedback (HRVB), and neuromodulation techniques, like cranial electrotherapy stimulation (CES), are able to enhance VM-HRV and the associated parasympathetic modulation of cardiovascular outcomes, and thus address autonomic imbalances associated with hypertension.

***Keywords***: stress; central autonomic network; hypertension; heart rate variability; biofeedback; cranial electrotherapy stimulation

**Citation**: Christou-Champi, S. (2021). Vagally mediated heart rate variability: A risk factor for hypertension. *NeuroRegulation*, *8*(3), 173–182. https://doi.org/10.15540/nr.8.3.173

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## Introduction

Despite steady improvements in global health, hypertension remains a leading cause of mortality, especially in upper-middle and high-income countries, and an important contributor toward disability-adjusted life years worldwide (Vos et al., 2020). This is not surprising given hypertension's association with stroke and ischemic heart disease (Boehme et al., 2017; Špinar, 2012; Wajngarten & Silva, 2019), which are currently considered as the leading causes of mortality and disability-adjusted life years worldwide. Several factors are thought to contribute toward individuals' risk to develop hypertension with the interaction between genetic (Lynch et al., 2020), behavioral (Hu et al., 2004), environmental (Bruno et al., 2017), and psychosocial (Cuffee et al., 2014) factors seen as accounting for the majority of hypertension cases (Ornosa-Martín et al., 2020; Singh et al., 2015). On this basis, stress is seen as having a significant role in modifying the impact of genetic factors on cardiovascular disease risk (Singh et al., 2015), and is considered an important pathogenic factor associating environmental stressors with high blood pressure as a result of maladaptation in various functional systems (Heine & Weiss, 1987).

Despite the well-documented link between the physiological bases of the stress response and blood pressure regulation, conclusions drawn from studies examining the relationship between exposure to psychosocial stressors and hypertension are hindered by the variability in the operational definitions used, and thus exposure to stressors and subsequent reactivity (i.e., initiation of the stress response; Player & Peterson, 2011; Sparrenberger et al., 2009). Given the variability in stressors and reactivity measures employed in studies examining the impact of psychosocial stressors and anxiety, it is very difficult to summarize the evidence for the association between a well-defined characterization of exposure to stressors, subsequent physiological reactivity, and hypertension (Liu et al., 2017; Mann, 2012).

The aforementioned is of particular importance as physiological reactivity constitute a prominent biological mechanism through which stressors impact blood pressure regulation and thus affect health (Brown et al., 2018). Indeed, individuals' reactivity to stressors matters more than mere exposure to it, especially when examining stressors' impact on health (Crosswell & Lockwood, 2020).

The present paper will initially discuss the role of stress in the regulation of blood pressure before examining the physiological mechanisms that allow vagally mediated heart rate variability (VM-HRV) to interface exposure to stressors with physiological reactivity. From there, it will discuss a substantial corpus of evidence linking VM-HRV with the development and progression of hypertension. Finally, it will examine self-regulation and neuromodulation techniques that can influence VM-HRV, and thus improve individuals' physiological reactivity to stressors and autonomic imbalances associated with the development and progression of hypertension.

## The Physiology of the Stress Response

Stress in physiology is seen as reflecting an organism's response to environmental pressures or demands (Selye, 1956). A system of interrelated brain structures regulating physiological arousal support stress responses. The central autonomic network (CAN) consist of both cortical areas including the insular cortex, anterior cingulate cortex, ventromedial prefrontal cortex (vmPFC), and subcortical structures like the central nucleus of the amygdala (CeA), hypothalamus, midbrain periaqueductal gray matter, parabranchial nucleus in the pons and medulla, nucleus of the solitary tract, ventrolateral reticular formation, and raphe nuclei (Benarroch, 1993). The CAN receives input from sensory processing areas regarding the external environment, as well as input from body organs regarding the physiological state of the body. These inputs, allow CAN to modify physiological arousal to accommodate for changes in the internal and external environment.

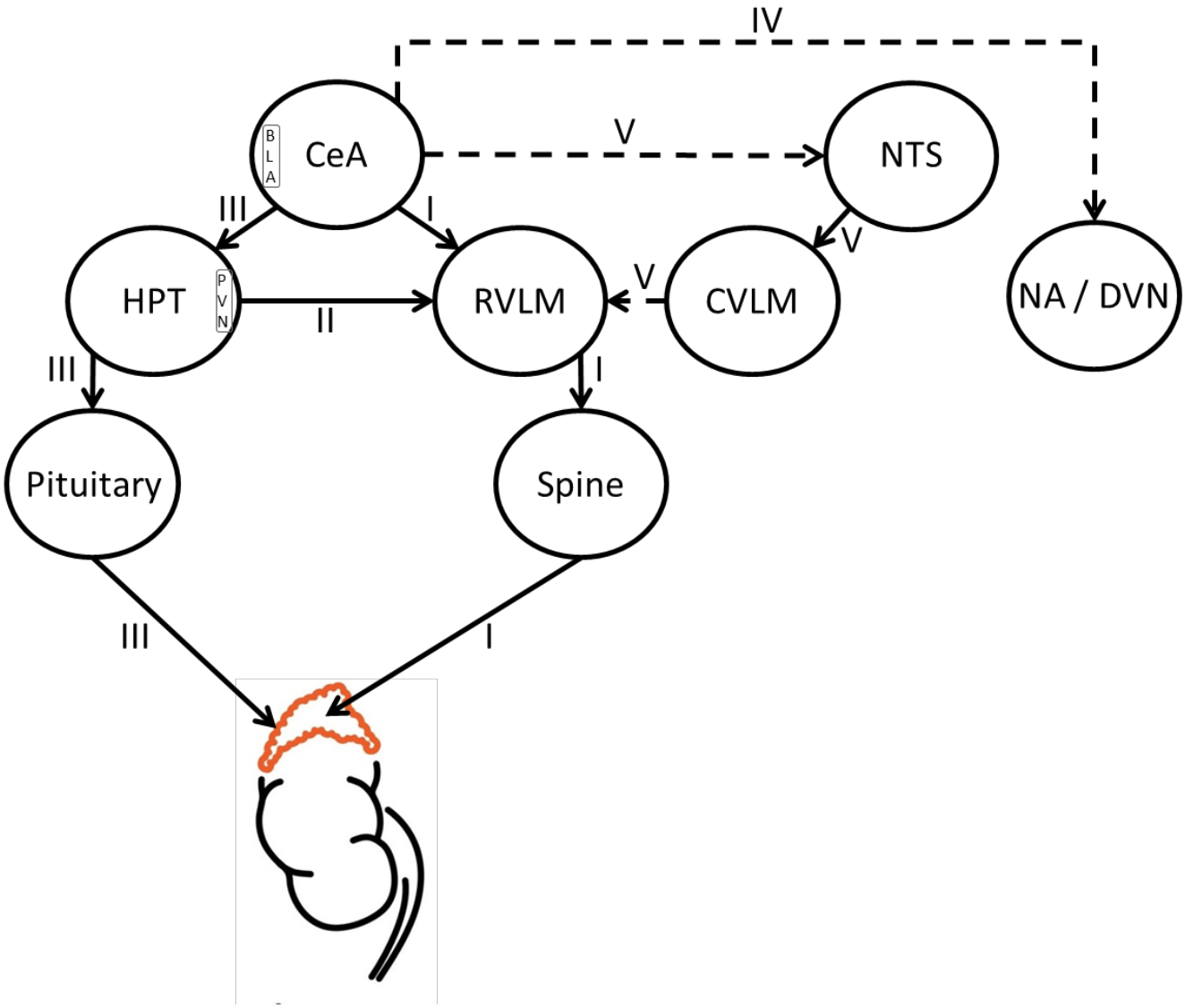
The amygdala nuclear complex is very important in the initiation of both the immediate, transient responses to stressors implemented through the sympathetic-adrenal medullary (SAM) axis, and delayed, prolonged responses carried out by the hypothalamic-pituitary-adrenal (HPA) axis. Within this framework, the CeA directly activates sympathetic rostral ventrolateral medullary (RVLM) neurons enhancing immediate SAM axis influence (Saha et al., 2005; Thayer et al., 2009). In addition, the CeA sends prominent projections to the hypothalamus which is involved in the activation of the sympathetic nervous system (SNS; LeDoux et al., 1988) via the HPA axis (Xu et al., 1999) and of the SAM axis via the paraventricular nucleus (PVN) that projects to RVLM (Badoer, 2001).

In essence, the CeA, through its projection to the hypothalamus, influences the activity of the HPA and SAM axes initiating the mechanisms of physiological arousal (see Figure 1). Under stress, the hypothalamus secretes corticotropin-releasing hormone (CRH). This provokes the release of adrenocorticotropic hormone (ACTH) from the pituitary. ACTH stimulates the adrenal cortex which secretes mineralocorticoids and glucocorticoids (aldosterone/cortisol). The best characterized physiologic effect of aldosterone is to increase sodium reabsorption and potassium and hydrogen ion excretion in an effort to increase blood volume and pressure (Komesaroff et al., 1994). However, recent evidence pointed out that aldosterone also has a powerful vasoconstriction effect (Kushibiki et al., 2007). In addition, aldosterone evokes a fibrotic response in the myocardium, and a profibrotic, hypertrophic, and inflammatory response in the vasculature, where it also minimizes nitric oxide bioactivity, thereby hindering vascular relaxation (Briet & Schiffrin, 2013). The abovementioned indicated that aldosterone is involved in the development of increased systemic vascular resistance and vascular and cardiac remodeling in a way that could sustain an elevated blood pressure (Freel & Connell, 2004; Xanthakis & Vasan, 2013). Cortisol has a pivotal role on metabolism as it prepares resources to provide energy through the catabolism of glycogen to glucose (Khani & Tayek, 2001) and protein to amino acids (Brillon et al.,

1995). This helps to overcome the increased metabolic demand presented by the stressor.

Besides the abovementioned, the CeA and hypothalamically mediated SAM input stimulates the adrenal medulla, which secretes catecholamines (epinephrine/norepinephrine). SAM mediated release of epinephrine and norepinephrine has immediate effects on the cardiovascular systems.

**Figure 1.** *Schematic Representation of CeA Influences on SAM (I & II) and HPA (III) Axes*.




**Note.** Both the CeA (I) and the PVN (II) innervate the RVLM which is involved in the activation of the adrenal medulla, via the spinal cord. The adrenal medulla secretes epinephrine and norepinephrine triggering an immediate but transient response to stressors. Also, the CeA projects to HPT (III) which in turn innervates the pituitary. The stimulation of the pituitary gland activates the adrenal cortex which secretes aldosterone and cortisol into the bloodstream initiating a delayed but prolonged response to stressors. Besides that, CeA inhibits the activity of vagal motor neurons in the NA and the DVN (IV), and thus reduces parasympathetic input. Moreover, CeA minimizes the parasympathetic input of the NTS (V) which in turn reduces CVLM's inhibitory input to the sympathetic neurons of the RVLM. The inhibition of parasympathetic neurons and simultaneous disinhibition of sympathetic neurons lead to increases in physiological arousal. CeA: central nucleus of the amygdala; BLA: basolateral amygdala; SAM: sympathetic-adrenal-medullary axis; HPA: hypothalamic-pituitary-adrenal axis; PVN: paraventricular nucleus of the hypothalamus; RVLM: rostral ventrolateral medulla; HPT: hypothalamus; NTS: nucleus of the solitary tract; CVLM: caudal ventrolateral medulla; NA: nucleus ambiguous; DVN: dorsal vagal motor nucleus.

Despite the vasodilation effect of low circulating epinephrine, high circulating concentrations shifts the balance of vasodilator and vasoconstrictor actions to net vasoconstriction (Klabunde, 2021). Similarly, norepinephrine increases cardiac output and systemic vascular resistance, resulting in an elevation in arterial blood pressure (Smith & Maani, 2020).

Moreover, the CeA minimizes parasympathetic input by simultaneously inhibiting vagal motor neurons in the nucleus ambiguous (NA) and the dorsal vagal motor nucleus (DVN). Furthermore, the CeA inhibits the parasympathetic input of the nucleus of the solitary tract (NTS). This in turn, minimizes inhibitory caudal ventrolateral medullary (CVLM) inputs to the sympathetic neurons of the RVLM. The simultaneous disinhibition of sympathetic neurons, and the inhibition of parasympathetic neurons, leads to an increase in physiological arousal resulting in elevated heart rate (HR) and a concomitant decrease of VM-HRV.

All of these responses promote physiological arousal in an effort to facilitate an individual's ability to withstand the stressor experienced, and thus adapt and thrive in a particular environment. The brain monitors the levels of cortisol secreted and once these rise, it terminates the secretion of CRH and ACTH completing the stress response cycle (Harbuz & Lightman, 1992; Tsigos & Chrousos, 2002). This negative feedback loop is designed to limit long-term exposure to cortisol's catabolic and immunosuppressive actions (Guilliams & Edwards, 2010).

## Heart Rate Variability: Integrating Stressors and Physiological Reactivity

Physiological arousal responses, including increases in blood pressure, are governed by the sympathetic division of the autonomic nervous system (ANS) and the associated SAM and HPA axes. The reciprocal interconnection between CAN's neural structures allows the prefrontal cortex (PFC) to inhibit subcortical structures, and thus the individual to respond to environmental pressures or demands in an effective manner (see Figure 2). Indeed, the sympathetic output of the CAN is under tonic inhibitory control via prefrontal cortical areas, including the medial prefrontal cortex (mPFC) and the orbitofrontal cortex (OFC), that inhibit the amygdala via networks of gabaminergic neurons (Gianaros & Wager, 2015; Shekhar et al., 2003; Thayer et al., 2009). Attenuation of PFC activity, via basolateral amygdala (BLA; Dilgen et al., 2013; Park et al., 2018), leads to disinhibition of the CeA that can directly activate the hypothalamus and sympathetic RVLM neurons.

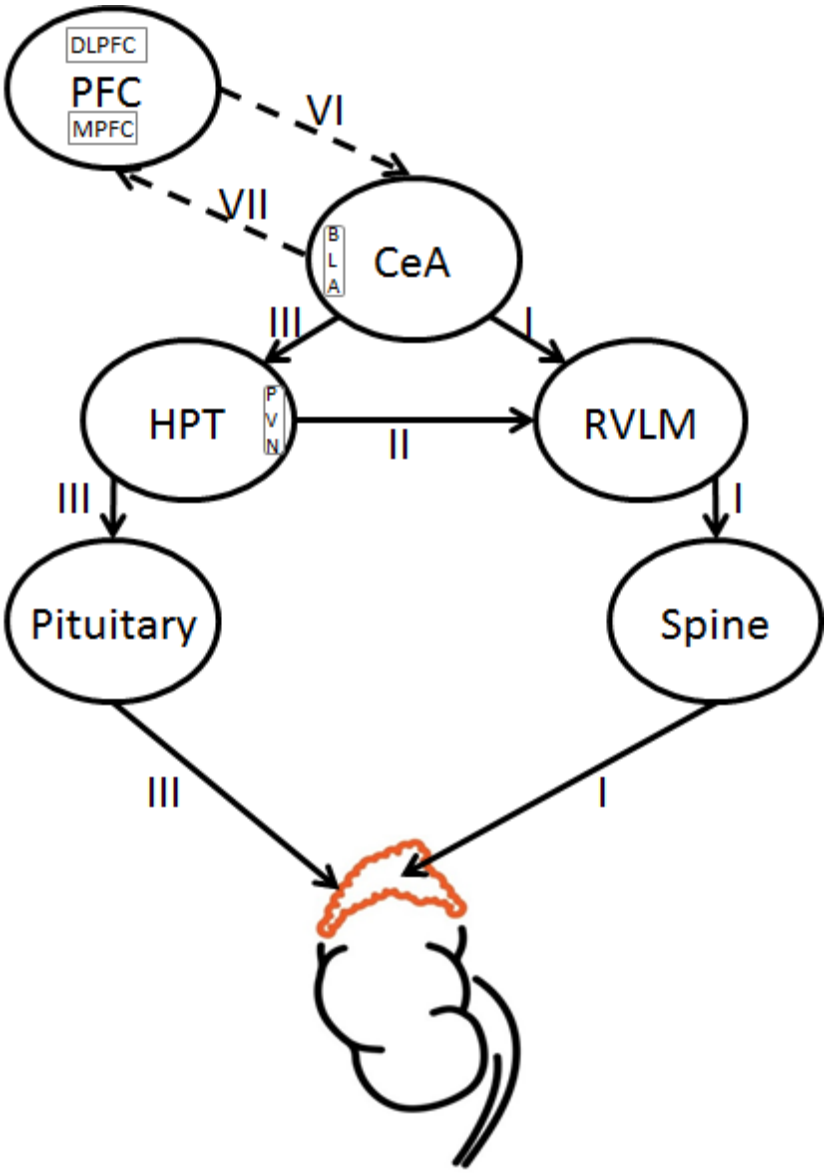
Evidence from relevant research supports the role of the PFC in the control of sympathetic neurons within the CAN, and thus cardiac output. For example, the deactivation of the PFC via intracarotid administration of sodium amobarbital led to increases in HR and concomitant decreases in VM-HRV (Ahern et al., 2001). Moreover, functional magnetic resonance imaging (fMRI) aiming to localize the central command network for induced cardiovagal activity indicated a positive correlation between VM-HRV and the dorsolateral PFC (Napadow et al., 2008). Likewise, fMRI paradigms examining the brain–heart interaction in a purely resting-state condition highlighted ventromedial PFC's role in the cortical generation of efferent vagal activity (Duggento et al., 2016; Ziegler et al., 2009).

Taken together, these evidences support the role of the PFC in the modulation of subcortical cardio-acceleratory circuits via an inhibitory pathway that is associated with vagal function that can be indexed by VM-HRV. Within this context, VM-HRV signifies the extent of the deactivation of the PFC, and thus the disinhibition of CAN's sympathetic input. As such, VM-HRV integrates stressors with individuals' reactivity capturing a prominent biological mechanism through which stressors impact health.

## Heart Rate Variability: Indexing Autonomic Imbalance and Hypertension

Lack of balance between the sympathetic and parasympathetic branches of the ANS minimizes the dynamic flexibility of the organism (Friedman & Thayer, 1998). An autonomic imbalance in which typically the sympathetic system is hyperactive and the parasympathetic system is hypoactive is associated with various risk factors and pathological conditions (Thayer et al., 2010). HRV can be used to assess such autonomic imbalances. For example, various measures of HRV have been successfully used to assess vagal activity (Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology, 1996). HRV measures in the time domain, including the standard deviation of R to R intervals (SDNN) and the root mean square successive differences (RMSSD), have been shown to be effective indices of vagal activity. Similarly, in the frequency domain, high frequency (HF: 0.15–0.40 Hz) spectral power has been successfully used to index vagal activity.

**Figure 2.** *Schematic Representation of PFC Inhibitory Influence on the CeA.*




**Note.** The sympathetic output of the CeA is under tonic inhibitory control from the PFC (VI), including the mPFC and the OFC. The reduction of PFC's inhibitory input to the CeA as a result of the activation of the BLA (VII) leads to the activation of the SAM and HPA axes (CeA's influences on SAM and HPA axes, I to III, are described in Figure 1).

The relationship between autonomic imbalances and hypertension is documented in both cross-sectional and prospective studies. For instance, prospective studies that examined the association between two minutes of supine HRV and hypertension over a 3-year follow-up period in a stratified random sample of 2061 black and white men and women from the Atherosclerosis Risk in Communities (ARIC) study reported an inverse relationship between HF-HRV and the development of hypertension (Liao et al., 1996). Those in the lowest HRV quartile had 2.44 greater risk of hypertension than those in the highest quartile. Additionally, cross-sectional analyses, adjusted for age, race, gender, smoking, diabetes, and education, indicated that the power of HF-HRV was significantly lower in both treated and untreated hypertensives compare to the normotensive group. Liao et al. (1996) results indicating that VM-HRV is

lower in pharmacologically treated hypertensives compared to normotensives are in line with relevant research (Cowan et al., 1993; Mussalo et al., 2001). In addition, prospective analyses over longer follow-up periods that examined the relationship between RMSSD and hypertension in 7099 men and women from the ARIC study reported that the lowest quartile of HRV adjusted for age, race, study center, diabetes, smoking, education, and BMI was associated with a hazard ratio of 1.36 for the development of hypertension 9 years later, compared to those in the highest quartile (Schroeder et al., 2003). Consistent with Liao et al. (1996) and Schroeder et al. (2003), cross-sectional analyses showed that HRV adjusted for relevant covariates was lower at baseline among individuals with hypertension.

Likewise, cross-sectional analyses examining the association between 2 hours of ambulatory HR recordings and hypertension in men and women participating in the Framingham Heart Study reported significantly lower HRV in hypertensives than in normotensives after adjusting for age, BMI, smoking, and alcohol consumption (Singh et al., 1998). More recent cross-sectional examinations of the relationship between VM-HRV and hypertension utilizing 5-min supine recordings reported similar results suggesting significantly lower VM-HRV in individuals displaying high blood pressure compared to normotensive groups (Goit & Ansari, 2016; Natarajan et al., 2014; Pal et al., 2011).

The aforementioned results from large-scale, prospective and cross-sectional epidemiological studies provide substantial evidence suggesting that decreases in parasympathetic input, as measured by VM-HRV, precedes the development of hypertension which is considered as the single most important risk factor for cardiovascular disease. In addition, these studies indicate that parasympathetic input, as indexed via VM-HRV, is lower in hypertensives than in normotensives even when these patients are treated with antihypertensive pharmacotherapy.

## Addressing Autonomic Imbalances Associated with Hypertension

Self-regulation techniques, like heart rate variability biofeedback (HRVB), and neuromodulation techniques, like cranial electrotherapy stimulation (CES), have been successfully used to improve VM-HRV, and therefore autonomic imbalances which correlate with increased mortality and poor functional outcomes including elevated human arterial hypertension.

### Heart Rate Variability Biofeedback

HRVB enables individuals to learn how to alter, and thus self-regulate, the variability and dominant rhythms of the cardiac function inducing beneficial adjustments in VM-HRV indices (Lehrer & Gevirtz, 2014). For example, a recent randomized controlled trial pointed out that HRVB increased VM-HRV indices in acute ischemic stroke patients that displayed autonomic deregulation, including cardiac autonomic dysfunction compared to sham biofeedback (Siepmann et al., 2021). As expected, patients included in the active HRVB condition also benefited from significant reductions in autonomic symptoms. Such changes in observed indices of VM-HRV following HRVB are associated with enhancements in functional connectivity between CAN's neural structures exerting prefrontal control and those responsible for its sympathetic output. For instance, the resting state functional connectivity between vmPFC and the amygdala was strengthened following HRVB (Schumann et al., 2021).

Despite the aforementioned, systematic reviews examining the effects of HRVB on hypertension produced inconsistent results (Costa Vital et al., 2021; Greenhalgh et al., 2010; Nagele et al., 2014; Nakao et al., 2003). The majority of these studies reported high heterogeneity highlighting differences in interventions and inconsistencies in the measurement of outcomes observed that prevented the characterization of the evidence for the association between HRVB and hypertension.

One important aspect contributing to the observed heterogeneity is the preexisting and concurrent use of antihypertensive pharmacotherapy along HRVB interventions (Linden & Chambers, 1994). This limits the potential effects of the HRVB intervention as the blood pressure levels of pharmacologically treated participants are often low when starting HRVB (McGrady, 2010). In support, randomized, double blind, placebo-controlled studies that included patients that had already been treated pharmacologically found no significant effect of HRVB on hypertension (Landman et al., 2013). On the contrary, randomized control trials that either included only unmedicated outpatients or statistically controlled for the effects of antihypertensive pharmacotherapy reported significant decreases in hypertension following HRVB compared to active control (Nolan et al., 2010; Palomba et al., 2011). In addition, studies examining the nature of cardiovascular reactions following HRVB suggested that this intervention is beneficial for patients treated with antihypertensive pharmacotherapy as it leads to

pronounced reactivity of vagal mechanism (Poskotinova et al., 2013). This is of particular importance given that hypertensives treated pharmacologically still display significant decreases in VM-HRV compared to normotensives (Cowan et al., 1993; Liao et al., 1996; Mussalo et al., 2001).

Taken together, the abovementioned research findings pointed out that HRVB is able to increase indices of VM-HRV and enhance functional connectivity between CAN's neural structures exerting prefrontal control with those responsible for its sympathetic output. Such evidence suggested that HRVB is able to influence the neural mechanisms controlling blood pressure regulation. Given that the majority of patients with hypertension are already being treated pharmacologically, and having in mind that HRVB leads to pronounced reactivity of vagal mechanism even in patients treated pharmacologically, HRVB represents a promising intervention that should supplement pharmacotherapy. Besides this, patients with prehypertension may thus be the ideal population for HRVB, since their blood pressure is elevated, but not to a level that it would prompt the prescription of antihypertensive medication (McGrady, 2010).

### Cranial Electrotherapy Stimulation

Noninvasive brain stimulation techniques, like CES, deliver low-intensity (50 μA to 4 mA) electrical current via electrodes attached to anatomical positions around the head to modulate the activity of the central and/or peripheral nervous system. Neuromodulation techniques can be an effective method to regulate the cardiovascular system given that noninvasive brain stimulation can influence autonomic imbalances that lead to hypertension (Cogiamanian et al., 2010). In point of fact, recent randomized, double blind, placebo-controlled trials reported significant increases in indices of VM-HRV following noninvasive CES as compared to sham CES (Altemus, 2019).

Likewise, randomized control studies examining the effect of CES on hypertension produced encouraging results supporting the use of noninvasive brain stimulation for the treatment of hypertension. For example, the early use of CES neuromodulation methods in hypertensive patients within a clinical pre–post paradigm resulted in an enhancement of parasympathetic modulation of cardiovascular outcomes and significant decreases in mean arterial blood pressure that stabilized within the normal range (Podzolkov et al., 1992). In addition, the preoperative administration of CES to hypertensive patients scheduled for surgery resulted in substantial (3–4 mmHg), albeit statistically nonsignificant, decreases in arterial blood pressure (Kang et al., 2020). Moreover, a recent randomized controlled trial pointed out that CES leads to a significantly improved blood pressure profile via the regulation of systolic and diastolic blood pressure (Mohammadi et al., in press).

On the whole, studies examining the effect of CES highlighted its ability to improve VM-HRV and produced promising results regarding its use for the treatment of hypertension. However, the limited number of relevant studies accounting for the floor effect created by antihypertensive pharmacotherapy and the observed variation in CES interventions, including target sites, obscures CES's effect on hypertension. As such, further studies are necessary to elucidate the association between CES and hypertension.

## Conclusion

The physiological substrates of the stress response, including prefrontal control, HPA, and SAM axes, support its role in the development and progression of hypertension. However, the examination of the relationship between exposure to stressors and hypertension was unsuccessful in confirming the underlying hypotheses in a decisive manner. Systematic reviews examining the effect of psychosocial stressors and anxiety on hypertension produced spurious results. The variability in the operationalization of stress and subsequent reactivity in these studies meant that relevant meta-analytic efforts suffered from strong heterogeneity that hindered the characterization of the evidence for the association between exposure, subsequent physiological reactivity, and risk for hypertension. This is of paramount importance as physiological reactivity to stressors constitutes a biological interface mechanism through which stressors affect blood pressure regulation.

The neural substrates of VM-HRV indicate that it is able to assimilate such an interfacing mechanism. In support, large-scale prospective and cross-sectional epidemiological studies provided substantial evidence linking decreases in VM-HRV with the development and progression of hypertension, hence indicating that individuals' reactivity to stressors, as measured via VM-HRV, amplify individuals' risk for the development and progression of hypertension. Within this context, VM-HRV can reinforce current screening initiatives in predicting future risk of hypertension and support treatment related prognosis.

Self-regulation techniques, like HRVB, and neuromodulation techniques, like CES, are able to enhance VM-HRV, and therefore the parasympathetic modulation of cardiovascular outcomes, thereby addressing autonomic imbalances associated with hypertension. Relevant evidence suggested that HRVB should supplement pharmacotherapy in hypertensive patients and be considered as a first line treatment for prehypertension. Similarly, neuromodulation methods, like CES, produced promising results for the treatment of hypertension. However, further studies are needed to clarify the observed relationship between CES and hypertension.

## Author Declaration

The author received no financial support for the research, authorship, and/or publication of this article.

The author declares no conflict of interest.

## References

Ahern, G. L., Sollers, J. J., Lane, R. D., Labiner, D. M., Herring, A. M., Weinand, M. E., Hutzler, R., & Thayer, J. F. (2001). Heart rate and heart rate variability changes in the intracarotid sodium amobarbital test. *Epilepsia, 42*(7), 912–921. https://doi.org/10.1046/j.1528-1157.2001.042007912.x

Altemus, M. (2019). *Effect of cranial electrical stimulation (CES) on autonomic regulation*. U.S National Library of Medicine. https://clinicaltrials.gov/ct2/show/results/NCT02163967

Badoer, E. (2001). Proceedings of the Australian physiological and pharmacological society symposium: The hypothalamus hypothalamic paraventricular nucleus and cardiovascular regulation. *Clinical and Experimental Pharmacology and Physiology, 28*(1–2), 95–99. https://doi.org/10.1046/j.1440-1681.2001.03413.x

Benarroch, E. E. (1993). The central autonomic network: Functional organization, dysfunction, and perspective. *Mayo Clinic Proceedings, 68*(10), 988–1001. https://doi.org/10.1016/S0025-6196(12)62272-1

Boehme, A. K., Esenwa, C., & Elkind, M. S.V. (2017). Stroke risk factors, genetics, and prevention. *Circulation Research, 120*(3), 472–495. https://doi.org/10.1161/CIRCRESAHA.116.308398

Briet, M., & Schiffrin, E. L. (2013). Vascular actions of aldosterone. *Journal of Vascular Research, 50*(2), 89–99. https://doi.org/10.1159/000345243

Brillon, D. J., Zheng, B., Campbell, R. G., & Matthews, D. E. (1995). Effect of cortisol on energy expenditure and amino acid metabolism in humans. *American Journal of Physiology–Endocrinology and Metabolism, 268*(3), E501–E513. https://doi.org/10.1152/ajpendo.1995.268.3.E501

Brown, E. G., Gallagher, S., & Creaven, A.-M. (2018). Loneliness and acute stress reactivity: A systematic review of psychophysiological studies. *Psychophysiology, 55*(5), e13031. https://doi.org/10.1111/psyp.13031

Bruno, R. M., Di Pilla, M., Ancona, C., Sørensen, M., Gesi, M., Taddei, S., Munzel, T., & Virdis, A. (2017). Environmental Factors and Hypertension. *Current Pharmaceutical Design, 23*(22), 3239–3246. https://doi.org/10.2174/1381612823666170321162233

Cogiamanian, F., Brunoni, A. R., Boggio, P. S., Fregni, F., Ciocca, M., & Priori, A. (2010). Non-invasive brain stimulation for the management of arterial hypertension. *Medical Hypotheses, 74*(2), 332–336. https://doi.org/10.1016/j.mehy.2009.08.037

Costa Vital, J. E., de Morais Nunes, A., Souza de Albuquerque Cacique New York, B., Araujo de Sousa, B. D., Nascimento, M. F., Formiga, M. F., & Fernandes, A. T. N. S. F. (2021). Biofeedback therapeutic effects on blood pressure levels in hypertensive individuals: A systematic review and meta-analysis. *Complementary Therapies in Clinical Practice, 44*, 101420. https://doi.org/10.1016/j.ctcp.2021.101420

Cowan, M. J., Pike, K., Burr, R. L., Cain, K. C., & Narayanan, S. B. (1993). Description of time- and frequency-domain-based measures of heart rate variability in individuals taking antiarrhythmics, beta blockers, calcium channel blockers, and/or antihypertensive drugs after sudden cardiac arrest. *Journal of Electrocardiology, 26*(Suppl. 1–13).

Crosswell, A. D., & Lockwood, K. G. (2020). Best practices for stress measurement: How to measure psychological stress in health research. *Health Psychology Open, 7*(2). https://doi.org/10.1177/2055102920933072

Cuffee, Y., Ogedegbe, C., Williams, N. J., Ogedegbe, G., & Schoenthaler, A. (2014). Psychosocial risk factors for hypertension: An update of the literature. *Current Hypertension Reports, 16*(10), 483. https://doi.org/10.1007/s11906-014-0483-3

Dilgen, J., Tejeda, H. A., & O'Donnell, P. (2013). Amygdala inputs drive feedforward inhibition in the medial prefrontal cortex. *Journal of Neurophysiology, 110*(1), 221–229. https://doi.org/10.1152/jn.00531.2012

Duggento, A., Bianciardi, M., Passamonti, L., Wald, L. L., Guerrisi, M., Barbieri, R., & Toschi, N. (2016). Globally conditioned Granger causality in brain–brain and brain–heart interactions: A combined heart rate variability/ultra-high-field (7 T) functional magnetic resonance imaging study. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences, 374*(2067), 20150185. https://doi.org/10.1098/rsta.2015.0185

Freel, E. M., & Connell, J. M. C. (2004). Mechanisms of hypertension: The expanding role of aldosterone. *Journal of the American Society of Nephrology, 15*(8), 1993–2001. https://doi.org/10.1097/01.ASN.0000132473.50966.14

Friedman, B. H., & Thayer, J. F. (1998). Anxiety and autonomic flexibility: A cardiovascular approach. *Biological Psychology, 49*(3), 303–323. https://doi.org/10.1016/S0301-0511(98)00051-9

Gianaros, P. J., & Wager, T. D. (2015). Brain-body pathways linking psychological stress and physical health. *Current Directions in Psychological Science, 24*(4), 313–321. https://doi.org/10.1177/0963721415581476

Goit, R. K., & Ansari, A. H. (2016). Reduced parasympathetic tone in newly diagnosed essential hypertension. *Indian Heart Journal, 68*(2), 153–157. https://doi.org/10.1016/j.ihj.2015.08.003

Greenhalgh, J., Dickson, R., & Dundar, Y. (2010). Biofeedback for hypertension: A systematic review. *Journal of Hypertension, 28*(4), 644–652. https://doi.org/10.1097/HJH.0b013e3283370e20

Guilliams, T. G., & Edwards, L. (2010). Chronic stress and the HPA axis: Clinical assessment and therapeutic considerations. *The Standard, 9*(2), 1–12. https://www.pointinstitute.org/wp-content/uploads/2012/10/standard_v_9.2_hpa_axis.pdf

Harbuz, M. S., & Lightman, S. L. (1992). Stress and the hypothalamo-pituitary-adrenal axis: Acute, chronic and immunological activation. *Journal of Endocrinology, 134*(3), 327–339. https://doi.org/10.1677/joe.0.1340327

Heine, H., & Weiss, M. (1987). Life stress and hypertension. *European Heart Journal, 8*(Suppl. B), 45–55. https://doi.org/10.1093/eurheartj/8.suppl_B.45

Hu, G., Barengo, N. C., Tuomilehto, J., Lakka, T. A., Nissinen, A., & Jousilahti, P. (2004). Relationship of physical activity and body mass index to the risk of hypertension: A prospective study in Finland. *Hypertension, 43*(1), 25–30. https://doi.org/10.1161/01.HYP.0000107400.72456.19

Kang, H. W., Kim, H. J., Kim, W. Y., Min, W. K., Min, T. J., Lee, Y. S., & Kim, J. H. (2020). Effects of cranial electrotherapy stimulation on preoperative anxiety and blood pressure during anesthetic induction in patients with essential hypertension. *Journal of International Medical Research, 48*(8), 300060520939370. https://doi.org/10.1177/0300060520939370

Khani, S., & Tayek, J. A. (2001). Cortisol increases gluconeogenesis in humans: Its role in the metabolic syndrome. *Clinical Science, 101*(6), 739–747. https://doi.org/10.1042/cs20010180

Klabunde, R. E. (2021). Cardiovascular physiology concepts (3rd ed.). Netherlands: Wolters Kluwer.

Komesaroff, P. A., Funder, J. W., & Fuller, P. J. (1994). 6 Mineralocorticoid resistance. *Baillière's Clinical Endocrinology and Metabolism, 8*(2), 333–355. https://doi.org/10.1016/s0950-351x(05)80256-3

Kushibiki, M., Yamada, M., Oikawa, K., Tomita, H., Osanai, T., & Okumura, K. (2007). Aldosterone causes vasoconstriction in coronary arterioles of rats via angiotensin II type-1 receptor: Influence of hypertension. *European Journal of Pharmacology, 572*(2–3), 182–188. https://doi.org/10.1016/j.ejphar.2007.06.017

Landman, G. W. D., Drion, I., van Hateren, K. J. J., van Dijk, P. R., Logtenberg, S. J. J., Lambert, J., Groenier, K. H., Bilo, H. J. G., & Kleefstra, N. (2013). Device-guided breathing as treatment for hypertension in type 2 diabetes mellitus: A randomized, double-blind, sham-controlled trial. *JAMA Internal Medicine, 173*(14), 1346–1350. https://doi.org/10.1001/jamainternmed.2013.6883

LeDoux, J. E., Iwata, J., Cicchetti, P., & Reis, D. J. (1988). Different projections of the central amygdaloid nucleus mediate autonomic and behavioral correlates of conditioned fear. *The Journal of Neuroscience, 8*(7), 2517–2529. https://doi.org/10.1523/JNEUROSCI.08-07-02517.1988

Lehrer, P. M., & Gevirtz, R. (2014). Heart rate variability biofeedback: How and why does it work? *Frontiers in Psychology, 5*, 756. https://doi.org/10.3389/fpsyg.2014.00756

Liao, D., Cai, J., Barnes, R. W., Tyroler, H. A., Rautaharju, P., Holme, I., & Heiss, G. (1996). Association of cardiac autonomic function and the development of hypertension: The ARIC study. *American Journal of Hypertension, 9*(12), 1147–1156. https://doi.org/10.1016/s0895-7061(96)00249-x

Linden, W., & Chambers, L. (1994). Clinical effectiveness of non-drug treatment for hypertension: A meta-analysis. *Annals of Behavioral Medicine, 16*(1), 35–45. https://doi.org/10.1093/abm/16.1.35

Liu, M.-Y., Li, N., Li, W. A., & Khan, H. (2017). Association between psychosocial stress and hypertension: A systematic review and meta-analysis. *Neurological Research, 39*(6), 573–580. https://doi.org/10.1080/01616412.2017.1317904

Lynch, S. M., Ward, M., McNulty, H., Angel, C. Z., Horigan, G., Strain, J. J., Purvis, J., Tackett, M., & McKenna, D. J. (2020). Serum levels of miR-199a-5p correlates with blood pressure in premature cardiovascular disease patients homozygous for the MTHFR 677C > T polymorphism. *Genomics, 112*(1), 669–676. https://doi.org/10.1016/j.ygeno.2019.04.019

Mann, S. J. (2012). Psychosomatic research in hypertension: The lack of impact of decades of research and new directions to consider. *The Journal of Clinical Hypertension, 14*(10), 657–664. https://doi.org/10.1111/j.1751-7176.2012.00686.x

McGrady, A. (2010). The effects of biofeedback in diabetes and essential hypertension. *Cleveland Clinic Journal of Medicine, 77*(7 Suppl. 3), S68–S71. https://doi.org/10.3949/ccjm.77.s3.12

Mohammadi, R., Javanmard, G. H., Alipour, A., & Zare, H. (in press). Effects of mindful breath awareness and muscle relaxation and transcranial electrical stimulation techniques on improving blood pressure status in patients with type 2 diabetes. *EXPLORE*. https://doi.org/10.1016/j.explore.2021.05.002

Mussalo, H., Vanninen, E., Ikäheimo, R., Laitinen, T., Laakso, M., Länsimies, E., & Hartikainen, J. (2001). Heart rate variability and its determinants in patients with severe or mild essential hypertension. *Clinical Physiology, 21*(5), 594–604. https://doi.org/10.1046/j.1365-2281.2001.00359.x

Nagele, E., Jeitler, K., Horvath, K., Semlitsch, T., Posch, N., Herrmann, K. H., Grouven, U., Hermanns, T., Hemkens, L. G., & Siebenhofer, A. (2014). Clinical effectiveness of stress-reduction techniques in patients with hypertension: Systematic review and meta-analysis. *Journal of Hypertension, 32*(10), 1936–1944. https://doi.org/10.1097/HJH.0000000000000298

Nakao, M., Yano, E., Nomura, S., & Kuboki, T. (2003). Blood pressure-lowering effects of biofeedback treatment in hypertension: A meta-analysis of randomized controlled trials. *Hypertension Research, 26*(1), 37–46. https://doi.org/10.1291/hypres.26.37

Napadow, V., Dhond, R., Conti, G., Makris, N., Brown, E. N., & Barbieri, R. (2008). Brain correlates of autonomic modulation: Combining heart rate variability with fMRI. *NeuroImage, 42*(1), 169–177. https://doi.org/10.1016/j.neuroimage.2008.04.238

Natarajan, N., Balakrishnan, A. K., & Ukkirapandian, K. (2014). A study on analysis of Heart Rate Variability in hypertensive individuals. *International Journal of Biomedical and Advance Research, 5*(2), 109–111. https://doi.org/10.7439/ijbar.v5i2.659

Nolan, R. P., Floras, J. S., Harvey, P. J., Kamath, M. V., Picton, P. E., Chessex, C., Hiscock, N., Powell, J., Catt, M., Hendrickx, H., Talbot, D., & Chen, M. H. (2010). Behavioral neurocardiac training in hypertension: A randomized, controlled trial. *Hypertension, 55*(4), 1033–1039. https://doi.org/10.1161 /HYPERTENSIONAHA.109.146233

Ornosa-Martín, G., Fernandez-Ballart, J. D., Ceruelo, S., Ríos, L., Ueland, P. M., Meyer, K., & Murphy, M. M. (2020). Homocysteine, the methylenetetrahydrofolate reductase 677C>T polymorphism and hypertension: Effect modifiers by lifestyle factors and population subgroups. *British Journal of Nutrition, 124*(1), 69–79. https://doi.org/10.1017/S0007114520000793

Pal, G. K., Adithan, C., Amudharaj, D., Dutta, T. K., Pal, P., Nandan, P. G., & Nanda, N. (2011). Assessment of sympathovagal imbalance by spectral analysis of heart rate variability in prehypertensive and hypertensive patients in Indian population. *Clinical and Experimental Hypertension, 33*(7), 478–483. https://doi.org/10.3109/10641963.2010.549275

Palomba, D., Ghisi, M., Scozzari, S., Sarlo, M., Bonso, E., Dorigatti, F., & Palatini, P. (2011). Biofeedback-assisted cardiovascular control in hypertensives exposed to emotional stress: A pilot study. *Applied Psychophysiology and Biofeedback, 36*(3), 185–192. https://doi.org/10.1007/s10484-011-9160-3

Park, A. T., Leonard, J. A., Saxler, P. K., Cyr, A. B., Gabrieli, J. D. E., & Mackey, A. P. (2018). Amygdala–medial prefrontal cortex connectivity relates to stress and mental health in early childhood. *Social Cognitive and Affective Neuroscience, 13*(4), 430–439. https://doi.org/10.1093/scan/nsy017

Player, M. S., & Peterson, L. E. (2011). Anxiety disorders, hypertension, and cardiovascular risk: A review. *The International Journal of Psychiatry in Medicine, 41*(4), 365–377. https://doi.org/10.2190/PM.41.4.f

Podzolkov, V. I., Mel'nikova, T. S., Suvorova, I. A., Churganova, L. I., & Starovoĭtova, S. P. (1992). [Cranial

electrostimulation—A new nondrug method of treating the initial stage of hypertension]. *Terapevticheskii Arkhiv, 64*(1), 24–27.

Poskotinova, L. V., Demin, D. B., Krivonogova, E. V., Dieva, M. N., & Khasnova, N. M. (2013). [The success of heart rate variability biofeedback parameters in persons with different levels of blood pressure]. *Vestnik Rossiiskoi Akademii Meditsinskikh Nauk, 7*, 20–23.

Saha, S., Drinkhill, M. J., Moore, J. P., & Batten, T. F. C. (2005). Central nucleus of amygdala projections to rostral ventrolateral medulla neurones activated by decreased blood pressure. *The European Journal of Neuroscience, 21*(7), 1921–1930. https://doi.org/10.1111/j.1460-9568.2005.04023.x

Schroeder, E. B., Liao, D., Chambless, L. E., Prineas, R. J., Evans, G. W., & Heiss, G. (2003). Hypertension, blood pressure, and heart rate variability: The Atherosclerosis Risk in Communities (ARIC) study. *Hypertension, 42*(6), 1106–1111. https://doi.org/10.1161/01.HYP.0000100444.71069.73

Schumann, A., de la Cruz, F., Köhler, S., Brotte, L., & Bär, K.-J. (2021). The influence of heart rate variability biofeedback on cardiac regulation and functional brain connectivity. *Frontiers in Neuroscience, 15*, 691988. https://doi.org/10.3389/fnins.2021.691988

Selye, H. (1956). *The Stress of Life*. New York, NY: McGraw-Hill.

Shekhar, A., Sajdyk, T. J., Gehlert, D. R., & Rainnie, D. G. (2003). The amygdala, panic disorder, and cardiovascular responses. *Annals of the New York Academy of Sciences, 985*(1), 308–325. https://doi.org/10.1111/j.1749-6632.2003.tb07090.x

Siepmann, T., Ohle, P., Sedghi, A., Simon, E., Arndt, M., Pallesen, L.-P., Ritschel, G., Barlinn, J., Reichmann, H., Puetz, V., & Barlinn, K. (2021). Randomized sham-controlled pilot study of neurocardiac function in patients with acute ischaemic stroke undergoing heart rate variability biofeedback. *Frontiers in Neurology, 12*, 669843. https://doi.org/10.3389/fneur.2021.669843

Singh, A., Babyak, M. A., Nolan, D. K., Brummett, B. H., Jiang, R., Siegler, I. C., Kraus, W. E., Shah, S. H., Williams, R. B., & Hauser, E. R. (2015). Gene by stress genome-wide interaction analysis and path analysis identify *EBF1* as a cardiovascular and metabolic risk gene. *European Journal of Human Genetics, 23*(6), 854–862. https://doi.org/10.1038/ejhg.2014.189

Singh, J. P., Larson, M. G., Tsuji, H., Evans, J. C., O'Donnell, C. J., & Levy, D. (1998). Reduced heart rate variability and new-onset hypertension: Insights into pathogenesis of hypertension: the Framingham Heart Study. *Hypertension, 32*(2), 293–297. https://doi.org/10.1161/01.hyp.32.2.293

Smith, M. D., & Maani, C. V. (2020). Norepinephrine. In *StatPearls* [Internet]. Treasure Island, FL: StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK537259/

Sparrenberger, F., Cichelero, F. T., Ascoli, A. M., Fonseca, F. P., Weiss, G., Berwanger, O., Fuchs, S. C., Moreira, L. B., & Fuchs, F. D. (2009). Does psychosocial stress cause hypertension? A systematic review of observational studies. *Journal of Human Hypertension, 23*(1), 12–19. https://doi.org/10.1038/jhh.2008.74

Špinar, J. (2012). Hypertension and ischemic heart disease. *Cor et Vasa, 54*(11), e433–e438. https://doi.org/10.1016/j.crvasa.2012.11.002

Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology. (1996). Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. *Circulation, 93*(5), 1043–1065. https://doi.org/10.1161/01.CIR.93.5.1043

Thayer, J. F., Hansen, A. L., Saus-Rose, E., & Johnsen, B. H. (2009). Heart rate variability, prefrontal neural function, and cognitive performance: The neurovisceral integration perspective on self-regulation, adaptation, and health. *Annals of Behavioral Medicine, 37*(2), 141–153. https://doi.org/10.1007/s12160-009-9101-z

Thayer, J. F., Yamamoto, S. S., & Brosschot, J. F. (2010). The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *International Journal of Cardiology, 141*(2), 122–131. https://doi.org/10.1016/j.ijcard.2009.09.543

Tsigos, C., & Chrousos, G. P. (2002). Hypothalamic–pituitary–adrenal axis, neuroendocrine factors and stress. *Journal of Psychosomatic Research, 53*(4), 865–871. https://doi.org/10.1016/S0022-3999(02)00429-4

Vos, T., Lim, S. S., Abbafati, C., Abbas, K. M., Abbasi, M., Abbasifard, M., Abbasi-Kangevari, M., Abbastabar, H., Abd-Allah, F., Abdelalim, A., Abdollahi, M., Abdollahpour, I., Abolhassani, H., Aboyans, V., Abrams, E. M., Abreu, L. G., Abrigo, M. R. M., Abu-Raddad, L. J., Abushouk, A. I., Acebedo, A., … Murray, C. J. L. (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *The Lancet, 396*(10258), 1204–1222. https://doi.org/10.1016/S0140-6736(20)30925-9

Wajngarten, M., & Silva, G. S. (2019). Hypertension and stroke: Update on treatment. *European Cardiology Review, 14*(2), 111–115. https://doi.org/10.15420/ecr.2019.11.1

Xanthakis, V., & Vasan, R. S. (2013). Aldosterone and the risk of hypertension. *Current Hypertension Reports, 15*(2), 102–107. https://doi.org/10.1007/s11906-013-0330-y

Xu, Y., Day, T. A., & Buller, K. M. (1999). The central amygdala modulates hypothalamic–pituitary–adrenal axis responses to systemic interleukin-1β administration. *Neuroscience, 94*(1), 175–183. https://doi.org/10.1016/S0306-4522(99)00311-5

Ziegler, G., Dahnke, R., Yeragani, V. K., & Bär, K.-J. (2009). The relation of ventromedial prefrontal cortex activity and heart rate fluctuations at rest. *The European Journal of Neuroscience, 30*(11), 2205–2210. https://doi.org/10.1111/j.1460-9568.2009.07008.x

**Received:** July 14, 2021
**Accepted:** September 10, 2021
**Published:** September 30, 2021