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Exploration of Brain Network Measures Across Three Meditation Traditions

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Abstract

Research into the similarities and differences between various forms of meditation practice is still in its early stages. Here, utilizing functional connectivity and graph measures, we present our work examining three meditation traditions: Himalayan Yoga (HT), Isha Shoonya (SNY), and Vipassana (VIP). EEG activity of the meditative block is used to build functional brain connections to exploit the resulting networks between various meditation traditions and a control group. Support vector machine is employed for binary classification, and models are built with features generated via graph theory measures. We obtain maximum accuracy of 84.76% with gamma1, 90% with alpha, and 84.76% with theta in HT, SNY, and VIP, respectively. Our key findings involve (a) higher delta connectivity in Vipassana meditators, (b) synchronization of theta networks in the left hemisphere inspected to be stronger in the anterior frontal area across meditators, (c) greater involvement of gamma2 processing observed among Himalayan and Vipassana meditators, (d) increased left frontal activity contribution for all meditators in theta and gamma bands, and (e) modularity engaged extensively in gamma processing across all meditation traditions. Furthermore, we discuss the implication of this research for neurotechnology products to enable guided meditation among naive practitioners.

Keywords: EEG signals; meditation; functional connectivity; graph measures; support vector machine; machine learning; brainwaves; Himalayan Yoga; Isha Shoonya; Vipassana

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Introduction

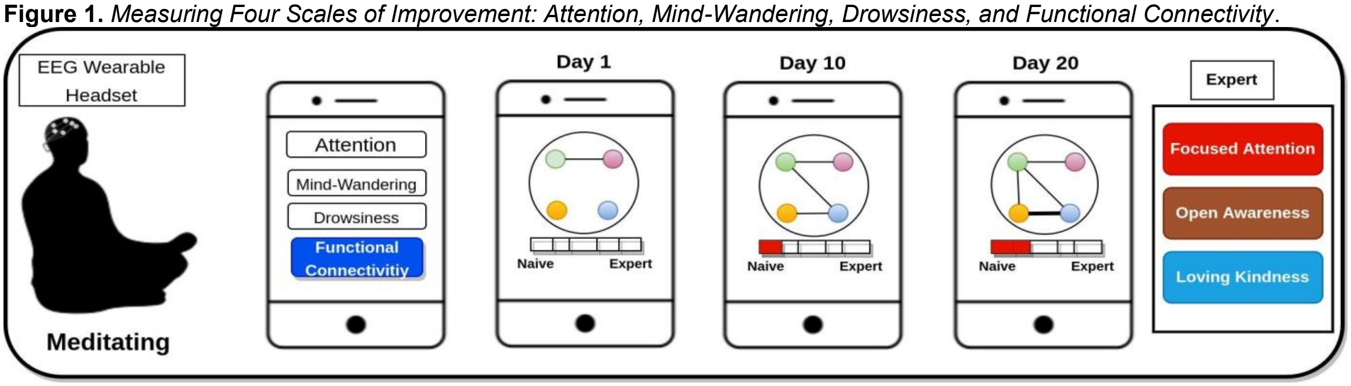
In recent years, neuroscientific research has focused on meditation as a mental practice. This is due to the large-scale benefit it offers, observed in numerous studies, such as improved attentional states, metacognitive awareness, cognitive control, compassion, self-regulation, decreased states of mind wandering, and so on (Brandmeyer & Delorme, 2018). Multiple studies determine how long- and short-term meditation practice (measured in hours of experience) impact the brain (in terms of neural oscillation and executive functioning tasks such as working memory). This approach is designed to integrate mindfulness-based practices like meditation in a clinical context to treat anxiety, depression, chronic pain, and stress (Yordanova et al., 2020). But most of the study misses out on the significance of each meditation type on distinct brain circuitry, frequency bands, and cognitive functions that is unique in itself and cannot be generalized fully to other types of meditation practices. As each meditation type can uniquely influence the person (both psychologically and physiologically) different meditation practices require careful observation and rigorous examination before making a causal interpretation and generalization. With neurotechnological advancements, meditation researchers are using electroencephalogram (EEG), functional magnetic resonance imaging (fMRI), magnetic resonance imaging (MRI), and single-photon emission computerized tomography (SPECT). EEG and fMRI techniques are commonly employed in meditation research. There are many types of meditation traditions practiced worldwide, for example, Himalayan Yoga (HT; focused attention), Vipassana (VIP; open monitoring) and Isha Shoonya (SNY; open awareness meditation), and Loving Kindness meditation.

Spectral analysis used in earlier studies on VIP revealed enhanced gamma activity over the parieto-occipital electrodes (Braboszcz et al., 2017; Cahn et al., 2010; van Lutterveld et al., 2017). Gamma band has been associated with cognitive processes such as attention, working memory, learning, consciousness, microsaccades, and visual imagery (Fries, 2009; Fries et al., 2007), and long-range neural communication (Nikolić et al., 2013). The sample entropy (SE) of VIP meditators was higher in the study by Vivot and colleagues (Vivot et al., 2020), especially in the alpha and low/high gamma bands. The alpha band (7–11 Hz) was identified to have a trait influence as observed in both the conditions of mind wandering and meditation in a recent study by (Braboszcz et al., 2017). According to studies on HT practitioners, their brainwaves are reported to have sensorimotor alpha, frontal-midline theta, and parieto-occipital gamma (Braboszcz et al., 2017; Brandmeyer & Delorme, 2018; Vivot et al., 2020). Working memory has linkages with alpha rhythms which are thought to be prevalent in HT meditation, since it emphasizes the mental repetition of the mantra and the breath (Braboszcz et al., 2017). SNY was linked to gamma frequency in the parieto-occipital, central, and frontal electrodes, according to a study by Braboszcz et al. (2017). Since the explicit focus is on "nothingness," it is unclear what kind of object is sent to the attentional system for SNY practitioners. Since higher gamma power over the frontal and parieto-occipital electrodes is demonstrated as a trait effect, this may indicate that SNY meditation engages attentional processes differently than VIP and HT meditation. According to the research by van Lutterveld et al. (2017), SNY meditators had greater separations in their thought charts observed using Hausdorff distance under the breath awareness condition. In the current study, the brain states connected to three crucial and distinctive types of meditation—HT, VIP, and SNY—are examined. This study's goal is to leverage functional network measurements to examine variations between control subjects and meditators on (a) frequency bands, (b) brain regions, (c) network measures, and (d) commonalities and discrepancies among mediators.

Complex network theory has recently gained prominence (Li & Yang, 2016). Research has demonstrated that EEG may be utilized to create brain networks that retain several crucial topological characteristics (Sun et al., 2019). The temporal correlation between distant neurophysiological events is often used to describe a functional connection in the brain (Friston, 1994). In recent decades, various neural coupling techniques have been put forth. Coherence (coh), a linear dependency measure between two nodes, has been used to assess functional connectivity (Jalili, 2016). However, coh is affected by volume conduction. Since volume conduction is likely to detect brain activity from the same sources, even if unrelated, it may result in incorrect correlations between nearby electrodes. To lessen the consequences of volume conduction, additional metrics have been incorporated. It has been shown that imaginary coherence (imcoh) can eliminate any instantaneous interactions that are caused by volume conduction (Nolte et al., 2004). The phase lag index (pli), a phase synchronization technique, is insensitive to the volume conduction effect and reveals the genuine coupling strength between pairs of channels by excluding interactions produced by zero phase differences (Stam et al., 2007). In the weighted phase lag index (wpli), a modification of the pli wherein observable phase leads and lags are weighted by the amplitude of the imaginary component of the cross-spectrum (Vinck et al., 2011). Corrected imaginary phase locking value (ciPLV), a metric for assessing synchronization in the presence of volume conduction or source leakage effects, was proposed by Bruña and colleagues (Bruña et al., 2018). We have used all five connectedness metrics because they can distinguish between functional networks that are similar and those that are distinct. Regardless of the coupling method, our main goal is to find the functional networks that discriminate between two groups.

Examining functional connectivity with various graph theoretical measures shows key topological characteristics of brain networks (Rubinov & Sporns, 2010). EEG/MEG, functional MRI, diffusion MRI, and structural MRI are just a few imaging modalities using graph theory analyses of human brain networks (He & Evans, 2010). Modularity, node betweenness, centrality, clustering coefficient, and the occurrence of highly connected hub regions are a few network features that have been addressed often (He & Evans, 2010; Sun et al., 2019; Wang et al., 2010). Additionally, it has been found that these network characteristics change over time under various conditions, such as normal development, aging, and pathological circumstances. Recent work by Hiroyasu and colleagues and a dearth of works on network modeling in meditation have shown how to categorize resting and meditative states using the centrality measure (Hiroyasu & Hiwa, 2017). In earlier research on long-term meditators, trait effects on meditators were examined (Braboszcz et al., 2017). These effects may indicate a change in the functional architecture of the human brain compared to controls. Our research examines the four network features between long-term practitioners of three meditation traditions and the control group. Machine learning classifiers are trained as the most practical method for spotting differences due to their strong pattern learning capabilities. Moreover, there has been a surge in studies using machine learning to categorize meditation states in recent years (Chaudhary et al., 2022; Pandey et al., 2022; Pandey & Miyapuram, 2020; Pandey & Miyapuram, 2021a, 2021c).

Figure 1. *Measuring Four Scales of Improvement: Attention, Mind-Wandering, Drowsiness, and Functional Connectivity*.



Note. A person is wearing an EEG headset while practicing meditation. Four scales of improvement can be examined on the mobile screen, and the last one indicates Functional Connectivity. Recording of Day 1 shows the initial connectivity. With progress in meditation, the application displays the change in connectivity after a few days and even explains the relation with the connectivity of expert meditators. This is an illustration generated by us to display the potential idea for neurotechnology.

Research and Technology Relevance

Cognitive Relevance

Years of neuroscience research have shown several advantages to meditation practice (Brandmeyer et al., 2019). A recent article offered a possible course of action with a unified framework (Dahl et al., 2020). The framework suggests awareness, connection, insight, and purpose as the four fundamental characteristics of well-being. The only way to acquire these qualities that offer direct access to one's well-being is through intentional mental training. A particular dimension denotes a specific method. A practitioner can, for instance, utilize concentrated attention to become aware of mind-wandering occurrences, maintain focus, and use loving kindness to cultivate fruitful relationships with others.

Neurotechnology

Many meditation applications are available to improve awareness and train attention (Migala, 2021). Since no feedback is provided, a novice practitioner feels pushed and gradually reduces their practice to the minimal effort until stopping altogether. Due to the availability of wearable EEG technology, the market has been able to create goods that can assist novice practitioners in learning meditation through real-time feedback and monitoring their progress over time, as demonstrated by the use of Muse and Neuphony meditation products. Here, we suggest a functional connectivity module enabling practitioners to see their incremental development and the changes in connectivity patterns that go along with it.

In Figure 1, three of the four modules can assess attention, daydreaming, and tiredness in real time. When the mind wanders, or a person feels sleepy, practitioners can receive immediate feedback so they can refocus on the meditation object. After some practice, people can evaluate their level of attention, the amount of time their minds wander, and whether they are awake or asleep while meditating. In the final module, users can compare their functional connectivity after a few sessions to that of potential specialists in various types of meditation. With the aid of neurotechnology, cognitive scientists, computer scientists, and signal processing experts can collaborate to identify the brain correlates of various stages of meditation. Therefore, it is conceivable to develop neural markers for various levels of meditation using signal processing and machine learning approaches.

Learning Representation

The most important step in separating the neural signals of experts and beginners so that neurofeedback can be implemented is through feature engineering. Robust feature extraction strategies are presented by deep learning and machine learning to categorize the various stages. Numerous articles from previous years have described the brain correlates of meditation. Pandey and Miyapuram describe a wavelet-based encoding of the oscillatory signature of meditators (Pandey & Miyapuram, 2020). In recent investigations, functional connectivity networks were examined to predict brain activity in meditators (Pandey et al., 2021). Convolutional neural networks are used to create a model that categorizes control and meditators' cognitive states (Pandey & Miyapuram, 2021b). The SHAP (Shapley Additive Explanations) explainable model, which employed three nonlinear dynamics to extract the significance of the scalp area, was used to analyze EEG data collected before and after mindfulness-based stress reduction (MBSR) training to determine the relevance of the data (Pandey & Miyapuram, 2021c). A recent study discusses and further categorizes various mental states associated with meditation using different machine learning approaches (Kora et al., 2021). Cognitive science and machine learning researchers have great potential to identify patterns and leverage them to create systems that can guide novice practitioners.

Data Description

Participants and Experimental Design

We used online open-access EEG data (Braboszcz et al., 2017). Data were collected at the Meditation Research Institute in Rishikesh, India, from 32 healthy control individuals and 20 meditators from the VIP school, and 27 meditators from the HT school, and 20 meditators from the SNY school. All meditators were chosen for the study based on their age, gender, and years of meditation practice. Control subjects were also selected for the study based on age, gender, and lack of meditation practice. Researchers wanted to investigate uniform groups of individuals for this study. Therefore, they constructed groups based on age and gender to match the individuals. As a result, there were four groups of 16 subjects in each meditation group: 16 controls (45 ± 10 years, five females), 16 HT meditators (43 ± 12 years, two females), 16 SNY meditators (40 ± 10 years, two females), and 16 VIP meditators (47 ± 15 years, five females). A single set of individuals was a control group for all three meditation traditions.

The experiment was divided into two 20-min sessions, one titled "Meditation" and the other "Instructed Mind Wandering." In the first 10 min of the Meditation block, subjects were instructed to focus on their breathing (breath focus or inhalation and exhalation) to prepare for their meditation practice. This task was used as a primitive practice period in all three meditation traditions to help people relax and deepen the depth of their meditation practice. After 10 min, they were notified to practice their specific meditation for the next 10 min. Both in the first and second half of the Meditation block, control participants were instructed to keep their focus on breath or inhalation and exhalation. In the Instructed Mind Wandering block, for the first 10 min, subjects were instructed to perform mind-wandering tasks, wherein they were asked to recall autobiographical events which were emotionally neutral such as routine childhood life, travels, etc. After the initial 10 min, they were directed to continue their instructed mind-wandering task for the next 10 min to preserve consistency with the Meditation condition. To avoid any order effects, the task sequence was counterbalanced; that is, in each of the meditation groups and control group, eight of the subjects either performed the mind-wandering task first or the meditation task first. In our study, we focused on comparing the second part of the Meditation block between controls (i.e., breath focus) and meditators (i.e., specific HT, VIP, SNY). We used preprocessed open access data, and preprocessing steps are mentioned in this article (Braboszcz et al., 2017). Participants all signed informed consent forms before participating. The Meditation Research Institute Indian ethical committee and University of California San Diego ethical committee approved the project (IRB project # 090731). Interested readers may refer to Braboszcz et al. (2017) for complete details.

Methods

Functional Connectivity

To create the functional connectivity matrix, we employed five coupling methods: coherence (coh), imaginary coherence (imcoh), phase lag index (pli), weighted phase lag index (wpli), and corrected imaginary phase-locking value (ciplv). We started from coh, the earliest measure of functional connectivity, to ciPLV, the latest measure, as every coupling method illustrates some similarities and differentiating synchronization patterns for the same dataset. In this study, we focus on capturing all the crucial connectivity relationships that can provide significant discrimination between control and meditator irrespective of the coupling method. Each brain connectivity preserves some network topology that can be scrutinized and reveal new insights into the meditative state. The subsection on spectral connectivity presents a brief description of five coupling methods (MNE, 2022). All the functional connectivity matrices were calculated every 5 s with a 2.5-s overlapping window for delta (1–4 Hz), theta (4–8 Hz), beta (8–12 Hz), alpha (12–20 Hz), gamma1 (20–60 Hz) and gamma2 (60–100 Hz) frequency bands along with regions described in Figure 2. Primarily four areas are left frontal (LF), right frontal (RF), left parietal (LP), and right parietal (RP). Based on these regions, intra- and interfunctional connectivity are computed. Bands are decided based on the recent article published on the same dataset (Vivot et al., 2020). Regions are determined based on the study discussing different meditation techniques (Yordanova et al., 2020).

Binarization of Brain Networks

The topology of functional networks is often obscured by faulty and weak connections (Sun et al., 2019). Thresholding, which involves removing a portion of the weakest links from the network, is a popular technique for maintaining a sparse network. However, deciding this threshold objectively remains inconclusive. In the recent work of De Vico Fallani and colleagues (De Vico Fallani et al., 2017), they introduce a criterion, the efficiency cost optimization (ECO), to identify the density threshold which filters the connections depending on the network size according to a power law. This method accentuates a network's intrinsic features while maintaining its sparsity. Hence, we used the ECO binarization method to remove the weak links. Obtained networks from coupling methods were binarized and quantitatively analyzed using graph theory measures.

Graph Theory Network Metrics

Several graph measures can characterize brain networks (Rubinov & Sporns, 2010). We computed functional segregation and integration measures of binary brain networks for each subject, including all coupling methods. The capacity for specialized processing to emerge within tightly interconnected clusters of brain regions is referred to as functional segregation. Functional integration in the brain quickly incorporates specialized information from various brain regions. We identified four widely employed network metrics. Functional integration metrics were node betweenness centrality (NB) and edge betweenness centrality (EBC). Functional segregation metrics were clustering coefficient (CC) and modularity (MU). The proportion of all shortest routes in a network that connects a particular vertex is known as NB, whereas the proportion of all shortest routes in the network that involves a particular edge is called EBC. Because the concept of betweenness centrality readily extends to linkages, it could be utilized to detect essential anatomical or functional connections. The CC is the number of triangles surrounding a node and is equal to the number of neighbors who are neighbors of each other. MU is a metric that measures how efficiently a network may be separated into distinct clusters. Mathematical equations and detailed explanations can be accessed in this paper (Rubinov & Sporns, 2010). Network measures were computed in a Matlab environment.

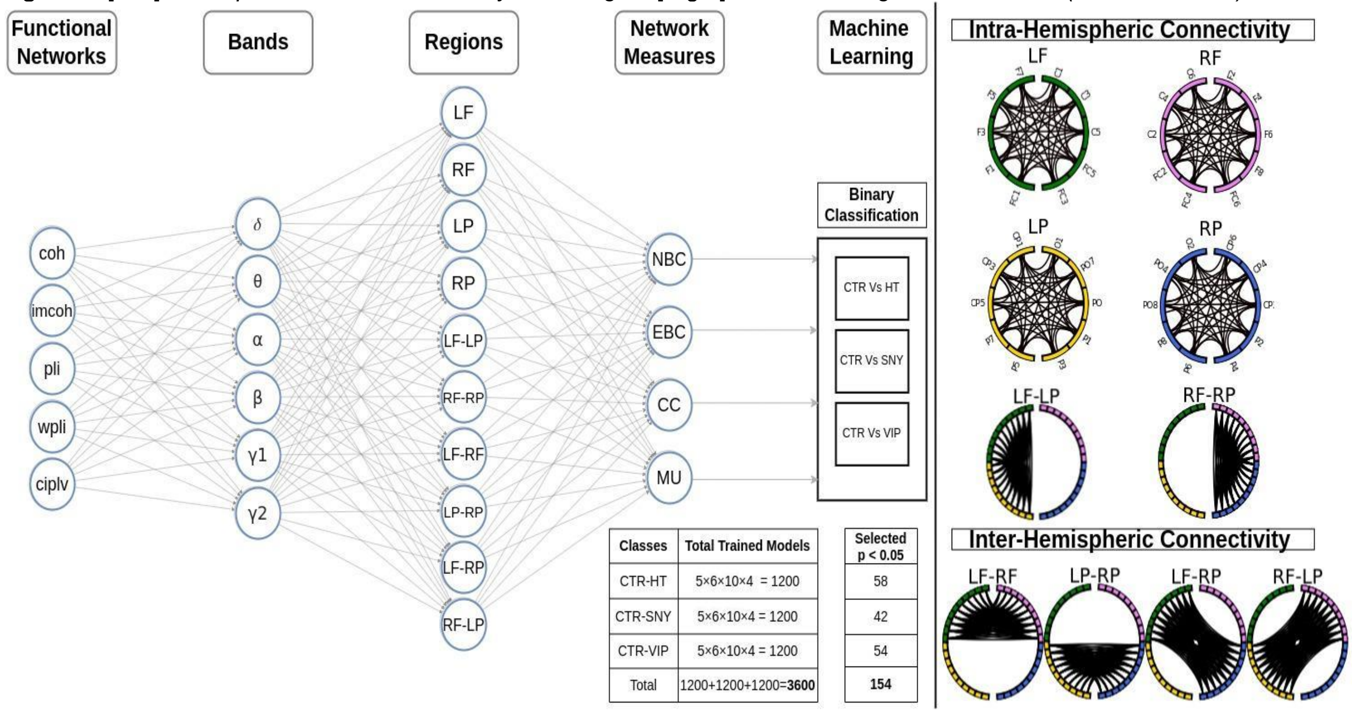
Machine Learning

Features generated from different network measures were used for classification. This study trained binary classifiers between the control and meditator groups. Support vector machine was selected for this research due to its well-established theory and more eloquent quality of easy interpretability. We trained models by tuning hyperparameters, and validation was performed using the 10-fold stratified technique. The classifier's performance was evaluated using accuracy, precision, recall, and F1 score. In line with this, we further assessed the statistical significance of the classifier using the permutation test with 10,000 rounds. Several articles have used this test (Ojala & Garriga, 2009) and discussed the effectiveness of the results via permutation tests. There were 1,200 models trained for each group encompassing connectivity methods, frequency bands, brain regions, and network measures. A total of 3,600 models were developed, of which only 154 models were selected based on the significance of $p < .05$, and division is provided in Figure 2. Since there was no class imbalance present in our data, we found accuracy and the *p*-value were sufficient for the presentation. Models were developed using scikit-learn python (Pedregosa et al., 2011). The outcome of classifiers between the control and meditators resulted from differences in network features and furthermore explained the differences in connectivity and synchronization patterns.

Results

The results presented in our study were based on 154 significant models ($p < .05$), selected using permutation tests as illustrated in Figure 2. Each model exhibited a unique combination of coupling methods, bands, regions, and network metrics. These values emphasized the discrimination between control and meditation traditions. We

Figure 2. [Left] *The Pipeline Illustrates Primarily Five Stages.* [Right] *Four Main Regions Are Shown (LF, RF, LP, RP).*



Classes	Total Trained Models	Selected p < 0.05
CTR-HT	5×6×10×4 = 1200	58
CTR-SNY	5×6×10×4 = 1200	42
CTR-VIP	5×6×10×4 = 1200	54
Total	1200+1200+1200=**3600**	**154**

Note 1 [Left]. The coupling method is selected, followed by the frequency band and region for constructing the brain network from EEG recordings. The topology of the connectivity graph is explored using graph theory network metrics. Binary classifiers are built based on the property of a graph. Permutation tests are performed to obtain the significant models (p < .05) for analysis.

Note 2 [Right]. A combination of 10 electrodes forms each region. All four intrahemispheric regions are further used to form two more intrahemispheric regions (LP-LF and RP-RF) and four interhemispheric regions (LF-RF, LP-RP, LF-RP, RF-LP), overall making a total of 10 regions.

focused our study on bands, regions, and network metrics. Hence, these 154 unique combinations were segregated and discussed.

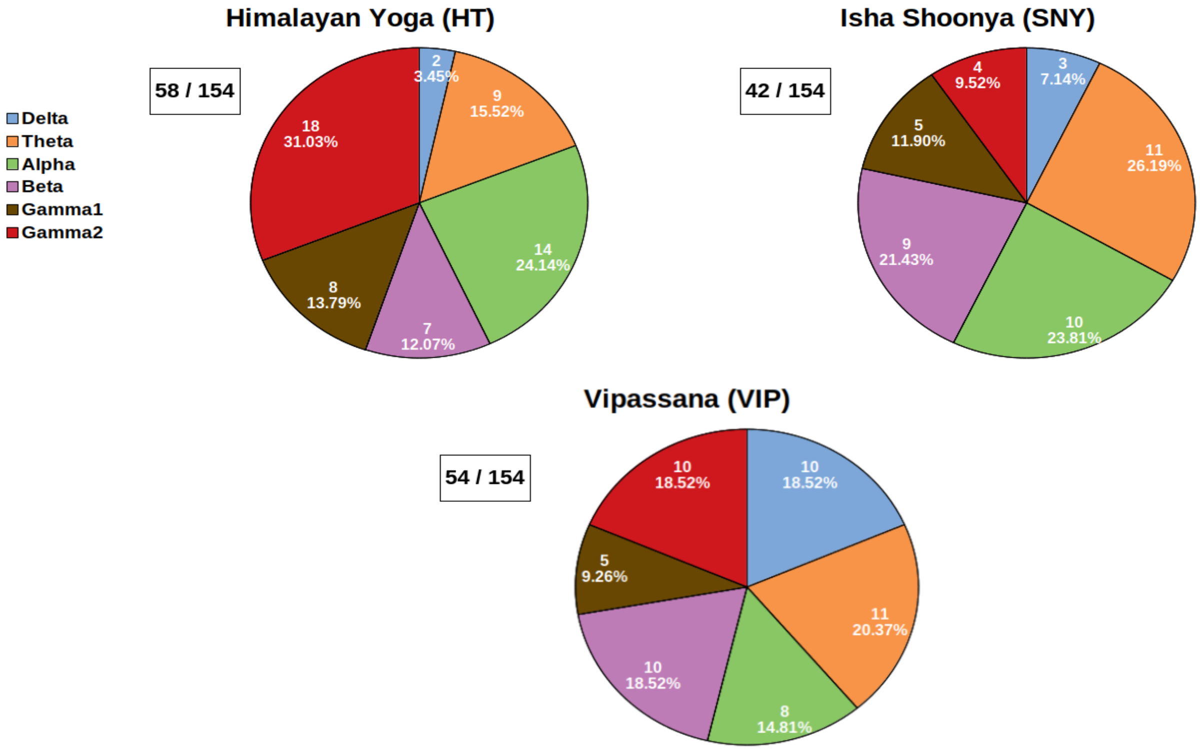
Role of Frequency Bands

For each meditation tradition, we have shown the spread of 154 significant values across all frequency bands in Figure 3. Each meditation type has some consistency and some degree of variability in the role played by a particular frequency band. Broadly, theta frequency band was found to be uniform across all meditators. For both HT and VIP meditators, gamma2 was more dominant. VIP meditators were found to have a greater amount of slow frequency delta waves than other meditators. For the CTR-HT group, all the accuracy was above 70% for most of the frequency bands except in the gamma1 band, whose accuracy was found to be around 85% (p < .01), as shown in Table 1. All bands appear to function well in distinguishing HT from control, but gamma1 played a more prominent role than the others. For the CTR-SNY group, most of the frequency bands, accuracy prediction was within 70% to discriminate controls from SNY meditators. The accuracy of alpha-band prediction, on the other hand, was found to be 90% (p < .01), with substantially higher efficiency. For the CTR-VIP group, accuracy predictions were within the range of 70–80%, except for the theta band, which had an accuracy of 85% (p < .01).

Participation of Regions

As shown in Figure 4, the synchronization of delta networks was significant for a few clusters in a variable fashion among all three meditation traditions (HT, SNY, VIP). For VIP, synchronization was found intrahemispheric in the LF, RF, and LP regions and interhemispheric between LF-RF, LF-RP, and LP-RP regions. During the synchronization of theta networks, among all the meditation traditions (HT, VIP, SNY), a stronger anterior-posterior connectivity in the left hemisphere (LF-LP), and anterior frontal connectivity (left to the right hemisphere; i.e., LF-RF regions were found to be

Figure 3. *A Significant Interaction of Bands With Meditation Traditions and Controls.*



Note. The significant counts ($p < .05$) were obtained by performing permutation tests. It represents how 154 significant models were distributed across each of the frequency bands, observed among meditators while they performed distinct meditation types (HT, VIP, SNY).

Table 1

Representation of Accuracy to Correctly Distinguish Controls With Distinct Meditative States in Frequency Bands.

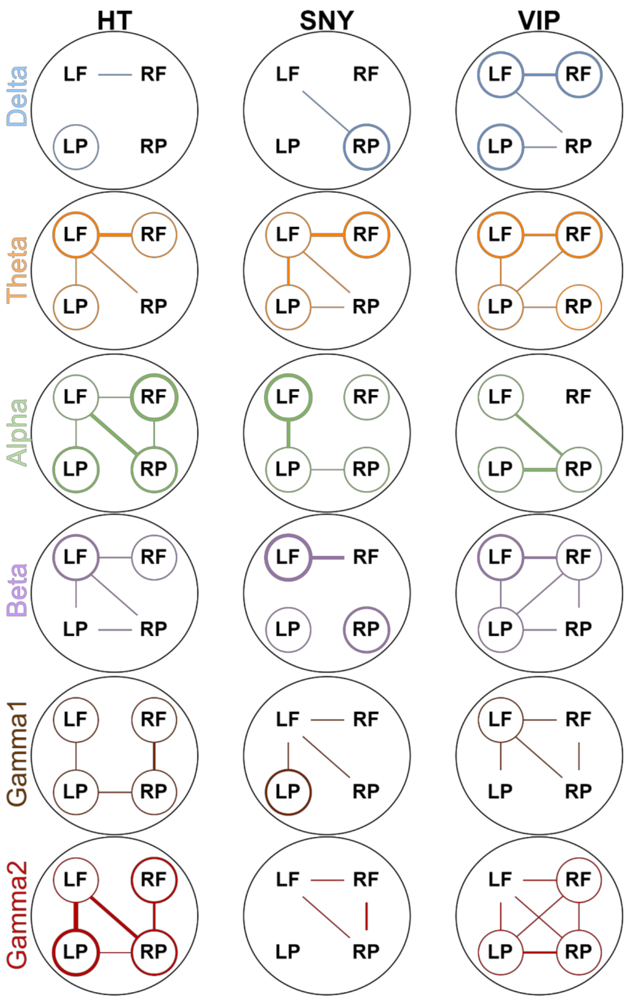
	CTR-HT		CTR-SNY		CTR-VIP	
Band	Accuracy (%)	*p*-value	Accuracy (%)	*p*-value	Accuracy (%)	*p*-value
delta	71.90	0.02	71.90	0.02	78.57	0.001
theta	78.57	0.003	75.71	0.01	**84.76**	**0.0004**
alpha	81.42	0.002	**0.90**	**0.0001**	79.04	0.001
beta	74.28	0.01	78.57	0.001	80.95	0.002
gamma1	**84.76**	**0.00009**	71.90	0.02	76.19	0.007
gamma2	80.95	0.001	75.71	0.008	80.95	0.003

All the *p*-values shown in the table are $p < .05$. Blue highlighted values suggest maximum accuracy in a particular column.

consistent). RF-LP regions were observed to have interhemispheric connections only in the VIP meditators. In the HT and SNY meditation, LF-RP interhemispheric connections were observed. During the synchronization of alpha networks, interhemispheric connections between LF-LP were common among HT and SNY meditators. A stronger connectivity in the LF-RP region among the HT and VIP meditators was observed. Moderate connections in the SNY and VIP groups were present in the LP-RP region. Overall, across all the meditators, synchronization in LF, LP, and RP clusters was indicative of its consistency.

Intrahemispheric connectivity in the RF and LF were more robust in the HT and SNY meditators, respectively. Higher intra- and interhemispheric connections were present in the HT meditators compared to the other two groups. During the synchronization of beta networks, a stronger LF

Figure 4. *Diagrammatic Representation of Statistically Significant Differences (p < .05), Based on the Allocation of 154 Values on Frequency Bands and Regions Across Three Meditation Traditions.*



Note. Circles indicate within-cluster (LF, LP, RF, RP) significance; lines designate intraconnectivity (LF-LP, RF-RP) and interconnectivity relationship (LF-RF, LP-RP, LF-RP, RF-LP). Stronger links are shown by denser circles and lines, based on the number of values obtained after the permutation test. Different colors represent frequency bands.

connectivity is observed for all meditators. Interhemispheric connectivity is observed in the LF-RF region and is seen across all meditators. A greater interhemispheric connection can be viewed in the HT and VIP meditators such as LF-LP, LP-RP, etc. During the synchronization of gamma1 networks, both intra- and interhemispheric connections were seen across meditators. Intrahemispheric LF-LP connectivity was common for all meditators. LP region had stronger connections among SNY meditators. Higher intra- and interhemispheric connections were found among HT meditators. RF-RP synchronization was found among VIP and HT meditators, whereas LP-RP connectivity was only observed in HT meditators. Interhemispheric connections in the LF-RF and LF-RP regions were consistent only in the SNY and VIP meditators. During the synchronization of gamma2 networks, consistent and higher intra- and interhemispheric connections are observed in HYT and VIP meditators (i.e., stronger connectivity in the LF-LP, LF-RP, LP-RP, RF-RP regions). Connectivity in the SNY meditators is not so dense both in the intra- and interhemispheric regions.

In Table 2, across all meditation traditions, the accuracy of most brain regions with frequency bands is greater than 70%. Across all intrahemispheric regions, the LF region was revealed to have the highest accuracy, especially for the HT (in gamma1) and VIP (in theta) meditation groups. For HT and SNY meditators, the alpha band was shown to play a role in the RF region, with an accuracy of 81% and 75%, respectively. In the RF-RP region, the SNY meditator's maximum accuracy was obtained in the LP region in the alpha band. In the LF-LP region, gamma2 was expressed in both HT and VIP meditator groups. Gamma2 bands can be seen for the mediators, notably for the HT and SNY groups. The beta band was observed only in RF and RF-RP regions for VIP and in the LF region for SNY meditators, but not for HT meditators. Broadly, most brain regions were found to have an accuracy within 70–80%, distinguishing frequency bands across all the meditation traditions, as shown in Table 3. In the anterior LF-RF region, a beta band is present across HT and SNY meditators, with 70% and 79%, respectively. In LP-RP region, maximum accuracy of 78% is obtained for HT group in gamma1 band and 90% in SNY group in alpha band. Maximum accuracy is obtained in the RF-LP regions for VIP meditators in the theta band, but RF-LP regions for HT and SNY meditators did not have significant accuracy.

Significance of Network Metrics

We observed the maximum number of allocations in modularity followed by NB as shown in Figure 5. EBC showed the maximum involvement between interconnectivity of the left and right frontal areas (LF-RF). The CC primarily engaged in the left and right frontal regions. In Figure 6 (regions), the interconnectivity of the left frontal and left parietal of SNY and VIP were observed in MU, NB, and EBC. In contrast, HT was engaged in MU and. NB was attributed across all regions in VIP, whereas MU was

Table 2
Maximum Classification Accuracy of Intrahemispheric Brain Regions Along With Frequency Bands.

	CTR-HT			CTR-SNY			CTR-VIP		
Region	Accuracy (%)	Band	*p*-value	Accuracy (%)	Band	*p*-value	Accuracy (%)	Band	*p*-value
LF	**84.76**	**gamma1**	**0.0009**	75.71	beta	0.005	**84.76**	**theta**	**0.0004**
RF	81.42	alpha	0.002	75.23	alpha	0.009	80.95	beta	0.002
LP	80.95	gamma2	0.001	**78.57**	**alpha**	**0.005**	78.57	delta	0.001
RP	70.47	gamma1	0.02	71.90	delta	0.02	69.04	gamma2	0.04
LF-LP	77.61	gamma2	0.005	75.71	theta	0.01	80.95	gamma2	0.003
RF-RP	76.19	gamma2	0.004	74.76	gamma2	0.02	78.57	beta	0.003

Blue highlighted accuracy values suggest maximum accuracy in a particular column. All the *p*-values shown in the table are $p < .05$.

Table 3
Maximum Accuracy Obtained to Distinguish Specific Meditation Traditions Based on Interhemispheric Regions and Frequency Bands.

	CTR-HT			CTR-SNY			CTR-VIP		
Region	Accuracy (%)	Band	*p*-value	Accuracy (%)	Band	*p*-value	Accuracy (%)	Band	*p*-value
LF-RF	70.47	beta	0.02	78.57	beta	0.001	76.19	gamma1	0.007
LP-RP	**78.09**	**gamma1**	**0.007**	**90.46**	**alpha**	**0.0001**	78.09	beta	0.007
LF-RP	77.61	alpha	0.005	72.38	gamma2	0.01	78.09	delta	0.003
RF-LP		-			-		**79.04**	**theta**	**0.003**

Blue highlighted accuracy values suggest maximum accuracy in a particular column. All the *p*-values shown in the table are $p < 0.05$.

involved in HT and SNY. VIP showed a greater number of connections in interconnectivity between left and right parietal, including EBC and NB. The right frontal of SNY was less involved than other groups, and network properties were captured with modularity and CC. Only VIP exhibited interconnectivity of the right frontal and left parietal with MU and NB. In Figure 6 (bands), VIP involved all network metrics in the delta and gamma2, whereas theta, alpha, and gamma2 in HT and SNY were involved in alpha and beta. NB and EBC were contributed across all bands in VIP, whereas MU in SNY. The similarity between all meditators was observed in frequency bands: (a) theta band engaged in left and right frontal interconnectivity via EBC, (b) more cross-connections involved in gamma processing using MU, and (c) beta waves in left frontal and interconnection with right frontal reflected connections with NB and EBC.

Discussion

Our findings show that (a) VIP practitioners have higher delta connectivity; (b) theta network synchronization in the left hemisphere is observed to be greater and more constant across meditators in the LF-LP region and in the anterior frontal area; (c) high levels of gamma2 processing in HT and VIP practitioners favorably correlated with the number of hours spent meditating in these two meditation traditions; (d) the left frontal activity contributes to theta and gamma bands for all meditators; (e) in contrast to EBC and CC, MU and NB are heavily weighted in graph measurements; and (f) MU is engaged extensively in gamma processing across all meditation traditions. Furthermore, left-right intra-inter hemisphere networks are engaged in varied ways, with each meditation state having unique synchronization patterns.

We observed that gamma2 was more noticeable in both HT and VIP meditators. This might result from

Figure 5. *This Image Illustrates an Overall Distribution of Network Metrics Across Regions and Bands, Including All Traditions.*

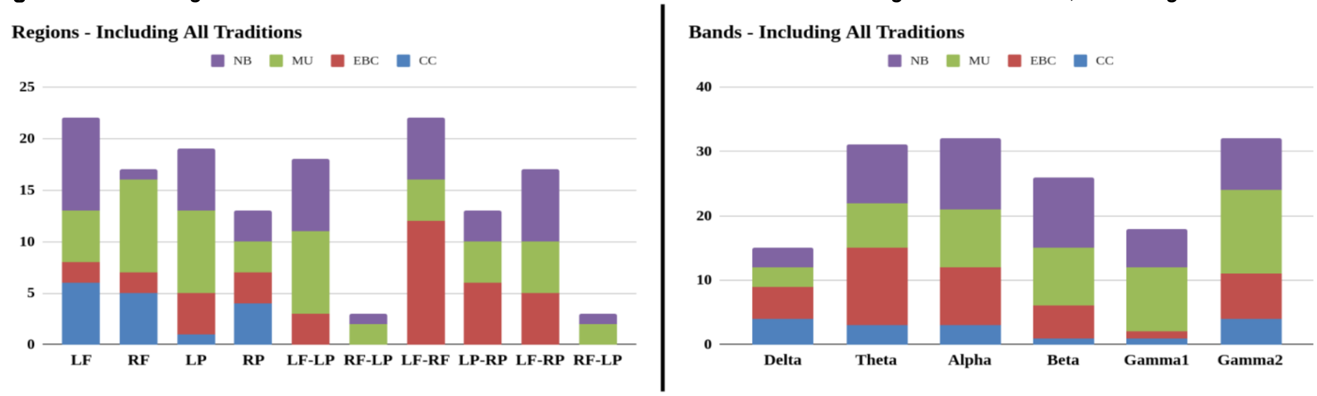
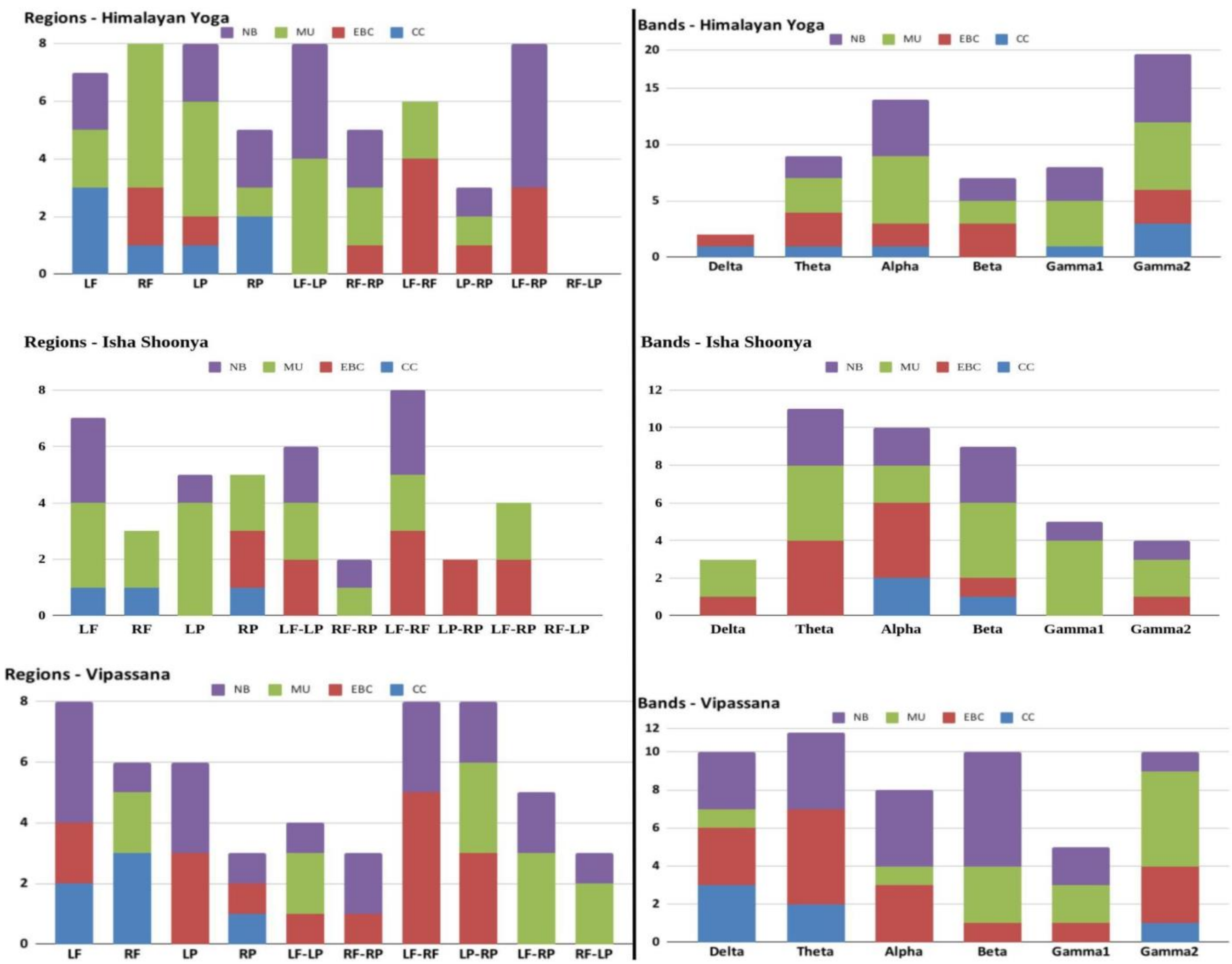


Figure 6. *Detailed Representation of Network Metrics Concerning Regions and Bands Across Meditator Traditions.*



more hours of meditation practice (Braboszcz et al., 2017), which can be presented as a trait effect exhibiting gamma2. Previous studies had observed high-frequency gamma band activity during meditation when participants had an increased hour of meditation experience (Ferrarelli et al., 2013; Hauswald et al., 2015).

Theta band activity was observed in the current study across all meditation practices. This can be linked with the cultivation of long-term meditation practice exhibiting theta activity over the frontal cortex, which is associated with sustained and internally directed attention states (Brandmeyer & Delorme, 2018). Theta activity is related to executive functioning tasks such as working memory and others that require cognitive control (Cavanagh & Frank, 2014; Cavanagh & Shackman, 2015). Theta rhythm was observed among all meditation traditions with stronger left anterior-posterior (LF-LP) and anterior frontal connectivity (LF-RF). Theta band's importance in meditation has been mostly related to top-down control mechanisms, such as heightened conflict monitoring and neural communication over long and broad networks related to cognitive processing (Cavanagh & Frank, 2014). In work by (Manna et al., 2010; Marzetti et al., 2014; Yordanova et al., 2020), similar observations of theta coupling across the left hemisphere anterior posterior (LF-LP areas) have been reported throughout three meditation traditions (focused attention, open monitoring, and loving kindness). The engagement of leftward asymmetry (Cahn & Polich, 2009), anterior frontal (Banquet, 1973), and frontal midline (Brandmeyer & Delorme, 2018) in the theta band has been observed consistently among meditators.

VIP practitioners were shown to have an increase in delta power. Past findings were found to support our results (Cahn et al., 2010; Cahn & Polich, 2009) and found that decreased frontal delta power in long-term VIP practitioners, while increased frontal delta in long-term meditators has been reported in zen (Faber et al., 2008) and qi-gong (Tei et al., 2009). VIP meditators may reflect a functional inhibition of brain appraisal systems in keeping detached from analysis, judgment, and expectation. For VIP meditators, delta power synchronizes intra- (LF, RF, LP) and interhemispheric (LF-RF, LF-RP, LP-RP). Prior research on meditation has shown that this increased frontal delta activity manifests as a baseline relative suppression of cognitive attention and a more vital detachment from current daily experiences (Faber et al., 2008; Tei et al., 2009).

The LF, LP, and RP clusters for alpha synchronization were seen among all meditation techniques. The LF, LP, and RP clusters of alpha synchronization were observed for all meditation practices. Alpha power is essential for processing and integrating somatosensory information, working memory, and cognitive entrainment during meditation (Brandmeyer & Delorme, 2018). According to studies, different meditation types may affect alpha power changes (Amihai & Kozhevnikov, 2015). This can be inferred to some extent from our study's observations of regional variability (inter- and intrahemisphere) due to different meditation practices, such as the increased power of alpha LF-LP frequently observed among HT and SNY meditators but not VIP practitioners.

The study by Yordanova et al. (2020) specifically for open monitoring meditation found left frontal coupling in beta bands, documented for all meditation traditions. We identified that lateralized increase in intra- and interhemispheric beta synchronization distinguished particular stages of meditation with shared involvement in the related clusters. The most frequently associated tasks with beta oscillations are endogenous, top-down regulated processing, and conscious processing, which promotes long-range re-entrant connections between cortical areas and greater communication through coherence. Lateralized beta connection may represent the amount of selected information (little vs. large) or the type of attentional process of selection (narrow/focused vs. wide/monitoring; Yordanova et al., 2020).

During the gamma1 synchronization, LF-LP connectivity was common for all meditation types. While LP-RP connectivity was only noticed in HT meditators, VIP and HT meditators displayed RF-RP synchronization. This is due to the function of gamma in the overall attentive state, working memory activation, information integration, and neuronal transmission underlying conscious awareness (Braboszcz et al., 2017; Cahn et al., 2013; Vivot et al., 2020). Neural coupling of gamma 2 frequency is primarily seen with higher inter- and intrahemispheric interaction between brain regions in HT and VIP meditators. It indicates the trait effect with increased hours of meditation practice, leading to neuroplastic change with the increase in neural connections.

Our research showed that modularity makes a considerable contribution. Modules are crucial for breaking more extensive networks into basic "building blocks," like internally highly connected clusters with weaker linkages. In neurobiology, modular divisions are significant because they distinguish brain parts with similar functions (Sporns, 2022). There appears to be ample room for future research to comprehend the underlying phenomena of modularity between two groups (meditators vs. controls).

Our results have been presented using a data-driven methodology, making them more interpretable and subject to further investigation for graph measures. However, this work offers a viable concept for consumer wearable headsets that can show how functional connectivity evolves as meditation practice progresses. The naive practitioner can comprehend the relationship between their functional connectivity patterns with different types of experienced meditators.

Conclusion

In this study, we compared three meditation traditions to a control group to find differences in frequency bands, regions, and network topological organization. Five coupling methods—including coh, imcoh, pli, wpli, and ciplv—were used to construct functional brain networks from the earliest to the most recent. Four separate graph theory network metrics (NBC, EBC, CC, MU), including functional segregation and integration, were used to examine six frequency bands, six intrahemispheric, and four interhemispheric connections. The 3600 models were reduced to 154 for examination using permutation tests, which provided diverse insights into the meditator groups. Left hemisphere theta synchronization (LF-LP) and anterior frontal (LF-RF) areas were visible for all meditation practitioners. Here, the presence of the gamma2 band (strong connections between the intra-interhemispheres) is consistently observed across HT and VIP meditators, indicating a characteristic influence (due to the increased hours of meditation practice). The research done in earlier literature on a comparable dataset supports this. Additional data showed the importance of various frequency bands and brain regions in differentiating between different styles of meditation, such as elevated delta power in VIP and improved left parietal (LP) connectivity in SNY practitioners. These neural connections among meditators are still in the early stages of research as to how and why they develop. Using brain connectivity and graph measurements, this study generally sheds light on the interaction effect of neural oscillations with intra- and interhemispheric brain areas during a particular meditative state, both globally and specifically. Future research can focus on the biomarkers found in graph measures for the various meditation traditions.

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Author Disclosure

The author declares no conflicts of interest.

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NeuroRegulation

EEG-Neurofeedback Training and Prolidase in Anxiety Disorders: An Exploratory Study

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Abstract

Objective: Prolidase is an enzyme that releases proline and is vital in extracellular matrix (ECM) remodeling, fueling white matter dynamics. Serum prolidase activity (SPA) is elevated in various neuropsychiatric conditions and may influence cognitive functions. Aim of the study was to explore the relation of SPA to neuropsychological functioning and its response to treatment in anxiety disorders. **Methods:** Twenty demographic-matched patients with anxiety were recruited. Six patients were given EEG-neurofeedback training (EEG-NFT), eight were treated pharmacologically (treatment as usual; TAU) with EEG-NFT, and six patients were treated only pharmacologically (TAU group). Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI) were used to assess anxiety and comorbid depression, respectively. **Results:** Symptom reduction was seen in all groups. SPA decreased considerably in EEG-NFT group. Mental speed and spatial working memory negatively correlated with SPA in EEG-NFT group. Focused attention, sustained attention, verbal working memory, and spatial construction ability negatively correlated with SPA in EEG-NFT+TAU group. Mental speed in TAU group was also inversely proportional to SPA. **Conclusion:** Inverse correlation between SPA and neuropsychological functions in EEG-NFT group is suggestive of prolidase-mediated microstructural changes in white matter, which may have an influence on cognitive enhancement in anxiety disorders (AD).

Keywords: anxiety disorders; prolidase; proline; EEG-neurofeedback training; neurocognitive functions; executive functions

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Introduction

Anxiety disorders (AD) are the most prevalent mental disorders worldwide (Stein et al., 2017). They are highly comorbid with other neuropsychiatric disorders. AD are a highly debilitating condition, posing significant disease burden and impacting quality of life (Sagar et al., 2020).

There is a dearth of definite biomarkers for AD owing to their invasive nature (cerebrospinal fluid) or cost effectiveness (neuroimaging methods). A need for peripheral biomarkers, which are economical, minimally-invasive and easy to obtain, is perceived (Vismara et al., 2020). Lately, serum prolidase activity has been studied in neuropsychiatric disorders such as schizophrenia (Güneş et al., 2016), bipolar disorder (Selek et al., 2011), major depressive disorder (Kokacya et al., 2014; Verma et al., 2017), Alzheimer's dementia (Krishna et al., 2020), and generalized anxiety disorder (GAD; Ercan et al., 2017) and is found to be elevated in comparison to controls.

Prolidase is an enzyme that cleaves iminodipeptides containing glycyl-proline and hydroxyproline at the carboxy terminal. During collagen metabolism, prolidase splits iminodipeptides, produces proline as an end product, and makes byproducts available for reuptake and recycling for protein synthesis, cell matrix remodeling, and cell growth (Namiduru, 2016). Extracellular matrix (ECM) is prominently made of collagen of which 20% consists of proline and hydroxyproline (Ramshaw et al., 1998). Increase in proline has been shown to decrease antioxidants in brain of rats, thus inducing oxidative stress (Delwing, Bavaresco, Chiarani, et al., 2003a; Delwing, Bavaresco, Wannmacher, et al., 2003b; Delwing, 2005). Proline is considered as an amino acid and its abundance in the brain gives it the status of a neurotransmitter (Lajtha & Toth, 1974). Defective ECM caused by altered serum prolidase activity (SPA) has shown to cause disorganized cytoarchitecture, defect of meninges, and compromised membranal integrity leading to mental deficiency (Insolia et al., 2020) and thus possibly causing impairments in cognitive functioning. Prolidase deficiency is a rare genetic disorder in which high levels of proline containing iminodipeptides in brain are seen to be associated with mental retardation (Namiduru, 2016). Proline is also implicated in modulation, that is, release and reuptake, of glutamate (Delwing et al., 2007) and activates NMDA receptors and thus depolarizing neurons (Ault et al., 1987). Glutamate is an excitatory neurotransmitter and excess of it leads to excitoxicity causing seizures or mental retardation and nerve cell death (Cohen & Nadler, 1997). It plays a role in neurodevelopment, cognition, learning, and memory in humans (Nasir et al., 2020). Hence, it is important to explore if SPA is associated with neuropsychological functioning due to its direct or indirect role through increased oxidative stress, inflammation, and ECM remodeling.

First line of treatment for AD has been pharmacotherapy (mostly selective serotonin reuptake inhibitors [SSRIs]) and cognitive behavior therapy (CBT; Garakani et al., 2020). However, a considerable number of patients do not respond to either of the treatments and that gives rise to the need of looking newer modalities of treatment. EEG-neurofeedback training (EEG-NFT) is a promising state-of-the-art treatment for AD (Micoulaud-Franchi et al., 2021). It enables a person to alter their cortical electrical activity through real-time feedback. Alpha-theta training has been effectively used to treat AD (Abdian et al., 2021; Hammond, 2005; Moore, 2000). EEG-NFT works on the electrophysiology of brain by synchronizing random electrical activity through training specific electrical waves repeatedly over a period of time. Electrical impulses to axons are known to induce myelination (Demerens et al., 1996; Ishibashi et al., 2006) which is a putative mechanism for training-induced white matter tract changes in the brain (Takeuchi et al., 2010). Electrocortical activity is associated with changes in the subcortical structures, and training brain waves through EEG-NFT is known to increase the cortical excitability and inducing neuroplasticity (Ros et al., 2010). Though, the cellular mechanism of these remain open to be explored.

We hypothesize that prolidase-mediated ECM alterations may influence synaptic plasticity in AD. With treatment, SPA may decrease in AD patients, thus impacting the brain regions involved in AD. As a consequence, cognitive functions are expected to improve with symptom reduction too. To our knowledge, this is the first study to explore serum prolidase levels in response to treatment in AD as assessed by clinical evaluations and neuropsychological functions.

Methods

Subjects

Patients of all genders between 18–45 years who were diagnosed with AD (i.e., social anxiety disorder, panic disorder with and without agoraphobia, or GAD) were recruited from a tertiary hospital in Southern India. Clinical diagnosis was made through clinical interview by a consultant psychiatrist based on ICD-10 criteria. Patients with presence or history of any neurosurgical, neurological, and severe mental illness; and those who were undergoing psychotherapy were excluded. Only right-handed people were included to maintain uniformity. The study was approved by the Institute Ethics Committee, NIMHANS. Informed consent was obtained from each patient before recruiting.

Clinical Assessments

Beck Anxiety Inventory (BAI) was administered to assess the severity of anxiety and patients with a score of >16 (moderate-severe anxiety) were recruited. Beck Depression Inventory (BDI) was administered to assess severity of depression.

Cognitive Assessments

Subtests from NIMHANS neuropsychology battery (Rao et al., 2004) were administered. Attention, executive functions, and memory were examined. Digit Symbol Substitution Test (DSST) for mental speed, Digit Vigilance Test (DVT) for sustained attention, Color Trails-1 (CT-1) for focused attention, and CT-2 for mental flexibility and response inhibition were used. *N*-back and spatial span from Wechsler Memory Scale-III (WMS-III) were used for verbal and visual working memory, respectively.

Controlled Oral Word Association Test (COWAT) was used to assess fluency. Rey's Auditory Verbal Learning Test (AVLT) and Complex Figure Test (CFT) were used to assess verbal and visual memory, respectively.

Blood Sample Analysis

Five ml of random blood was drawn through venipuncture by a trained staff nurse in the morning. It was left at room temperature for an hour for clotting to occur. The serum was then separated on the same day by spinning the sample in a centrifuge at a speed of 5000 rpm for 15 min. Once separated, serum was transferred to a new set of tubes and was stored at −80º celsius until batch analysis. Spectrophotometric method was used to measure the proline released through SPA (Chinard, 1952; Myara et al., 1982). SPA is reported in U/ml.

Treatment

EEG-NFT

20 sessions of 30 min each were provided to patients on alternate days by a trained clinical psychologist. The training was given at O1 and O2 location to enhance alpha and theta waves; that is, a reward in terms of points (auditory) would be given if the thresholds for alpha and theta to increase were met. The thresholds were set on auto mode; that is, an average of the last three min of alpha and theta activity was taken and the next threshold was set at that limit. The training was conducted on Atlantis Module (produced by BrainMaster Technologies, Inc., Oakwood Village, Ohio).

Treatment as Usual (TAU)

Patients who were on psychotropic medications and no other treatment modality formed the treatment as usual group. Patients in both groups were stabilized on medication for at least three weeks before conducting any assessments and EEG-NFT.

Statistical Analysis

IBM SPSS version 28 for Windows was used for statistical analysis. Mean and standard deviations of socio-demographic variables, clinical symptoms and SPA at baseline are presented. Wilcoxon Signed Rank test was used to measure the pre to post change in all variables within groups. Effect sizes are determined by dividing the *Z* scores by square root of observations of the respective variables. Spearman's rank correlation was used to find correlations between SPA, clinical, and cognitive variables.

Results

In this exploratory study, age, sex, and educational status matched subjects were included in the order of six patients in the EEG-NFT group (five males and one female) with a mean age of 29.33 ± 4.59, eight patients in the EEG-NFT+TAU group (six males and two females) with a mean age of 26.13 ± 5.16, and six patients in TAU group (five males and one female) with a mean age of 33.83 ± 9.84 years. All the recruited subjects' BAI, BDI, and cognitive indices scores were statistically similar across groups at baseline (Table 1).

Upon treatment, neuropsychological functions improved in all groups. Significant improvement is seen in anxiety and comorbid depressive symptoms in all the groups after treatment. Highest improvement is seen in EEG-NFT group, followed by EEG-NFT+TAU group (See Table 2).

Table 1
Sociodemographic and Clinical Variables at Baseline

Variables	EEG-NFT	EEG-NFT+TAU	TAU	Sig.
Age in years	29.33 ± 4.59	26.13 ± 5.16	33.83 ± 9.84	0.226
Duration of illness in years	2.67 ± 1.50	2.38 ± 2.07	4.17 ± 3.37	0.285
Education in years	17.00 ± 4.64	16.25 ± 1.98	12.50 ± 6.05	0.414
Beck Anxiety Inventory	26.00 ± 3.84	39.88 ± 11.56	31.00 ± 6.57	0.074
Beck Depression Inventory	22.83 ± 12.70	30.88 ± 8.72	21.83 ± 10.62	0.257
Serum prolidase activity U/ml	8.65 ± 1.48	8.01 ± 3.02	7.38 ± 2.66	0.729

Table 2
Wilcoxon Signed Rank Test to Assess the Change with Treatment in Variables in Different Groups

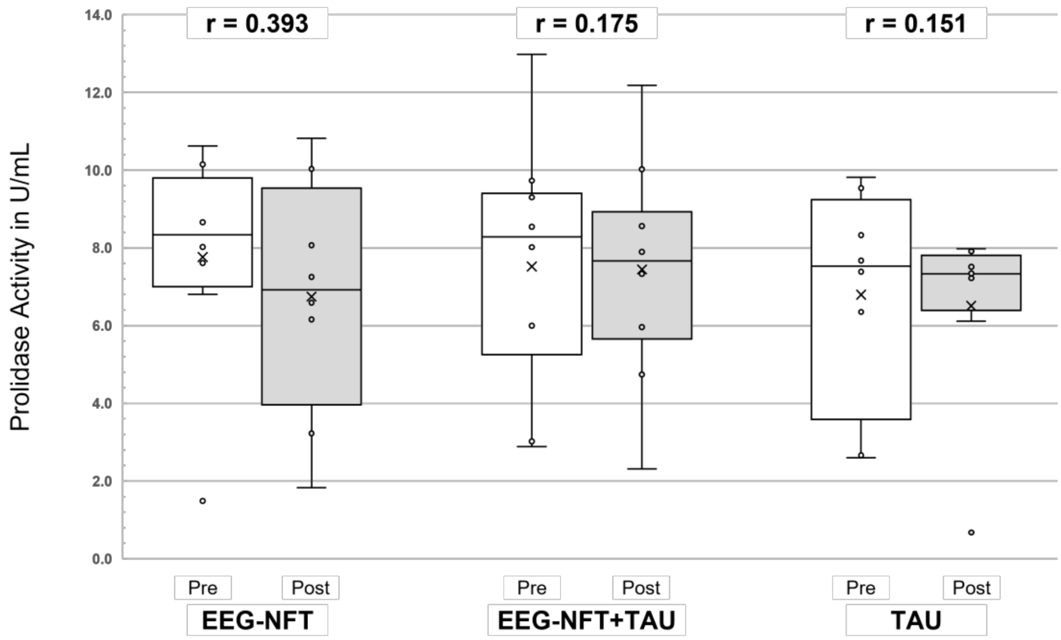
	Groups								
	EEG-NFT			EEG-NFT+TAU			TAU		
Measures	*Z*	*r*	*S*ig. (2-tailed)	*Z*	*r*	*S*ig. (2-tailed)	*Z*	*r*	*S*ig. (2-tailed)
Beck's Anxiety Inventory	−2.207	−0.64**	0.03#	−2.524	−0.63**	0.01#	−2.214	−0.64**	0.03#
Beck Depression Inventory	−2.201	−0.64**	0.03#	−2.100	−0.53**	0.04#	−2.201	−0.64**	0.03#
DSST	−2.207	−0.64**	0.03#	−0.980	−0.25	0.33	0.000	0.00	1.00
Color Trails-1	−1.572	−0.45*	0.12	−0.350	−0.09	0.73	0.000	0.00	1.00
Color Trails-2	−1.153	−0.33*	0.25	−1.051	−0.26	0.29	−1.826	−0.53**	0.07#
Digit vigilance total time	−0.943	−0.27	0.35	−1.680	−0.42*	0.09	−1.826	−0.53**	0.07#
Digit vigilance - errors	−1.461	−0.42*	0.14	−1.620	−0.41*	0.11	−0.365	−0.11	0.72
COWAT	−2.032	−0.59**	0.04#	−1.556	−0.39*	0.12	−0.272	−0.08	0.79
N-Back 2 hits	−1.511	−0.44*	0.13	−2.060	−0.52**	0.04#	−0.272	−0.08	0.79
N-Back 2 errors	−1.473	−0.43*	0.14	−2.401	−0.60**	0.02#	−1.095	−0.32*	0.27
Spatial span forward	−1.289	−0.37*	0.20	−0.986	−0.25	0.32	−0.921	−0.27	0.36
Spatial span backward	−0.756	−0.22	0.45	−1.354	−0.34*	0.18	−0.184	−0.05	0.85
Spatial span total	−1.633	−0.47*	0.10	−0.341	−0.09	0.73	−0.535	−0.15	0.59
AVLT total	−1.572	−0.45*	0.12	−2.371	−0.59**	0.02#	−1.826	−0.53**	0.07#
AVLT immediate recall	−2.070	−0.60**	0.04#	−2.041	−0.51**	0.04#	−1.604	−0.46*	0.11
AVLT delayed recall	−1.089	−0.31*	0.28	−2.032	−0.51**	0.04#	−1.633	−0.47*	0.10
CFT COPY	−1.604	−0.46*	0.11	−1.604	−0.40*	0.11	−0.816	−0.24	0.41
CFT immediate recall	−1.166	−0.34*	0.24	−2.328	−0.58**	0.02#	−1.289	−0.37*	0.20
CFT delayed recall	−1.572	−0.45*	0.12	−2.176	−0.54**	0.03#	−0.730	−0.21	0.47
Serum prolidase activity	−1.363	−0.39*	0.17	−0.700	−0.18	0.48	−0.524	−0.15	0.60

Significant at 0.05 level, * Moderate effect size < − .30, ** Large effect size < −.50. DSST- Digit Symbol Substitution Test, COWAT- Controlled Word Association Test, AVLT- Rey's Auditory Verbal Learning Test; CFT- Complex Figure Test.

With respect to prolidase activity, a considerable reduction in the EEG-NFT group and marginal reduction in the other two groups noted (Figure 1). A positive correlation was found between prolidase and comorbid depression at the baseline in the EEG-NFT group $r(4) = 0.943$, $p = .005$. This is in agreement with previous studies conducted in major depressive disorder (Kokacya et al., 2014; Verma et al., 2017). However, no significant correlation was found between symptom reduction and decreased prolidase activity (Table 3).

Interestingly, when the cognitive scores were closely scrutinized, mental speed $r(4) = −0.899$, $p = .015$ and spatial working memory $r(4) = −0.899$, $p = .015$ negatively correlated with prolidase in EEG-NFT group. Focused attention $r(6) = −0.714$, $p = .047$; sustained attention $r(6) = 0.708$, $p = .05$; mental flexibility and set-shifting ability, verbal working memory *N*-back hits $r(6) = −0.778$, $p = .023$ and *N*-back errors $r(6) = 0.876$, $p = .004$; and spatial construction ability $r(6) = −0.791$, $p = .019$ negatively correlated with prolidase in EEG-NFT+TAU group. Mental speed $r(4) = −0.812$, $p = .05$ in TAU group is also negatively correlated with prolidase (See Table 3).

Figure 1. *Change in SPA Across Groups After Treatment.*



Note. Mean (marked as x) and median values are presented of EEG-NFT group (n = 6), EEG-NFT+TAU group (n = 8) and TAU group (n = 6). Wilcoxon Signed Rank test was used to analyze and effect size was calculated using $r = Z/\sqrt{N}$.

Table 3
Correlations Between SPA and Neuropsychological Scores Presented as Spearman's Rho

		Correlations		
		EEG-NFT	**EEG-NFT+TAU**	**TAU**
DSST	Correlation Coefficient	−0.899*	−0.429	−0.812*
	p-value	0.015	0.289	0.050
CT-1	Correlation Coefficient	−0.143	−0.714*	−0.174
	p-value	0.787	0.047	0.742
DVT-e	Correlation Coefficient	−0.493	0.708*	−0.290
	p-value	0.321	0.050	0.577
NB2-H	Correlation Coefficient	0.058	−0.778*	0.698
	p-value	0.521	0.023	0.123
NB2-E	Correlation Coefficient	0.118	0.876**	−0.696
	p-value	0.824	0.004	0.125
SS-fw	Correlation Coefficient	−0.899*	0.061	−0.058
	p-value	0.015	0.885	0.913
CFT-COPY	Correlation Coefficient	−0.638	−0.791*	−0.334
	p-value	0.173	0.019	0.518

** correlation is significant at 0.01 level (2-tailed), * correlation is significant at 0.05 level (2-tailed). DSST - Digit Symbol Substitution Test, CT-1 - Color Trails-1, DVT-e - Digit Vigilance Test errors, NB2-H - Verbal *N*-Back-2 hits, NB2-E - Verbal *N*-Back-2 errors, SS-fw - Spatial span - forward, CFT-COPY - Complex Figure Test copy.

Discussion

The role of SPA is now being explored in neuropsychiatric disorders. These conditions are associated with neuropsychological deficits. SPA is observed to be elevated in common mental disorders like depression and GAD. Present study is an exploration of the effect of EEG-NFT for anxiety on prolidase activity and its relation to cognitive functions. We had hypothesized, with decrease in SPA, clinical symptoms and cognitive functions will improve.

Deficits in spatial working memory and spatial long-term memory is seen in an inherited disorder of amino acids called hyperprolinemia type II which is characterized by excessive proline (Bavaresco et al., 2005). Higher proline levels are shown to destroy cells in hippocampus, which is an important region for memory consolidation and retention (Nadler et al., 1988). Surprisingly, no correlations between SPA and short-term and long-term memory were found. However, mental speed and spatial working memory negatively correlated with prolidase in EEG-NFT group. Focused attention, sustained attention, verbal working memory, and spatial construction ability negatively correlated with prolidase in EEG-NFT+TAU group too. Mental speed in TAU group is also negatively correlated with prolidase. The tests assessing these functions are not susceptible to practice effects, and we can safely attribute the improvement to the treatment. The aforementioned cognitive functions are the building blocks for executive functions and targeting these have shown to be effective for higher cognition as well. As seen on performance of Color Trails-2, patients' mental flexibility and set-shifting ability and response inhibition improved along with attention and verbal working memory. These cognitive functions are a part of executive functions and are largely governed by fronto-parietal networks (Coull et al., 1996; Figueroa-Vargas et al., 2020; Scolari et al., 2015). The present intervention-neurofeedback training, has shown to bring about microstructural changes in white matter pathways connecting the frontal and parietal regions (Ghaziri et al., 2013). The ECM provides a support framework to the synapses and thus the subcortical regions and is essential for neuroplasticity (Burnside & Bradbury, 2014). Prolidase plays an important role in ECM remodeling. Findings from the present study imply that NFT-induced, possibly prolidase-mediated microstructural changes in white matter have therapeutic influence in AD. It warrants further large-scale studies to confirm these observations.

Limitations and Future Directions

The limitation of the study was small sample size. Hence, the findings should be interpreted with caution. However, we found that prolidase activity responds to existing treatment modalities. We also saw a reduction in prolidase of a moderate effect size through EEG-NFT. The mechanisms of these remain to be explored. It was interesting to see the reduction in SPA also correlated with multiple neuropsychological functions independently of the clinical symptoms. This is indicative of the role of SPA in strengthening the ECM and sustaining the cognitive networks and pathways. We speculate that the enhanced synapses through EEG-NFT are supported by the ECM through SPA and thus reinforce the cognitive enhancement. These are preliminary findings and further controlled studies with a bigger sample are required for establishing the role of SPA in AD.

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Author Disclosure

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NeuroRegulation

A Feasibility Study of LORETA *Z*-Score Neurofeedback Training in Adults with Schizophrenia-Spectrum Disorder Experiencing Treatment-Resistant Auditory Verbal Hallucinations

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Abstract

Introduction: The incomplete effectiveness of interventions demands new ways to help people diagnosed with schizophrenia who experience auditory verbal hallucinations (SZ-AVH). We aimed to perform a feasibility study of low-resolution electromagnetic tomography analysis (LORETA) neurofeedback with people exhibiting treatment-resistant SZ-AVH. **Methods:** We examined changes in resting-state quantitative electroencephalogram (qEEG) in four people with SZ-AVH (three male, one female) after LORETA *Z*-score neurofeedback training. **Results:** The study design had to be amended due to a national COVID-19 lockdown. Neurofeedback was well tolerated and no participants dropped out. Recruitment was the main feasibility issue. Barriers included a lack of knowledge of neurofeedback by patients and mental health teams, as well as the travel and time commitment involved. For the only patient who completed all 20 sessions, elevated frontal, central, and temporal theta absolute power measured at baseline normalized after treatment, but decreased temporal delta and an increase in coherence for all frequency bands were also found. **Conclusions:** Two key lessons were drawn for the feasibility of trials of EEG neurofeedback in this population. First, significant effort is needed to educate mental health professionals and patients about neurofeedback. Second, the equipment employed for neurofeedback training needs to be physically based at a site where patients routinely attend.

Keywords: schizophrenia; auditory verbal hallucinations; EEG; LORETA; neurofeedback; qEEG; theta power

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Introduction

Auditory verbal hallucinations (AVH), the perception of voices in the absence of auditory stimuli, are reported by between 60–80% of people with a diagnosis of schizophrenia and can cause significant distress (McCarthy-Jones et al., 2017; Thomas et al., 2007). Some people prefer treatments that “turn towards” their voices and engage with them (De Jager et al., 2016), such as cognitive-behavioral therapy or the approaches of the Hearing Voices Movement (Jauhar et al., 2014; Longden et al., 2018; Schnackenberg et al., 2017; Van Der Gaag et al., 2014). Others prefer to “turn away” from their voices (De Jager et al., 2016) and utilize treatments such as antipsychotic medication or neurostimulation. Yet, antipsychotic medications have limited effectiveness, with up to a third of patients not benefitting from these drugs (Shergill et al., 1998), and neurostimulation techniques have a mixed evidence-base (Fröhlich et al., 2018; Slotema et al., 2014).

The present study aimed to explore the feasibility of EEG-based neurofeedback training (NFT) in the framework of the turning away approach, which may appeal to some people who hear voices. This is a noninvasive intervention in which self-regulation of brain activity is sought through operant conditioning (Strehl, 2014). The therapeutic value of NFT has been explored in multiple populations, including people diagnosed with attention-deficit/hyperactivity disorder (Arns et al., 2014; Van Doren et al., 2019; Wangler et al., 2011), epilepsy (Schoenberg & David, 2014), and autism (Thompson et al., 2010). Yet, questions remain over whether NFT is an effective treatment in some areas of psychiatry and well-designed studies are still required to assess this (Begemann et al., 2016).

Proof-of-concept work has already been performed for fMRI-based NFT in people diagnosed with schizophrenia with AVH (Orlov et al., 2018). However, EEG-based neurofeedback offers a more cost-effective, accessible and convenient approach, which deserves investigation (McCarthy-Jones, 2012). Case studies have also been published using EEG-based neurofeedback in schizophrenia (Surmeli et al., 2012). However, there is the need for work that assesses the feasibility of NFT for treating specifically treatment-resistant SZ-AVH, which is the population with whom this approach will be tested.

EEG-based neurofeedback appears promising due to the documented EEG changes detected in SZ-AVH. Lower alpha band coherence between auditory cortical areas has been found in people diagnosed with schizophrenia who experience AVH (Henshall et al., 2013). This has been proposed to be associated with the disruption of central auditory processing, which may affect the interhemispheric transfer within auditory circuits (Henshall et al., 2013). Increased resting-state beta activity has also been found in people diagnosed with schizophrenia experiencing AVH, when compared to those without AVH, in speech-related areas of the brain (left inferior parietal lobule, left medial frontal gyrus; Lee et al., 2006). Moreover, both increased alpha and beta-band activity in auditory regions have been found to be associated with state experiences of AVH (Ishii et al., 2000; Ropohl et al. 2004; Sritharan et al., 2005).

Other findings suggest a positive correlation between increased frequency of hallucinations and low frequency oscillations (i.e., delta and theta; Gattaz et al., 1992; Juszczak, 2011), which might also play a role in the generation of the emotionally charged hallucinations of abusive voices expressing personal insults (Nayani & David, 1996). More specifically, recent research has demonstrated the link between fronto-central theta power abnormalities and sensory processing deficits (Roa Romero et al., 2016), also proposing a role for fronto-temporal delta connectivity (Ford et al., 2002) and frontal/central/temporal theta power/coherence dysfunctions in patients with paranoid schizophrenia experiencing auditory hallucinations (Zheng et al., 2015).

Furthermore, lower theta power in the hippocampus has been shown to precede AVH (Van Lutterveld et al., 2012). This may be due to its effects on the temporal coordination of local network oscillations in the gamma range (Lisman & Buzsáki, 2008), the disruption of normal activity in auditory networks, or its impact on the functioning of the salience network (Hare et al., 2018). Such changes fit with models of AVH that focus on alterations within and between speech production and speech perception regions of the brain (Ford & Mathalon, 2005).

Quantitative EEG (qEEG) can be used to suggest possible altered activity in the brain, relative to the nonpsychiatric population, and to guide NFT (Surmeli et al., 2012). More specifically, low-resolution electromagnetic tomography analysis (LORETA) NFT uses a qEEG-guided method that allows the localization of the activity generators (modules or hubs) underlying the EEG signals that are measured at the cortex. While this requires a 19-electrode cap for every session (which can be set up in minutes), it can yield results with fewer sessions (Thatcher & Lubar, 2014).

This study aimed to investigate the feasibility of using 20 weekly sessions of LORETA NFT in people diagnosed with schizophrenia and with treatment-resistant AVH, employing tailored intervention protocols based on both baseline qEEG recordings and behavioral symptoms or complaints.

Methods

Recruitment

This feasibility trial was registered with ClinicalTrials.gov (NCT03852706). The study aimed to recruit 40 participants who were to be randomized to treatment and waiting-list control conditions. Randomization was to be performed through a local Clinical Research Facility. Ethical approval for the study was sought and granted from an appropriate Human Research Ethics Committee. Recruitment was first undertaken through local mental health teams, under the supervision of a Consultant

Psychiatrist. The research team attended meetings of the mental health teams and discussed the nature of the study with them. The teams agreed to identify potential participants and to provide them with a researcher-generated information sheet about the study. Interested patients would then contact the research team for more information. A second recruitment strand involved directly approaching patients attending an outpatient clozapine clinic, to provide them with information about the study.

Inclusion criteria were that patients should 1) be aged between 18 and 65 years, 2) have received a diagnosis of a schizophrenia-spectrum disorder, 3) have experienced AVH for at least one year, 4) have a score of two or more on the *current frequency* item of the auditory hallucinations subscale of the Psychotic Symptom Rating Scale at the time of initial assessment (representing voices occurring at least once a week), 5) have been deemed refractory to antipsychotic treatment (defined as still hearing voices despite 4–6 weeks of treatment with antipsychotics), 6) be on a stable dose of antipsychotic medication for the three months prior to study enrolment, 7) be right-handed, and 8) be able to give written informed consent. Exclusion criteria were 1) a diagnosis of substance abuse disorder, 2) prior head injury with loss of consciousness for more than five minutes, 3) immediate risk of harm to self or others.

For reasons discussed in the Results section, related to both the specific nature of this trial and a national COVID-19 lockdown, recruitment to the trial proved extremely difficult. After discussion with the trial's independent steering committee, the design of the study was revised to a case-study approach in which all patients enrolled in the trial would receive the neurofeedback intervention.

Participants who indicated an interest in the study were invited to visit Actualise Psychological Services (https://www.actualise.ie), the private neurofeedback clinic which was partnering with the research team to provide the neurofeedback. Participants who wished to proceed with the study then gave written informed consent to participate. They were formally assessed using the Edinburgh Handedness Inventory (Oldfield, 1971), the Quality of Life Enjoyment and Satisfaction Questionnaire (Revicki et al., 2014), the Psychotic Symptom Rating Scales (Haddock et al., 1999), the Auditory Hallucination Rating Scale (Hoffman et al., 2003), and the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983).

On the same day, a pretreatment (baseline) resting-state (eyes-open) EEG was recorded for approximately 5 minutes. NFT commenced a week later. Each session took place approximately weekly and consisted of a 5- to 10-min setup plus seven NFT rounds, with each round lasting 5 min. A week after completion of the last NFT session, posttreatment assessments were made employing the same EEG and clinical measures taken at baseline.

Participants

Four patients participated in the study (three male, one female). Patients were aged between 30 and 59 years of age, had their first episode between 18 and 27 years of age, were 100% right-handed, had received a formal diagnosis of a schizophrenia-spectrum disorder, and were currently taking clozapine. One patient smoked (15 cigarettes/day) and one patient used alcohol (16 ml ethanol/week). This data is reported here is in narrative format, rather than in traditional tabular form for data protection reasons. Other data on study variables relating to participants is reported in Table 1.

Table 1
Assessment Scores of Participants.

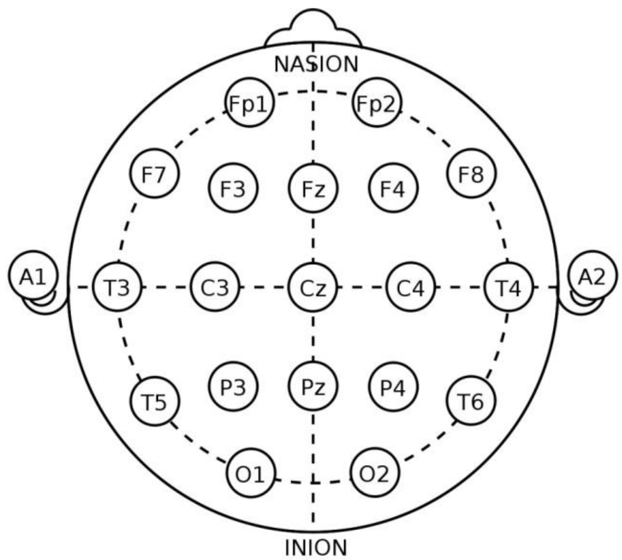
	Patient A 20 sessions		Patient B 11 sessions		Patient C 8 sessions		Patient D 14 sessions	
Study measures	Baseline	End	Baseline	End	Baseline	End	Baseline	End
PSYRATS-AH	21	15	21	28	20	16	23	27
PSYRATS-D	16	11	16	15	*	12	15	15
AHRS	20	24	21	20	15	10	33	31
HADS (anxiety)	10	13	5	13	10	12	10	5
HADS (depression)	5	5	4	5	8	10	9	8
Q-LES-Q-SF	50	64	84	61	25	70	54	59

Note. PSYRATS-AH = Psychotic Symptom Rating Scale – Auditory Hallucinations Subscale; PSYRATS-D = Psychotic Symptom Rating Scale – Delusions Subscale; AHRS = Auditory Hallucination Rating Scale; HADS = Hospital Anxiety and Depression Scale; Q-LES-Q-SF = Quality of Life, Enjoyment, and Satisfaction Questionnaire. * = missing data.

EEG Data Aquisition

All data were recorded and NFT administered using a Deymed Truscan 32-channel EEG amplifier (Deymed Diagnostics, Payette, Idaho). EEG data were collected simultaneously at 19 of the International 10-20 standard sites (Figure 1) using 19-channel Flexicaps (Deymed Diagnostics, Payette, Idaho; Jurcak et al., 2007).

Figure 1. *The 10-20 International System of EEG Electrode Placement*.



Truscan Acquisition (v.7.0.5.122) software recorded the data, which was read in real time by NeuroGuide software (Applied Neuroscience Inc., Seminole, Florida; v3.0). All amplifier parameters were consistent across all patients. Since all patients were regularly treated with psychoactive medication, a Laplacian montage was used to minimize widespread/unselective effects on the resting-state waveform (Yao et al., 2019).

All recordings took place in a quiet room while patients were seated in a comfortable chair that provided adequate support for the neck and shoulder muscles. Spontaneous EEG was acquired at rest with the patient's eyes open a week before starting NFT and a week after completion of treatment, where possible (only patient A completed the full 20-week treatment). Each recording included a minimum of 5 minutes of raw EEG data.

Neurofeedback Training

LORETA *Z*-score NFT was used for the treatment sessions. This method makes continuous calculations that compare the participant's EEG activity to a normative database. These norms are based on the participant's age and gender, with moment-to-moment statistical comparisons occurring during the NFT session. Positive feedback was provided when brain activity (depending on the protocol created ad hoc for each participant) moved closer to the normalised function (i.e., closer to $z = 0$). LORETA is a source localization method that estimates the location of the deep underlying brain generators (called modules or hubs) and networks of the patient's EEG activity within a given frequency band. This allows to translate qEEG data into a three-dimensional representation of the brain and locate the anatomical source of selected EEG activity.

NFT Protocols

Protocols for LORETA *Z*-score NFT were automatically created by NeuroGuide, based on baseline EEG recordings and on the patient's symptoms/complaints. Electrophysiological and behavioral information were combined and integrated together by NeuroGuide to create a protocol.

Brodmann areas to train (left and right hemisphere) were automatically selected by NeuroGuide using the *LifeSpan* normative database as a reference. Protocols involved the differential modulation of the absolute power, phase and intra-/inter-hemispheric coherence for delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–25 Hz), high beta (25–30 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta1 (12–15 Hz), beta2 (15–18 Hz), beta3 (18–25 Hz). All the protocols employed for each of the four patients recruited are available from the researchers on request.

Regions of Interest and Target EEG Measures

Based on previous research into EEG changes associated with AVH, we explored generalised alpha band activity (8–12 Hz) changes as measured by qEEG and also frontal alpha amplitude asymmetry between the left and right hemispheres (Fp1 and Fp2). We also investigated posttreatment changes in frontal/central/temporal delta (0.5–4 Hz) and theta (4–8 Hz) band power/coherence. Similarly, in an attempt to detect activity changes in speech/auditory related areas we tested for temporal beta band activity changes after NFT, exploring qEEG in T3, T4 and T5. Beta coherence between the left and right temporal cortices (T3-T4) were also explored. Finally, in line with previous schizophrenia qEEG research showing reduced alpha coherence in auditory cortical regions, we explored posttreatment effects on alpha coherence for the electrode pairs C3-C4, C5-C6, T3-T4, P5-P6, and F7-F8.

qEEG Data Analysis

The main EEG analyses focused on changes measured after NFT, focusing on absolute frequency band power, coherence and amplitude asymmetry changes. After treatment, changes in EEG absolute power were analyzed using NeuroGuide 3.0. Individual EEG files were edited to remove non-EEG artefact such as electromyographic and drowsiness-related signals. Edited data were then statistically analyzed for split-half reliability and test-retest reliability by NeuroGuide to assure consistency and integrity (Charter, 2003). A minimum of 60 seconds of artefact-free EEG data with a split-half reliability Pearson's coefficient ratio of at least 0.95 and test-retest reliability ratio of 0.90 was used as a cutoff value for data inclusion, which allowed to select enough data for EEG testing (Gasser et al., 1985; Thatcher et al., 2003).

Analysis of edited data was then performed by comparing the patient's EEG to the Lifespan Normative Database of "healthy normal" individuals (Applied Neuroscience Inc., Seminole, Florida). This database includes the EEG of 625 healthy subjects, acquired in both eyes-open and eyes-closed conditions, with age ranging from 2 to 82 years.

Measures of interest, that is, frequency band absolute power, coherence and amplitude asymmetry were derived from the EEG spectral analysis. NeuroGuide computes *z*-score statistical values derived from the standard normal distribution, setting the mean to 0 and standard deviation to 1. Thus, *z*-scores provided an estimate of a subject's EEG deviation from the age-matched values included in the normative database, that is, when absolute values of *z*-scores were 1.5 or greater ($|z| \geq 1.5$), the deviation was deemed statistically significant (Walpole et al., 2012).

Results

Feasibility of Recruitment

Recruitment to the trial and the NFT protocol being delivered to three patients were halted by the COVID-19 lockdown. For budgetary reasons, recruitment could not be started again once the lockdown had been lifted. However, significant difficulties had been experienced in recruitment prelockdown.

No patients were able to be recruited through Consultant-led efforts in local mental health teams. The three patients who were referred to the study through Consultant-led efforts were found not to meet the study inclusion criteria (cessation of AVH). Follow-up with Consultants indicated a variety of reasons for the unsuccessful recruitment. Consultants had been able to locate patients who they believed met the inclusion criteria for the study and provided them with information sheets about the study. However, patients typically declined.

Reasons for patients not wanting to take part in the study, as reported by the Consultants, varied. Many patients did not want to undertake repeated cross-city travel to attend the neurofeedback clinic where the treatment was to be delivered. Other patients were reported to want to do activities not related to their illness. Some patients simply did not find neurofeedback appealing. Paranoia seemed to be a specific barrier to some patients, due to concerns about the nature of the intervention. Patients were also not keen to enter a study in which they could be randomized to a wait-list condition and not receive the actual intervention. Despite the participant information sheet, some prospective participants also reported being unclear as to what the procedure involved. Consultants also reported their teams being demotivated by not being able to find patients interested in the trial, which led to reduced efforts at recruitment.

Recruitment was more successful from an outpatient clozapine clinic, which was attended in person weekly by one of the research team. However, most patients still did not meet the inclusion criteria for the study. This was because patients were either not reporting AVH or exhibited conditions that would prevent them from regularly attending the neurofeedback clinic (e.g., cognitive impairment, poor mobility or alertness). Overall, a total of 80 hours spent in recruitment activities resulted in the recruitment of four patients into the study.

Participants

Of the four patients who took part to the study, one completed the full 20-week NFT protocol (Patient A), one completed 11 sessions (Patient B), one completed 8 sessions (Patient C) and one completed 14 sessions (Patient D).

qEEG

We report the before-after qEEG results for each patient. At baseline, Patient A had increased theta power at frontal, central and temporal sites (Table 2), and increased temporal coherence (Table 3). At the end of the intervention, nearly all initially nonnormative power was normal in this patient

(Table 2). However, Patient A now had decreased delta power at temporal sites (Table 2) and widespread hypercoherence for all frequencies (Table 3). Before and after qEEG head maps are shown in Figure 2.

Patient B exhibited nonnormative theta power in a range of frontal, central and temporal sites both before and after NFT, as well as some nonnormative alpha and beta power in temporal regions (Table 2). The latter was largely normalized at the end of NFT (Table 2). There was nonnormative temporal beta coherence at the start, but not after NFT (Table 3). However, at the end of the trial there was nonnormative coherence between a range of other frontal, temporal and central areas in the theta frequency band (Table 3).

Patient C showed mostly normal power at the start of the trial, but had nonnormalized theta and delta power in a number of sites at the end of NFT (Table 2). At both the start and end of NFT, both normative and nonnormative coherences were detected (Table 3). Patient D showed nonnormative theta power at a range of sites and nonnormative delta coherence after, but not before NFT (Table 2). They showed nonnormative frontal amplitude asymmetry for the alpha frequency band before but not after NFT (Table 4).

Table 2
EEG Power (Z-Scores Pre-/Postneurofeedback Training)

	Delta				Theta			
Electrode	Patient A	Patient B	Patient C	Patient D	Patient A	Patient B	Patient C	Patient D
Fp1	-	-	-	-	2.38/ns	2.06/2.61	1.98/2.09	ns/2.24
Fp2	-	-	-	-	2.22/ns	2.01/2.60	-	ns/2.12
F3	-	-	-	-	2.20/ns	2.38/3.20	ns/2.45	ns/2.67
F4	-	-	-	-	2.22/ns	2.44/3.34	ns/2.34	1.97/2.62
F7	-	-	ns/2.53	-	2.53/ns	2.68/3.37	-	ns/2.03
F8	-	-	-	-	2.40/ns	2.55/3.44	-	-
Fz	-	-	-	-	1.98/ns	2.37/2.91	ns/2.53	ns/2.64
C3	-	-	ns/2.74	-	-	-	-	ns/2.43
C4	-	-	ns/2.45	-	-	-	ns/2.30	ns/2.09
Cz	ns/−2.27	-	ns/2.94	-	-	2.56/3.10	-	ns/2.30
T3	2.03/−2.07	-	-	-	2.03/ns	2.60/3.16	-	ns/2.11
T4	ns/−2.30	-	-	-	-	3.01/3.40	ns/2.35	ns/2.05
T5	ns/−2.35	-	-	-	-	2.87/2.62	-	ns/2.00
T6	ns/−2.06	-	-	-	-	3.47/3.71	-	-

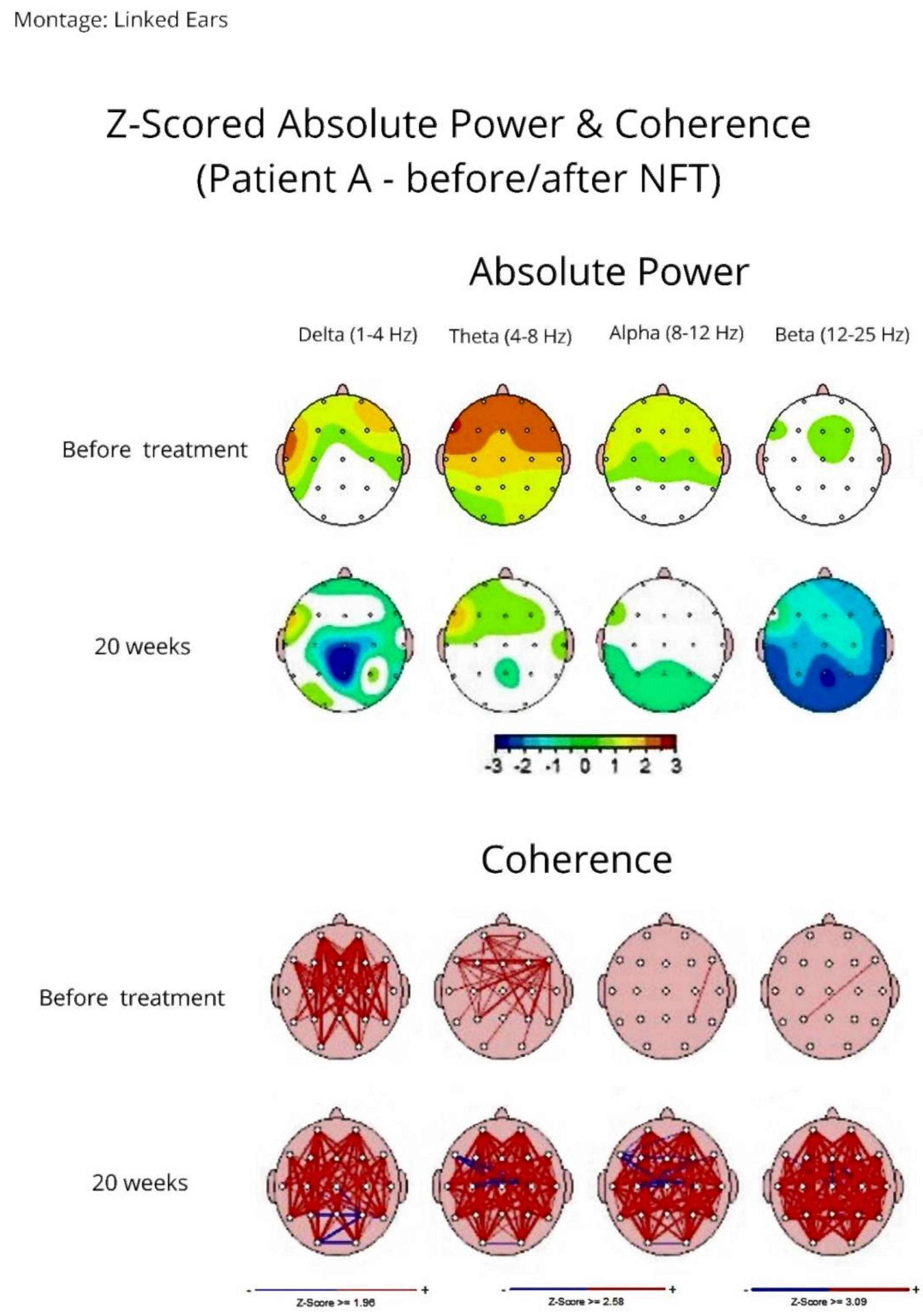
Note. ns = not significant.

Table 3
EEG Coherence (Z-Scores Pre/Postneurofeedback Training)

		Z-score Pre/Postneurofeedback Training			
	Electrode pair	Delta	Theta	Alpha	Beta
Patient A	Fp1-C3	ns/3.47	ns/3.94	ns/2.69	ns/2.66
	Fp1-T3	ns/2.65	ns/4.03	ns/3.99	ns/4.39
	Fp1-T5	ns/4.67	ns/6.04	ns/6.85	ns/7.65
	Fp2-C4	ns/2.72	ns/2.97	-	-
	Fp2-T4	ns/2.91	ns/4.24	ns/4.30	ns/5.56
	F3-T3	-	ns/2.28	ns/2.61	ns/2.55
	F3-T5	ns/2.73	ns/2.91	ns/3.24	ns/3.72
	F4-T4	-	ns/2.46	ns/2.75	ns/2.74
	F7-T3	-	-	-	ns/2.20
	F7-T5	ns/3.30	ns/2.33	-	ns/2.93
	F8-T4	ns/2.15	ns/2.23	ns/2.21	ns/2.41
	C3-C4	-	-	ns/−3.19	-
	T3-T5	ns/2.30	2.38/ns	-	-
	T3-T4	ns/4.64	2.22/ns	ns/3.38	-
	T5-T6	-	ns/2.33	ns/2.55	ns/2.33
Patient B	Fp1-C3	-	ns/2.57	-	-
	Fp2-C4	-	ns/2.47	-	-
	F4-C4	-	ns/−2.59	-	-
	F4-T4	-	ns/−2.28	-	-
	T5-T6	-	-	-	2.44/ns
Patient C	Fp1-T5	−2.02/ns	−1.96/−1.99	-	-
	Fp2-T6	ns/−2.22	-	-	-
	Fp2-P4	-	ns/−2.22	-	-
	Fp1-T5	−2.02/ns	−1.96/−1.99	-	-
	F4-T6	ns/2.09	-	-	-
	C3-C4	−2.18/−2.59	−2.18/−5.12	ns/−3.39	−2.33/ns
	T3-T4	-	-	-	−3.12/ns
	T5-T6	−2.72/−2.44	−2.46/−2.57	-	-
Patient D	Fp2-C4	ns/−3.05	-	-	-
	F4-C4	ns/−4.07	-	-	-
	C3-C4	ns/−3.74	-	-	-
	C4-F8	ns/−2.52	-	-	-
	C4-T6	ns/−2.15	-	-	-
	Fp2-C4	ns/−3.05	-	-	-

Note. ns = not significant.

Figure 2. *Before and After Treatment qEEG of Patient A After 20-Week Neurofeedback Training*.



Note. qEEG compares the data to normal controls with color coding based on *SD* - green color indicates regions where values of power were between 0 and 1 *SD*s above the database mean. Yellow color between 1 and 2 *SD*s; red color values of power between 2 and 3 *SD*s.

Table 4
Amplitude Asymmetry in the Alpha Frequency Band

Patient	Fp1 µV Sq (pre/post)	Fp2 µV Sq (pre/post)	*Z*-score (pre/post)
A	15.04/5.34	15.28/5.12	ns/ns
B	10.42/13.55	9.60/13	ns/ns
C	91.44/6.12	66.21/6	ns/ns
D	14.03/1.24	17/1.18	−2.47/ns

Note. ns = not significant.

Discussion

This study aimed to test the feasibility of using LORETA *Z*-score NFT as an intervention for AVH in people diagnosed with schizophrenia deemed treatment-resistant. Feasibility issues were identified with recruitment. The NFT itself was well tolerated, with no patients dropping out during the treatment and no adverse events being reported. Lessons were learned about how the feasibility of future trials of this approach could be improved.

Feasibility of Recruitment

A key barrier to recruitment was that potential participants did not want to undertake cross-city travel to attend the private neurofeedback clinic. The benefits of collaborating with a private clinic, in which extensive experience of providing neurofeedback was available, were hence offset by patients with the disabling effects of treatment-resistant schizophrenia not wishing to travel.

We had anticipated that this may be a barrier and planned to solve this problem by either encouraging family to support the patient or by providing private transport. However, this was not able to overcome this travel-related barrier. There is hence the need, in this population, to arrange for NFT to be administered where patients already regularly visit, in order to increase the feasibility of the approach.

A second barrier was the lack of clear understanding by the clinical teams involved in recruiting patients of what neurofeedback involved, to be able to appropriately explain it to potential participants. This was despite the researchers visiting the teams to explain the approach, and the details given in information sheets relating to the trial. In future trials, providing a live, on-site demonstration of NFT to clinical teams would seem to be useful and may help recruitment. Again, this was not possible in the current setup because of the off-site nature of the equipment. Having the equipment based at the clinical sites would again help overcome this barrier. This approach would fit with the notion that a strong collaboration and effective communication between clinical staff and researchers is key to meeting recruitment goals in schizophrenia studies/trials. This appears to be particularly the case with relatively novel treatments such as NFT.

Finally, in order to allow the NFT procedure to be better explained to prospective participants, to aid their informed decision as to whether to participate or not, we would recommend employing the experience of previous patients who have used NFT, as paid consultants to a trial. Their experience could help design the participant information sheet and also answer questions that potential participants might have. This was not possible in the current trial, as it had to be halted before patients could feedback on their experiences.

The interruption of the trial by the COVID-19 lockdown meant that we are not able to feedback to teams the results that were being found from the trial. It is also anticipated that this would increase interest in the trial and recruitment efforts.

Neurofeedback

After NFT, qEEG results showed normalization for some of the target frequency bands in our regions of interest. In particular, after 20 sessions/weeks, the increases in theta absolute power were normalized in Patient A (Figure 2). Previous qEEG research has found that widespread delta and theta activity is increased in nondepressed patients with schizophrenia (Begić et al., 2009), and our results might suggest that our neurofeedback intervention normalized deviant theta activity in multiple frontal, central, and temporal sites. However, in the same patient, delta power was also found to be abnormally decreased at temporal sites after treatment and while in Patient B no power change was found after treatment, theta power was greatly increased frontally, centrally and temporally after NFT in two other patients (Patients C and D).

Remarkably, there was marked heterogeneity in the four patients' EEG differences as compared to a normal template at baseline. Two patients showed widespread nonnormative theta power, whereas two others did not. This could represent altered EEG activity associated with specific subtypes of AVH (Jones, 2010). If so, this suggests the importance of personalizing NFT, based on an individual's EEG profile, rather than a one-size-fits-all approach. However, it may be that such differences were not associated with AVH or other symptoms, but with medication use, as clozapine and other psychotropic medications have been reported to impact EEG readings (Aiyer et al., 2016; Kim et al., 2019). To minimize widespread effects of medication however, we used a Laplacian montage, which does not rely on one single reference point but uses nearby electrodes as a combined reference. As such, this montage is more sensitive to local variations in EEG activity and is recommended when recording from patients regularly treated with psychoactive drugs (Yao et al., 2019).

Of note, we found that some EEG activity which differed to a normal template at baseline no longer differed at the end of NFT. Conversely, some EEG activity that was nonnormative at baseline did differ at the end of NFT. In this regard, it is worth considering how targeting nonnormal activity in one region or band may result in compensatory brain activity resulting in nonnormal activity in other regions or bands and the complaint-level changes associated with this.

Important considerations may arise from the reduction in temporal delta power and the increase in coherence after 20 sessions of NFT in Patient A, and from the movement away from a normal qEEG profile in Patients C and D after 8 and 14 NFT sessions, respectively. These results suggest that delta and theta abnormalities, at least in some patients, might arise from separate neural generators, separate neurochemical imbalances or from differential modulation of brain activity associated with pharmacotherapy. Of note, previous research employing LORETA functional imaging found region-specific changes in beta power when nonmedicated patients where compared with patients treated with clozapine (Tislerova et al., 2008), which suggests that interactions between NFT and clozapine cannot be ruled out in some patients. Such considerations however, should be confirmed in a heterogeneous population studied at a group level and also speak to the need to consider how treatment duration and ad hoc protocols should be optimized in the attempt of balancing power and coherence changes.

In conclusion, the present study suggests that LORETA *Z*-score NFT is tolerable in people diagnosed with schizophrenia with treatment-resistant AVH. However, for research to be feasible in this population, both patients and clinical teams involved in recruitment need to better understand what the process of NFT involves. Demonstrating and performing NFT on-site, for both patients and clinical teams may help overcome this barrier. We also recommend that individual-level analyses be undertaken, in addition to group-level analyses, and the potential for compensatory EEG changes examined.

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NeuroRegulation

Interactive Brain Stimulation Neurotherapy Based on BOLD Signal in Stroke Rehabilitation

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Abstract

Interactive brain stimulation is a new generation of neurofeedback characterized by a radical change in the targets of cognitive (volitional, adaptive) influence. These targets are represented by specific cerebral structures and neural networks, the reconstruction of which leads to the brain functions' restoration and behavioral metamorphoses. Functional magnetic resonance imaging (fMRI) in the neurofeedback contour uses a natural intravascular tracer, a blood-oxygenation-level-dependent (BOLD) signal as feedback. The subject included into the "interactive brain contour" learns to modulate and modify his or her own cerebral networks, creating new ones or "awakening" pre-existing ones, in order to improve (or restore) mental, sensory, or motor functions. In this review we focus on interactive brain stimulation based on BOLD signal and its role in the motor rehabilitation of stroke, briefly introducing the basic concepts of the so-called "network vocabulary" and general biophysical basis of the BOLD signal. We also discuss a bimodal fMRI-EEG neurofeedback platform and the prospects of fMRI technology in controlling functional connectivity, a numerical assessment of neuroplasticity.

Keywords: interactive brain stimulation; cerebral networks; functional magnetic resonance imaging (fMRI); BOLD; bimodal fMRI-EEG neurofeedback platform.

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Introduction

Interactive brain stimulation (IBS) is a recently developed type of neurofeedback that involves the organization of a feedback "target" based on a hemodynamic response signal recorded by functional magnetic resonance imaging (fMRI). Biofeedback technologies in general, and neural interfaces in particular, have recently attracted increasing attention (Sulzer et al., 2013; Wang, Collinger, et al., 2010). The term "interactive brain" is closely related to neural interface technologies (or, in other words, neuro-prosthetics technologies), which are considered in the context of the prospects for creating algorithms for controlled neuroplasticity. The search for these neurofeedback algorithms is especially in demand for the recovery of the consequences of acute cerebrovascular accident, since stroke-induced motor, cognitive, and sensory impairments deprive survivors of independence for many years and increase the burden on their caregivers. It is generally accepted that the basis for motor functions recovery and improvement after a stroke is the innate anatomical and physiological plasticity of the brain enhanced by motor exercises and sensory stimulation (Kim & Kang, 2022; Kwakkel & Kollen, 2013; Nudo, 2003; Nudo et al., 1996; Schaechter et al., 2006; Sokolova et al., 2010;

Wang et al., 2006). This is the basis of the principle of poststroke rehabilitation, although it is known that even with intensive special training and general aerobic exercises recognized as the "gold standard" of poststroke rehabilitation, no more than 20% of surviving patients recover, and 33–60% of them remain disabled (Duncan et al., 2000; Feigin et al., 2016, 2017; Kwakkel & Kollen, 2013). In this regard, there is a strong need to identify the main involved brain structures and stimulation methods that can radically affect the current efficiency of the neurorehabilitation. The identification of such cerebral formations and, most importantly, their real-time interactions requires using modern technologies of functional noninvasive neuroimaging and neurofeedback systems.

Neuroimaging and Neurofeedback

FMRI of the Brain*.* FMRI is based on the fact that a decrease in blood oxygenation produces the increase of brain MRI image contrast (Ogawa & Lee, 1990; Ogawa et al., 1998). This contrast, which depends on the level of blood oxygenation (blood oxygenation level-dependent, BOLD), results from the conversion of diamagnetic oxyhemoglobin into paramagnetic deoxyhemoglobin. It is assumed that the observed signal changes are closely correlated with the neuronal activity (Bentley et al., 2016; Gauthier & Fan, 2019; Lecrux & Hamel, 2016; Miller et al., 2001), and, in fact, BOLD is a natural MRI contrast that indirectly reflects the level of oxidative processes in the brain tissue. At the same time, the fMRI experiment makes it possible to localize cerebral areas up to one cubic millimeter with high spatial resolution, including deep parts of the brain (Birn et al., 1999; Buckner, 1998; Matthews & Jezzard, 2004; Ogawa et al., 1998). Today, it can be argued that BOLD signal recording is the optimal tool of mapping the neuronal activity, precisely, the functional state of neural ensembles (NE) during volitional reconstruction of cerebral networks (Shtark et al., 2012).

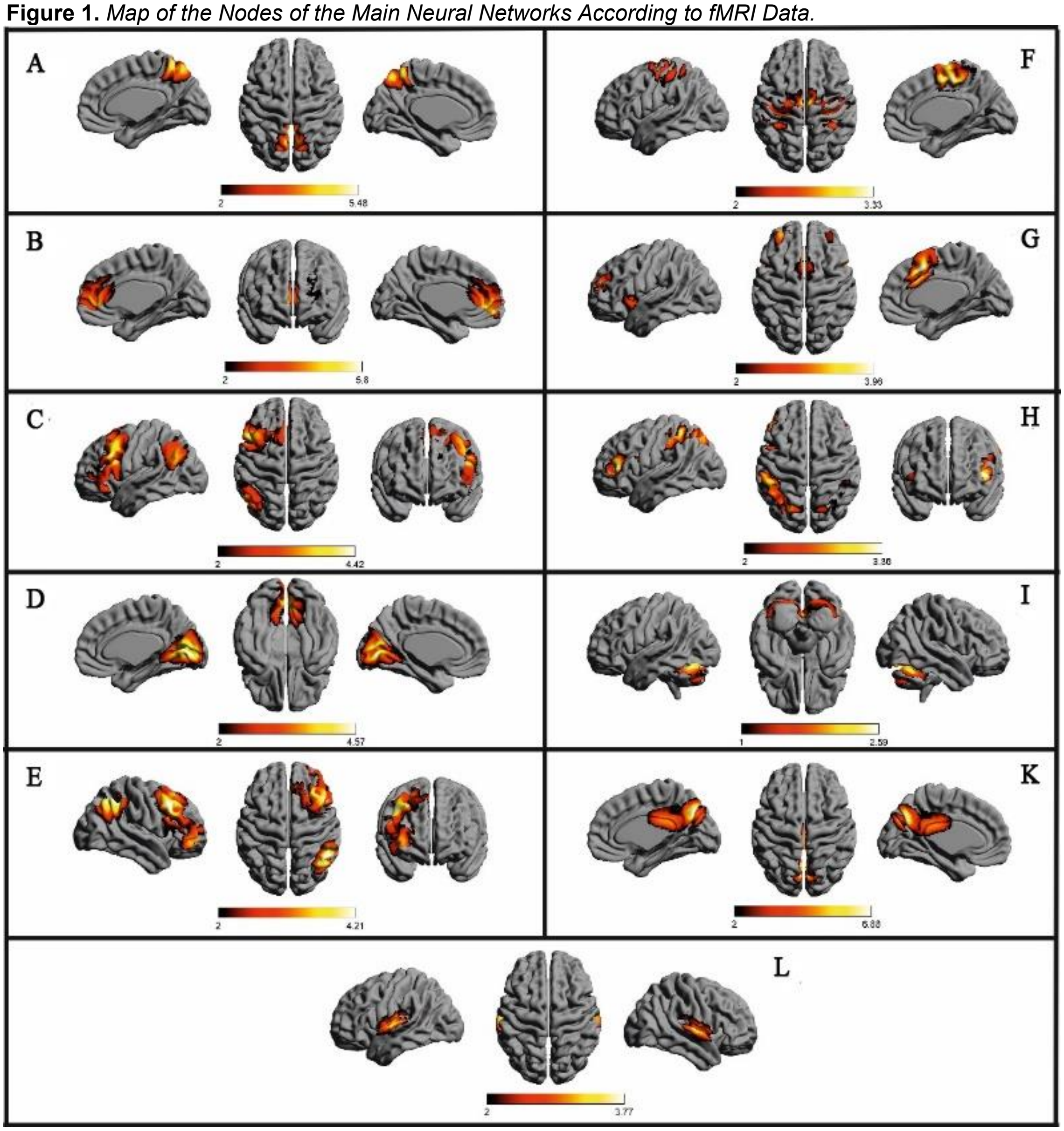
Electroencephalographic Neurofeedback; Bimodal fMRI-EEG Neuroimaging Platform EEG*.* The accuracy of mapping the brain activity zones based on electroencephalogram (EEG) recording from the surface of the scalp is very conditional, because the resultant is the sum of the signals from a huge number of neurons which is distorted due to the resistance of the cerebrospinal fluid, meninges, skull bones, muscles, and scalp. To some extent the problem is solved by increasing the number of EEG leads to 64 or even more (Luu et al., 2001), but in terms of spatial resolution the MRI technology, including fMRI, is beyond competition. Besides, applying correlation analysis in fMRI gives a clear idea of the relationship between distant brain regions (functional connectivity). However, its ability to determine the direction of the information flow (effective connectivity) in each NE is very limited. From this point of view, the EEG, which has a higher temporal resolution, is better suited for studying the dynamic processes of the brain (Lopes da Silva, 2013).

Obviously, the combination of both methods seems attractive for observing spatiotemporal neural dynamics of the human brain (Herrmann & Debener, 2008). This became possible due to improvements in EEG recording devices and methods of processing the artifact noise generated in the magnetic field of an MR scanner (Bonmassar et al., 1999; Ives et al., 1993; Ullsperger & Debener, 2010). Studies have shown that EEG-fMRI "concordia" links electrophysiological and hemodynamic measurements together and generates new understanding of brain function, which is not possible if these technologies are used separately (Huster et al., 2012; Philiastides et al., 2021; Ritter & Villringer, 2006; Shtark et al., 2015). Considering that both EEG and fMRI signals are directly related to the activity of specific neural associations and act as physiological markers of the functional anatomy of the brain, these signals are of specific interest as neurofeedback targets either individually or together. Whereas EEG neurofeedback has a long history (Evans et al., 2019; Shtark, 2019), the IBS based on the fMRI signal is still evolving. However, before moving to the essence of IBS based on the BOLD signal in poststroke motor rehabilitation, it is feasible to discuss the network organization of the brain and its changes after a stroke.

Network Organization of the Brain and Its Reconstruction After Stroke

Major Cerebral Networks*.* Modern neurophysiology considers the brain macrostructural organization as a composition of interacting neural networks (fMRI products), each of which includes several areas that are functionally interconnected and have a certain specialization, which is manifested by activation or deactivation in response to a specific task. Network neuroscience was initiated in the 1990s, when the first cerebral network, the sensorimotor network (SMN), was described (Biswal et al., 1995; Golanov et al., 1994). Later other networks were discovered that determine different levels of brain organization, from small NE to large-scale networks, including widely spread areas of cortical and subcortical structures that provide mainly complex cognitive operations (Buckner & DiNicola, 2019; Marek & Dosenbach, 2018; Menon, 2011; Petersen & Sporns, 2015; Raichle et al., 2001). The main networks are frontal-parietal network (FPN) or central executive network, (CEN), salience network, cinguloopercular network (CON), default mode network (DMN), ventral and dorsal attention network (VAN, DAN), visual network (VN), and auditory network (AN), see Figure 1.

Figure 1. *Map of the Nodes of the Main Neural Networks According to fMRI Data.*



Note. A - default ventral network (vDMN): precuneus, superior parietal lobule; B - dorsal default network (dDMN): anterior cingulate, middle and superior frontal gyrus; C - left fronto-parietal network (LFPN): inferior, middle and superior frontal gyrus, infero-parietal lobule, supramarginal gyrus; D - primary visual network (PVN): wedge, lingual and posterior cingulate gyrus, precuneus; E - right fronto-parietal network (RFPN): middle, inferior and superior frontal gyrus, inferior parietal lobule, supramarginal gyrus; F - sensorimotor network (SMN): middle frontal, postcentral and precentral gyrus; G - anterior significant stimulus identification network (ASN): cingulate gyrus, superior, inferior and middle frontal gyrus, insular cortex; H - visuospatial information processing network (VSN): inferior and superior parietal lobule, inferior and middle frontal, postcentral gyrus; I - cerebellar network (CN): cerebellar clivus; K - precuneus network (PN): precuneus, posterior cingulate gyrus; L - auditory network (AN): superior temporal gyrus, insular cortex, postcentral gyrus, Heschl gyrus, precentral gyrus (Bezmaternykh et al., 2018).

The FPN includes the dorsolateral prefrontal and posterior parietal cortex, and it is one of the most important centers of cognitive control that ensures the alignment of goal-directed behavior that is relevant to the task. The FPN interacts closely with the attentional, visual, sensorimotor, and auditory networks, as well as with the cortical regions nearby, and its activity is characterized by a reciprocal relationship with DMN activity (Marek & Dosenbach, 2018).

One of the most extensive and well-studied is the DMN which, according to recent data, includes several subnetworks and has numerous connections with other cerebral networks (Buckner & DiNicola, 2019). The DMN belongs to the so-called “resting networks,” the activity of which is recorded in the state of calm wakefulness (Raichle et al., 2001). DMN is believed to provide "introspective" cognitive processes involving mental resources that are far beyond direct sensory perception of the environment, such as prediction, self-perception, and autobiographical memories, hypotheses about the thoughts and feelings of another person (Buckner & DiNicola, 2019; Molnar-Szakacs & Uddin, 2013; Raichle et al., 2001). One of the main properties of DMN is its deactivation in response to a task that requires concentration on external stimuli from the environment. In this view, there is a need of the whole variety of options mentioned above under the conditions of long-term "training" in the MRI tomograph.

Structural and Dynamic Parameters of Neural Networks. The modern neuroscience usually considers the brain network organization in terms of graph theory, the essence of which is the mathematical modeling of paired relationships between objects (Alionte et al., 2022). Bassett et al. (2006) described interactions within cerebral networks in view of the “small world” concept. From the small world perspective, the cerebral network model is a system of nodes and connections (vertices and edges) where most of the edges are assembled to form small amounts of strongly connected clusters, while the rest are involved in maintaining connections between them (Sporns & Honey, 2006). In a more conditional “neuroanatomical” language, nodes (clusters) in relation to neural networks are represented by neurons or anatomical regions of the brain, and edges (connections) are represented by axons (tracts). Thus, in the neural architecture any network can be defined as structurally separated areas of the brain that exhibit activation patterns that correlate over time (Alionte et al., 2022). These activation patterns can be measured using fMRI, and they necessarily have direct connections, which, by the way, can also be discovered using diffusion-weighted MRI methods.

Temporal correlations of activation of neural network nodes dispersed in the brain are described by the concept of functional connectivity (FC) which is defined as a statistical relationship between distant neurophysiological events (Friston, 2011). At the same time, integration paths in a complex hierarchically built system are better understood in terms of effective connectivity (EC) which explains both the correlation and vector components of the information flow between brain regions (Friston, 2011). Obviously, the basis for both dynamic characteristics of the neural networks viability is provided by structural connectivity (SC) represented by the corresponding signal conductors (paths), but it is neither sufficient nor a complete description of connectivity in relation to the purpose of the neural network (Friston, 2011). Understanding that the brain functions as a network of interconnected neural circuits is critical in determining approaches to the neurofeedback and IBS after a stroke, since structural damage to a single node (or several nodes) in a network can affect all the structures of this network, and vice versa, while the nods outside the affected network can take over the functions of the affected nods providing the recovery.

Cerebral Networks and Stroke. From the view of the brain network organization, stroke can no longer be considered as an exclusively focal disease of the central nervous system. The existence of various functional connections between nodes within a particular network (for example, motor areas of the sensorimotor network) and complex internetwork interactions can largely explain the global nature of changes in the brain and allows considering stroke as a disease of the whole brain, a "network disease."

On the one hand, damage to a certain area of the brain due to stroke results in a dysfunction of remote areas functionally related to the affected node; on the other hand, the remaining intact nodes of the damaged network are able to restore the impaired function (Carter, Astafiev, et al., 2010; Carter, Shulman, et al., 2012; Guggisberg et al., 2019). This was convincingly demonstrated in an experiment on mice where motor relearning after a stroke in the primary motor cortex (M1) was associated with activation of the medial premotor cortex (mPMC), which under normal conditions does not play a significant role in the implementation of movement, and ischemia of mPMC itself does not lead to paralysis (Zeiler et al., 2013). Modeling the network effects of damage showed that the lesions induce specific patterns of altered FC between distant cortical regions, often affecting both hemispheres. At the same time, the degree of these effects depends, among others, on localization and partially can be predicted by the properties of the structural network of the lesion site. In particular, lesions near the temporoparietal junction cause particularly severe and widespread changes in FC, while lesions in primary sensory or motor areas remain more localized (Alstott et al., 2009).

Functional neuroimaging based on the BOLD signal provides important information about the dynamics of the reorganization of cerebral networks after a stroke. It was shown that during one year after subcortical ischemic stroke, as movements are restored, the motor network gradually acquires a more complex, chaotic structure as compared to healthy people (Wang, Yu, et al., 2010). Apparently, such chaotic connections in a poststroke brain result from a formation of many new connections, or activation of preexisting connections, not active under normal conditions, that compensate for the destroyed nerve pathways. These new connections are less stable, but they are effective and provide at least partial restoration of the impaired function (Fornito et al., 2015; Guggisberg et al., 2019; Li et al., 2014; Rowe, 2010). In general, the poststroke reorganization of motor networks is reduced to a decreased inter- and intrahemispheric FC of the motor areas of the ipsilateral hemisphere (Carter et al., 2010; Larivière et al., 2018; Siegel et al., 2016; Tang et al., 2016; van Meer et al., 2010; Yuan et al., 2021) and an increased intra-hemispheric connectivity of contralateral motor areas (van Meer et al., 2010). It is noteworthy that the FC between motor areas and cognitive networks, specifically DMN, salience network, VAN, and DAN, weakens (Almeida et al., 2017; Cheng et al., 2021). At the same time, it was suggested that functional improvement after a stroke is provided by the preservation/restoration of the FC of motor and nonmotor networks (Almeida et al., 2017). Larivière and colleagues drew attention to the lack of proper reciprocal inhibition in the DMN after activation of the motor network, which is apparently associated with insufficient signal strength of the latter (Larivière et al., 2018). The evolution of the motor network poststroke reorganization is manifested as the restoration of the motor areas activity and an increase in their interhemispheric FC, which strongly correlates with the improvement in motor function (Carter et al., 2010; Guggisberg et al., 2019; van Meer et al., 2010; Zhang et al., 2016). Thus, by affecting the motor areas and/or their connections based on IBS it becomes possible to noninvasively and purposefully modulate the course of neuroplasticity after a stroke.

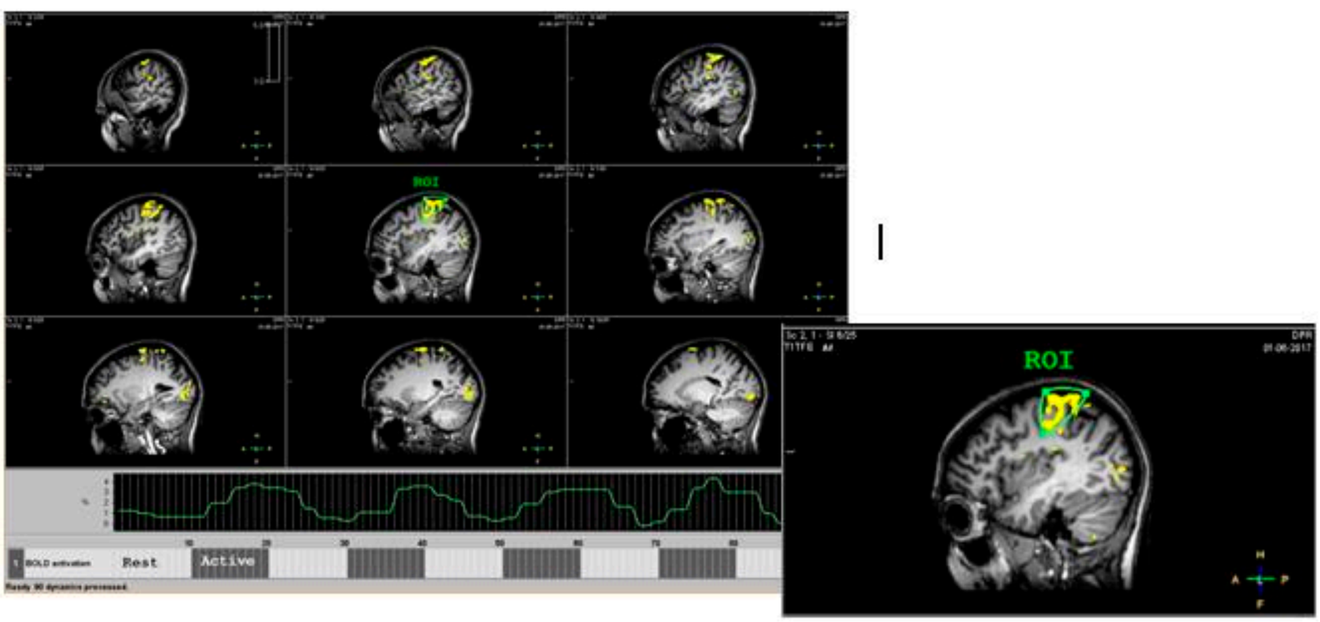
Neurofeedback Based on BOLD Signal in Poststroke Motor Rehabilitation

BOLD signal neurofeedback, or IBS, is a new generation of neurotherapy in the sense of a radical change of the target; from the traditional volitional influence on the peripheral domains characteristics (cardiovascular, respiratory, or muscular system) to the control of the brain region of interest (ROI). In the fMRI training paradigm, during performance of task the BOLD signal provides a subject information about the current brain activity almost in real time (response delay is only 4–6 s). At the same time, the fundamental advantage of fMRI over other methods of functional neuroimaging (EEG, functional near-infrared spectroscopy [fNIRS], magnetoencephalography [MEG]) is related to its high spatial resolution, which makes it possible to map activation patterns and show functional connections between cerebral network nodes with an accuracy up to several millimeters, including subcortical structures. At the same time, fMRI IMS not only allows to focus on the ROI in the research paradigm with good accuracy, but also provides “the necessary flexibility to adapt to frequent changes in brain network configurations that are typical for newly formed networks" (Paret et al., 2019). Here can be seen the prospects of controlling not only individual cerebral structures, but also the dynamics of functional connections between them, as well as the activity and coherence of neural networks, become well-formed (Mel'nikov et al., 2017). Without going into details of the technical and mathematical support of fMRI training, the next section will briefly touch on the methodological foundations of constructing sessions of IBS.

General Principles for Organizing IBS Sessions Based on the BOLD Signal. Defining a target (ROI) for BOLD IBS is determined by the specific therapeutic task and is usually based on the relationship of the selected brain structure with the target symptom(s). At the same time, the design of the fMRI-IBS training can be built specially to teach a patient to manage both "tonic" symptoms that are stabile (for example, hemiparesis, neglect, major depression episode, etc.), and "phasic," that are symptoms periodically and quickly developed (for example, hallucinations, obsessions, tics, etc.). Finally, IBS protocols can be aimed at enhancing the existing compensatory models (Fovet et al., 2015). The ROI for a particular subject is identified by selecting the desired structure according to MRI data or by functional localization during a separate short fMRI session aimed at determining the gray matter volume for an individual performing the task (Mel'nikov et al., 2017). A combination of the two methods is also possible. Some protocols use more than one target ROI (Rance, et al., 2014; Scharnowski et al., 2015). In addition to the target ROI, another one is recruited which obviously does not participate in the performance of the target function but serves to level the activation estimation error due to global processes in the brain. The network neurofeedback lexicon is presented more distinctly in the studies where the subject receives back the signal of the strength of the connection between the nodes of his/her cerebral network (Koush et al., 2013; Liew et al., 2016; Morgenroth et al., 2020).

Existing studies in the fMRI neurofeedback indicate the possibility of presenting a feedback signal in visual, auditory, and tactile modalities (Stoeckel et al., 2014). But perhaps the most common is the visual form. The signal metaphor can vary in complexity, from a simple graph or thermometer to game scenes and realistic maps of brain activation (Yoo & Jolesz, 2002). Before and after IBS sessions the subject passes behavioral and/or psychological tests depending on the symptom being studied, for a quantitative assessment of the dynamics of the trained skill. A number of research protocols suggest a follow-up in several months after training completion. Before the start of the training, a preliminary "calibration" MRI session is performed during which the subject's individual brain structure is specified, the ROI is determined, and the equipment is adjusted for a particular participant (Figure 2).

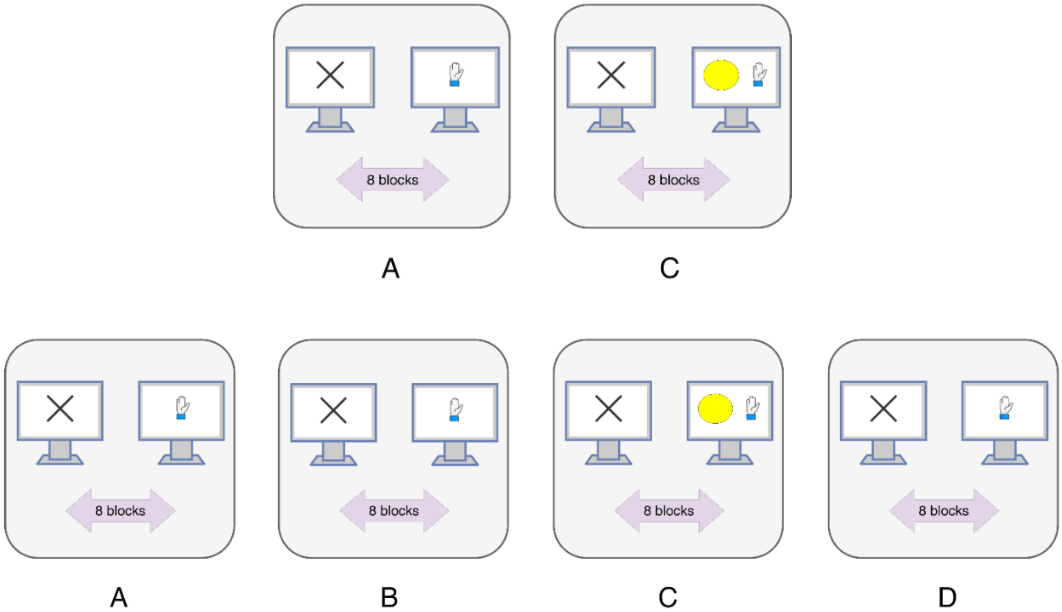
Figure 2. *Isolation of a ROI During an fMRI-IBS Calibration Session.*



Note. Actual hand work causes activation of the M1 (Brodmann area 4) which appears as a yellow area at the anatomical image of the brain. The operator can manually outline the ROI to later use it as a biofeedback target (green outline around the yellow area). The magnitude of the BOLD signal in the ROI is shown as a curve at the figure bottom (Savelov et al., 2019a).

In the first as well as in the final session, the characteristics of interest are measured for a subsequent detailed offline analysis. In the poststroke motor recovery paradigm, training sessions are performed daily or at 1- to 2-day intervals, typically for 3–4 weeks. During each session, the participant alternates periods of active regulation using a feedback signal and rest periods (Figure 3). One training session takes 40–60 min, including preparation. In several protocols, a "transfer run" can also be provided to test the independence of the trained skill compared to the experimental settings during which the subject does not receive feedback when performing the task.

Figure 3. *IBS Design Optimized for Teaching Self-Regulation Skills (Top) and for Demonstrating the Degree of Skill Formation (Bottom).*



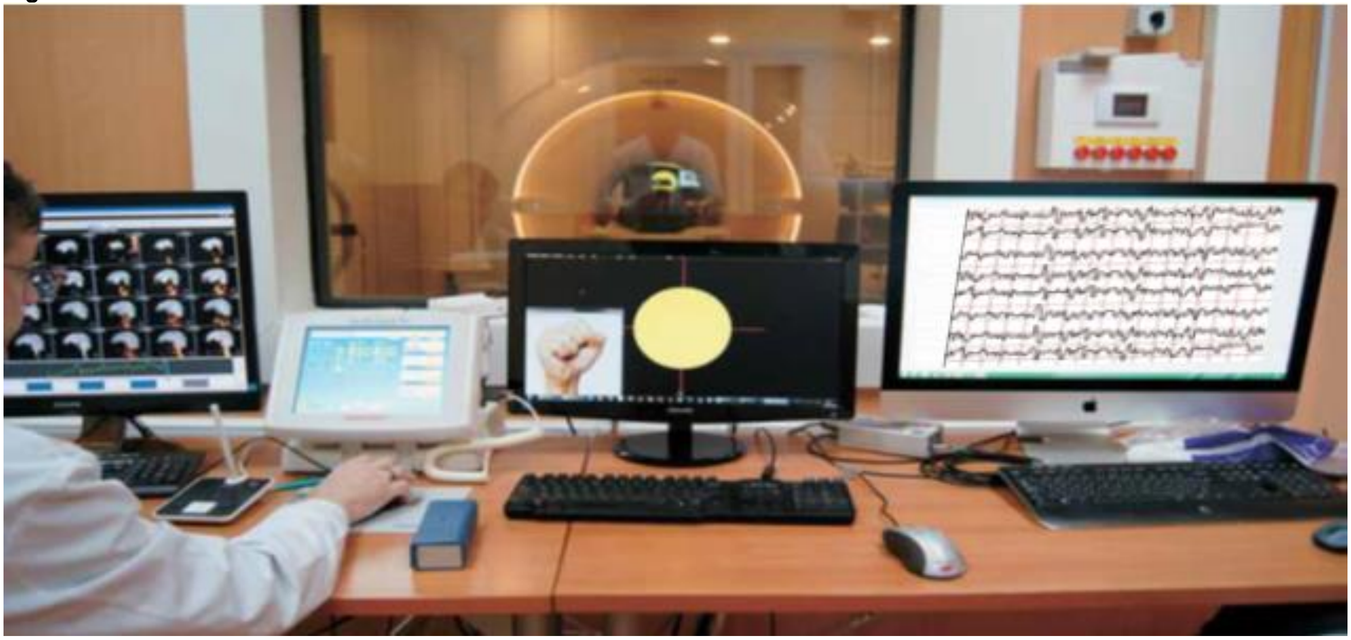
Note. A - functional localization: eight 25-s cycles of "rest–work" (squeezing the ball with the hand). B, C, D - hand movement imagination with feedback (C) and without it (B, D): eight cycles of 25 s of rest / 75 s of work (Savelov et al., 2019a).

For most research and therapeutic tasks, the described monomodal training model is sufficient. However, the simultaneous registration and analysis of two neurophysiological signals at once leads to a qualitatively different level of understanding the mechanisms of neuroplasticity and reorganization of cerebral networks under the impact of IBS. Let us analyze the neurofeedback circuit based on the bimodal platform for fMRI-EEG signals recording.

Bimodal fMRI-EEG Neurofeedback Platform: Advantages and Prospects. Improvements in the mathematical and statistical processing of fMRI and EEG signals made it possible to combine the strengths of each of the technologies (meaning their high spatial and temporal resolution, respectively) and obtain more information about the current brain activity (Figure 4). To organize NFB based on the bimodal fMRI-EEG platform the key problem is to ensure a high level of synchronization between both platform subsystems and the protocol. If this requirement is fulfilled, the simultaneously arriving signals of each modality reflect the brain activity caused by the protocol task with minimal delay. In most studies involving the simultaneous fMRI and EEG recording the real-time feedback is presented only for one of the modalities, and the signals of the other modality are processed offline to assess the electrophysiological (EEG) and hemodynamic (BOLD) correlates of the NFB (Mano et al., 2017; Shtark et al., 2015; Zotev et al., 2014).

As far as we know, the first experimental online integration of signals of both modalities for the purposes of NFB was performed by Zotev et al. (2014). In Zotev's experiment (2014) healthy volunteers practiced emotional self-regulation by simultaneously controlling the BOLD fMRI signal in the ROI of the left amygdala and EEG frontal power asymmetry in the high beta range (21–30 Hz). In this research the participants were asked to evoke positive emotions using happy autobiographical memories. The integrated signal flow of both modalities was presented to the participants at the screen as a red bar, the level of which had to be raised to the target (blue line). The results of this study showed the fundamental feasibility of simultaneous regulation of hemodynamic (BOLD) and electrophysiological (EEG) activity of the human brain and inspired optimistic prospects for the development of new research paradigms and cognitive approaches to the treatment of major neuropsychiatric disorders (Zotev et al., 2014). Later, the results of using the bimodal NFB fMRI-EEG platform in the stroke rehabilitation were published, which we discuss in the next section.

Figure 4. *IBS Session on the Bimodal fMRI-EEG Platform.*



Note. The patient in the MRI tomograph is asked to imagine the movement of the paretic hand. The monitor in the center of the picture shows a hand-shaped hint and a feedback metaphor (a yellow circle), the size of which depends on the success of the hand movement imagination task, being proportional to the magnitude of the BOLD signal in ROI. The same image is duplicated on the patient's monitor behind the tomograph. The monitor on the left displays brain activation zones according to the BOLD fMRI signal; right monitor shows simultaneous EEG recording (Savelov et al., 2019a).

Neurofeedback by BOLD Signal After a Stroke: "Birth" of an Interactive Brain. The first study that confirmed the possibility of poststroke restoring of the functions of the brain motor areas using fMRI NFB was published in 2012. Six subjects (two patients with hemiparesis after a subcortical stroke in more than one year and four healthy volunteers with an average age of 25.3 years) during three training sessions were instructed to increase the activity of the ventral premotor cortex (vPMC), one of the secondary motor areas. All participants learned to voluntarily increase the BOLD signal in the vPMC, however, the strength of the pinch grip (assessed as a behavioral end point) remained unchanged in one patient and one volunteer. An interesting finding of this study was revealed while comparing the levels of intracortical inhibition/facilitation with the degree of change in the BOLD signal during training. It turned out that initially high level of intracortical facilitation or a low level of intracortical inhibition assessed using transcranial magnetic stimulation (TMS) correlated with the success of self-regulation of the BOLD signal in vPMC. Moreover, the increase of the BOLD signal in vPMC, in turn, suppressed intracortical inhibition, revealing the reciprocal relationship of these two processes. Since the study was conducted during the development of the method and the main aim was to study the feasibility of learning the self-regulation of vPMC activity, the relationship of the studied neurophysiological changes with the functional outcomes was not evaluated. In addition, the limitations of the applied TMS protocol did not allow the authors to understand whether the increase of M1 excitability during fMRI IBS training was direct or indirect, through the modulating effects of vPMC (Sitaram et al., 2012).

Another study included four patients who had a stroke more than 6 months before the start of the training (two 2-hour sessions during 1 week). Participants practiced increasing the strength of the functional connections of two regions: 1) the motor cortex at the border of the affected area and 2) the thalamus of the same hemisphere. Three patients showed a significant increase of the characteristic value; two patients were able to reproduce this effect without feedback during a special test (transfer run), which confirmed the formation of the self-regulation skill. At the same time, the training was found to be most effective in subjects who demonstrated the most severe impairments of motor functions before the start of the training (Liew et al., 2016). Regretfully, the relations between neurobiological and behavioral characteristics were not considered in these studies. However, it should be emphasized that it was the first study of using fMRI NFB in stroke rehabilitation where network vocabulary was used and patients were trained to control not the signal from the motor areas, but the FC between them.

A recent pilot study by Lioi et al. (Lioi, Butet, et al., 2020; Lioi, Fleury, et al., 2018) was aimed to educate patients with poststroke hemiparesis to self-regulate the activity in the ipsilateral supplementary motor area (SMA) using both the BOLD signal and the EEG signal (in case the EEG signal of the event-associated cortical rhythm desynchronization [ERD] was assessed). The study included two patients with left-sided hemiparesis after a stroke that occurred more than 6 months before the start of the training. During two training sessions (5 min each) the patients were instructed to imagine the movement of the paretic arm, while the result of ROI activation was presented to them in the form of a visual signal. The first part of the study (Lioi et al., 2018) proved the feasibility of such a paradigm in patients with hemiparesis and revealed their high motivation to participate in training sessions based on animation and feedback. In the second part (Lioi et al., 2020) the study protocol was extended: after the first bimodal training session three NFB EEG sessions were conducted, followed by fMRI-EEG bimodal training (five training sessions in total). Motor functions were assessed before and after the training. A very important feature of the NFB design, in our opinion, was an adaptive character of training, specifically, the reward for the activation of each of the two ROIs chosen by the researchers changed consequently: at the first training session SMA activation was rewarded higher, and at subsequent sessions the reward for M1 activation was greater. For all four patients (stroke at least 1 year before the training; two of them had ischemic stroke) their work on the strategy of paretic arm movement pattern resulted in an increase in the and ERD signals in the SMA and M1 (according to the Wilcoxon test p = 0.004 and 0.006, respectively). For two patients who showed the most significant increase in M1 activation in the ipsilateral cortex at the end of training there was also a functional improvement according to the Fugle-Meyer test (hand subscale): from 19 to 25 points for one patient and from 50 to 53 for the other. The patient with less marked activation of M1 showed no changes in hand function after training. This outcome may have been affected by a significant impairment of the corticospinal tract (CST) integrity—the fractional anisotropy (FA) asymmetry index was 0.105. It is relevant to note that the two patients mentioned above had relatively intact CST, with FA asymmetry index 0.04 and 0.06, respectively. However, for the fourth patient the CST preservation (FA index = 0.05) was not sufficient for the motor function progress: the Fugle-Meyer score decreased from 41 to 37, and M1 activation in NBU sessions was found weak (although SMA was activated well). It can be assumed that this failure is associated with the cortical localization of the lesion (three other patients suffered a subcortical stroke).

A fundamentally different research, treatment and rehabilitation approach characterized by a change the targets, from cognitive impact of specific brain areas to a more global and holistic view of cerebral networks, was demonstrated in the works of Savelov et al. (Savelov, Shtark, Kozlova, et al., 2019; Savelov, Shtark, Mel’nikov, et al., 2019b). The outcome of IBS on the bimodal fMRI-EEG platform was assessed not only in terms of restoration of the paretic arm functioning, but mainly in terms of FC dynamics and remodeling of cerebral network elements dispersed throughout the brain (Figures 5–8).

Figure 5. *Distribution of Activated Voxels in the Patient's Brain During Actual Work with the Paretic Limb at Different Stages of the IBS Course*

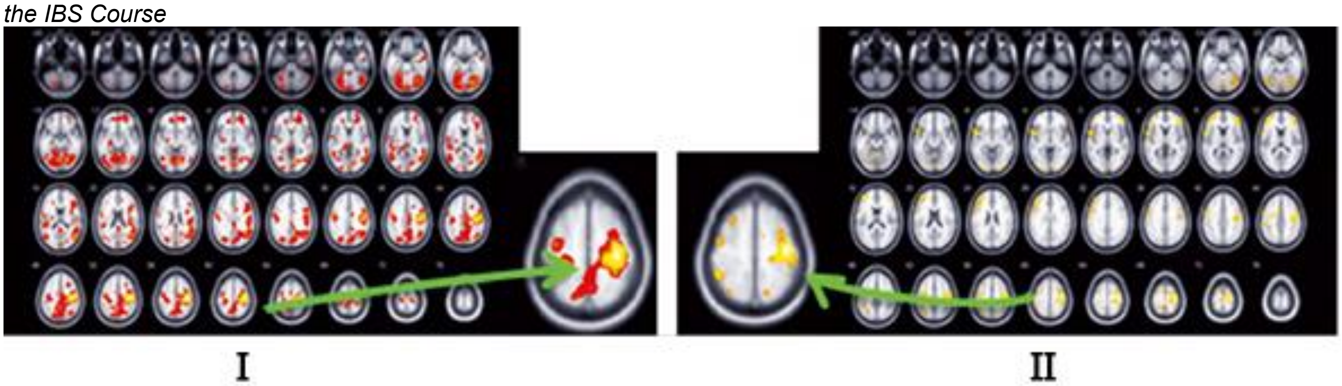
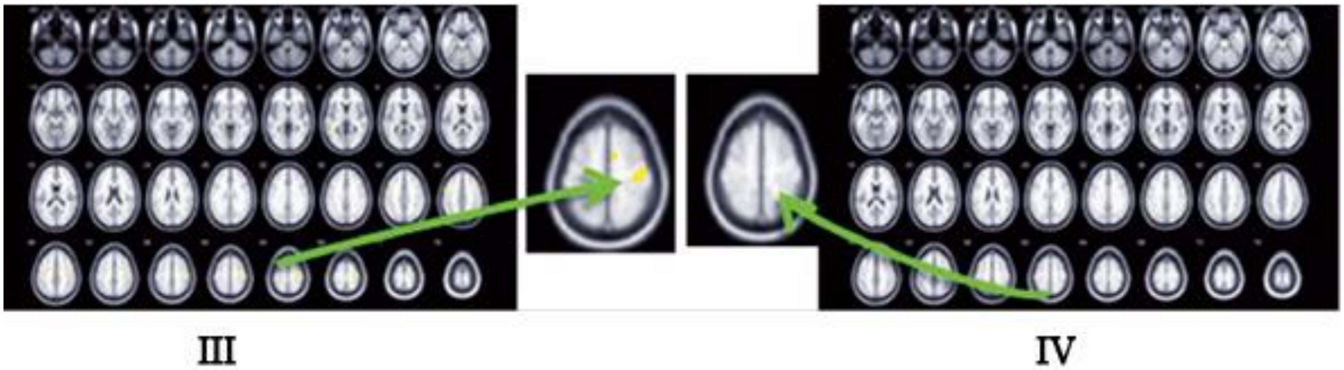
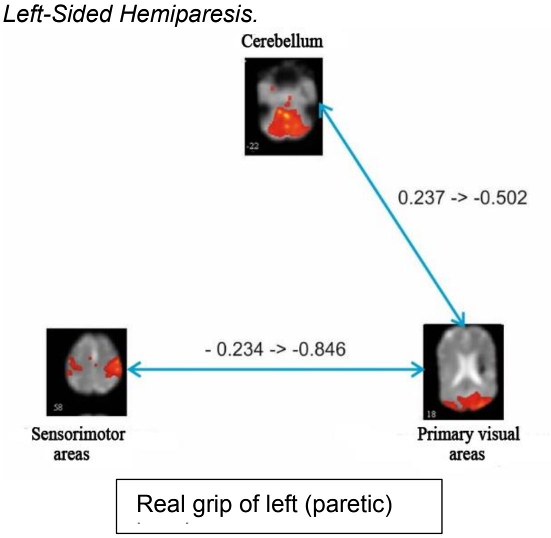


Figure 5. *Distribution of Activated Voxels in the Patient's Brain During Actual Work with the Paretic Limb at Different Stages of the IBS Course*

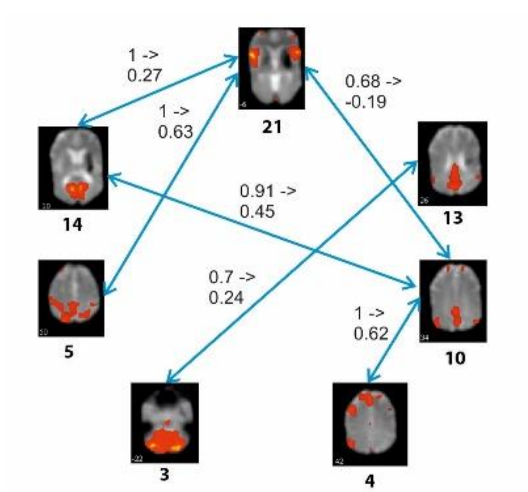


Note. During the IBS course (stages I, II, III, and IV), while performing a real hand movement, the activity of irrelevant cerebral regions (in particular, the occipital lobes) decreases, as well as the intensity of the ROI signal, which, apparently, is associated with the skill acquisition and ability to perform with less energy consumption (Savelov et al., 2019b).

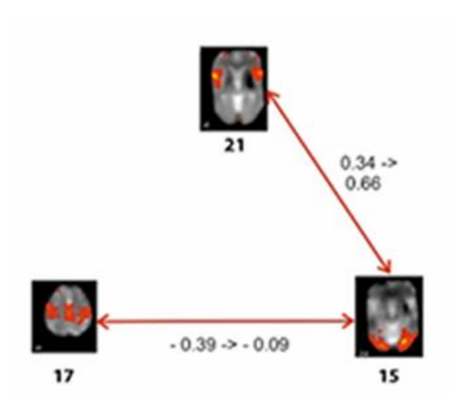
Figure 6. *Evolution of Functional Relationships of Independent Components from First to Fifth IBS Session in a Patient with Left-Sided Hemiparesis.*



Note. The patient demonstrated reciprocal connections between the primary visual and sensorimotor areas and the cerebellum during a real grip of the left (paretic) hand. This was probably due to a patient's poor proprioception, as a result of which precise movements can only be performed under visual control. During training the proprioceptive function is restored, and vision does not play a leading role in the coordination of movements (see also Figure 5). Arrows - statistically significant change of FC in a pair of components during training (correlation coefficient of temporal dynamics in a pair of networks for 1 and 5 sessions, respectively). Each component corresponds to a number: 3 - cerebellum (cerebellar network); 4 - lateral frontal region (FPN on the left); 5 - precentral gyrus, precuneus (network of spatial perception); 10 - lateral frontal region, posterior cingulate gyrus, precuneus (dorsal network of passive work); 13 - precuneus, wedge (precuneus network); 14 - posterior cingulate gyrus, precuneus (primary visual network); 15 - lingual gyrus, wedge (network of the highest level of visual processing); 17 - pre- and postcentral gyrus (sensorimotor network); 21 - superior temporal, inferior frontal gyrus (search network for significant stimuli) (Savelov, Shtark, Kozlova, et al., 2019).

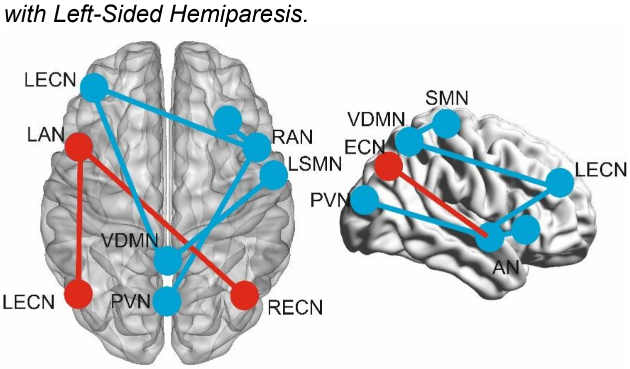


BS at right Brodmann area 4



IBS at left Brodmann area 4

Figure 7. *Evolution of the Coefficients of the Strength of Functional Connections of the Components From the First to the Fourth Biofeedback Session in the Right Motor Zone (No Significant Connections on the Left) in a Patient with Left-Sided Hemiparesis.*

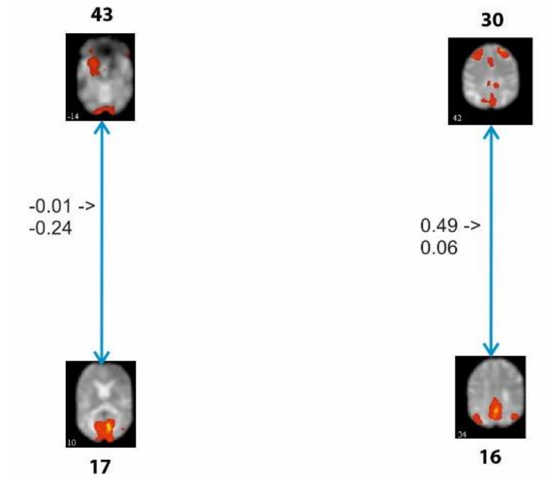


Note. Red lines - increase in the strength of functional connections, blue lines - decrease. L(R)ECN - left (right) CEN (FPN); VDMN - default network; L(R)AN - left (right) auditory network; PVN, primary visual network; SMN - sensorimotor network (Savelov, Shtark, Kozlova, et al., 2019).

In the study (Savelov et al., 2019b) dynamics of the BOLD and EEG signals was evaluated: the values of spectral power and coherence were calculated in the standard ranges of α, β, and θ separately for the attempts of paretic hand actual move and of imagining this action. At the end of the training (eight IBS sessions with an interval of 3–4 weeks) a significant clinical improvement was demonstrated in parallel with the reorganization of the Brodmann areas (BA) activities considering the power of the EEG rhythms (Figure 9). In general, the EEG and fMRI characteristics indicated an increasing similarity between the fragments of functional communications realized during real and imaginary movements during the training course. According to the authors opinion, the observed patterns revealed a "common neural pathway" that can be used in IBS to restore the skill of hand physical contraction with the lowest energy costs (Savelov et al., 2019b).

Another study attempted to compare the clinical and neurophysiological effects of a mono- and bimodal IBS platform (i.e., fMRI IBS and fMRI EEG IBS) in motor stroke rehabilitation (Bezmaternykh et al., 2021). Assessing the sample as nonrepresentative (one patient for each method), the authors concluded that both patients learned to increase C3/C4 coherence with other central leads in the EEG μ-band on the basis of feedback, and both of them improved their functional performance. However, the patient who trained on the bimodal platform mastered the regulation of EEG activity to a

Figure 8. *Evolution of the Coefficients of Functional Connections of the Components from the First to the Fifth Biofeedback Session Along the Left (Left) and from the First to the Fourth Session Along the Right (Right) Brodmann Zone 4.*

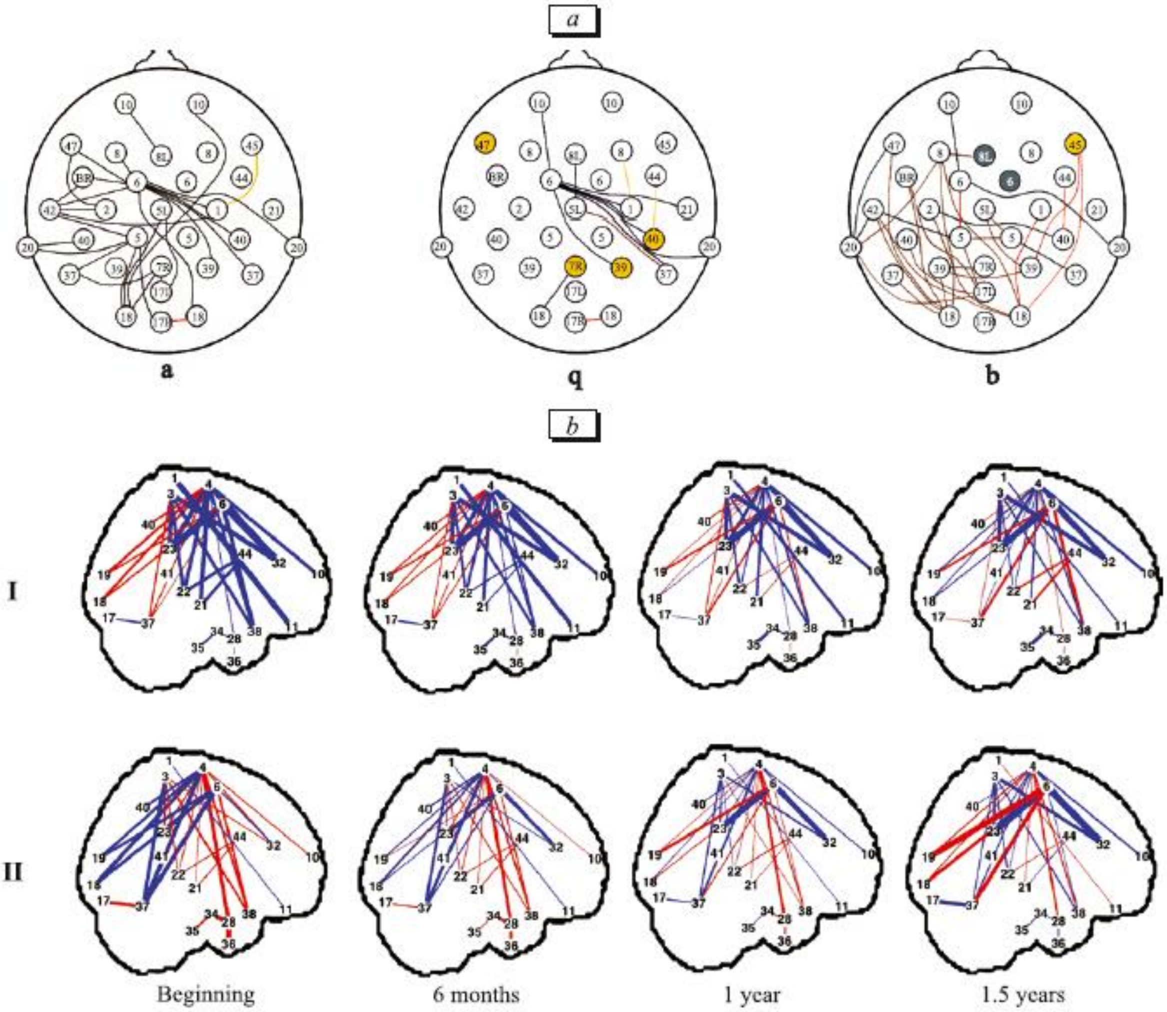


Note. In the context of ISM in the left motor area, there was an increase in desynchronization of the primary visual network with a component that included the lingual and inferior frontal gyrus; i.e., reduced integration in the processing of visual stimuli. The biofeedback of the right Brodmann zone 4 was accompanied by a decrease in the connectivity strength of the passive mode network and the relevant stimulus search network, which corresponds to the normal relationship of these systems and may reflect a decrease in cognitive control over the task. Arrows - statistically significant change in FC in a pair of components during the course (correlation coefficient of temporal dynamics in a pair of networks for 1 and 5 sessions, respectively). A number is indicated for each component: 16 - precuneus, posterior cingulate gyrus (passive mode network); 17 - wedge, lingual gyrus (primary visual network); 30 - superior and middle frontal gyrus, precuneus (relevant stimulus search network); 43 - lingual, inferior frontal gyrus (Savelov, Shtark, Kozlova, et al., 2019).

greater extent. This seems logical at first glance, although further research is certainly needed to explain the significance of the observation for the restoration of function.

Recently preliminary data from the proof-of-concept (PoC) study of a new paradigm were published where participants practiced not only to activate the ROI, but also to regulate the degree of this activation—the so-called "graded fMRI neurofeedback" (Mehler et al., 2020). This paradigm was previously tested in healthy volunteers (Mehler et al., 2019; Sorger et al., 2018), then transferred later to the stroke population (Mehler et al., 2020).

Figure 9. *Representation of Linear Trends in the Changes of (A) EEG Parameters and (B) the Strength of fMRI-Reported Functional Connections During Neurofeedback Course.*



Note. a) *α*, *β*, and *θ* EEG rhythms. The numbers indicate (BA) corresponding to EEG leads. The colored circle (BA) marks a trend in the power of EEG rhythm at the corresponding lead. The lines between circles (BA) illustrate the trends of coherence within the given frequency range between two leads. The red (black) color marks the coherences and spectrum powers which respectively increased (decreased) during imaginary or real work with the paretic wrist. The brown (yellow) color marks the coherences and spectrum powers which respectively increased (decreased) during real work and decreased (increased) during the imaginary one. b) The numbers indicate BA. The red and blue lines mark the positive and negative connections, respectively, while the line thickness corresponds to connection strength. I and II: patterns of real and imaginary wrist clench, respectively (Savelov et al., 2019b).

The hypothesis was that using the fMRI NFB contour a poststroke patient was able to create an image of the paretic arm movement in such a way as to 1) steadily activate the SMA of the ipsilateral hemisphere and 2) independently control SMA activity to achieve the discrete (high and low) target levels. Following strict selection criteria of the study five patients were recruited, heterogeneous in terms of the severity of upper limb dysfunction, including one patient with complete motor recovery. The patients underwent two training sessions of movement imagination of the paretic hand based on the BOLD feedback signal from the SMA at the lesion side and learned to activate the signal from the SMA. The authors keep open the confirmation of the hypothesis of the ability to regulate the degree of this activation and invite to discuss this topic (Mehler et al., 2020). We would like to emphasize the boldness of the declared paradigm that considers the model of neurofeedback as reinforcing the "interactive brain" concept.

Table 1
IBS in Poststroke Motor Rehabilitation

№	Автор	Patients/ control, *n*	Platform Modality	ROI	Number of Sessions	Outcome
1	Sitaram et al., 2012	2/4	fMRI	vPMC	3	All participants learned to activate ROI signal. Pinch grip strength increased in four subjects (three healthy subjects and one patient).
2	Liew et al., 2016	4/0	fMRI	FC iM1 - iThal	2	Three participants learned to activate ROI signal, activation more manifested in patients with severe paresis. Skills were tested at transfer run. Motor function was not assessed.
3	Lioi et al., 2018	2/0	fMRI-EEG	iSMA	2	All participants learned to activate ROI signal.
4	Savelov, Shtark, Mel'nikov, et al., 2019b	1/0	fMRI-EEG	iM1; ERD at BA	8	Activity zones were reorganized throughout the brain. Hand motor function improved.
5	Savelov, Shtark, Kozlova, et al., 2019	12/0	fMRI-EEG	iM1	3–8	Formation of reciprocal connections between primary visual areas, cerebellum and sensorimotor areas with real grip of the paretic hand.
6	Lioi et al., 2020	4/0	fMRI-EEG	iM1 and iSMA	2+3*	Neurofeedback adaptive model. All participants learned to activate ROI signal. Motor function restoration was better in case of relatively intact CST and subcortical stroke.
7	Mehler et al., 2020	5/0	fMRI	iSMA	2	All participants learned to activate ROI signal.
8	Bezmaternykh et al., 2021	2/0	fMRI-EEG	iPreM, iSMA, cSMA	6	Both participants learned to activate ROI signal. C3/C4 coherency with other central leads in EEG μ-band. Both participants also improved their ability to imagine movements.

Note. *n* - number of observations; ROI - region of interest; fMRI - functional magnetic resonance imaging; EEG - electroencephalography; vPMC, ventral premotor cortex; SMA - supplementary motor area; CST - corticospinal tract; FC - functional connectivity; Thal - thalamus; M1 - primary motor cortex; i - ipsilateral; c - contralateral; ERD - event-related cortical rhythm desynchronization; BA - Brodmann area; PreM - premotor cortex * - two sessions were conducted on a bimodal fMRI-EEG platform and three sessions on an EEG-monomodal platform

Conclusion

In February 2015, a conference was held in Gainesville (Florida, USA) dedicated to the "birth" of the trimodal platform; that is, integration of the fMRI-EEG tandem into the adaptive (cognitive, etc.) feedback contour (Sulzer et al., 2013). The targets of the neurofeedback were cerebral structures and neural networks. We called this entire methodological structure an interactive therapy (stimulation) of the brain (Mel'nikov et al., 2017). Thanks to the IBS a person, healthy or sick, has an opportunity to learn, being in a tomograph, to control the characteristics of visualized intracerebral formations; that is, cognitively rebuild the stereometry of neural networks, that leads to therapeutic and behavioral metamorphoses. The authors of the article participated in a conference in the United States and then entered the circle of this continually developing scientific community (Maastricht - Aachen, the Netherlands - Germany, 2017; Nara, Japan, 2019). Today, this direction is an undoubted trend in neurosciences that provides methodology, neurotechnology, and tools for modern neurobiological problems of any complexity.

What can be attributed to the basic knowledge of this direction?

1. First of all, the phenomenon of a polymodal platform that allows solving problems of

spatial and temporal resolution. Built into the feedback contour, this format allows combining online volitional control of cerebral hemodynamics and electrogenesis using both modalities simultaneously.

2. New essence: FC becomes the target of the interactions, drawing the recovery process (for example, after stroke) to *in vitro* situation. We assume that the development of this option will provide a basis for the “transplantation” of a neural network created on a 3D printer in the future.
3. The concept of "network neurology", largely a product of fMRI, that allows us considering stroke and its consequences as "network diseases," which changes the view on many stroke aspects: diagnosis, treatment, recovery, and prognosis. The patient's medical history involves a new lexical and semantic vocabulary, and FC becomes a numerical expression of brain neuroplasticity.
4. The so-called phenomenon of BOLD-dependent EEG that arose in connection with the need to expand the applicability of the IBS, which was prevented by two complicating circumstances: a close "local" binding with a tomograph and, of course, the commercial component of the whole technology. The studies in this direction appeared in Israel and were conducted in the frameworks of the fMRI-EEG tandem, demonstrating a real transition to BOLD-dependent EEG using the example of affective disorders (Meir-Hasson, Keynan, et al., 2016; Meir-Hasson, Kinreich, et al., 2014; Keynan, Cohen, et al., 2019; Keynan, Meir-Hasson, et al., 2016) and similar transformations in relation to stroke (Rudnev et al., 2021).
5. Finally, diffusion characteristics reflecting the transformations of the brain microstructure (in terms of "network vocabulary," the dynamics of neural networks SC) are being considered as possible predictors of stroke itself (Alves et al., 2022; Zhuravleva et al., 2022) and its outcomes (Spampinato et al., 2017; Yu et al., 2020), and become one of the potentially “controllable” characteristics.

Thus, due to fMRI, neurofeedback technology is now undergoing a period of “revolutionary” reformation moving into a coordinate system of network neuroscience that promises a new understanding of the structural and functional organization of the brain.

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NeuroRegulation

Healing Chronic Back Pain

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Abstract

This case report describes the self-healing process by which a 28-year-old woman who had scattered her L3 vertebra, broken both sides of her jaw, and fractured her left shoulder in a motorcycle accident. After the accident, she underwent two surgeries to replace her shattered L3 as well as fuse her L2 and L4 vertebrae. A year later, she continued to take 5–10 mg of Baclofen and 300 mg of Gabapentin three times a day to control her pain. After one year, she enrolled in a holistic health class that included self-healing practices. She implemented self-healing imagery and other self-regulation strategies, and after three weeks she stopped all medication. At the 18-week follow-up, she is pain free. Discussed are the steps of the self-healing strategies she implemented to improve her health.

Keywords: back pain; imagery; visualization; holistic health; self-care; relaxation

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Introduction

> In at the beginning of 2021, I broke my L3 vertebra during a motorcycle accident and underwent two surgeries in which surgeons replaced my shattered L3 with a metal "cage" (looks like a spring) and fused this cage to the L4 and L2 vertebrae with bars. I also broke both sides of my jaw and fractured my left shoulder. I felt so overwhelmed and totally discouraged by the ongoing pain. A year later, after doing the self-healing project as part of the university class assignment, I feel so much better all the time, stopped taking all prescription pain medications, and eliminated the sharp pains in my back. This project has taught me that I have the skill set needed to be whole and healthy.
>
> —J.C., 28-year-old college student

Chronic pain is defined as a pain that persists or recurs for more than 3 months (Treede et al., 2019). It is exhausting and often associated with reduced quality of life and increased medical costs (Yong et al., 2022). Pain and depression coexacerbate physical and psychological symptoms and can lead to hopelessness (IsHak et al., 2018; Sheng et al., 2017; Von Korff & Simon, 1996). To go to bed with pain and anticipate that pain is waiting for you as you wake up is often debilitating. One in five American adults experience chronic pain, most frequently in their back, hip, knee, or foot (Yong et al., 2022). Patients are often prescribed analgesic medications (pain killers) to reduce pain. Although the analgesic medications can be effective in the short term to reduce pain, the efficacy is marginal for relieving chronic pain (Eriksen et al., 2006; Tan, & Jensen, 2007). Recent research by Parisien et al. (2022) reported that anti-inflammatory drugs were associated with increased risk of persistent pain. This suggests that anti-inflammatory treatments might have negative effects on pain duration. In addition, long-term medication use is a major contributor to the opioid epidemic and increased pain sensitivity (Higgins et al., 2019; Koob, 2020; NIH-NIDA, 2022). Pain can often be successfully treated with a multidisciplinary approach that incorporates nonpharmacologic approaches. These include exercise, acceptance and commitment therapy, as well as hypnosis (Warraich, 2022). This paper reports how self-healing strategies as taught as part of an undergraduate university class can be an effective approach to reduce the experience of chronic pain and improve health.

Each semester, about 100 to 150 junior and senior college students enroll in a holistic health class that focuses on a whole-person Holistic Health curriculum. The class includes an assessment of complementary medicine and holistic health. It is based upon the premise that the mind and emotions affect body, and that the body affects the mind and emotions, that Green et al. (1970) called the psychophysiological principle.

> Every change in the physiological state is accompanied by an appropriate change in the mental emotional state, conscious or unconscious, and conversely, every change in the mental emotional state, conscious or unconscious, is accompanied by an appropriate change in the physiological state. (p. 3)

The didactic components of the class include an overview of the role of posture; the psychophysiology of stress, respiration, lifestyle and other health factors; reframing internal language; guided imagery, and self-healing imagery. Students in the class are assigned self-healing projects to improve their own health using techniques that focus on awareness of stress, dynamic regeneration, stress reduction imagery for healing, and other behavioral change techniques adapted from the book *Make Health Happen* (Peper et al., 2002).

The focus of the last 6 weeks of the class is to identify, develop, and implement a self-healing project to optimize personal health. The self-healing project can range from simple lifestyle changes to reducing chronic pain. Each student identifies their project, such as increasing physical activity, eating a healthy diet (reducing sugar and junk food), stopping vaping or smoking, limiting screen time, reducing anxiety or depression, stopping hair pulling, reducing headaches or back pain, etc. At the end of the semester, 80% or more of the students reported significant reduction in symptoms (Peper, Harvey, et al., 2022; Peper, Lin, et al., 2014; Peper, Miceli, et al., 2016; Peper, Sato-Perry, et al., 2003). During the last five semesters, 13% of the students focused on reducing pain (e.g., migraines, neck and shoulder pain, upper or lower back pain, knee pain, wrist pain, and abdominal pain). The students report that they successfully reduce their symptoms an average of 8.8 on a scale from 0 (*no benefit*) to 10 (*total benefit*). The success for improving their symptoms correlates 0.63 with their commitment and persistence to the project (Heinz et al., 2022).

The purpose of this case example is to describe how a student with severe back pain reduced her symptoms and eliminated medication by implementing an integrated self-healing process as part of a class assignment and offers recommendations on how this could be useful for others.

Methods

Participants

A 28-year-old woman (J.C.) had broken her L3 vertebra in a motor cycle accident on January 28, 2021. She underwent two surgeries in which surgeons replaced her shattered L3 with a metal "cage" (which she describes as looking like a spring) and fused this cage to the L2 and L4 vertebrae with bars. She also broke both sides of her jaw and fractured her left shoulder. More than a year later, she was taking 5–10 mg of Baclofen and 300 mg of Gabapentin three times a day to reduce pain.

As a report about an effort to improve the quality of a classroom activity, this report of findings was exempted from Institutional Review Board oversight.

Goal of the Self-Healing Project

To decrease the sharp pain and discomfort in her lower back that resulted from the motorcycle accident and, although not explicitly listed, to decrease the pain medications.

Self-Healing Process

During the last 6 weeks of the 2022 Spring semester, the student implemented her self-healing practices for her personal project which consisted of the following steps.

1. To create a self-healing plan that included exploring the advantages and disadvantages of her illness.
2. To create a step-by-step plan with specific goals to relieve the tension and pain in her lower back. This practice allowed her to quantify her problem and the solutions. Like so many people with chronic pain, she focused on the problem and feelings (physical and emotional) associated with the pain. As a result, she often felt hopeless and worried that it would not change.
3. To observe and evaluate when her pain sensations changed. She recognized that

she automatically anticipated and focused on the pain and anxiety whenever she needed to bend down into a squat. She realized that she anticipated pain even before she began to squat. This showed that she needed to focus on healing before and during the movement of this area of her body. Through her detailed observations, she realized that her previous general rating of back pain could be separated into two components: muscle tightness/stiffness and sharp pain. With this realization, she changed the way she was recording her pain level.

4. To ask questions of her unconscious through a guided imagery practice of accessing an inner guide (for detailed instructions, see Peper et al., 2002, p. 197–206). In this practice, the person relaxes and imagines being in a special healing place where they feel calm, safe, and secure. Then as they relax, they become aware of another being (wise one or guide) approaching them (the being can be a person, animal, light, spirit, etc.). The being is wise and knows them well. In their mind, they ask this being questions such as, "What do I need to do to assist in my own healing?" Then they wait and listen for the answer. The answers may take many forms such as in words, pictures, a sense of knowing, or it may come later in dreams or in other forms. When students are assigned this practice for a week, most report experiencing some form of guide and many find the answers meaningful for their self-healing project.

Through this imagery of the inner guide script, she connected with her higher self and the wise one told her, "Wait." This connecting with the wise one was key in accepting that the project was not as daunting as she initially thought. She realized that pain was not going to be forever in her future. She also interpreted that as reminder to have patience with herself. Change takes time and practice, which she previously experienced while correcting her posture to manage her emotions and edit her negative thoughts into positive ones (Peper et al., 2022). Whenever she would have pain or feel discouraged because of external circumstances, she would remind herself:

- I need to have patience with myself.
- I have all the healing tools inside of me, and I am learning to use them.
- If I do not make time for my wellness, I'll be forced to make time for my illness.

5. To practice the self-healing imagery as described by Peper et al. (2002) and adapted from the work by Dr. Martin Rossman (Rossman, 2000). Imagery can be the communication channel between the conscious/voluntary and the unconscious /autonomic/involuntary nervous system (Bresler, 2005; Hadjibalassi et al., 2018; Rossman, 2019). Imagery appears to act as the template and posthypnotic suggestion to implement behavior change and may offer insight and ways to mobilize our self-healing potential (Battino, 2020). Imagery is dynamic and changeable.

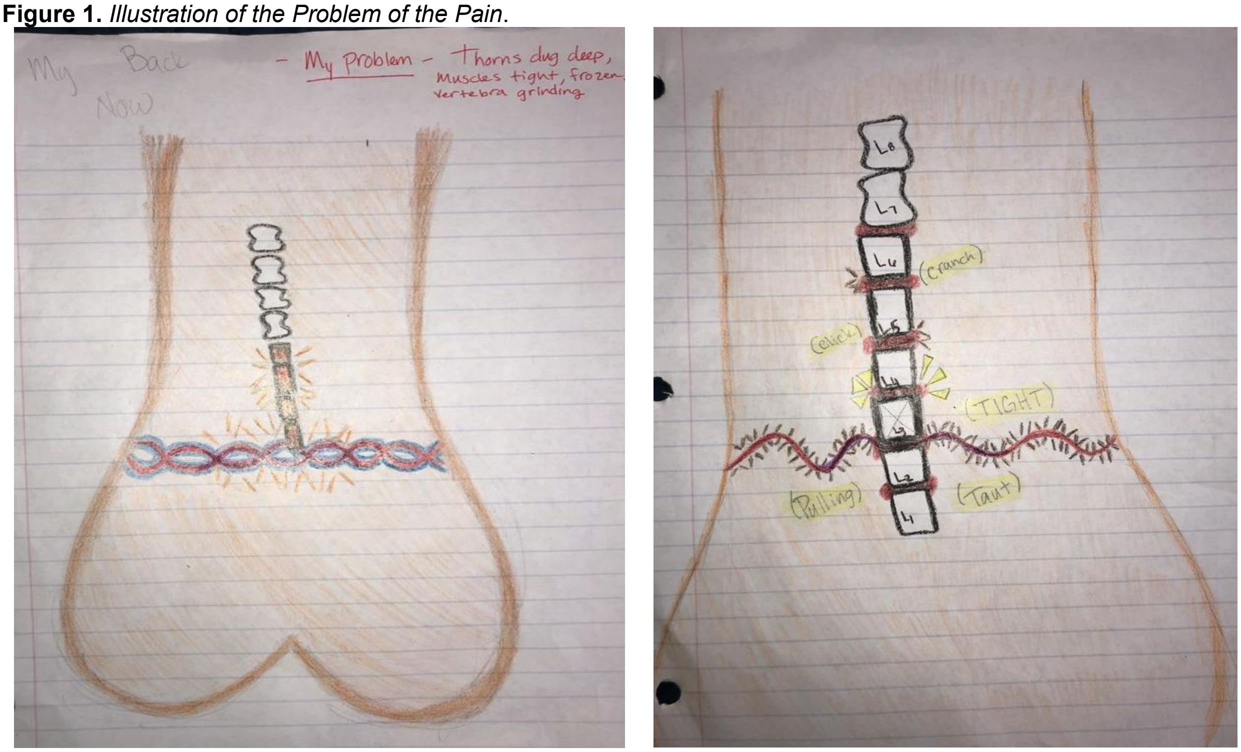
The process of self-healing imagery consists of three parts.

1. To Inspect the problem and create a graphic illustration of the problem as it is experienced at the present moment of time.
2. To illustrate graphically how that area or problem would look when being completely well/whole or disappeared.
3. To create a self-healing process by which the initial problem is transformed into health (Peper et al., 2002, p. 217–236). This focuses on what the person could do for themselves; namely, each time they thought of or became aware of the problem, they would focus on the self-healing process. It also implies that there is hope and they could become well.

The drawings of inspection of the pain and problem she experienced at that moment of time are shown in Figure 1. The resolution of the problem and being well and whole are illustrated in Figure 2.

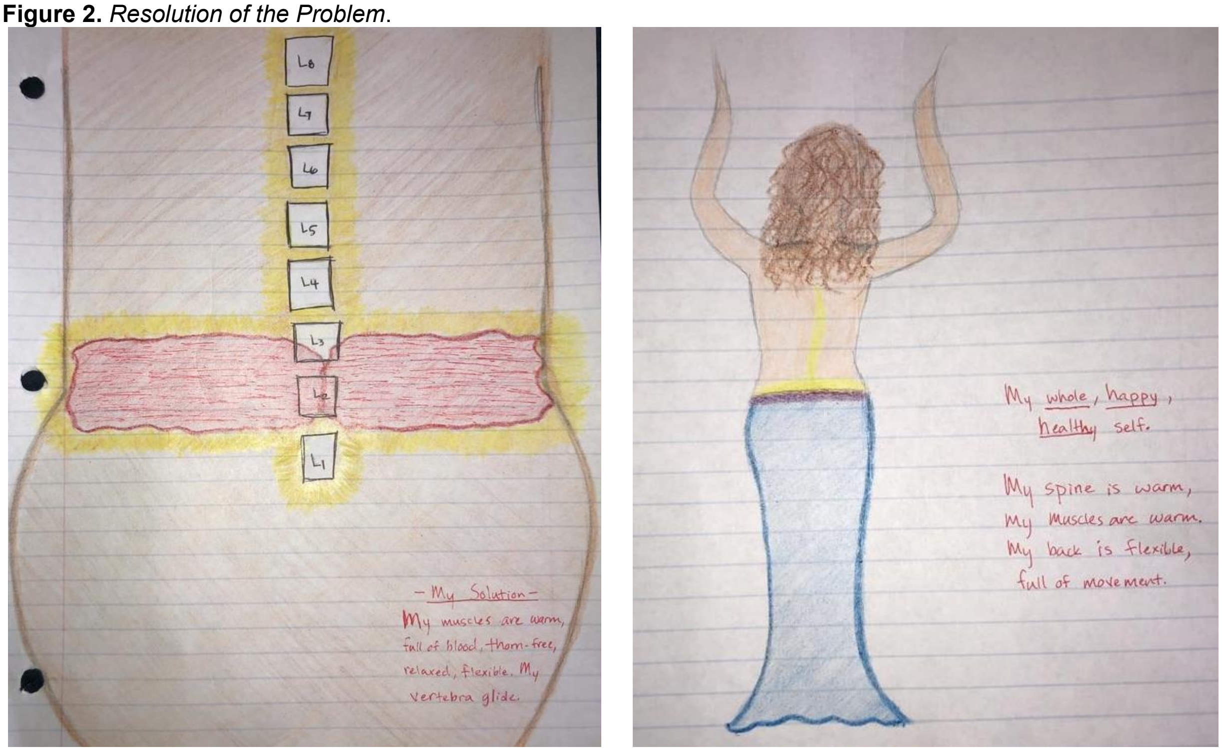
During the weeks of practice, she utilized the first image of the muscles warm, full of blood, free of thorns, relaxed, and flexible. Her second image of her fully being healed was inspired through a religious statue of Yemaya that she had in her room (Yemaya is a major water spirit from the Yoruba religion Santeria and Orisha of the seas and protector of women). Each time she saw the statue, she thought of the image of herself fully healed and embodying the spirit Orisha. Therefore, this image remained important to her all the time. Her healing imagery process by which she transforms the image of inspecting of the problem to being totally well are illustrated in Figure 3.

Figure 1. *Illustration of the Problem of the Pain*.



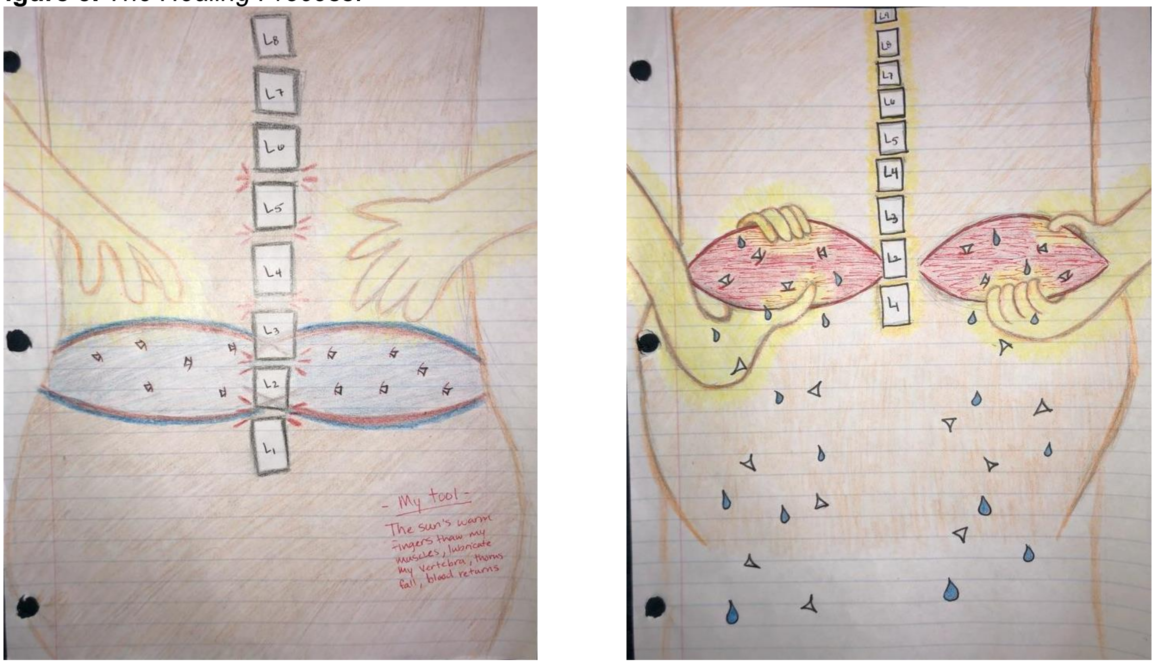
Note. Thorns dug deep, muscles tight, and frozen vertebrae grinding.

Figure 2. *Resolution of the Problem*.



Note. Resolution of the problem in which her muscles are warm, full of blood, free of thorns, relaxed and flexible; and being whole happy and healthy in which her spine is warm. Her muscles are warm, and her back is flexible and full of movement.

Figure 3. *The Healing Process*.



Note. The sun's warm fingers thaw my muscles, lubricate my vertebra, thorns fall out, and blood returns.

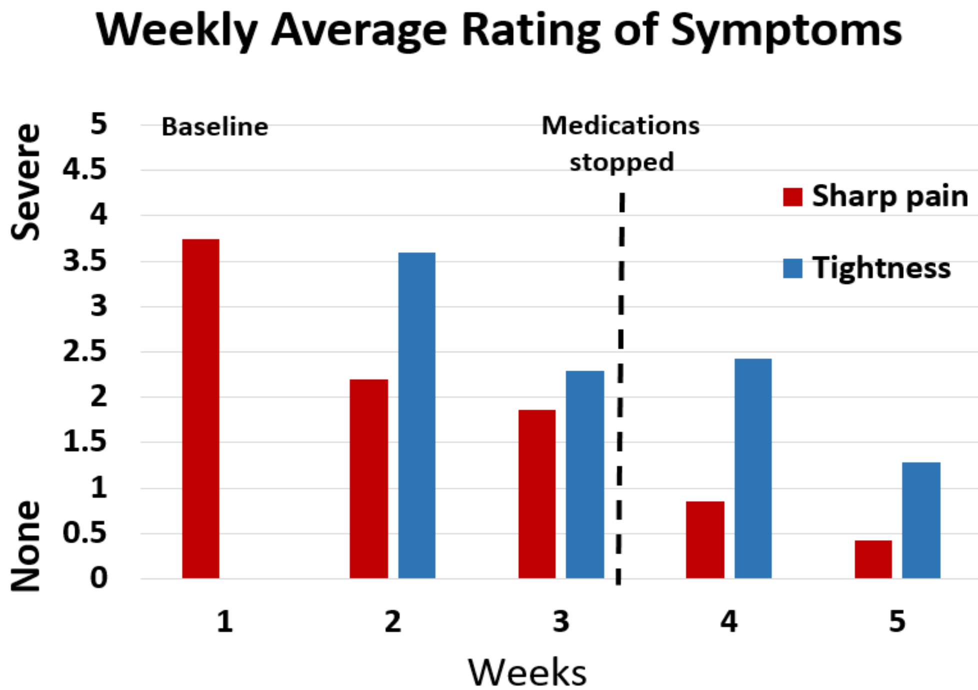
For 5 weeks she implemented her self-healing project by creating a self-healing plan, asking questions of her unconscious, and drawing her self-healing imagery. She also incorporated previously learned skills from the first part of the semester such as diaphragmatic breathing, hand warming, shifting slouching to upright posture, and changing language. Initially she paired hand warming with the self-healing imagery. She could feel an increase in body warmth each time she practiced the imagery. J.C. practiced the self-healing imagery as an in-depth daily practice and throughout the day when she became aware of her back as described in her log entries:

> I repeated the same steps as the day prior today. I did my practice in the early morning but focused on the details of the slowed down movements of the sun's hands. I saw them as they stretched out to my back, passed through my skin, wrapped around my muscles, and began to warm them. I focused on this image and tried to see, in realistic detail, my muscles with a little ice still on them, feeling hard through and through, the sun's glowing yellow-orange fingers wrapped around my muscles. I imaged the thorns still in my muscles, though far fewer than when I started, and then I imaged the yellow-orange glow start to seep out from the sun's palms and fingers and spread over my muscles. I imaged the tendons developing as the muscle tissue thawed and relaxed, the red of the muscle brightened, the ice on and within my muscles started to melt, and the condensation formed as it ran down into collected droplets at the bottom of my muscles. I imaged the thorns lose their grip and fall out, one at a time, in tandem with the droplets falling. I continued this process and imaged my muscles expanding with warmth and relaxation as they stayed engulfed in the warmth of the sun.
>
> At the end of my practice, I did a small stretch session. I felt extremely refreshed and ready for yet another extremely busy day between internship, graduation, and school. I would say I felt warm and relaxed all the way into the afternoon, about six hours after my practice. This was by far the most detailed and impactful imagery practice I have had.
>
> The self-healing imagery practice provided me with the ability to conceptualize more than my problem, as it showed me the tools to (and the importance of) conceptualizing my solution, both the tool and end result.

Results

Pain and tightness decreased, and she stopped her medication by the third week as shown in Figure 4.

Figure 4. *Self-Rating of Sharp Pains and Tightness During the Self-Healing Project*.



At the 18-week follow-up, she continues to improve, experiences minimal discomfort, and no longer takes medication. As J.C. stated, "I was so incredibly shocked how early on [in the project] I was able to stop taking pain medications that I had already taken every day for over a year."

Discussion

This individual case example provides hope that health can be improved when shifting the focus from pain and discomfort to focusing on actively participating in the self-healing. As she wrote,

> The lesson was self-empowerment in regard to my health. I brought comfort to my back. There is metal in my back for the rest of my life, and this is something I have accepted. I used to look at that as a horrible thing to have to handle forever. I now look at it as a beautiful contraption that has allowed me to walk across a graduation stage despite having literally shattered a vertebra. I am reintegrating these traumatized parts of my body back into a whole health state of mind and body. Doctors did not do this, surgeries did not, PT (physical therapy) didn't and neither did pain medications. MY body and MY mind did it. I did this.

The self-healing project was the culmination project for the class that included attending the weekly class session and completing assigned homework practices. These included discussion about placebo/nocebo, the role of hope, examples of self-healing with visualization, the role of nutrition, the psychophysiology of stress, and factors associated with healthy aging across cultures. Although self-healing imagery appears to be the major component that facilitated her healing, it cannot be parceled out from the many other concepts and practices that she learned such as hand warming and learning slow diaphragmatic breathing.

In the class discussions it was pointed out that not everyone may return to health; however, they can always be whole. For example, if a person loses a limb, the limb will not regrow; however, the healing process probably includes acceptance and creating new goals to achieve and live a meaningful life.

To encourage a shift in perspective, students were assigned to watch and comment on videos of people who had overcome serious illness. These included Janine Shepherd's 2012 TED Talk, *A broken body isn't a broken person,* and Dr. Terry Wahl's 2011 TEDxIowaCity Talk, *Minding your mitochondria.* Janine Shepherd shared how she recovered from a very serious accident in which she became paralyzed to becoming an acrobatic pilot instructor, while Dr. Terry Wahl shared how she cured and got out of her wheelchair and cure her severe Multiple Sclerosis with diet (Shepherd, 2012; Wahl, 2011). In addition, they were assigned to watch Madhu Anziani's presentation, *Healing from paralysis-Music (toning) to activate health*, in which he discussed how he recovered from being a quadriplegic to becoming an inspirational musician (Anziani & Peper, 2021). Finally, the students read and commented on other students' case examples of reversing acid reflux, irritable bowel and chronic headaches (Peper, 2018, 2022; Peper, Covell, et al., 2021; Peper, Mason, Harvey, et al., 2020; Peper, Mason, & Huey., 2017a, 2017b). By seeing how others overcame chronic disorders, the class provided an educational approach by which she reduced her chronic back pain.

Lessons extracted from this case example that others may be able use to mobilize health.

- Take action to shift from being hopeless and powerless to becoming empowered and an active agent in the healing process.
- Change personal beliefs that healing and improvement are possible through experiential practices and storytelling.
    - Teach the person self-regulation skills—such as slower breathing, muscle relaxation, cognitive internal language changes, and hand warming—by which the person experiences changes.
    - Provide believable role models who shared their struggles in overcoming traumatic injury, such as inspirational talks, and previous clients' or students' self-reports who have improved.
- Transform the problem from a global description into specific behavioral specific parts. For example, being depressed is a global statement; however, if it can be broken down into specific behaviors such as, "my energy is too low to do exercise" or "I have negative thoughts*.*" The intervention will then focus on resolving the specific behavior such as increasing exercise or changing thoughts. In J.C.'s case, she changed the general rating of pain into muscle tightness and sharp pains. This provided the bases for strategies to relax and warm the muscles.
- Focus on what you can do at this moment versus focusing on the past, what happened, who caused it, or blaming yourself and others. Explore and ask what you now can do now to support your healing process and reframe the problem as a new opportunity for growth and development.
- Practice, practice, and practice with a childlike exploratory attitude. Focus on the small positive benefits that may occur. It is not mindless practice; it is practice while being present and being gentle with yourself. The benefits accrue as you practice more and more which many people have experienced when learning to play a musical instrument or master a sport. Even though many participants believe that practicing 15 min a day is enough, it usually takes much more time. Reflect on how a baby learns to walk or climb. The toddler practices daylong and takes naps to regenerate and grow. When the toddler is not yet successful in walking or climbing, it does not give up or interpret it as failure or self-blame, it just means practice more.
- Have external reminders to evoke the self-healing practices. In J.C.'s case, the small statue of Yemaya in her room was the reminder to think of herself fully healed each time she saw it.
- Guide yourself through the wise one imagery, ask yourself a question, then listen and act on the intuitional answers.
- Develop a self-healing imagery process that transforms the dysfunction to health or wholeness. Often the person only perceives the limitations and focuses on describing the problem. Instead, acknowledge, accept what was and is, and focus on developing a process to promote healing. What many people do not realize is that when they think or imagine how their injury or illness was caused, it may reactivate and recreate the initial trauma. We forget that our thoughts change physiology. For example, when one imagines eating a lemon, the person will probably salivate (a parasympathetic response). Thus, focus on processes that support healing.
- While practicing the imagery, experience it as if it is real and feel it happening inside yourself. Many people initially may find this challenging as they see it outside themselves. One way to increase the "felt sense" is to incorporate more body involvement such as acting out the imagery with hand and body movements.
- When having a relapse, remind yourself to keep going. Every morning is the beginning of a new day, do each practice anew. To increase motivation, reflect on something that was challenging in the past but that you successfully overcame. Focus on that success. As J.C. wrote, "I was also successful in that I gave myself slack and reminded myself that relapses will happen and what matters more are the steps I take to move forward."

- Make healing a priority—that means making yourself a priority. This means doing it often and during the day. Allow the self-healing imagery and process to run in the back of the head just as a worry can be present in the background most of the day. So often people practice for a few minutes (which is great and better than not practicing at all); however, at other times during the day they are captured by their worry, negative thoughts, or limitations caused by their disorder.

  When a person focuses on the limitations, it may interrupt the self-healing process. The analogy we often use is that the healing process is similar to healing from a small cut in the skin. Initially a scab forms, and eventually the scab falls off and the skin is healed. On the other hand, if you keep moving the skin or pick at the scab, the healing is much slower. By focusing on the limitations and past visualization of the injury, self-healing may be reduced. This is similar to removing the scab before the skin has healed. As J.C. stated, "'If you don't make time for your wellness, you'll be forced to make time for your illness' was 100% a motivating factor in my success."
- Explore resources for providers and people living with pain. Dr. Rachel Zoffness provides a trove of high-quality articles, books, videos, apps, and podcasts on her website https://www.zoffness.com/resources

In summary, we do not know the limits of self-healing; however, this case example illustrates that, by implementing self-healing strategies, health and recovery are possible. As J.C. wrote:

> To have broken a vertebra in my back and experience all the injuries that came with the accident when I already did not have the strongest mind-body connection was incredibly intense and really heartbreaking and discouraging in my life. That made things difficult because I was not able to 100% focus on my healing because I felt so overwhelmed by the feeling of discouragement that I felt. Experiencing this self-healing project and seeing the imagery that helped me not just feel so much better all the time but be able to stop taking all prescription pain medications and eliminate the sharp pains in my back have taught me that I have the skill set needed to be whole and healthy.

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