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EEG Activation During a Mindfulness Session and Its Effects on Memory Encoding

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Abstract

This paper investigates the potential impact of a single mindfulness session on explicit memory recall, employing quantitative electroencephalography (qEEG) to compare a study group to a control group. Phase synchronization in alpha, theta, and gamma frequency bands across various brain regions involved in memory processes was analyzed. Twenty-eight adults, balanced in gender and age, participated in both groups. Memory encoding and retrieval were assessed using word lists presented over four successive sections, with EEG recordings taken before, during, and after mindfulness sessions. Results revealed increased theta and decreased gamma band activation in the right hemisphere during mindfulness, with synchronization between temporal and parietal cortices and frontal cortex during encoding. Higher gamma activation in specific brain regions correlated with better recall. While the study group showed no significant decline in posttest scores compared to controls, suggesting mindfulness may serve as a protective factor in free recall, further research with larger datasets is needed for validation.

Keywords: mindfulness; explicit mnesic enhancement; quantitative EEG (qEEG)

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Introduction

Memory is a process where learning is accumulated (Elsey et al., 2018; Ruiz Rodríguez, 2004). Traditionally, the memory neural bases research focused on the specific brain locations analyzes trying to discover where this information is stored. However, this localizationist trend has been replaced by a more current one seeking to understand the nervous system as a sequential and whole, encoding and retrieving this information, and considering the spatiotemporal synchronization or coherence in different wavebands between these neural areas (Elsey et al., 2018; Polanía et al., 2012).

In memory functioning, the working memory receives the information, and it is automatically transferred to the long-term memory. The latter functions as storage where learning is retained for an unlimited time, as long as it is used and considered helpful for survival or adaptation to the environment; otherwise, it is forgotten (Ruiz Rodríguez, 2004). This potentially permanent storage has been intensively

studied in neuroscience. In explicit learning, the recording, processing of stimuli, information storage, and retrieval are associated with parahippocampal, perirhinal, entorhinal cortices, dentate circumvolution, hippocampus, amygdala, frontal, temporal, parietal lobes, and different cortical association areas (Buschke, 1984; León, 2008; Rodríguez-Ledo et al., 2018; Schoeberlein & Sheth, 2015; Sugiura, 2004; Zeidan et al., 2010). During an explicit learning process, such as retaining a word list or recalling it, the EEG activity studies have shown that phase synchronization for theta and gamma bands in frontal and temporoparietal structures seems crucial (Aftanas & Golocheikine, 2001; Field, 2013; Goleman, 2016; Homan et al., 1987; Horta-Barba et al., 2020; Labos et al., 2008; Neamțu et al., 2021; Pérez-Elvira, Oltra-Cucarella, Carrobles, Moltó, et al., 2021; Pérez-Elvira, Oltra-Cucarella, Carrobles, Teodoru, et al., 2021). More details related to different brain regions' connectivity for encoding and retrieving explicit information are presented in Appendix A.

On the other hand, the study of attentional mechanisms is of great interest since they are related to human memory and learning (Chica Martinez & Checa Hernández, 2013). Mindfulness is a type of attention that has been associated with better cognitive performance and better scores in working memory (Jha et al., 2010; Mrazek et al., 2013; Shapiro & Walsh, 2003; Yakobi et al., 2021). This type of sustained, open, and voluntary attention has been of interest to clinical neuropsychology. Mindfulness meditation could alleviate cognition. Mindfulness is related to the increase of power in the theta, alpha, and, perhaps, gamma bands in frontal areas of the cerebral cortex (Aftanas & Golosheykin, 2005; Andresen, 2000; Bennett & Trinder, 1977; Dunn, 1999; Ehrlichman & Wiener, 1980; Fell & Axmacher, 2011; Fenwick, 1987; Harne & Hiwale, 2020; Lutzenberger et al., 2002; Pagano & Warrenburg, 1983; Sarnthein et al., 1998; Serrien et al., 2003; Travis et al., 2002; West, 2016). Some reports have already shown that mindfulness improves different aspects of cognitive performance, or those related to it, such as academic performance (León, 2008; Schoeberlein & Sheth, 2015), learning, anxiety (Rodríguez-Ledo et al., 2018; Schoeberlein & Sheth, 2015; Sugiura, 2004), information processing speed (Zeidan et al., 2010), memory (Mrazek et al., 2013; Zeidan et al., 2010), attention, and impulse control (Mrazek et al., 2013; Zeidan et al., 2010). Moreover, mindfulness shows protective effects of memory decay and could be used as an effective technique to enhance cognitive performance in the learning process (Jha et al., 2010; Appendix A).

This research approach aimed to study the EEG activity during memorization or mnesic encoding and retrieval tasks. To this goal, we analyzed the behavior of alpha, theta, and gamma waveband amplitude and the coherence related to frontal, temporoparietal cortices, and medial temporal structures during a single mindfulness session to explore its role for a possible improvement or protection in the recall of the explicit mnesic material. To the best of our knowledge, current literature is scarce regarding the mindfulness role in this respect.

Materials and Methods

Subjects

This prospective study was conducted in NEPSA Rehabilitación Neurológica, a neurological rehabilitation clinic certified by the Government of Castilla y León (Spain), in collaboration with the Research and Telemedicine Center for Neurological Diseases in Children in Sibiu, Romania, for data analysis (Ethical Commitee: 5/2021).

The sample of this study consisted of 28 healthy adult participants aged between 24 and 35 years (mean age = 30.64, *SD* = 4.00), all of them medium–high cultural and socieconomic adult volunteers. The sample was collected at the neuropsychophysiology laboratory of NEPSA Rehabilitación Neurológica (Salamanca, Spain), and each participant was randomly assigned to the experimental or control group (by rolling dice). The participants in the experimental group totaled 14 people (7 men = 50%; mean age = 29.21, *SD* = 3.90). The participants in the control group accounted for a total of 14 people as well (8 men = 57.1%; mean age = 28.60, *SD* = 4.56). The inclusion criteria were: (a) no psychiatric or neurological pathology, and (b) no previous experience in meditation. The participants were informed in writing about the research design, and all of them gave their explicit written consent to carry out this study. The anonymity of the responses and scores of all participants was guaranteed and respected according to the Helsinki Declaration guidelines.

Instruments

Memory Test. The ad hoc list of words used in our study is presented in Appendix B (Buschke, 1984; Horta-Barba et al., 2020; Labos et al., 2008). The purpose of this list is to evaluate the memory encoding of the verbal material and its subsequent

retrieval. Participants were given 20 s to try to memorize the six words that appeared on a computer screen. After these 20 s, a semantic cue was associated with each word to selectively ease the recall in later phases when they were asked to remember and name the words. Once these 20 s had passed, they were offered another six words, and once again the cue was selectively provided. This was done in repeated sections, four sections with 80 s of coding and 24 words to remember. After finishing these four sections, the participants were asked to try to remember and vocalize freely all the words they remembered in the desired order. This part is known as free recall. Once the subjects indicated they could not remember any more words, they were offered the cues and asked again to remember the word associated with the related cues, known as cued recall.

The word-list test was applied in the pre- and postmindfulness session, with two analogous versions of the same test where the words were changed but the same cues were maintained, with the idea that one version and the other were not significantly different in terms of difficulty of encoding and recall. Half of the participants received version A first and then received version B after the mindfulness session. The other half received version B first and then received version A after the mindfulness session (Table 1, Appendix B). For each trial, the participants were asked to freely recall as many items as possible, and the category cues were provided for items not retrieved by total free recall. The same procedure of recalling (freely and cued) was done after the mindfulness session. The subjects were required to freely remember the words, and the category cues were provided for items not retrieved freely. The measures evaluated here were total free recall (cumulative sum of free recall from the 4 sections of the test; range 0–24) and total recall (TR; cumulative sum of free recall + cued recall from the four sections of the test, range 0–24).

Electroencephalography Amplifier. Discovery 20-channel device (BrainMaster Technologies, Bedford OH) was used. It provides a 24-bit conversion with an internal sampling rate of 1024 samples/s and 256 samples/s data rate to the computer, providing 20 high-resolution and aliasing-free signals. A 50-Hz notch filter was used.

EEG Cap. Medium-size free-cap (Neurofeedback-Partner, Munich, Germany), which is an EEG electrode application technique with 19 channels located according to International System 10-20 (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2; Homan et al., 1987) and using a Linked Ears montage. The electrodes on the standard caps were positioned according to the International 10-20 method of electrode placement. The spongy electrodes reservoir carried a sponge soaked with saline to record the EEG.

EEG Acquisition Software. BrainAvatar 4.6.4 software (BrainMaster Technologies, Bedford OH) recorded the EEG.

QEEG Analysis Software. NeuroGuide v. 2.9.1 (Applied Neuroscience, Inc., St. Petersburg FL) and BrainAvatar Analyzer (BrainMaster Technologies, Bedford OH) software were used for the EEG computation and analysis.

Mindfulness Session CD-ROM. Goleman (2016) recorded a brief mindfulness session of breathing meditation employed.

Procedure

Prior, during, and after the memory test, EEG data were collected to perform a descriptive study analyzing the brain activation in participants with no previous experience with this type of meditation.

Initially, an EEG baseline was recorded in eyes-closed and resting conditions for a period of time between 3 and 6 min (Pérez-Elvira, Oltra-Cucarella, Carrobles, Teodoru, et al., 2021). After this, the EEG activity was collected in the premnesic coding condition with eyes open and for a timeframe of about 80 s. Then, the EEG signals were collected during the guided mindfulness meditation session performed by the experimental group in the eyes-closed condition and for the duration of the session: 10 min and 27 s. During the same time, the subjects in the control group simply performed any activity they wished as long as it had nothing to do with the memory test, allowing them to check their cell phone, read, or chat with other people. Then, the EEG was recorded during the memory test performed postmindfulness procedure. As mentioned previously, to avoid the test–retest effect, the premindfulness test was designed in two versions (A and B). Hence the subjects receiving version A in the premindfulness test get version B in the postmindfulness test and vice versa. We also wanted to control the possible difference in the difficulty of versions A and B of the test, so the studied subjects and the control ones were balanced so that the potential differences between versions would not affect the results. The complete design of this study is shown in the following table (Table 1).

Table 1
Study Design

	Stage 1	Stage 2	Stage 3	Stage 4
Experimental type 1 (*N* = 8)	Baseline ***(EEG)***	Pretest (test version A), ***EEG***	Meditation *Mindfulness* (***EEG***)	Posttest (test version B), ***EEG***
Experimental type 2 (*N* = 6)	Baseline (***EEG***)	Pretest (test version B), ***EEG***	Meditation *Mindfulness* (***EEG***)	Posttest (test version A), ***EEG***
Control type 1 (*N* = 7)	Baseline (***EEG***)	Pretest (test version A), ***EEG***	Pause (***EEG***)	Posttest (test version B), ***EEG***
Control type 1 (*N* = 7)	Baseline ***(EEG)***	Pretest (test version B), ***EEG***	Pause (***EEG***)	Posttest (test version A), ***EEG***

The EEG records were imported into NeuroGuide version 2.9.1 (Applied Neuroscience, Inc., St. Petersburg, FL) software for editing and removing artifacts. The artifacts removal was done manually. Then, the files were further imported to the Brain Analyzer of BrainAvatar (BrainMaster Technologies, Bedford, OH). Brain electrical activity was reconstructed by combining the sLORETA localization algorithm with a real-time reference database and creating accurate 3D images of brain activation in the EEG component bands of interest. All 6,239 voxels of brain activity were computed in real-time (8 images per second) in eight frequency bands and converted into amplitude. Using the analysis in the qEEG option from BrainAvatar software, we selected EEG segments of 1-s epochs and performed the statistical analysis providing sLORETA 3D images. We used the summary values for amplitude and connectivity metrics for every frequency in each channel (Pérez-Elvira, Oltra-Cucarella, Carrobles, Moltó, et al., 2021).

Data Analysis

Analyses of the gathered EEG recordings were made using a general linear model analysis in the form of a repeated-measures study (MANOVA performed in SPSS version 25; α level of 0.05; Neamțu et al., 2021). The first objective was to study the EEG changes considering the dependent variable, the mean amplitude of each frequency range or, more simply put, activation in the meditation phase, while the independent variable was the same measure in its basal form (baseline EEG). Then, a similar analysis was carried out with repeated measures to test whether there was an improvement in memory performance after the mindfulness session. Specifically for this objective, the dependent variable was the score in the free recall part of the ad hoc list of word test (postmindfulness test), while the independent variable was the fact of having performed a mindfulness meditation in the case of the experimental group, or not (in the case of the control group; the categorical variable). The scores of the postmindfulness test were compared with those obtained before meditating or resting to evaluate the change produced. For both analyses (the EEG metrics pre-, during, and postmindfulness, and memory test scores pre- and postmindfulness), the Pillai trace (F) and Eta partial square (η_p^2) were employed to measure the effect size, being $\eta_p^2 < 0.06$ small, $0.06 < \eta_p^2 < 0.14$ medium, and $\eta_p^2 > 0.14$ large (Field, 2013).

The data on the synchrony between frontal, temporal, and parietal cortices during mnestic encoding were analyzed by the bivariate correlation between the regions of interest. This type of statistical analysis allowed us to know the degree to which two variables vary jointly so that we could study the synchrony or coherent joint activation of two cortical areas. The Pearson's correlation coefficient (*r*) and the strength of the correlation was interpreted as low $0 < r < 0.3$, medium $0.3 < r < 0.6$, and high $0.6 < r < 0.9$ (Field, 2013).

Results

We separately present the results with a focus on three dependent variables: (a) alpha, theta, and gamma waveband amplitude and coherence related to frontal, temporoparietal cortices, and temporoparietal structures during a single mindfulness session; (b) the study of the EEG activity during memorization or mnesic encoding tasks; and (c) exploring the role of the mindfulness session for a possible improvement in the recall of the explicit mnesic material.

Mindfulness Meditation Session Waves Versus Basal Condition

The results of the repeated measures analysis comparing basal and meditation activation levels in terms of the mean amplitude of each of the frequency bands in the zones of interest based on previous literature are presented in Table 2.

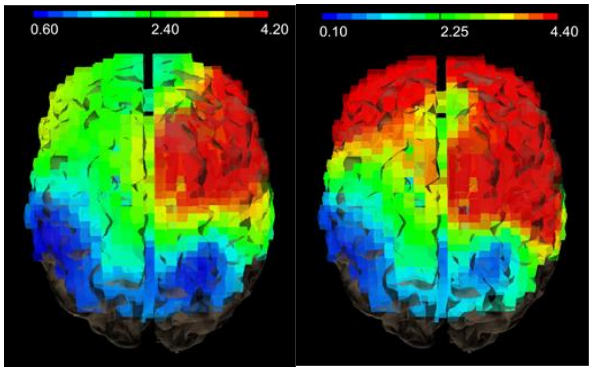
The comparative analysis of activation levels in the alpha, theta, and gamma bands in the frontal cortex and in the sum of all locations offered different significant results. The first result is related to the increase of the theta wave in the right frontal cortex (η_p^2 = 0.297 and p < .05) during meditation compared to the basal activation of the participants. This effect is illustrated for better understanding in Figure 1.

Table 2

Mean Amplitude by Frequency Band and Zone of Interest

	Basal	Meditation	Effect size	Sigma
	M (*SD*)	*M* (*SD*)	η_p^2	*p*
	Amplitude (uV)			
Left frontal cortex				
Alpha (α)	1.39 (0.43)	1.36 (0.39)	0.008	.747
Theta (Θ)	1.29 (0.35)	1.37 (0.19)	0.112	.223
Gamma (γ)	0.13 (0.33)	0.12 (0.28)	0.234	.067
Right frontal cortex				
Alpha (α)	1.57 (0.49)	1.48 (0.39)	0.128	.191
Theta (Θ)	**1.41 (0.41)**	**1.58 (0.24)**	**0.297**	**.036**
Gamma (γ)	0.14 (0.41)	0.12 (0.24)	0.257	.054
All left cortices				
Alpha (α)	1.85 (0.77)	1.96 (0.79)	0.037	.489
Theta (Θ)	0.92 (0.27)	0.96 (1.18)	0.033	.518
Gamma (γ)	0.91 (0.32)	0.76 (0.17)	0.265	.050
All right cortices				
Alpha (α)	1.39 (0.39)	1.34 (0.39)	0.028	.549
Theta (Θ)	**1.02 (0.30)**	**1.18 (0.18)**	**0.369**	**.016**
Gamma (γ)	**0.12 (0.27)**	**0.10 (0.19)**	**0.335**	**.024**

Figure 1. *Amplitude in the Theta Range During Mindfulness Meditation of Two Types of Participants—(A) Basal Activation and (B) During Meditation (the Color-Coded Scale Represents Microvolts).*



This increase is also in the sum of all locations (η_p^2 = 0.369 and p < .05), with a large effect size in both cases. Similarly, we noticed a large effect size but related to a decrease in the level of gamma activation in the sum of all locations, again in the right hemisphere (η_p^2 = 0.335 and p < .05). Table 3 presents the relationship between frontal cortex activation and its synchrony with the temporal and parietal ones, based on the alpha, theta, and gamma frequency bands (preferentially related to each other in these regions). We highlighted the bivariate correlations between these key cortical regions and the alpha, theta, and gamma bands.

Table 3
Synchrony in Codification (Bivariate Correlations)

	Left Frontal Θ	Right Frontal Θ	Left Frontal α	Right Frontal α	Left Frontal γ	Right Frontal γ
Left Temporal Θ	**.823****	**.536***	.291	.128	.378	.350
Right Temporal Θ	**.605***	**.729****	**.761****	**.662****	.523	**.563***
Left Temporal α	.133	.491	**.576***	**.624***	.460	.333
Right Temporal α	.128	.376	**.726****	**.780****	.344	.300
Left Temporal γ	.474	.126	.050	−.156	**.747****	.518
Left Temporal γ	**.749****	**.596***	.232	.090	.529	**.596***
Left Parietal Θ	**.708****	**.691****	**.740****	**.644***	.443	**.679****
Right Parietal Θ	.507	**.600***	**.750****	**.656***	.481	**.624***
Left Parietal α	−.055	.328	**.732****	**.823****	.216	.267
Right Parietal α	−.064	.243	**.667****	**.781****	.077	.138
Left Parietal γ	**.786****	.405	.276	.081	.471	.458
Right Parietal γ	**.814****	**.712****	.423	.285	.335	.507

Note. N = 14 for all results; * = significative correlation at level .05; ** = significative correlation at level .01 (2 tails).

Our results pointed to clear synchrony between the frontal cortex and the temporal and parietal cortex during the encoding of verbal material. There was a marked tendency for the temporal and parietal cortices to synchronize with the frontal cortex, responding in the same frequency range: (a) when the frontal cortices of the left and right hemispheres showed activity in the theta rhythm (Θ), the temporal and parietal cortices were synchronized in the same frequency range with an exception, the lack of coherence between the left frontal and contralateral parietal (Figure 1); (b) When the left and right hemisphere frontal cortices showed activity in the alpha (α) rhythm, the temporal and parietal cortices were synchronized in the same frequency range without exception; and (c) When the frontal cortices of the left and right hemisphere showed a gamma (γ) rhythm synchronization, this coherence occurred only in the same frequency range in the ipsilateral temporal cortex, but not in the contralateral or parietal cortex.

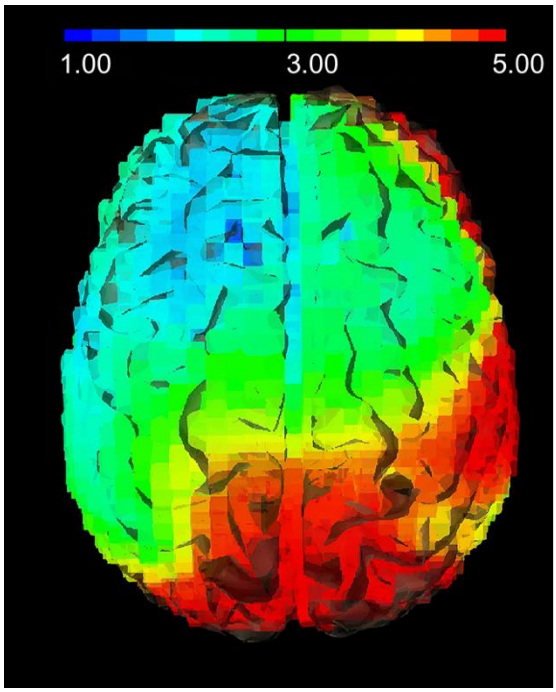
On the other hand, the analyzed data also informed us about the synchrony between frontal and temporal and parietal cortices in different frequency ranges. The ipsilateral parietal cortices and the

contralateral temporal and parietal cortices responded synchronously in gamma rhythm when the left frontal cortex responded synchronously in the theta rhythm. The same effect was found for the right frontal cortex when it responded with increased activation in theta rhythm. However, only the ipsilateral temporal and parietal cortices were synchronized with it in the gamma rhythm. Synchronous activation in the alpha rhythm of frontal and temporal, and parietal cortices was also noticed in the theta frequency range. In this case, both right and left parietal cortices responded to such a pattern, while only the right temporal cortex was activated in the theta frequency range. Finally, it was shown how the activation in the gamma range of the right frontal cortex correlated in the theta range with the ipsilateral temporal and parietal cortices, and with the contralateral temporal cortex. Note that, in all cases, the strength of the correlation was medium or high, so the results obtained should be taken into consideration.

Memory Encoding Associated With Mindfulness

Regarding the encoding of verbal material, the analysis of the bivariate correlation between the different areas of the cortex studied, frontal, temporal, parietal, and the sum of all neocortices revealed a significant correlation between the score achieved in the free recall test and the increased activation in the γ range in (a) the right temporal cortex (r = 0.638 and p < .05), (b) the left and right parietal cortex (r = 0.544 and r = 0.596, p < .05), and (c) the sum of all neocortices of the left hemisphere (r = 0.605 and p < .05; Figure 2).

Figure 2. *Amplitude in the Gamma Range During Encoding of Verbal Material of a Subject (the Color-Coded Scale Represents Microvolts)*.



The results of the repeated measures analysis comparing the pre–post measure scores on the free recall test of verbal material showing the improvement in recall after the brief mindfulness meditation session are presented in Table 4.

Table 4
Effect of Mindfulness Meditation on Memory

	Free words recall Premindfulness $M(SD)$	Free words recall Postmindfulness $M(SD)$	Size effect η_p^2	Sigma p
		Scores		
Experimental (N = 14)	12.64 (4.32)	12.29 (3.89)	0.006	.779
Control (N = 14)	**13.36 (4.05)**	**10.07 (4.75)**	**0.504**	**.003**

Note. Both experimental and healthy controls followed the same assessment.

Our results showed a predictable worsening in the free recall of the verbal material learned in the second part (post) compared to the first part (pre) in either the experimental or the control group, perhaps due to a primacy effect or due to the interference of the first items learned over the second ones. However, this pattern was significant in the control group (η_p^2 = 0.504 and p < .05) and not significant in the experimental group suggesting a protective role of the mindfulness session.

Discussion

In this study, we had the following objectives: to analyze the electroencephalographic activation during a brief session of mindfulness meditation carried out by participants with no previous experience with this type of meditation versus a control group, to study the synchrony between the frontal cortex and the temporal and parietal cortex during a memory task, and to explore the influence of mindfulness on the free recall of verbal material.

The results obtained during mindfulness meditation highlighted a specific activation pattern characterized by increased alpha, theta, and gamma frequency bands compared to the baseline activity of the subjects. The brief mindfulness meditation session participants did present an increased activation of the right frontal cortex in the theta wave range, which is consistent with previous studies (Aftanas & Golocheikine, 2001; Andresen, 2000; Dunn, 1999; Harne & Hiwale, 2020; Shapiro & Walsh, 2003; Travis et al., 2002). This suggests that when people with no previous experience follow the guided meditation instructions (Goleman, 2016), greater frontal activation in the theta frequency range is generated. Furthermore, the lateralization found towards the right hemisphere is in agreement with several authors' findings (Aftanas & Golosheykin, 2005; Ehrlichman & Wiener, 1980; Fenwick, 1987; West, 2016), and in opposition to other reports (Bennett & Trinder, 1977; Pagano & Warrenburg, 1983). With respect to previous literature, in our study we only found this significantly increased activation in the theta range, not occurring in the other two frequency bands shown in the literature (alpha and gamma). In fact, the gamma frequency showed a significant reduction when studied in all right hemisphere locations as a whole.

We have found a particular pattern of wave synchrony that occurred when participants were trying to store or encode verbal material. The frontal cortex presented a high coherence with the temporal cortex in the theta and gamma frequency ranges and the parietal cortex in the gamma range. These results are in line with those found by other authors (Fell & Axmacher, 2011; Harne & Hiwale, 2020). These synchronizations in the theta and gamma range between the frontal cortex and temporal and parietal lobe have been previously related to the retention of information in the working memory (Sarnthein et al., 1998; Serrien et al., 2003) as well as with the workload and information retention in short-term memory (Babiloni et al., 2004; Lutzenberger et al., 2002), which predicts the individual working memory capacity (Kopp et al., 2006; Plaska et al., 2021). Furthermore, our approach has pointed out the importance of gamma in memory processes. According to our results, the higher activation of this frequency in the right temporal cortex and the left and right parietal cortex predicts a better result in the free recall test performed.

Finally, regarding the facilitation effect of the encoding and recall of explicit verbal material, our results showed a worsening in the performance but statistically significant only in the control group, not in the study group practicing mindfulness. This could be explained by the primacy effect or by the interference of the learned material in the first part of the test. The former refers to the possibility that the semantic relationship between the words in the list improves the recall of the initial words, but not latter items (Glanzer & Cunitz, 1966). On the other hand, the latter has to do with the retroactive inhibition it produces because when learning the two lists, each of them acts as a system of independent habits that compete at the time of retrieval (McGeoch, 1932). The greater the similarity between the lists, the greater the likelihood of these effects appearing, which is something that might have happened in this case, since the ad hoc design of both parts has been arranged so that both trials are analogous. However, the results also informed us of an effect that supports the usefulness of this type of mindfulness technique. In the control group, the worsening is evident in the posttest in relation to the pretest, however, this effect was not significantly observed in the group that meditated. The mindfulness technique has probably acted as a protective factor against this worsening, with a positive effect on the cognitive capacity, which is in line with the findings of relatively similar studies but on the working memory performance (Jha et al., 2010; Mrazek et al., 2013).

Future research to address the limitations in our study should envisage larger samples to explore further and strengthen our results regarding the mindfulness protective role in worsening in the posttest versus pretest scores due to primacy and or to the interference of the first presented items. Likewise, it would be very useful to use simultaneous EEG-fMRI or EEG-PET neuroimaging techniques with a higher spatial resolution to study activation in the cortical regions and the deeper regions of the brain. Using the brief guided mindfulness meditation approach, it would also be very interesting to study different brain regions' connectivity in encoding and retrieving explicit

information in expert meditators versus beginner participants.

Conclusion

Mindfulness markedly synchronized temporal and parietal cortices with the left and right frontal cortex in the same frequency range when encoding the verbal material enhanced the studied group's cognitive performances. Mindfulness might be a protective factor in free recall in a series of multiple memory tests.

Author Disclosure

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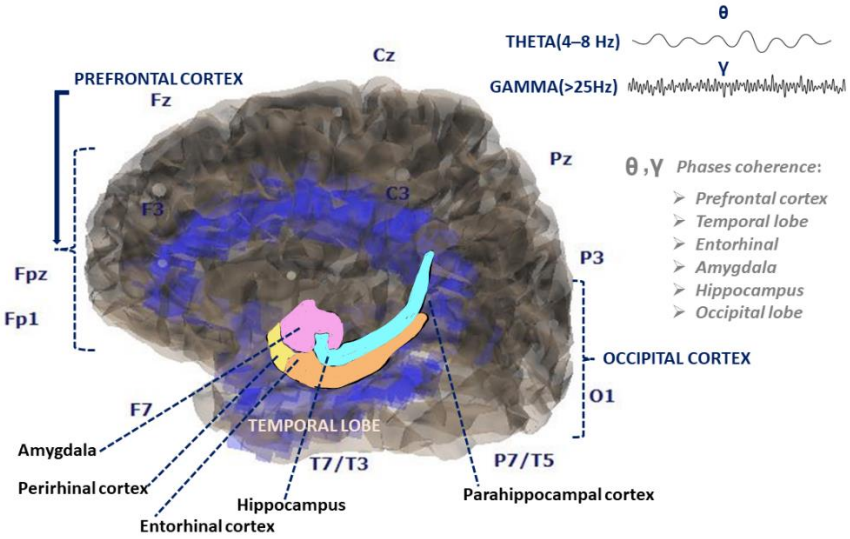
Appendix A

Memory, Mindfulness, and qEEG

Memory and qEEG. In explicit learning, the memory acquisition process begins with the recording and processing of stimuli arriving from outside in one or more heteromodal association cortices and sent further along to the parahippocampal and perirhinal cortices (Figure 1). Then, the information subsequently reaches the entorhinal cortex, which sends it to the dentate circumvolution through the perforant pathway to be finally transferred to the hippocampus (Androver-Roig et al., 2013). In addition, the hippocampus receives information from the amygdala, which has a modulatory role on learning by enhancing declarative learning of stimuli and emotionally charged situations (Redolar Ripoll, 2013). Once the encoding process carried out by the hippocampus ends, the information returns back to the cortex, reaching the medial structures that are basic for the definitive storage of information, according to Eichenbaum (2008; Figure A).

Figure A. *Explicit Learning Neural Substrate and the Wavebands Synchronization (Phases Coherence)*.



The neural substrate of explicit learning is mainly located in the medial temporal lobe, while the explicit memory is stored in the different cortical association areas (Eichenbaum, 2008). In the encoding and retrieval processes, the left prefrontal cortex seems to be more involved in the encoding process while the right prefrontal cortex in the information retrieval. For example, the semantic process in the explicit learning of the words seems to start with the occipital lobe and continues with the left temporal lobe. The inferior left frontal lobe is involved in word selection and retrieval, while the temporal lobe seems to have a crucial role in naming and reading words (Camina & Güell, 2017).

Hippocampus has a vital role in the transfer of information from immediate to long-term memory systems, initially consolidating the acquired information (Gilmore et al., 2021; Squire & Zola, 1996; Suzuki, 2005). Moreover, different wavebands synchronization (particularly in the theta and gamma range) seems to be crucial for the connectivity between the brain regions in the memory processes. According to Fell and Axmacher's (2011) meta-analysis, many studies support the correlation between the synchronization of anterior and posterior brain regions during encoding and retrieval of declarative information. The aforementioned authors pointed out that phase synchronization in medial temporal structures, specifically between the entorhinal cortex and the hippocampus, predicts subsequent word recall in humans.

This phase synchronization was also reported in studies by Pavlides et al. (1988), showing how an increased theta and gamma coherence in the hippocampus, amygdala, and neocortex predicts the immediate recall in a verbal retrieval task. In these brainwaves frequency ranges, Fell and Axmacher (2011) indicated that the phase

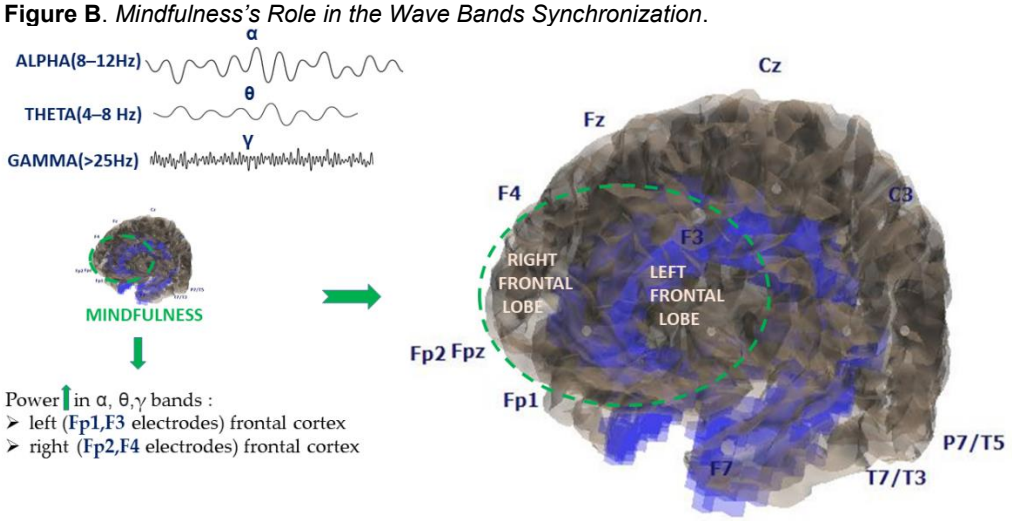
synchronization between frontal and temporal areas had a crucial importance for explicit memory. Moreover, theta synchronization between the prefrontal cortex and medial temporal lobe has been shown to occur during the maintenance of information in working memory (Sarnthein et al., 1998; Serrien et al., 2003). Furthermore, theta coherence between the frontal cortex and temporoparietal cortex regions increased workload and predicted individual working memory capacity (Kopp et al., 2006; Plaska et al., 2021). In short-term memory studies, this synchrony was noticed not only in theta but also in the gamma range between frontal areas during the retention of information (Babiloni et al., 2004; Lutzenberger et al., 2002; Plaska et al., 2021).

Mindfulness and qEEG

Grossman and colleagues (2004) comprehensively define mindfulness as maintaining a moment-by-moment awareness of our thoughts.

The EEG activation generated in people while performing mindfulness meditation has been studied. Increments in the power of the theta and alpha frequency bands in the frontal cortex have been found in addition to a decrease in the other frequency bands (Andresen, 2000; Shapiro & Walsh, 2003). This increase of alpha power in the frontal cortex is often observed when people are meditating, compared to control conditions (Aftanas & Golocheikine, 2001; Khare & Nigam, 2000; Lee et al., 2018; Figure B).

Figure B. *Mindfulness's Role in the Wave Bands Synchronization*.



Moreover, this frequency band acquires greater amplitude while people who meditate are resting than nonmeditating control groups (Aftanas & Golosheykin, 2005; Ehrlichman & Wiener, 1980; Harne & Hiwale, 2020; Travis et al., 2002), suggesting that both alpha activations are related to mindfulness meditation practice (Delmonte, 1984) both in their state or temporal form during meditation and in their trait. It seems to be sustained over time, even without meditation.

On the other hand, an increase in the theta frequency band has also been associated with state or temporary (Aftanas & Golosheykin, 2005; Aftanas & Golocheikine, 2001; Harne & Hiwale, 2020; Travis et al., 2002) and trait or permanent mindfulness, finding greater activity in this band in advanced meditators compared to beginners (Cahn & Polich, 2006). Expert meditators exhibit higher trait alpha and theta power compared to controls during meditation and baseline measurements (Aftanas & Golocheikine, 2001; Andresen, 2000; Delmonte, 1984).

In addition to the alpha and theta frequency ranges, the relationship between mindfulness meditation and the increase of frequency bands above 40Hz or gamma has also been documented. In this sense, increments in

frontal activity are found to be greater in meditators during the mindfulness session compared to their resting state (Lutz et al., 2004). Also, Carter et al. (2005) found a higher mean gamma frequency activation during meditation while comparing expert and beginner meditators. Using low-resolution electromagnetic tomography analysis (LORETA; Pascual-Marqui et al., 1994), Lehmann et al. (2001) indicate that gamma is the only band that demonstrates differential spatial distributions in the frontal cortex comparing meditators and control EEG baseline. Mindfulness meditation could alleviate cognition. Mindfulness is related to the increase of power in the theta, alpha, and, perhaps, gamma bands in frontal areas of the cerebral cortex (Aftanas & Golosheykin, 2005; Andresen, 2000; Bennett & Trinder, 1977; Dunn, 1999; Ehrlichman & Wiener, 1980; Fell & Axmacher, 2011; Fenwick, 1987; Harne & Hiwale, 2020; Lutz et al., 2004; Pagano & Warrenburg, 1983; Sarnthein et al., 1998; Serrien et al., 2003; Travis et al., 2002; West, 2016). In fact, some reports have already shown that mindfulness improves different aspects of cognitive performance, or those related to it, such as academic performance (León, 2008; Schoeberlein & Sheth, 2015), learning, anxiety (Rodríguez-Ledo et al., 2018; Schoeberlein & Sheth, 2015; Sugiura, 2004), information processing speed (Zeidan et al., 2010), memory (Mrazek et al., 2013; Zeidan et al., 2010), attention and impulse control (Mrazek et al., 2013; Zeidan et al., 2010). Moreover, mindfulness shows protective effects of memory decay and could be used as an effective technique to enhance cognitive performance in the learning process (Jha et al., 2010)

Appendix B

Table 1

Category	Neutral (0) or emotional (1)	Item	RL1 (Free recall)	RF1 (Cued recall)
Reading Material	0	**Encyclopedia**		
Vegetable	0	**Bell pepper**		
Family	1	**Mother-in-law**		
Bird	0	**Canary**		
Dedication of time	1	**Job**		
When life does not go on	1	**Death**		
Reptile	0	**Crocodile**		
Physical sensation	1	**Pain**		
Tool	1	**Gun**		
Construction material	0	**Wood**		
Building	0	**Museum**		
Intense emotion	1	**Sadness**		
Economic status	1	**Poverty**		
Furniture	0	**Shelf**		
Verb tense	1	**Future**		
Musical instrument	0	**Harmonica**		
Event	1	**Accident**		
Vehicle	0	**Bus**		
Plant	0	**Margarita**		
Improvement	1	**Ascent**		
Family	1	**Son**		
Disease	1	**Cancer**		
Sports	0	**Basketball**		
Cooking utensil	0	**Strainer**		
		Sums	**0**	**0**
		Total Free Recall		
		Total Facilitated Recall		
		Deferred Recall Total		
		Total Recall		

Table 2

Category	Neutral (0) or emotional (1)	Item	RL1 (Free recall)	RF1 (Cued recall)
Game	0	**Ball**		
Electricity	0	**Plug**		
Show of happiness	1	**Laughter**		
Capturing reality and storing it	0	**Photography**		
Insect	1	**Spider**		
Element of terrorist aggression	1	**Pump**		
Body part	0	**Ear**		
Criminal act resulting in death	1	**Murder**		
Long-lasting interaction with a person	1	**Relation**		
To step on at home	0	**Carpet**		
For stargazing	0	**Telescope**		
Profession	1	**Police**		
Fluid inside the body	1	**Blood**		
To fly	0	**Balloon**		
When you have no stress	1	**Peace of mind**		
Viewing utensil	0	**Glasses**		
When someone does not tell the truth	1	**Liar**		
To drink	0	**Bottle**		
Electronic utensil	0	**Computer**		
When nails and slate or fork and plate	1	**Squeak**		
When you believe that good things are going to happen to you	1	**Hope**		
Family	1	**Primo**		
Space-Astronomy	0	**Moon**		
Eating utensil	0	**Spoon**		
		Sums	**0**	**0**
		Total Free Recall		
		Total Facilitated Recall		
		Deferred Recall Total		
		Total Recall		

NeuroRegulation

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Loss of an Eye: A Case Study of a First Responder's Neurofeedback Treatment

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Abstract

A case study is presented of a first responder injured in the line of duty who experienced the loss of an eye and sought neurofeedback treatment. That there are no known studies reporting qEEG or ERP findings, nor the efficacy of neurofeedback for the condition, emphasizes the importance of reporting on this case. A literature review of neuroanatomical and neurophysiological studies relevant to the loss of binocular vision is presented with application to the case at hand. Hypotheses regarding the measurable effects of monovision on qEEG and ERP assessments, and the possible efficacy of neurofeedback treatment, are explored in light of the findings. Possible improvements in visual processing were found after a course of neurofeedback treatment as measured by pre-post qEEG and ERP assessments.

Keywords: EEG; ERP; qEEG; neurofeedback; first responders; eye injury

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Introduction

This compelling case of a person in their thirties employed as a first responder began with an eye injury sustained during the course of duty which resulted in complete loss of sight in one eye and subsequent surgical removal of the eyeball. Fortunately, there was no encroachment of the trauma into the brain. The individual was referred for a quantitative electroencephalogram (qEEG) and event-related potentials (ERP) workup and neurofeedback (NFB) treatment. Approximately 1 month following the injury presented for the initial assessment. The individual had been medically cleared to return to work, with some limitations due to the effects of monocular vision and the sudden loss of binocular vision—namely on reduced peripheral vision and depth perception. The individual was also medically cleared to drive. In addition to the physical injury, there were concerns over the psychological impacts of the injury, so mental health checklists were also administered. The subject and clinicians agreed that the case was of research interest due to the rare opportunity to study the effects of the loss of binocular vision on qEEG/ERP measurements as well as to measure the effect of NFB treatment. While there was no qEEG/ERP data collected on the subject prior to the injury, we fortuitously had qEEG/ERP samples of many of the person's first responder cohort, which served as a comparison. Finally, two normative databases were employed, giving a comparison to theoretical healthy subjects.

In this paper we will analyze the data collected on the subject as well as research on potential NFB approaches for individuals experiencing similar injuries. Additionally, a review of pertinent neuroanatomical and neurophysiological literature will be reviewed.

First Responders

First responders are defined by 2003 presidential directive as "individuals who in the early stages of an incident are responsible for the protection and preservation of life, property, evidence, and the

environment, including emergency response providers" (Johnson, 2007). Historically, the work of first responders has been considered to pose to them a higher risk for injury and death. To assess the occupational risks for first responders, Reichard and Jackson (2010) compiled various agency reports on the respective classifications of emergency medical services (EMS), fire, and law enforcement showing how these groups are at significant risk for work-related injuries. They estimated that police officers and career firefighters have the highest rates of injuries among first responders at 8.5% and 7.4% of the respective workforces (Reichard & Jackson, 2010).

Statistics for specific types of injuries for first responders are difficult to ascertain, possibly due to reporting limitations and inconsistencies. For example, Reichard and Jackson (2010) found a lack of unanimity among reporting criteria and no specificity about eye injuries, with the nearest classification being injuries to the face. Of interest for this study, statistics for assaults on law enforcement offices in Australia from 2014 to 2020 show that approximately 0.3% of injuries sustained from an assault result in eye disorders (Orr et al., 2023). The Centers for Disease Control and Prevention estimates that the risk of eye injury is 1.2% of all injuries sustained by workers in the general population, with no classification for first responders (Centers for Disease Control and Prevention, 2022).

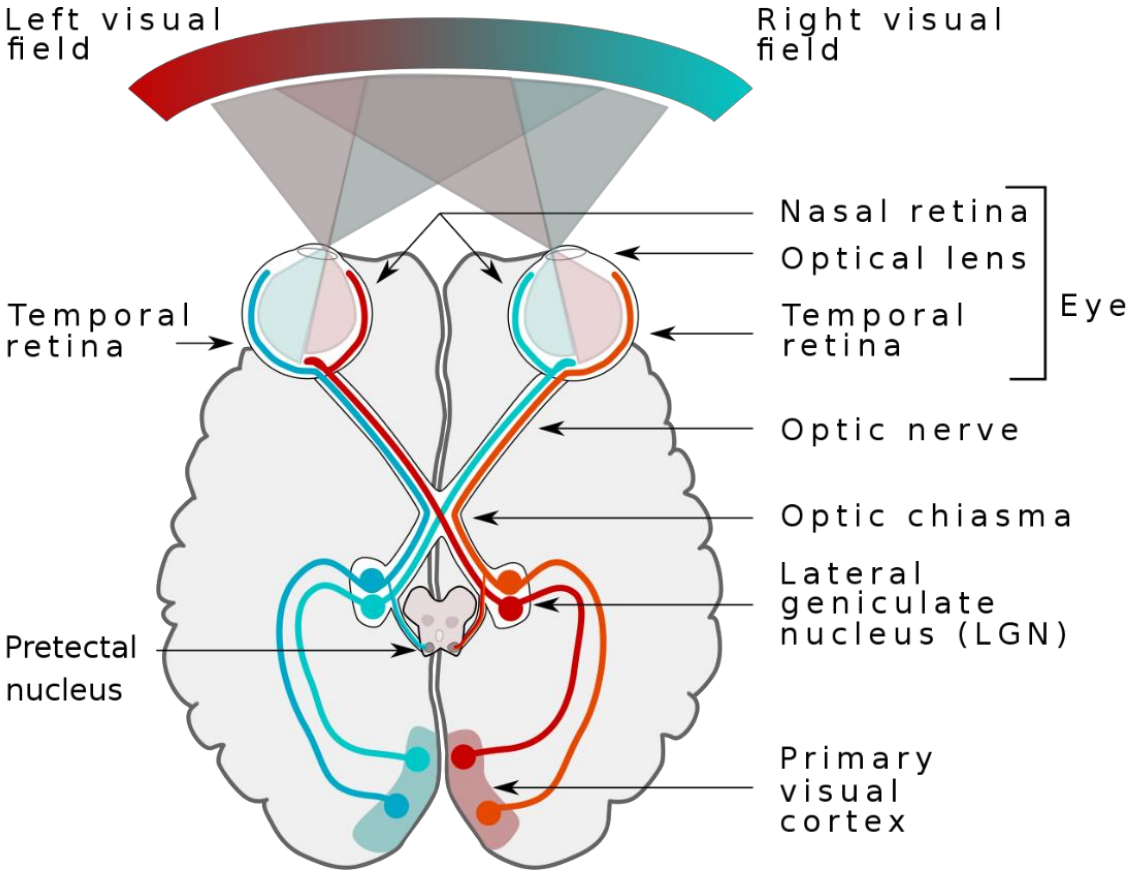
While the injury sustained by the subject of this study may or may not be representative of others in the field, the opportunity to study qEEG and ERP measurements may provide some insight into the nature of monocular vision after a sudden loss of binocular vision. Additionally, the effect of the chosen NFB protocol may provide important data as well.

The goals for NFB treatment were twofold: to address any posttraumatic stress and to enhance visual processing. While the literature is replete with research and evidence-based protocols for treating posttraumatic stress, a literature review returned no studies on treating vision loss from such an injury with NFB. A review of relevant neuroanatomical and neurophysiological aspects of vision gave limited guidance on appropriate NFB targets. As part of the retrospective analysis of the qEEG, ERP, and NFB data, and further literature review, additional insights were gained which may form the basis for additional treatment and study.

The Visual System

The human visual system involves levels of duplication and division of resources (see Figure 1). Roughly speaking, visual perception may be said to begin with the focus of photons from external sources on the retina with the light from the right visual field being refracted through the cornea and lens onto the left side of the retina, and vice versa with the left visual field. Ostensibly because the nose blocks the way, an arc of the far-right visual field is only accessible to the right eye, and vice versa with the far-left visual field to the left eye. The optic nerve conveys the sensory information from the retina to the lateral geniculate of the thalami where it is then sent to the primary visual cortex. En route from the retinas, tracts of the optic nerve route through the optic chiasm. Some tracts of the optic nerve are then routed to the thalamus of the same hemisphere with projections onto the visual cortex of the same hemisphere. Other tracts of the optic nerve make a crossover at the optic chiasm and are then routed to the thalamus of the opposite hemisphere with projections onto the visual cortex of that hemisphere. Projections from the left thalamus go to the left visual cortex and projections from the right thalamus to the right visual cortex. The result is that the input from the left side of the retina (right visual field) of the left eye (left temporal hemiretina) proceeds to the left thalamic lateral geniculate with information then passed on to the left visual cortex, and the input from the right side of the retina (left visual field) of the right eye (right temporal hemiretina) proceeding to the right thalamic lateral geniculate with information then passed on to the right visual cortex. The sensory input from the right side of the retina of the left eye (left nasal hemiretina) crosses over to the right thalamic lateral geniculate with information then passed on to the right visual cortex. Conversely, input from the right nasal hemiretina flow to the left thalamic lateral geniculate with information then passed on to the left visual cortex. The result is that sensory information for both the right and left visual fields is duplicated into the right and left visual cortices, respectively (Wurtz & Kandel, 2000).

Figure 1. *A Simplified Schema of the Human Visual Pathway*.



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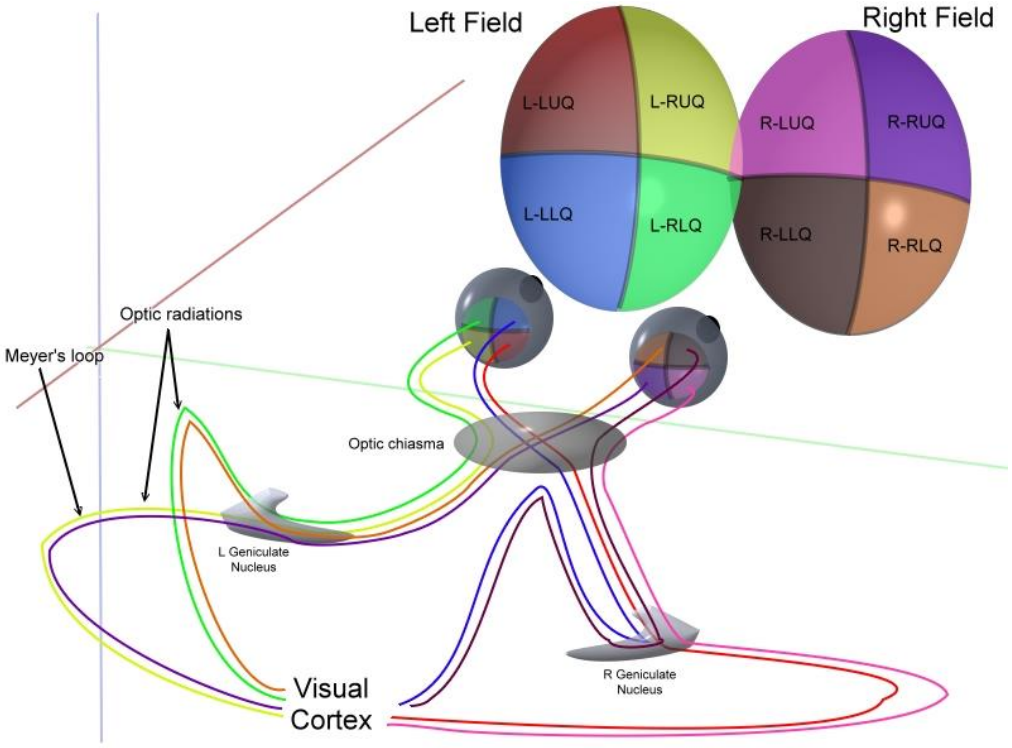
Sensory input from the thalami into the visual cortices has an added level of complexity in that the tracts from the left and right sides of the retinas remain segregated in the thalamic lateral geniculate nuclei via magnocellular (M) and parvocellular (P) layers, which then form parallel pathways to different locations of the respective visual cortex (see Figure 2). The cells in the M and P pathways respond differently to color contrast, with the P cells being more sensitive to changes in colors and the M cells more sensitive to the luminance contrast (brightness) of the colors. In addition, P cells are more sensitive to spatial changes while M cells are more sensitive to temporal changes. Moreso, optic nerve tracts carry input from regions of the retina which are populated with rods and cones, which varying degrees of sensitivity to light and color, respectively, with higher densities of cones in the fovea, where spatial acuity is highest (Wurtz & Kandel, 2000).

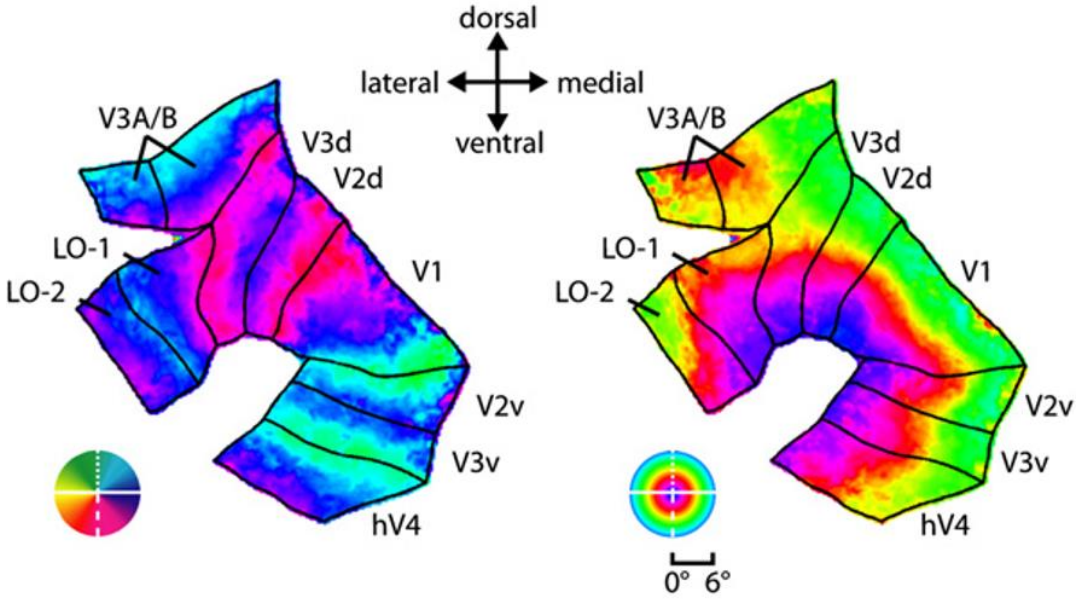
The axonal tracts from the thalami lateral geniculate nuclei to the respective regions of the visual cortices have been mapped in some detail (Avarez et al., 2015). At the visual cortices in the medial occipital lobes, a representation of visual stimuli is plotted like a matrix corresponding to areas of the retinas (Larsson & Heeger, 2006; Tootell et al., 1998; Wurtz & Kandel, 2000; see Figure 3).

Figure 2. *A Less Simplified Schema of the Human Visual Pathway*.



Note. From Ratznium at en.wikipedia, CC BY-SA 3.0 <https://creativecommons.org/licenses/by-sa/3.0/>, via Wikimedia Commons.

Figure 3. *Human Retinotopic Map*.



Note. Larsson, Heeger, CC BY 3.0 <https://creativecommons.org/licenses/by/3.0>, via Wikimedia Commons.

Hypothesis 1: Measurable Effects

While the qEEG—as normed against a database of healthy subjects—can provide significant information regarding the brain's activity in a resting state, ERPs may be of much greater utility for assessing our subject's visual processing (Woodman, 2010). The hypothesis posited here is that even though our subject's monocular vision would be represented in both hemispheres in a way comparable to binocular vision, the amount of the sensory input would be halved, and the reduced input would be reflected in the ERPs, and possibly in the qEEG. This hypothesis might be supported in the literature of luminance perception, which indicates that attention is more influenced by luminance contrast as measured from lower to higher luminance levels (perceived as brightness; Eroğlu et al., 2020; Fimreite et al., 2015; Martinovic et al., 2011; Skiba et al., 2014). These luminance studies, however, were based on subjects' binocular vision and not specifically applicable to the focus of this study.

It is known that deprivation of sight in one eye early in life, such as with amblyopia, produces profound developmental differences in the related visual systems, namely, a depression of visual neurophysiology occurs for the deprived eye. Conversely, it has been shown that the visual system related to the nondeprived eye takes over and compensates (even to the extent of greater acuity). Most of the studies found which addressed the effects of monocular deprivation have focused on the effects of amblyopia. In the case of amblyopia, however, there is not a complete loss of vision in the affected eye, but a reduction in spatial detail (Freeman, 2009; Freeman & Bradley, 1980).

Lunghi et al. (2015) studied pre–post visual evoked potentials (VEP) following 150 min of monocular deprivation using a translucent patch over the nondominant eye. They reported an increased VEP in the deprived eye and decreased VEP in the nondeprived eye. Likewise, evoked alpha power increased in the deprived eyes and decreased for the nondeprived eye. EEG sites of interest were Cz, Pz, Poz, Oz, PO7, and PO8 (central, parietal, and occipital).

Kwon et al. (2009) studied pre–post fMRI BOLD responses in the visual cortices (V1 and V2) when subjects were fitted with contrast-reducing goggles for 4 hr. The result was an increase in BOLD responses in visual cortices, which supported a theory that prolonged deprivation from normal contrasts results in compensatory changes.

Studies showing the effects of totally obscuring vision in one eye are scarce. Frenkel and Bear (2004) chemically blinded one eye in adolescent mice and reported a potentiation of responses driven by the unblinded eye. These effects resembled similar procedures for adult mice. Rittenhouse et al. (1999) had previously demonstrated that the nondeprived eye potentiation was greater when mice were temporarily exposed to monocular deprivation using eyelid sutures than when the eye was chemically blinded for the same time period. This indicates that some level of low light gradient with low contrast (through eye lids) has an additive effect on the development of nondeprived eye dominance. We may assume, therefore, that total blindness of one eye has a potentiation effect on vision with the remaining eye, but perhaps not to the extent as with partial blindness such as the loss of contrast discrimination. So, even though the visual input is halved at the level of ocular input, the visual system is likely to compensate with increased potentiation, and possible increased acuity.

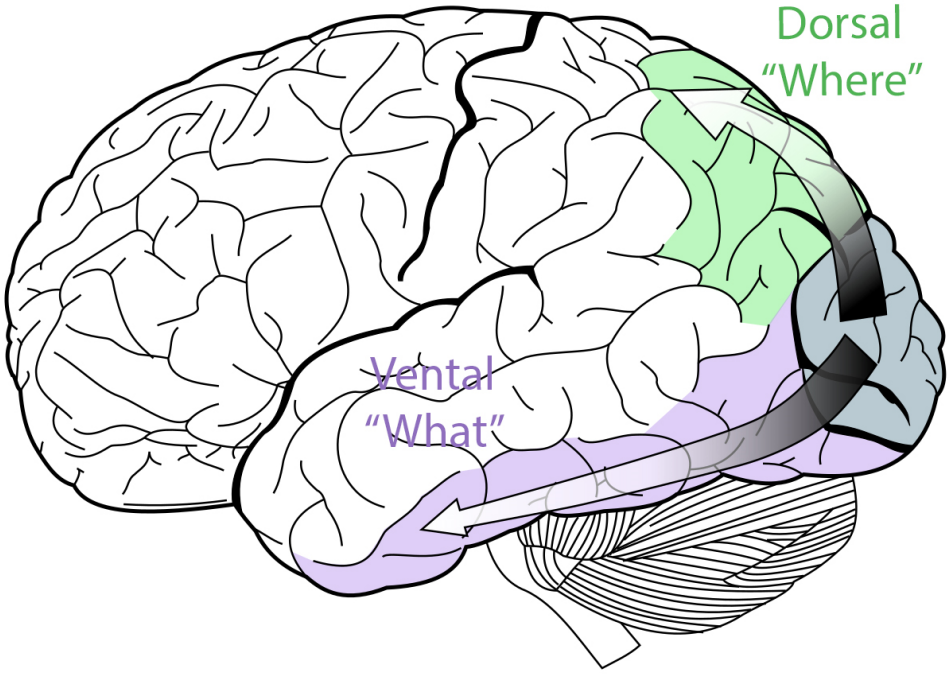
Hypothesis 2: Benefits From Neurofeedback

At the initial assessment it was clear that the subject's interest was in performance enhancement due to the significance of stringent demands of the vocation. Furthermore, the subject denied any psychological problems associated with the injury, as surprising as this was to the clinicians. A second hypothesis, then, was that NFB geared toward enhancing visual processing may serve the subject's desire to improve performance, given the limitations of depth perception and peripheral vision. Numerous potential protocol targets were considered, including amplitude training (beta enhancement) over occipital, parietal, or posterior temporal sites to enhance visual processing. In addition, coherence training was considered to be an option in this regard.

Returning to the neuroanatomical discussion to inform our strategy for determining a protocol, from the thalamic lateral geniculate nuclei, the distinct parallel M and P pathways set the stage for some of the ways visual input is processed once it reaches the visual cortices in the occipital lobes, and ultimately how the sensory information is processed downstream by related brain structures. At this point, two distinct circuits might be affected, namely the dorsal and ventral streams (Goodale & Milner, 1992) which have been labeled as generally involving a determination of the "what" (ventral) and the "where" (dorsal; see Figure 4). Joel Norman elaborated on the two-pathway model as including the respective functions of the streams as recognition and

identification (ventral) and visually guided behavior (dorsal) with the source input for the streams as foveal (ventral) and retinal-wide (dorsal). He further posited that the ventral stream is less affected by monocular vision (Norman, 2002). More recent studies have shown a dynamic interplay between various aspects of the dorsal and ventral streams (Alvarez et al., 2015) which is also highly contextual (Gilbert & Li, 2013). An earlier study by Zanon et al. (2010) demonstrated that activating the left parietal cortex with transcranial magnetic stimulation (TMS) activated both the dorsal and ventral with prefrontal regions streams as measured by EEG ERPs.

Figure 4. *Ventral and Dorsal Visual Streams*.



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No NFB studies were found that specifically addressed monocular vision. An EEG NFB study to address visuospatial neglect of right hemisphere stoke patients using alpha power downtraining in the parietal region demonstrated a promising improvement in visuospatial search measurements (Ros et al., 2017). Of interest are fMRI NFB experiments demonstrating control over subject-specific regions of the retinotopic visual cortex with measured enhancement of visual perceptual sensitivity (Schamowski et al., 2012; Shibata et al., 2011; Wang et al., 2021).

Methods

The Subject

To protect the identity of the subject, no exact age, gender identity, or job title is given. The subject is in his or her thirties and is a first responder. The subject gave written consent for his or her data to be used for the purpose of research. This study complies with the Declaration of Helsinki and was performed according to ethics committee approval.

Symptom Assessments

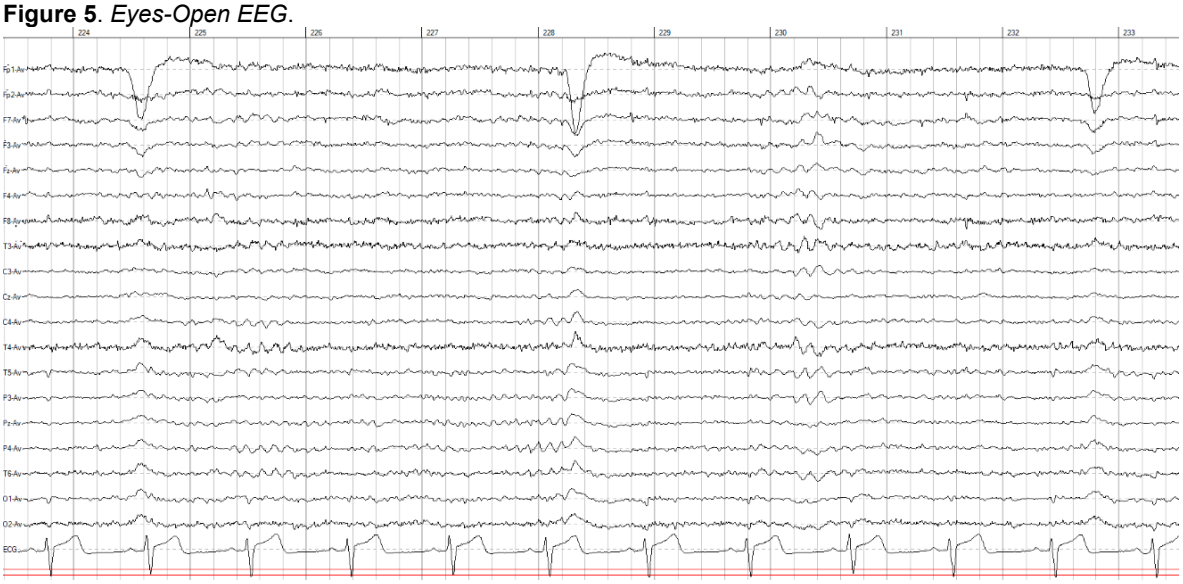
The Achenbach Behavior Checklist (ASEBA) Adult Self-Report and Zung Self-Rating Anxiety Scale were administered at pretreatment and posttreatment.

EEG and ERP Recordings

For each assessment session, eyes-closed and eyes-opened resting state EEG data for the subject was recorded for 5 min, respectively, and a Visual Continuous Performance Test (VCPT) ERP recording for 20 minutes, from 19 electrode locations (Fp1, Fp2, F3, F4, F7, F8, Fz, C3, C4, Cz, P3, P4, Pz, T3, T4, T5, T6, O1, and O2) positioned on the scalp according to the international 10/20 system using a standardized electrode cap (Electro-Cap International, Inc., Eaton, Ohio, USA) with a linked-ears reference (see Figure 5).

Preparation of electrodes was performed in a manner adequate to achieve impedance levels of less than 5,000 ohms (Jones, 2015). An ECG channel was also collected to assist with identifying ECG artifacts. Recordings were made with a Mitsar 201 high-impendence 21 channel amplifier with WinEEG version 2.136.109 software (Mitsar Co. Ltd., St. Petersburg, Russia) using a Windows-based laptop. The ERP visual continuous performance test (VCPT) was administered using the included PsyTask version 1.55.19 presentation software on an ethernet cable-connected second Windows-based laptop with calibration done according to the manufacturer's specifications.

Figure 5. *Eyes-Open EEG*.



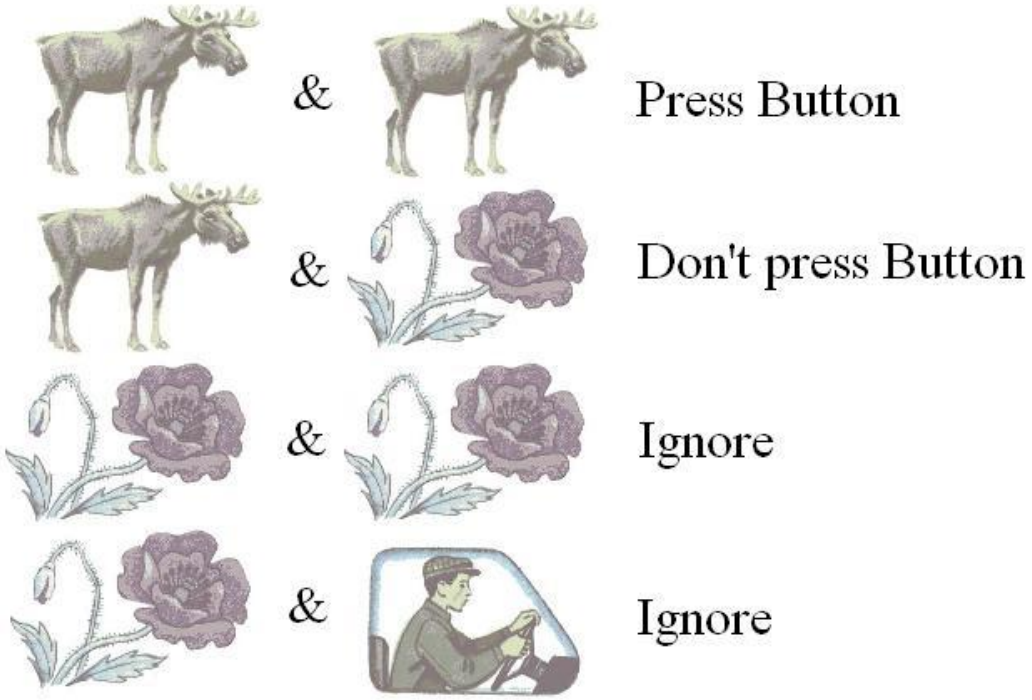
Note. Sample of 19 channel eyes open EEG showing unilateral eye movements during blinks.

The VCPT trials were set up to present go/no-go trials in which a subject is presented with two images, each displayed on screen consecutively, one second apart. The images are of animals, flowers, and people. The go condition is comprised of two animals in sequence. The no-go condition is comprised of an animal followed by a flower. Other presentations are interspersed which entail the presentation of a flower followed by a flower and a flower followed by a person with a tone sounding simultaneously with the image of a person. An example of this schema is shown in Figure 6.

qEEG and ERP Processing

qEEG processing was accomplished using WinEEG software and the Human Brain Index normative database (HBimed AG, Switzerland) and NeuroGuide version 3.0.4 software and the LifeSpan normative database (Applied Neuroscience, Inc., Largo, FL). ERP processing was done using WinEEG and the Human Brain Index normative database.

Figure 6. *ERP VCPT Visual Stimuli*.



Note. "Press Button" is the go condition whereas "Don't press Button" is the no-go condition.

Neurofeedback

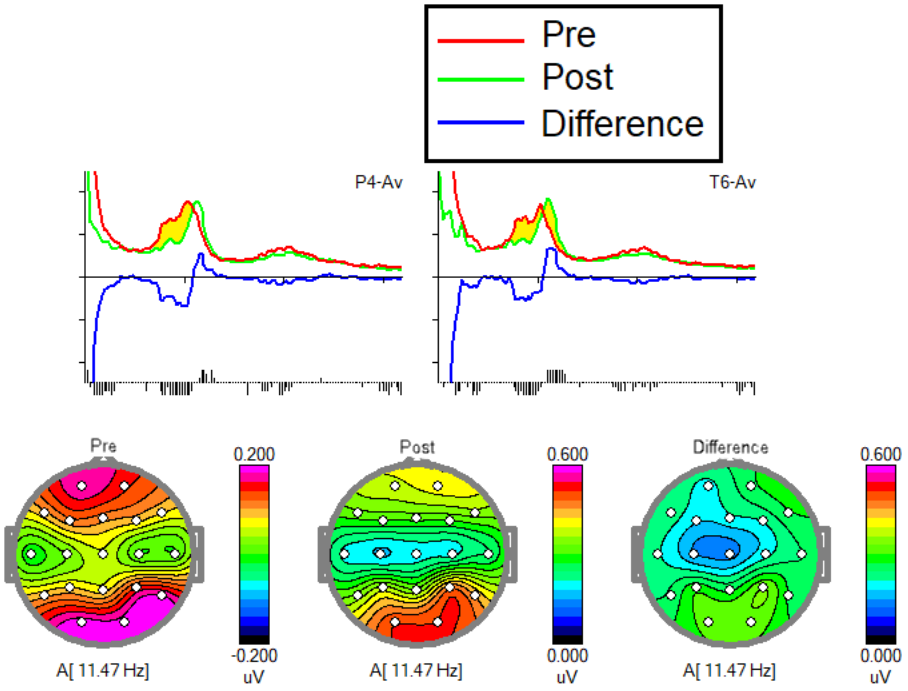
NFB sessions were conducted using BioExplorer software (CyberEvolution, Inc., Seattle, WA) with the Neurobit Optima+4 high impedance amplifier (Neurobit Systems, Poland). Preparation of electrodes was performed in a manner adequate to achieve impedance levels of less than 5 kΩ (Jones, 2015). The subject received a total of eight sessions of NFB training: two sessions per week for 4 weeks. Two-channel amplitude training was accomplished with active electrodes at P3 and P4, with reference electrodes placed at A1 and A2, respectively. The ground electrode was placed at Cz. Placements on the scalp were in accordance to the International 10-20 system. Gold-plated Grass electrodes were used (Natus Medical, Inc., Middleton, Wisconsin, USA). Frequency bands trained were 4–10 Hz (decrease), 12–18 Hz (increase), and 25–35 Hz (decrease). Operant-conditioning audio-visual feedback was provided using screen brightening and volume increase as positive reinforcement while the subject watched cartoon animations, by manually adjusting the individual frequency band thresholds at equal levels of success in order to maintain and an average overall success percentage at approximately 50–60%.

Results

Salient differences in the pre–post qEEG measures as processed with WinEEG/HBI indicated that (a) the occipital alpha rhythm peak frequency was faster after the completion of the NFB regimen, from 10.5 Hz to 11.2 Hz, with an inhibition of low frequency content of the posterior alpha, and (b) the increased level of the posterior cortex activation after the NFB sessions (see Figure 7).

Pre–post calculations in NeuroGuide/LifeSpan found a similar increase in the alpha peak frequency, from 9.94 Hz to 10.44 Hz at O1 and O2 (see Table 1). The decrease in alpha 1 (8–10 Hz) activity was also statistically significant ($p < .001$).

Figure 7. *Pre- and Post-qEEG Spectra in Eyes-Closed Condition*.



Note. WinEEG and HBI.

Table 1
Pre–Post Changes in Alpha Peak Frequency

Pre–Post	Site	APF (Hz)	
Pre	O1	9.91	
Pre	O2	9.97	
		9.94	Average
Post	O1	10.44	
Post	O2	10.44	
		10.44	Average
		0.5	**Difference**

Note. NeuroGuide.

Behavior characteristics that reflect response accuracy, response time (RT) in milliseconds (ms), and variability of RT (in ms) were captured during the ERP trails. Norms for these measures are included in the database. This potentially gives a picture of a subject's ability to accurately identify the stimuli and respond accordingly, and the speed with which the subject responds—from the time of the stimulus presentation to the time of response (clicking the button). Furthermore, by comparing behaviors during both the pre- and posttreatment assessment, a probable measure of treatment effects on response characteristics is obtained. During this subject's ERP trials, pre- and posttreatment errors were zero, and response time (RT) and RT variability decreased at the postassessment. All posttreatment measures were below the normative database average (Table 2).

Table 2
Pre- and Post-ERP Behaviors

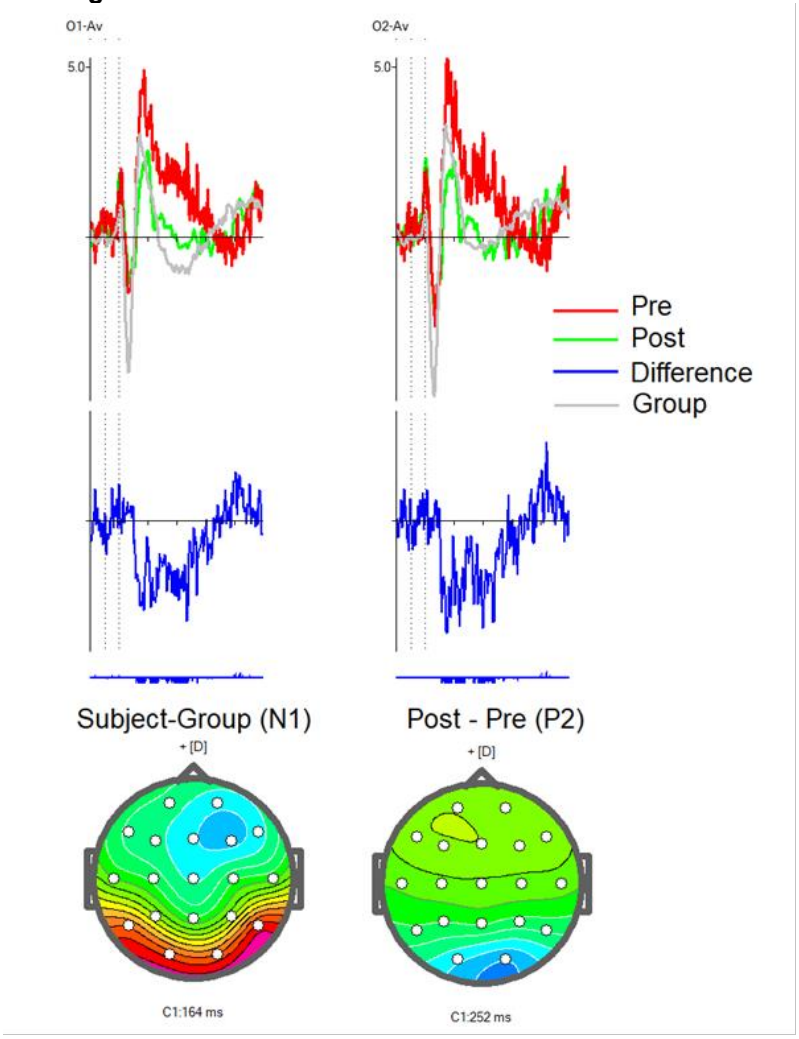
Pre–Post	Omission Errors	Commission Errors	Response Time (ms)	Variability (RT)
Pre	**0**	**0**	**430**	**8.3**
Post	**0**	**0**	**363**	**4.1**
Norm	**1.9**		**379**	**6.8**

Note. WinEEG and HBI.

In examining pre- and posttreatment responses to the first visual stimulus in go (a*) trials, additional comparisons were made to the normative database and to a group of the subject's peers which was conducted in an earlier study, as shown in Figure 8.

The visual N1 wave of occipital temporal topography (see the left map), reflecting the level of the ventral stream activation, is significantly reduced in comparison to the group norms. This result probably reflects the effect of the injured eye. Before the NFB sessions, a late positive component of the ERP in the occipital sites (O1, O2) is abnormally increased. This result probably reflects the increased sensitivity of neurons participating in formation of the poststimulus visual trace. But this late component is significantly reduced after NFB, possibly reflecting a normalization of the component—and an improvement in ventral stream function. If so, the subject's ability to process the "what" in visual processing may have been improved.

Figure 8. *ERPs in the Cued Go/No-Go Task*.



Note. WinEEG and HBI.

Surprisingly, the subject's pre- and posttreatment symptom checklists were within normal limits. All of the ASEBA scales, for example, were below clinical levels. The Zung anxiety scale results were in the normal range, as well. The reason for normal symptomatology following a traumatic event is unknown but may be attributed to the intense level of training the subject had received and her or his level of resilience.

Conclusions

Case studies can be of value when a clinician provides assessment and treatment in a highly unusual situation and may yield insights

unobtainable through conventional research methods. This study examined a unique case in which a first responder's loss of an eye is hypothesized to cause reduced visual processing which may be measurable with qEEG and ERP assessments. Relevant findings were presented. In addition, the study examines the possibility of enhancing subsequent visual processing in the case of sudden injury-related monovision by the application of parietal amplitude-based NFB. Pre- and posttreatment analysis of certain ERP markers were presented that may indicate the efficacy of NFB in this regard.

Limitations of the study include the fact that only one subject is studied. This is due, for the most part, to the rarity of the situation. An internet search shows that there may be a few additional somewhat similar cases related to first responders occurring on an infrequent basis, which conceivably may yield a broader population to study.

That the subject's pre- and posttreatment ERP components reflect a plausible improvement, or normalization, of the ventral stream, these changes cannot be attributed solely to the NFB provided. Research was presented in the literature review that indicates the possibility of the brain's ability to adapt to the loss of an eye with the improvement to certain aspects of visual processing. The mere passage of time may therefore account for the documented improvements as spontaneous neuroplastic changes are more significant during the early months following an injury. On the other hand, early intervention may enhance functional recovery. In this case, a highly motivated, high-functioning individual demonstrated improvements that may not be seen across the general population.

As clinicians develop treatment protocols for injured public servants, it is hoped that this study may shed some light on similar cases. As for this subject, future possibilities for EEG NFB may include further beta enhancement amplitude training of the parietal, occipital, or temporal-parietal regions. Additionally, the parietal alpha suppression protocol studied by Ros et al. (2017) is of interest for addressing any visuospatial issues. The study by Zanon et al. (2010) suggested possibilities for parietal-prefrontal coherence training as a means of enhancing dorsal and ventral visual streams. And finally, the cited fMRI studies, demonstrating subject's ability to control visual cortex activity with resulting improvement in visual perceptual sensitivity (Scharnowski, 2012; Shibata et al., 2011; Wang et al., 2021) and concomitant EEG LORETA studies demonstrating motor imagery localization (Cebolla, et al., 2017) may provide a rationale for LORETA ROI NFB which enables the targeting of the visual cortices with source localization methods.

Author Disclosure

Authors have no grants, financial interests, or conflicts to disclose.

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Quantitative EEG Significantly and Clinically Differentiates Acute Mild TBI Patients From Matched Neurotypical Controls: Power Spectral and Connectivity Analyses

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Abstract

Concussive head injuries result in not only coup–contrecoup trauma to neurological tissue at injury sites but also a mechanical shearing of neurological pathways throughout the brain. Unfortunately, however, the diagnosis of concussion has long been based largely on self-reports of overt symptoms and virtually never includes an assessment of involved neurological tissues and pathways. This deficiency then leads to premature return to play or duty, to the risk of subsequent neurological reinjury and, in worse cases, to chronic traumatic encephalopathy. We offer here a test of quantitative EEG (qEEG) as a convenient, low-cost remedy to this problem in the evaluation of acute head injury in 19 diagnosed concussion patients matched to neurotypical controls. Results of qEEG indicate numerous Brodmann area functional clusters of highly significant and very large effect sizes in the differentiation of these two groups in EEG connectivity measures of coherence and phase difference. These findings indicate that qEEG can be used as a "hard" neurological measure of traumatic brain injury that directly assesses this neuronal shearing process as well as direct tissue injury and may offer an essential biomarker of readiness to return to play or duty and the avoidance of subsequent retraumatization of the brain.

Keywords: qEEG; power spectral; connectivity; coherence; phase difference; concussion

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Introduction

Quantitative Electroencephalography

Quantitative electroencephalography (qEEG) is a methodology for transforming analog raw signals from the standard clinical EEG into digital information that can be further entered into mathematical algorithms that represent a number of important characteristics of brain electrical activity. Two general categories of these characteristics are EEG spectral power, or the relative amount of energy contained in frequency components of the signal, and neurological connectivity, or the integrity of connections among neural pathways throughout the brain. Once digitized, these qEEG values for the individual patient can be compared with similar characteristics from selected normal control individuals or with established normative databases of typical, or "neurotypical," individuals. The latter have been challenged as perhaps not representative of the population from which the targeted individuals have been derived, although such criticisms have

been disputed (Tenney et al., 2021; Thatcher, 2016; Thatcher & Lubar, 2009).

Over the past century, outcome measures from the EEG and qEEG have been related to a broad variety of neurological functions as well as to neuropathologies. One of the earliest applications of the clinical EEG was to identify differences in the amplitudes of certain frequencies, both within and across homologous brain regions. For example, it has been well documented that neurological pathologies are frequently associated with increased slow-wave (delta, 0–4 Hz; theta, 4–8 Hz) amplitudes (Alexander et al., 2006; Ianof & Anghinah, 2017; Jelic, et al., 2000; Moretti, 2015; Pourmand, 1994; Thatcher, 2009; Thatcher et al., 2001; Wallace et al., 2001) and reduced faster wave (alpha, 8–12 Hz; beta, 12–30 Hz; and gamma, 30–100 Hz) amplitudes (Thatcher, 2009). Additionally, amplitude differences within a frequency and across homologous cortical regions have long been observed. Such amplitude asymmetries, most frequently and easily noticed in the alpha frequency, were thought to be indicative of neurological dysfunction (e.g., from documented cortical lesions) in early clinical reports, although nonpathological asymmetries were frequently found in neurotypical participants as well (Pourmand, 1994; Strobos, 1960). Focal amplitude asymmetries have been statistically associated with epileptiform activity, early infantile autism, lower intelligence, and individual differences in affective and motivational dispositions and are generally recognized as indicative of neuropathology when other supportive factors are present (e.g., neurotrauma; Dawson et al., 1982; Hagemann, 2004; Seneviratne et al., 2016; Thatcher et al., 2005).

More recently in the history of qEEG has been the discovery and assessment of connectivity measures among neurological networks. Such measures are rather commonsensical in the understanding of neurological trauma from blunt-force injuries to the brain, given the coup–contrecoup damage that results from viscous neurological tissue coursing back and forth from the site of injury to contralateral bony structures. The shearing of neurological tissue from such injuries results in serious structural and biochemical disturbances from diffuse axonal stretching and tearing in neurological networks across the brain (Bigler, 2013; Giza & Hovda, 2014; Mustafi et al., 2018; Seifert & Shipman, 2015; Thatcher et al., 1991). Millisecond electrical quantification of connectivity disturbances has only been obtainable with the development of qEEG algorithms. These measures include *coherence* and *phase differences* between related waveforms.

Coherence is an important statistical measure of the degree of linkage or coupling of two distinct areas of the brain, primarily in the cortex, and is often used as a measure of the functional association of different neural networks (Lubar, 1997; Thatcher, 2012). Coherence reflects the temporal stability of EEG waveform phase angle differences between two sites on the cortex, or phase locking. In the multichannel EEG, coherence is typically computed across all pairs of electrodes and frequencies. Although conceptually it is scored like a simple zero-order correlation coefficient between 0–1 and historically was computed as the simple correlation of amplitude, or power, over time, the more contemporary computation of coherence is much more complex. It involves phase and power relationships, is designed to be free of volume conduction properties of the brain, and is independent of amplitude alone (Hindriks, 2021; Thatcher, 2009; Thatcher et al., 1986). Coherence output is best interpreted as taking an inverted U-shape form, with low coherence (hypocoherence) reflecting either regional differentiation and specialization of functions or, in the case of documented neuropathology, impaired connections among neural networks, and high coherence (hypercoherence) suggesting a compensatory lack of differentiation or increased redundancy in cortical functioning. Both extremes are often seen in the reduced information processing efficiency with certain neuropathologies (Jelic et al., 1996; Thatcher, 2016; Wallace et al., 2001). Neurologically, a perfect coherence of 1 indicates a constant phase difference over time between signals and suggests some functional connectivity, and a coherence of 0 indicates random phase differences and less organized functionality. Thatcher (2016) has proposed a two-compartment model for coherence, with this measure reflecting phase synchrony among (a) long-axon pyramidal thalamo-cortical cells and (b) short-axon stellate and Martinotti cortico-cortical cells, and with the latter cells contributing the most to coherence measures among more proximal electrodes.

Phase differences reflect the cyclical differences between waveforms that one is interested in comparing. These differences occur quite commonly in the EEG when the wave patterns across any two channels do not coincide; overlapping waves having the same cycle are in-phase waves and those with different cycles are out of phase. Very simply, one can measure the phase difference between waves

having the same frequency by comparing analogous points on each wave in degrees of phase difference (e.g., 15 degrees out of phase). Obviously, with very complex and rapidly changing waveforms across multiple electrode sites such as seen in the EEG, the algorithms for calculating these phase differences are quite mathematically sophisticated (see Thatcher et al., 2009, for a guide in calculating EEG phase differences). In short, phase difference metrics reflect the degree of entrainment and synchronization, or locking, of EEG oscillations within a specified frequency band and represent a somewhat purer and more immediate measure of EEG connectivity than the time-averaged coherence measure (Chaturvedi et al., 2019; Thatcher et al., 2009; Thatcher et al., 2005). As with coherence, diminished or excessive phase synchronization can be suggestive of cognitive dysfunction. Thus, phase desynchronization has been reported for mild cognitive impairment, with excessive phase synchronization indicated for some stages of Alzheimer's disease (Alexander et al., 2006; Moretti, 2015). A related connectivity measure *phase lag index* which also quantifies phase synchronization, can suggest chaotic signal relationships across cortical networks for low values and synchronized or perfect phase locking and connectivity for high values (Stam et al., 2007; Thatcher et al., 2008). Phase measures are also free of volume conduction and amplitude characteristics of the EEG signal and serve as a measure of directional flow of information among electrode sites (Kuang et al., 2022; Stam et al., 2007; Thatcher, 2012).

Brodmann areas represent the most widely known and frequently cited mapping system of the primate brain, commonly utilized in MRI, qEEG, and other imaging programs. In the early 1900s, Korbinian Brodmann undertook an exhaustive cytoarchitectural study of the primate cerebral cortex, including humans, utilizing Nissl cell staining procedures to examine the histological structure and organization of brain cells (Brodmann, 1909; Garey, 2010). Using this process, Brodmann identified 52 regions that differed in cell structure and, over the decades since, these Brodmann areas have been closely associated with various functions. Contemporary neuroimaging software can target specific cortical regions and associate those regions with Brodmann areas having defined functions. For example, Broca's speech and language areas have been consistently localized to Brodmann areas 44 and 45 in the human brain. Comprehensive Brodmann maps have been prepared and may be utilized to identify brain regions corresponding to normal and pathological functioning, as in traumatic brain injury (TBI; Trans Cranial Technologies, 2012).

Concussion/Traumatic Brain Injury

One of the most common sources of neurological trauma is TBI. A review of the reported incidence of concussive head injuries over the past 3 decades indicates that TBI has reached epidemic proportions in the United States. Head injuries occur across the lifespan and from multiple sources, including recreational activities, sports, accidents, and military operations. Military and sport-related injuries share common characteristics in the diagnosis, treatment, and prognosis of TBI (Lew et al., 2007). For example, from 2000 to 2016, 352,612 military personnel were diagnosed with TBI, approximately 20% of U.S. combatants in the Iraq and Afghanistan theaters of war, with 82% of those suffering mild TBI (mTBI; Logan et al., 2013; Swanson et al., 2017). Indeed, TBI has been considered the "signature wound" of U.S. combatants (Connelly et al., 2017; Swanson et al., 2017). Additionally, as many as 3.8 million concussions from competitive sports occur yearly in the United States, with approximately 25% of all patients presenting to hospital emergency departments (ED) for sports and recreational head injuries (Daneshvar et al., 2011; Harmon et al., 2013; Kelly et al., 2001). The Centers for Disease Control (CDC) has reported increasing rates of mTBI-related ED visits between 2001 and 2010, with an 800% increase relative to all ED visits between 2006 and 2010 (Wright et al., 2013; Zhang et al., 2016). These statistics spotlight sport-related concussions as the leading cause of mTBI ED admissions among children and teens—with rugby, hockey, and American football having the highest frequency of concussion and with the NCAA reporting a doubling of concussion incidence in 2010 (Pfister et al., 2016; Zuckerman et al., 2015). Unfortunately, due to poor, uncertain, and avoidant diagnoses, as many as 50% of sport-related concussions go unreported and untreated, with evidence of cumulative effects following repeated injury (Harmon et al., 2013; Langlois et al., 2006; Pfister et al., 2016).

Strategies for the diagnosis of concussion/TBI (C/TBI) are variable and are heavily influenced by patient self-report. Although exams vary considerably in comprehensiveness, the current "gold standard" of concussion diagnosis is the medical examination, including a neurological evaluation of hearing, vision, reflex, balance, coordination, strength, sensation, memory, and attention span. Physicians sometimes follow up with referral for a formal cognitive test, such as the

ImPACT, and, if symptoms warrant, an imaging test (e.g., CAT scan). However, in lieu of rare formal neuroimaging, the diagnosis and recovery of mTBI are almost exclusively based on the self-report of the patient and testing for "soft," more peripheral, neurological signs. Even the medical neurological exam tests peripheral nerve and motor function rather than directly observing brain physiology. This omission is critical for judgements of return to play or duty, which involve the risk of repetitive injury.

It is well documented that athletes commonly hide and underreport symptoms and that a commanding officer will often waive the postconcussion recovery period if the injured military combatant is deemed critical to the mission and to the survival of fellow soldiers (Marshall et al., 2012; Teel et al., 2014). A recent review of return-to-play or -duty decisions found that most relied on symptom reports to determine recovery (Haider et al., 2017). The risks of neurological retraumatization based on self-reports of questionable validity—added to the diagnosis of concussion also based in large part on self-reports and visual observation of symptoms—have led the 2017 International Concussion in Sport Group (CISG) and the CDC to recommend the development of improved neurological measures of C/TBI (McCrory et al., 2017; Centers for Disease Control and Prevention [CDC], 2018). The most recent CDC clinical guidelines on mTBI point to weak diagnostic consistency; primary use of subjective judgments in identification, treatment, and return to play; and the critical need for objective evidence-based diagnostic and intervention strategies (CDC, 2018). These guidelines also encourage the use of computerized assessments for the multifactorial evaluation of mTBI and call for research-based evidence to improve diagnostics and treatment (CDC, 2018).

Given the unique and very specialized power and connectivity measures of "hard," more direct and centralized, neurological functioning available in the computer-administered qEEG, this technology is certainly poised to be a critical diagnostic and prognostic assessment tool for TBI. Indeed, over the past decades, qEEG has developed into a targeted TBI assessment instrument. The application of normative databases to plot departures from normality can be used to quantify and to localize brain trauma and to track return to normality during recovery, more confidently and accurately deciding recovery and return to play or duty without premature retraumatization (Slobounov et al., 2012; Thatcher, 2009). One normative database includes an empirically validated TBI Severity Index which reports the patient's severity and likelihood of TBI with confidence intervals across mild, moderate, and severe levels. Research on the Severity Index has reported a classification accuracy of 96.39%, a sensitivity index (true TBI positive) of 95.45%, and a specificity index (true TBI negative) of 97.44% (Thatcher et al., 2001; Thatcher et al., 1989). qEEG has been used to document concussions in sports-related injuries (Donaldson et al., 2018; Fickling et al., 2019; Thompson et al., 2005), civilian accidents (Thatcher et al., 1989), and in combat veterans (Lewine et al., 2019; Trudeau et al., 1998).

In a sample of 608 civilian chronic mTBI patients compared with 108 neurotypical controls, Thatcher et al. (1989) found three classes of neurophysiological injuries: (a) increased coherence and decreased phase in frontotemporal regions, (b) decreased anterior-posterior power differences, and (c) reduced posterior alpha EEG power. Similarly, in a well-controlled EEG study of 71 active duty and veteran personnel with chronic mTBI compared with 82 neurotypical control participants, Lewine et al. (2019) found significantly (a) increased relative theta power, (b) decreased relative alpha power, and (c) decreased interhemispheric beta coherence in mTBI patients relative to controls. These findings have been supported by MRI Diffusion Tensor Imaging (DTI) outcomes (Mustafi et al., 2018). In addition to these legacy, normative, localization, diagnostic, and quantitative advantages of the qEEG, it is important to note that EEGs are much less expensive (~1/10th the cost) and far more portable (e.g., can be taken to the locker room of a sporting event or to a military field hospital) than MRIs and other imaging techniques. McLoughlin et al. (2014) have noted that EEG is the most portable and noninvasive among neuroimaging methodologies and holds remarkable promise for the identification of neuropathology biomarkers.

Recovery from mTBI is conventionally split into three phases: acute, subacute, and chronic. In general, the acute phase occurs within the first 24–48 hr postinjury; the subacute phase is from 2 days up to 3 weeks postinjury; and the chronic phase extends from 3 weeks and beyond (Liu et al., 2008; Svetlov et al., 2015; Toshkezi et al., 2018; Tshibanda et al., 2009; Weiss et al., 2007). An informal review of 30 EEG controlled-research investigations published over the past 2 decades reveals only five studies that examined the truly acute effects of diagnosed concussion on the EEG, and these studies utilized a reduced montage of frontal electrode measurements and a proprietary machine learning algorithm (Bazarian et al., 2021; Hanley et al., 2018; Hanley et

al., 2017; Jacquin et al., 2018; Wilde et al., 2020). The vast majority of studies of qEEG effects of concussion have been chronic investigations. It has been well documented that most mTBI patients either recover symptomatically after approximately 10 days and return to play or duty, risking further neurological injuries which obfuscate subsequent neurological measures, or they seek alternative medical or other therapy treatments for their injuries if their symptoms continue, treatments which can have an impact on subacute and chronic phase EEG testing (Marshall et al., 2012; Slobounov et al., 2012; Swanson et al., 2017; Wallace et al., 2001). It is the purpose of this research project to examine the more immediate and purer acute effects of diagnosed concussion on comprehensive 19-channel qEEG assessment measures.

Methods

Participants

As noted above, studies of concussion/mTBI patients during the acute phase of injury have been uncommon in the qEEG literature. No doubt this is a result of the difficulty in accessing patients at the time of injury and of administering a complex, computer-based, multichannel scan of their brain activity. Certainly, in the military combat situation, immediate access to injured combatants is nearly impossible and must await movement and care of the injured to a field medical facility. As well, on the professional or recreation sports field, access to an injured player must wait for their transport to an off-field waiting area, locker room, or field medical facility. Most frequently, patients are not accessible for a formal EEG study for days or even weeks to months postinjury. Even though EEG technology has become quite miniaturized, with multichannel units now book-sized and either self-contained or operating from a computer laptop, acute patient access for research purposes remains a difficulty.

At Northern Arizona University (NAU), we found ourselves in a somewhat fortuitous situation for the implementation of an acute concussion study of this nature. Flagstaff, Arizona, is a relatively small town located at the base of a dormant volcano, within close proximity to the Grand Canyon and to many other major hiking, cross-country and downhill skiing, snowboarding, mountain-biking, and rock-climbing venues, and known for its outdoors lifestyle. Additionally, Flagstaff is home of a large, young, residential, and quite active university community characterized by students who ride motorized and self-propelled skateboards around campus, often at high speeds, and must often walk to classes on icy and snow-packed streets and sidewalks. Additionally, as for most any university, there are many collegiate and intramural sports activities occurring throughout the year. As a result of these many rather high-risk activities, the NAU Campus Health Services (CHS) reports between 50–70 cases of diagnosed concussion/mTBI per academic year. And, while the ages of our university students are very similar to those of young military combatants who suffer head injuries, most of the concussions reported to CHS occur during the performance of enjoyable recreational activities, lessening the conflation of mTBI with PTSD diagnoses more common in combat and other traumatic injuries. Furthermore, potential concussion participants need only walk across the street from CHS or a short distance from their dormitory to our laboratories to participate in a research study to be accessed rather soon after injury. We still must schedule participant runs around their busy academic and work schedules, producing some delays, but we have found that we can generally access concussion patients within 3 days postinjury, most often sooner.

Consequently, we recruited a cohort of 24 acute concussion patients from CHS for participation in a larger investigation of the enhanced diagnostics, prognostics, and treatment of concussion/mTBI utilizing combined computer-brain interface and standard protocols. Recently concussed patients, each formally diagnosed by a CHS physician, were given a flyer for the study with contact information. Those interested in participating signed an internal HIPAA release form giving their physician permission to share their medical information with the PIs of the study. The CHS physician administered the routine Acute Concussion Evaluation (ACE) concussion assessment (Gioia et al., 2008) and a standard neurological examination and rendered an ICD-10 diagnosis. Concussed patients then contacted the primary PI and were interviewed via phone regarding the participation criteria. Inclusion criteria were (a) age 18–40 years, (b) physician-diagnosed concussion/mTBI within 24–48 hr of injury, (c) no other history of concussion/TBI within 1 year, (d) not currently taking any psychoactive medications or drugs or able to undergo a 24-hr washout, and (e) no diagnosed neurological disorder within 5 years of the study. A matched control cohort of 20 neurotypical participants was also recruited from a local online research participation recruitment website. Controls were individually matched to concussed patients by age range, biological gender, handedness, student status, and quality of the EEG recording and met

identical inclusion criteria with the exception of a recent concussion.

Procedures

All concussion patients were scheduled for their initial assessments within a target date of 24–48 hr postinjury. Due to scheduling conflicts, some of the patients had to be scheduled outside of this window but they were required to still be experiencing the same level of symptoms as immediately after injury. Control participants were scheduled within the same academic semesters as the concussion patients. All participants were invited to the laboratories for a 2.5-hr assessment session and initially completed informed consent, demographic, and contact forms. Additionally, all participants completed the Post-Concussion Symptom Scale (PCSS), a 22-item self-report Likert rating checklist of concussion symptoms (McLeod & Leach, 2012); the Brief Symptom Inventory (BSI), a 53-item self-report Likert rating inventory of psychopathology and psychological distress including measures of somatization, obsessive-compulsivity, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism, and general psychological distress (Derogatis & Melisaratos, 1983), the latter instrument included as an overall measure of psychological distress and to assess psychopathology which could potentially influence the EEG (Tenney et al., 2021); and a battery of standard concussion assessment instruments not analyzed in this report of acute outcomes.

Each participant also received a 19-channel qEEG comprised of, in this order, 10 min eyes closed, 10 min eyes open, and 22 min of a cognitive/attentional challenge (Test of Variables of Attention [TOVA]), with each EEG recorded continuously and stored in separate data files. The TOVA is a computerized continuous performance, go/no-go task that assesses attentional abilities across five dimensions: response time, response time variability, inattention (errors of omission), impulse control (errors of commission), and *d* prime (ratio of hits to false alarms, or the ability to discriminate target from nontarget events in one's environment; The TOVA Company, 2024). In addition to allowing the recording of cortical electrical activity during a rather demanding cognitive/attentional challenge for both concussed and neurotypical participants, the TOVA results allowed a further comparison of both cohorts on each of these attentional measures. The qEEGs were recorded with a Mitsar 201 24-channel amplifier, utilizing WinEEG recording and processing software (Mitsar Co. Ltd, St. Petersburg, Russia), further processed with ANI NeuroGuide neuroanalysis software (Applied Neuroscience, Inc., St. Petersburg, Florida), and a 24-channel International 10-20 electrocap system (Electro-Cap International, Eaton, Ohio) with impedances adjusted to < 5 kΩ. EEG data were sampled at 250 Hz, referenced to linked earlobes, and bandpassed at 0.3–50 Hz with notch filter set at 55–65 Hz. All data were carefully and individually artifacted utilizing ANI NeuroGuide Automatic Editing software with automated rejection of drowsiness, eye movement, and muscle artifact exceeding a *Z*-score threshold of 2.00. All files were additionally visually and blindly inspected by the PI for any remaining artifacts, including evidence of sleep onset, with offending epochs removed, and split-half and test–retest reliabilities held at > .90. Absolute EEG amplitude was computed from the 19 scalp electrodes for delta, theta, alpha, and beta frequency bands. EEG coherence and phase differences were computed for all electrode pairs utilizing automated computations of algorithms described in Thatcher et al. (2001, 2009).

Participants were debriefed at the conclusion of the study, and each participant was compensated for their participation. As the concussed participants were active medical patients, any worsening of symptoms at any point in the study was noted and such patients were referred back to their health care professional at CHS for further care. Each patient had improved by conclusion of the study and had returned to normal activities. All procedures were previously approved by the NAU Institutional Review Board for the protection of human subjects.

Design and Analysis

Our hypotheses were that acute concussion and neurotypical groups would significantly differ in low frequency, delta and theta, power with the concussed groups scoring with higher power in these frequencies, and would significantly differ in hyper- or hypocoherence and phase differences at selected frequencies. We predicted that these effects would be seen in all three assessment conditions, with most remarkable differences seen in the eyes-closed and TOVA conditions. We also predicted that the concussion group would score in a more impaired direction on the PCSS and on all five TOVA measures compared with the neurotypical group. The outcomes reported here represent a 2 (groups) x 3 (conditions) between dependent (matched) groups design, with concussed and neurotypical groups individually matched by biological gender, age range (within 1–3 years over 18–24 years of age), handedness, student status,

and quality of the EEG recording and examined across three conditions (eyes closed, eyes open, and cognitive/attentional challenge). Dependent variables were EEG absolute power and amplitude asymmetry across four frequencies (delta, theta, alpha, and beta) and two connectivity measures (coherence and phase difference) across the same four frequencies. All EEG statistical and neuroimaging analyses were conducted utilizing ANI NeuroGuide NeuroStat and NaviStat statistical computational software available within the ANI NeuroGuide EEG analysis platform. The software utilized for our neuroimaging targets the center voxel of each Brodmann area in order to estimate the current source density of the respective area and to plot connectivity patterns. Demographic and questionnaire analyses were conducted utilizing SPSS statistical software (Version 29.0.0.0, 2022, IBM Corp., Armonk, NY). For all analyses, assessment conditions, power and connectivity functions, EEG frequencies, and Brodmann areas were treated by convention as orthogonal measures, and hypothesized effects were evaluated as planned comparisons with no corrections for potential inflation of Type I error. However, all comparisons were further subjected to Bonferroni corrections conducted within conditions, functions, frequencies, and Brodmann areas to reduce the potential false discovery rate (Lewine et al., 2019; Pagano, 2010).

A statistical power analysis was conducted to determine if our planned cohort numbers were sufficient to generate satisfactory power. For a moderate effect size of 0.5 and alpha = 0.05, a total dependent groups *t*-test sample size of 36 would be sufficient to produce a power of 0.90 for each analysis. Thus, our total paired sample size of 38 was adequate to test for potential significant effects.

Results

Sample Characteristics

Demographic and questionnaire data for each of our 24 concussed and 20 neurotypical control participants are presented here in text and in Table 1. As noted above, each of our participants reported no head injuries nor unconsciousness within 1 year nor diagnosed neurological disease within the previous 5 years of the study. Although participants were matched by age range, biological gender, handedness, and student status, mean age did not significantly differ between groups (concussed, 20.33; neurotypicals, 19.70, $t(42) = .93$, $p = .36$). Our sample was primarily female (66%), with 10 and 5 males in the concussed and neurotypical groups, respectively, necessitating omitting 5 males from the dependent groups comparisons (5 males with excessively noisy EEGs or who prematurely dropped from the full study were omitted from the paired-subjects' comparisons). There were two matched left-handed participants in each group, and all participants were enrolled students. Additionally, both groups did not significantly differ in cultural identity (concussed/neurotypical: White American, 19/14; Hispanic American, 4/5; African American, 0/1; Unidentified, 1/0; $\chi^2 = 2.53$, $p = .47$), current pregnancy (0/0), prior epilepsy (0/0), current chronic pain (4/1, Fisher's Exact $p = .36$), current peripheral neuropathy or nerve damage (0/0), current antianxiety medication use (4/0, Fisher's Exact $p = .11$), current asthma medication use (0/0), current birth control use (5/4, Fisher's Exact $p = 1.00$), current blood pressure medication use (0/0), current diabetic medication use (0/0), current heart medication use (0/0), current prescription pain medication use (0/0), current unspecified other medications (5/1, Fisher's Exact $p = .20$), or in current use of the following recreational drugs more than 1 time per week: amphetamines (0/0), cocaine (0/0), pain killers (4/0, Fisher's Exact $p = .11$), downers (0/0), uppers (0/0), ecstasy (2/1, Fisher's Exact $p = 1.00$), and other unspecified recreational drugs (2/0, Fisher's Exact $p = .49$). Our sample of participants did show trends toward between-group differences in current antidepressant medication use (5/0, Fisher's Exact $p = .05$) and in marijuana use more than once per week (7/1, Fisher's Exact $p = .05$), and significantly greater alcohol use more than once per week for the concussion group (11/0, Fisher's Exact $p < .001$). Thus, our participants also matched quite well culturally and in most medications and recreational drug usages, with the exception of more frequent alcohol use and somewhat greater antidepressant medication and marijuana use in our concussion patients. All participants using medications or drugs abstained from use within 24 hr of testing.

Each concussion participant entered the study with a formal ICD-10 diagnosis of concussion rendered by a medical doctor and a completed ACE concussion assessment. On some occasions, ACE scores had to be completed by the PI based on PCSS scores at point of entry. As ACE scores are based on a patient self-report checklist in the ACE questionnaire which is identical to the patient-completed checklist on the PCSS, minus one item, unavailable ACE scores could easily and accurately be generated for the few patients with missing physician ACE scores. Similarly, ACE scores were completed by the PI for each neurotypical participant on the basis of their PCSS self-report of symptoms. Each participant also

completed a PCSS concussion symptom checklist and a BSI assessment of psychological distress at the initial assessment, and during their qEEG each participant completed the TOVA test. Only the BSI/GSI average total score is reported here, as BSI psychopathology sub-scores were not a critical part of this analysis. ACE, PCSS, and BSI questionnaires were blindly scored by the researchers and are here reported as raw scores. The TOVA test is automatically and blindly scored and reported by the TOVA software. As noted above, the TOVA scoring generates multiple measures of cognitive/attentional abilities, including errors of omission (inattentiveness), errors of commission (impulsivity), response time (reaction time), response time variability (variability in reaction time), and an overall attentional measure called *d* prime. Additionally, two experimental indices were considered in our analyses, an Impulsivity Index and an Attention Comparison Score, the latter comparing the score with those from independently diagnosed ADHD individuals. These raw score measures are standardized and are then compared with the current, relevant TOVA normative database for departures from normality. For ease of explication, these standardized scores may then be converted into *Z*-scores having a mean of 0 and a standard deviation of 1. Each *Z*-score thus represents the number of standard deviation units the individual score differs from the mean of the normative group. The greater the departure from 0, the more different from the norm the score is, and, in general, the more negative the score, the poorer the performance. Group means, standard deviations, and significance statistics for each of these instruments are presented in Table 1.

Review of Table 1 indicates that on average our concussion participants endorsed over 14 of the 22 symptoms of concussion on the ACE instrument, significantly higher than the 1.65 symptoms identified by our neurotypical controls. Rating the severity of these symptoms on the PCSS revealed a similar significant difference between the two groups, with the mean of 43.33 placing the concussed patients at the top end of the *very high* (just below *extremely high* and near the 98th percentile) concussion symptom score classification range relative to healthy young women in the Lovell et al. (2006) normative study.

BSI Global Severity Index (GSI) scores were used as a measure of psychological distress for this study. BSI/GSI scores were likewise significantly different between groups, with our concussion sample scoring significantly higher on psychological distress than our neurotypical controls. However, GSI average scores for our concussed patients (.85) were only somewhat higher (+.33 *SD* units), and means for our neurotypical participants (.17) were much lower (−1.29 *SD* units) than those values

Table 1
Assessment Variable Statistics by Group

Variable	Concussion Group		Neurotypical Group		*t*	*p*
	n	*M* (*SD*)	*n*	*M* (*SD*)		
ACE	24	14.46 (3.54)	20	1.65 (2.60)	13.43	< *.001*
PCSS	24	43.33 (14.74)	20	3.70 (5.29)	12.26	< *.001*
BSI/GSI	20	0.85 (0.46)	20	0.17 (0.16)	6.32	< *.001*
TOVA Omission Errors	24	−4.36 (8.50)	20	−0.95 (3.70)	−1.77	*.043*
TOVA Commission Errors	24	−1.30 (2.38)	20	−0.72 (1.30)	−0.97	.17
TOVA Response Time	24	0.29 (1.34)	20	1.25 (0.89)	−2.85	*.003*
TOVA Response Variability	24	−2.10 (3.22)	20	−0.79 (2.19)	−1.55	.06
TOVA *d* Prime	24	−1.37 (1.29)	20	-0.82 (1.05)	−1.55	.07
TOVA Impulsivity Index	24	1.35 (1.24)	20	1.45 (0.67)	−0.33	.37
TOVA Attention Comparison	24	−1.44 (4.30)	20	1.70 (3.30)	−2.67	*.005*

Note. ACE = Acute Concussion Evaluation; PCSS = Post-Concussion Symptom Scale; BSI/GSI = Brief Symptom Inventory Global Severity Index Average Scores; TOVA = Test of Variables of Attention. ACE, PCSS, and BSI scores are raw scores. TOVA scores are standardized *z*-scores having a mean of 0 and a standard deviation of 1. All *t*-tests are 1-tailed as per *a priori* predictions.

reported for normal college females (.71) in an earlier study by Cochran and Hale (1985). These results suggest that while our sample of concussion patients reported significantly more psychological distress following their injury than our neurotypical controls, our concussed patients were not significantly more distressed than a normative sample of college females.

TOVA testing during the qEEG also revealed, as predicted, significant differences between groups. Relative to neurotypicals, concussion participants showed significantly more errors of omission, $t(32.6) = -1.77$, $p = .04$, and slowed response time $t(40.11) = -2.85$, $p = .003$, with trends toward increased response time variability, $t(42) = -1.55$, $p = .06$, and increased d prime, $t(42) = -1.55$, $p = .07$. Additionally, TOVA concussed patients' overall responses during qEEG were much more similar to responses of attention-deficit/hyperactivity disorder (ADHD) patients than were those of our neurotypical group, $t(42) = -2.67$, $p = .005$. These results indicate that our head injury patients were having attentional, reaction time, and stimulus discrimination difficulties (problems differentiating relevant from nonrelevant events in one's environment) and were responding more like ADHD individuals.

Quantitative EEG Results

Eyes-Closed Assessment. The qEEG paired comparisons between conditions (concussed minus neurotypicals, $N = 19$ matched pairs) outcomes for the eyes-closed assessment condition are presented in Table 2 for FFT absolute power, amplitude asymmetries across homologous sites, coherence, and phase differences across each frequency (delta, theta, alpha, beta). Significance values and effect sizes are presented for Brodmann area hubs (concentrated regions of neural interconnectivity within a Brodmann area) and not for electrodes or electrode pairs as the former are more meaningful and relevant to concussion symptom manifestation.

Table 2

Eyes-Closed qEEG Power and Connectivity Group Differences by Frequency Statistical Significance, Effect Size, and Brodmann Areas

Function	Delta *p Value, Effect Size, and Brodmann Area*	Theta *p Value, Effect Size, and Brodmann Area*	Alpha *p Value, Effect Size, and Brodmann Area*	Beta *p Value, Effect Size, and Brodmann Area*
Absolute Power	+*.037*, 1.06, (L)8,9	n.s.	n.s.	n.s.
	+*.045*, 1.02, (R)10	n.s.	n.s.	n.s.
	+*.043*, 1.03, (R)7	n.s.	n.s.	n.s.
Amplitude Asymmetry	n.s.	n.s.	n.s.	n.s.
Coherence	n.s.	−*.047*, 1.01, (L)10-37	n.s	n.s.
	n.s.	−.035, 1.07, (L)8,9-4,3	n.s.	n.s.
	n.s.	−.009, 1.38, (L)8,9-7	−*.005*, 1.51, (L)8,9-7	n.s.
	n.s.	−.046, 1.01, (R)8,9-7	n.s.	n.s.
	n.s.	−.038, 1.06, (L)8,9-18	n.s.	n.s.
	n.s.	−*.002*, 1.70, (L)8,9-37	n.s.	n.s.
	n.s.	−.039, 1.05, (R)8,9-37	n.s.	n.s.
	n.s.	−*.004*, 1.55, (L)4,3-7	−*.006*, 1.47, (L)4,3-7	−*.001*, 1.85, (L)4,3-7
	n.s.	−.028, 1.13, (L)4,3-18	−*.003*, 1.62, (L)4,3-18	n.s.
	n.s.	−*.006*, 1.47, (L)4,3-37	−*.016*, 1.25, (L)4,3-37	−.027, 1.13, (L)4,3-37
	n.s.	−.047, 1.01, (L)7-21	−*.015*, 1.27, (L)7-45	n.s.
	n.s.	−*.008*, 1.41, (L)7-37	n.s.	−.040, 1.04, (L)7-31
	n.s.	−.030, 1.11, (R)7-37	n.s.	−*.016*, 1.25, (R)7-37
	n.s.	−*.025*, 1.15, (L)18-21	n.s.	−.035, 1.07, (L)18-37
	n.s.	−*.006*, 1.47, (L)45-37	n.s.	−.032, 1.10, (R)18-37
	n.s.	−*.010*, 1.36, (L)21-37	n.s.	n.s.
	n.s.	−*.022*, 1.18, (R)21-37	n.s.	n.s.

Table 2 (Cont.)
Eyes-Closed qEEG Power and Connectivity Group Differences by Frequency Statistical Significance, Effect Size, and Brodmann Areas

Function	Delta *p Value, Effect Size, and Brodmann Area*	Theta *p Value, Effect Size, and Brodmann Area*	Alpha *p Value, Effect Size, and Brodmann Area*	Beta *p Value, Effect Size, and Brodmann Area*
Phase Difference	−*.029*, 1.12, (R)10-4,3	−*.038*, 1.06, (R)10-8,9	+.049, 1.00, (L)10-18	n.s.
	n.s.	n.s.	+.040, 1.04, (R)10-47	n.s.
	−.048, 1.00, (R)8,9-4,3	n.s.	+*.011*, 1.34, (L)8,9-18	n.s.
	−*.013*, 1.30, (L)8,9-45	+*.003*, 1.62, (R)8,9-21	−*.003*, 1.62, (L)8,9-45	n.s.
	n.s.	n.s.	+.038, 1.06, (L)8,9-37	n.s.
	−.041, 1.04, (R)4,3-18	+*.016*, 1.25, (L)4,3-37	n.s.	n.s.
	−.026, 1.14, (L)4,3-45	n.s.	n.s.	n.s.
	−*.037*, 1.06, (R)7-18	n.s.	+*.044*, 1.02, (R)7-21	n.s.
	−*.046*, 1.01, (R)18-37	n.s.	+*.021*, 1.19, (L)18-45	n.s.
	n.s.	n.s.	+*.043*, 1.03, (L)45-37	+*.022*, 1.18, (L)45-37

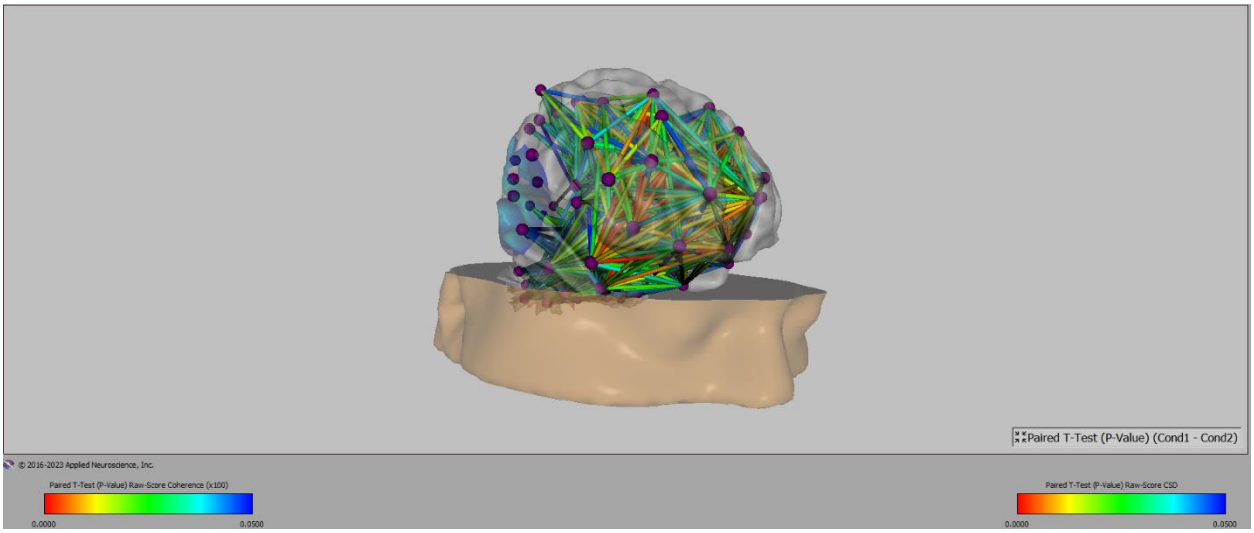
Note. + = concussed group higher; − = concussed group lower; for coherence and phase, a dash (-) between Brodmann areas indicates neural connectivity pathway between the indicated Brodmann areas. Bonferroni adjusted significant *p* values are in italics. Cohen's (1988) effect size ranges: small = .00–.20; medium = .21–.79; large = .80+.

For the eyes-closed condition, absolute power differences between groups were scant and marginally significant for higher delta power in the concussed group, but with large effect sizes observed across four Brodmann areas, 7, 8, 9, and 10. These areas are involved in personal spatial orientation and visual-spatial attention and focus (R7), muscle and executive control and planning, working memory, language processing, verbal fluency, empathy, and emotional processing (L8 and 9), and attention, recognition, and recall and risk benefit analysis (R10; Trans Cranial Technologies, 2012). Increased very slow-wave power in these regions may suggest impaired functioning in these activities. There were no significant amplitude asymmetry differences between groups.

For coherence, there were highly significant and very large effect size differences between groups within the theta band, with fewer effects in the alpha and beta bands, all indicating hypocoherence (impaired communication) across frequencies for the concussed group. Most frequent were theta hypocoherence connectivities between Brodmann areas 8 and 9 (frontal eye fields and dorsolateral-prefrontal cortex [DL-PFC]) on the one hand and areas 3, 4, 7, 18, and 37 (postcentral gyrus, primary motor cortex, somatosensory association cortex, secondary visual cortex, and fusiform gyrus, respectively) on the other, suggesting potential communication difficulties between frontal executive planning and control and working memory processes (8 and 9) and sensorimotor processing, control, and execution (3 and 4), spatial orientation and visuomotor coordination (7), visuomotor organization (18), and visual analysis, recognition, and association (37) processes. Hypocoherence connectivity anomalies were likewise found across the theta, alpha, and beta frequencies between Brodmann areas 3 and 4 on the one hand and 7, 18, and 37 on the other, suggesting potential sensorimotor processing and execution difficulties involved in visuospatial analyses. Similar visuospatial orientation, association, analysis, self-referential, empathic, and related semantic expression deficits are consistent with theta, alpha, and beta hypocoherences between areas 7, 18, 21, 31, 37, and 45. Figure 1 presents swLORETA neuroimages of eyes-closed concussed minus neurotypical significant theta coherence differences.

Phase difference effects were somewhat mixed, with lower phase differences (synchronization) for the concussed group within the delta band and higher phase differences (desynchronization) for the concussed group primarily within the alpha band. Interestingly, these phase difference connectivity anomalies were largely localized to the same Brodmann areas as found for coherence, suggesting desynchronization of these waveforms and the same communication impairments for theta, alpha, and beta. However, in the delta band, waveforms within these same Brodmann areas appeared to be significantly and highly synchronized, which could further interfere with communication during synchronized slow-wave activity in these areas.

Figure 1. *ANI NaviStat swLORETA NeuroImage of Eyes-Closed Concussed Minus Neurotypical Significant Theta Coherences Differences, Right Frontal View*.



Note. Purple spheres represent center voxels of Brodmann areas referred to in text. Colored bars represent the significance of connectivity pathways among Brodmann areas. Colored scales reflect significance levels of differences (red end of color bar → difference p = .0000). Note significant frontal executive processing connectivity anomalies.

Eyes-Open Assessment. Outcomes for the eyes-open resting focus assessments are presented in Table 3 for FFT absolute power, amplitude asymmetries, coherence, and phase differences across the same frequencies of delta, theta, alpha, and beta. Similarly, statistical significance and effect size values are presented for respective Brodmann areas.

Generally, the eyes-open assessment condition revealed involvement of the same Brodmann areas, but with a somewhat different configuration of coherence and phase difference effects. Again, absolute power was only significant for an increase in delta power for the right somatosensory association cortex (Brodmann area 7) suggesting impaired functioning in spatial orientation and visual spatial attention and focus during eyes-open attention. There were no significant amplitude asymmetry effects for this condition.

Theta and beta coherence measures indicated the same hypocoherences in communication pathways involving frontal executive planning, control, and working memory (areas 8 and 9), sensorimotor processing, control, and execution (areas 3 and 4), spatial orientation and visuomotor organization (areas 7 and 18), visual analysis, recognition, and association (area 37), and self-referential, empathic, and semantic processing (areas 21, 31, and 45). Functions involving these areas would correspondingly be expected to be impaired for concussed patients with these observed hypocoherences. Within the delta band, there were significant hypocoherences between the left DL-PFC (area 9) and the frontal eye fields (area 8) executive motor planning areas on the one hand and primary sensorimotor cortices (areas 3 and 4) on the other, between primary sensorimotor areas (3 and 4) and somatosensory association cortex (area 7), and between somatosensory association cortex (area 7) and the fusiform gyrus (area 37), all suggesting visuo-sensorimotor integration difficulties. Interestingly, there were no coherence anomalies for the alpha band.

Table 3

Eyes-Opened qEEG Power and Connectivity Group Differences by Frequency Statistical Significance, Effect Size, and Brodmann Areas

Function	Delta *p Value, Effect Size, and Brodmann Area*	Theta *p Value, Effect Size, and Brodmann Area*	Alpha *p Value, Effect Size, and Brodmann Area*	Beta *p Value, Effect Size, and Brodmann Area*
Absolute Power	+*.027*, 1.13, (R)7	n.s.	n.s.	n.s.
Amplitude Asymmetry	n.s.	n.s.	n.s.	n.s.
Coherence	n.s.	n.s.	n.s	−.026, 1.14, (L)10-18
	n.s.	−*.042*, 1.03, (L)10-37	n.s.	−*.012*, 1.32, (L)10-37
	−*.042*, 1.03, (L)8,9-4,3	−*.002*, 1.70, (L)8,9-4,3	n.s.	n.s.
	n.s.	−*.006*, 1.47, (L)8,9-7	n.s.	n.s.
	n.s.	−.022, 1.18, (R)8,9-7	n.s.	n.s.
	n.s.	−.035, 1.07, (L)8,9-18	n.s.	n.s.
	n.s.	−*.004*, 1.55, (L)8,9-37	n.s.	n.s.
	n.s.	−.033, 1.09, (R)8,9-37	n.s.	n.s.
	−*.032*, 1.10, (L)4,3-7	−.011, 1.34, (L)4,3-7	n.s.	−*.004*, 1.55, (L)4,3-7
	n.s.	−.039, 1.05, (L)4,3-18	n.s.	n.s.
	n.s.	−.036, 1.07, (R)4,3-47	n.s.	−.038, 1.06, (L)4,3-45
	n.s.	−*.010*, 1.36, (L)4,3-37	n.s.	−.015, 1.27, (L)4,3-37
	n.s.	n.s.	n.s.	−.032, 1.10, (R)4,3-37
	n.s.	−*.010*, 1.36, (L)4,3-37	n.s.	−.015, 1.27, (L)4,3-37
	n.s.	−.028, 1.13, (L)7-45	n.s.	−.022, 1.18, (L)7-45
	−*.046*, 1.01, (L)7-37	−*.010*, 1.36, (L)7-37	n.s.	−.047, 1.01, (L)7-37
	n.s.	n.s.	n.s.	−.019, 1.21, (R)7-37
	n.s.	n.s.	n.s.	−*.046*, 1.01, (R)18-37
	n.s.	−*.017*, 1.24, (L)45-37	n.s.	−*.022*, 1.18, (L)45-37
	n.s.	−*.016*, 1.25, (R)47-37	n.s.	n.s.
	n.s.	−*.041*, 1.04, (L)21-37	n.s.	n.s.
Phase Difference	+*.008*, 1.41, (L)10-8,9	n.s.	+*.038*, 1.06, (R)10-4,3	n.s.
	+*.008*, 1.41, (L)10-21	n.s.	n.s.	n.s.
	−*.039*, 1.05, (R)4,3-18	n.s.	n.s.	n.s.
	−*.044*, 1.02, (R)7-18	n.s.	n.s.	+*.046*, 1.01, (L)45-37

Note. + = concussed group higher; − = concussed group lower; for coherence and phase, a dash (-) between Brodmann areas indicates neural connectivity pathway between the indicated Brodmann areas. Bonferroni adjusted significant *p* values are in italics. Cohen's (1988) effect size ranges: small = .00–.20; medium = .21–.79; large = .80+.

Phase differences during the eyes-open condition were again mixed and much less in number than for eyes closed. Desynchronized (+) executive and self-reflective functional connectivity within the delta and alpha bands from the left frontal pole of the DL-PFC (area 10) to proximal executive motor planning (left areas 8 and 9) and more distal semantic processing areas (left area 21) and to sensorimotor areas (3 and 4) suggest impaired functions within these sensorimotor domains. Similarly desynchronized beta phase connectivity between Broca's area (45) and the fusiform gyrus (area 37) would suggest word-finding and verbal expressive difficulties as well. Negative delta phase difference scores between right sensorimotor cortex (areas 3 and 4) and the somatosensory association cortex (area 7) on the one hand and secondary visual cortex (area 18) on the other would indicate slow-wave synchronization of these visual sensorimotor functions.

TOVA Assessment. Given the high cognitive information processing demands required for our college student population, we chose to administer an additional cognitive/attentional assessment challenge to our participants. The TOVA test required sustained attention for 22 min to a repetitive and monotonous go/no-go task necessitating immediate button press to a defined target and inhibition of presses to a nontarget. Table 1 results above demonstrated significant reaction time delays and inattention in our concussed participants, with trends toward increased variability in reaction time and in overall attentional skills, and with significant similarity to diagnosed ADHD patients relative to matched neurotypicals. To determine potential EEG anomalies that might suggest these attentional deficits, we computed the same absolute power, amplitude asymmetries, coherence, and phase differences between our concussed patients and our matched controls during the TOVA challenge. Table 4 shows these results.

As for the eyes-closed and eyes-open conditions, there were minimal to no significant between-groups differences in absolute power or in amplitude asymmetry during the TOVA test. Only a significant increase in alpha and beta asymmetry was found for Brodmann area 7, the somatosensory association cortex. This effect could possibly indicate a significant deterioration in visual-motor coordination, particularly in purposeful skilled movements such as reaching and grasping for an object, or perhaps reaction time in pressing the TOVA switch for our concussed patients.

Table 4

TOVA qEEG Power and Connectivity Group Differences by Frequency Statistical Significance, Effect Size, and Brodmann Areas

Function	Delta *p Value, Effect Size, and Brodmann Area*	Theta *p Value, Effect Size, and Brodmann Area*	Alpha *p Value, Effect Size, and Brodmann Area*	Beta *p Value, Effect Size, and Brodmann Area*
Absolute Power	n.s.	n.s.	n.s.	n.s.
Amplitude Asymmetry	n.s.	n.s.	+*.009*, 1.38, (R)7	+*.017*, 1.24, (R)7
Coherence	−*.019*, 1.21, (L)8,9-4,3	−*.003*, 1.62, (L)8,9-4,3	−.047, 1.01, (L)8,9-4,3	n.s.
	n.s.	−.048, 1.00, (R)8,9-4,3	n.s.	n.s.
	n.s.	−*.002*, 1.70, (L)8,9-7	n.s.	−*.006*, 1.47, (L)8,9-7
	n.s.	−.030, 1.11, (R)8,9-7	n.s.	n.s.
	n.s.	−.030, 1.11, (L)8,9-18	n.s.	−.026, 1.14, (L)8,9-18
	n.s.	−.015, 1.27, (L)8,9-21	n.s.	n.s.
	n.s.	−*.005*, 1.51, (L)8,9-37	n.s.	−*.005*, 1.51, (L)8,9-37
	n.s.	−.034, 1.08, (R)8,9-37	−.026, 1.14, (R)8,9-37	n.s.
	n.s.	−*.003*, 1.62, (L)4,3-7	n.s.	−*.001*, 1.85, (L)4,3-7
	n.s.	−.041, 1.04, (L)4,3-18	n.s.	n.s.
	n.s.	−.025, 1.15, (R)4,3-47	n.s.	n.s.
	n.s.	−.013, 1.30, (L)4,3-37	n.s.	−.027, 1.13, (L)4,3-37
	n.s.	n.s.	n.s.	−.022, 1.18, (R)4,3-37
	n.s.	−.017, 1.24, (L)7-45	n.s.	−.039, 1.05, (L)7-45
	n.s.	−.029, 1.12, (R)7-47	n.s.	n.s.
	n.s.	-*.008*, 1.41, (L)7-37	n.s.	n.s.
	n.s.	−.034, 1.08, (R)7-37	−*.040*, 1.04, (R)7-37	−*.013*, 1.30, (R)7-37
	−*.023*, 1.17, (L)18-37	−*.011*, 1.34, (L)18-37	n.s.	n.s.
	n.s.	−*.011*, 1.34, (L)45-37	n.s.	−*.035*, 1.07, (L)45-37
	n.s.	−*.045*, 1.02, (R)47-37	n.s.	n.s.
	n.s.	−*.041*, 1.04, (L)21-37	n.s.	n.s.

Table 4 (Cont.)
TOVA qEEG Power and Connectivity Group Differences by Frequency Statistical Significance, Effect Size, and Brodmann Areas

Function	Delta *p Value, Effect Size, and Brodmann Area*	Theta *p Value, Effect Size, and Brodmann Area*	Alpha *p Value, Effect Size, and Brodmann Area*	Beta *p Value, Effect Size, and Brodmann Area*
Phase Difference	−.035, 1.07, (L)10-8,9	n.s.	n.s.	n.s.
	−.018, 1.23, (R)10-8,9	n.s.	n.s.	n.s.
	−*.004*, 1.55, (R)10-4,3	n.s.	n.s.	n.s.
	−.046, 1.01, (L)10-18	n.s.	n.s.	+*.042*, 1.03, (L)10-7
	−.035, 1.07, (L)10-45	n.s.	n.s.	n.s.
	−*.001*, 1.85, (R)10-21	n.s.	n.s.	n.s.
	−.013, 1.30, (R)10-37	n.s.	n.s.	n.s.
	−.040, 1.04, (R)8,9-4,3	n.s.	n.s.	n.s.
	−.034, 1.08, (R)8,9-37	+*.046*, 1.01, (L)8,9-21	n.s.	n.s.
	−*.008*, 1.41, (L)4,3-7	n.s.	n.s.	n.s.
	−.041, 1.04, (L)4,3-18	n.s.	n.s.	n.s.
	−.038, 1.06, (R)4,3-18		+*.035*, 1.07, (L)4,3-37	n.s.
	−*.005*, 1.51, (R)4,3-37	n.s.	n.s.	+*.028*, 1.13, (L)7,21

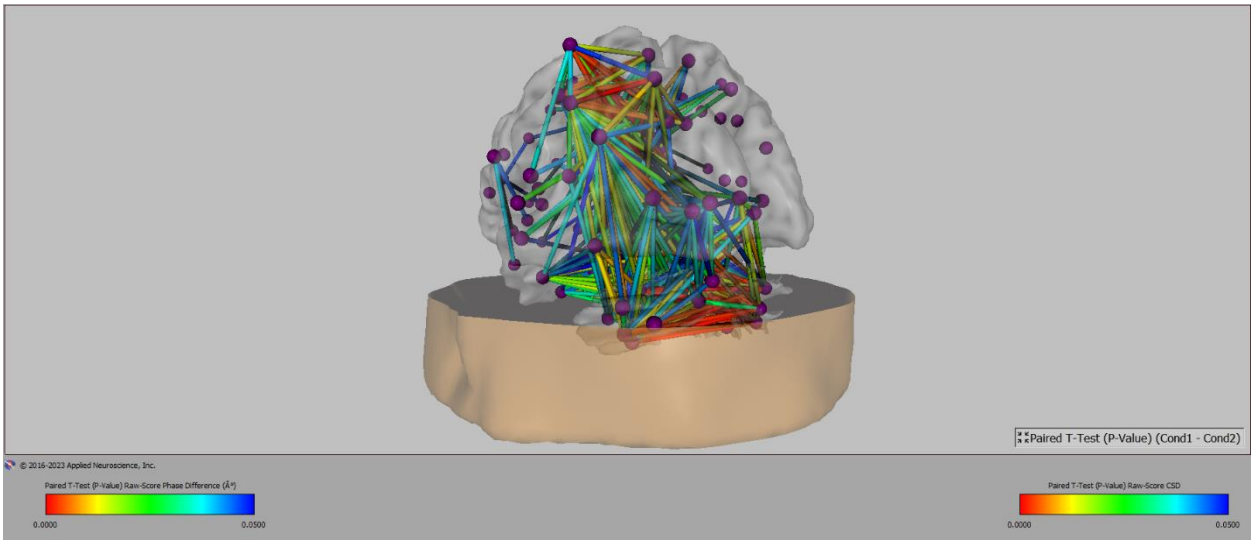
Note. + = concussed group higher; − = concussed group lower; for coherence and phase, a dash (-) between Brodmann areas indicates neural connectivity pathway between the indicated Brodmann areas. Bonferroni adjusted significant *p* values are in italics. Cohen's (1988) effect size ranges: small = .00–.20; medium = .21–.79; large = .80+.

Significant differences between groups were found toward remarkable hypocoherences within the theta and beta frequencies. The same configuration of Brodmann areas was found involved for both of these frequencies for the TOVA condition as for the eyes-closed and eyes-open conditions, but with many more significant theta anomalies than for the eyes-open resting focus condition reported in Table 3. These hypocoherence effects suggest similar difficulties during a cognitive/attentional task in frontal executive planning, control, and working memory (areas 8 and 9), sensorimotor processing, control, and execution (areas 3 and 4), spatial orientation and visuomotor organization (areas 7 and 18), visual analysis, recognition, and association (area 37), and language processing (areas 21, 45, and 47). Somewhat fewer differences were found for the beta frequencies but these were largely within the same Brodmann areas as theta anomalies and for focused eyes open. An important exception for the beta band was an increase in hypocoherences for Brodmann areas 8 and 9 projecting to areas 7, 18, and 37, suggesting impaired information processing during executive functions directed at visuomotor and spatial orientation, recognition, analysis, and association. In the alpha band, areas 7, 8, and 9 experienced significant hypocoherences in connectivity to areas 3, 4, and 37, indicating impaired planning, control, and execution of sensorimotor visuospatial experiences. And, only one hypocoherence was found for the delta band, in the slowed communication of left secondary visual cortex (area 18) with the fusiform gyrus (area 37), suggesting potential word-finding difficulties (e.g., aphasia) in expressing visual experiences.

The most salient differences among the three assessment conditions may be seen in phase differences for the TOVA delta frequency condition. Although remarkably elevated delta *power* was not found across any condition, the synchronization of delta frequencies within the TOVA cognitive/attentional challenge was indeed noteworthy. Across left and right primary somatosensory (area 3), primary motor (area 4), frontal eye fields (area 8), and DL-PFCs (areas 9 and 10), communication among these areas and with somatosensory association cortex (area 7), secondary visual cortex (area 18), middle temporal gyrus (area 21), fusiform gyrus (area 37), and Broca's area 45 were hypersynchronized. Given the very slow frequency characteristics of delta rhythms, these hypersynchronized connectivities would suggest slowed and phase-locked, diminished flexibilities across primary processing, association, and linguistic activities for our concussed patients.

On the other hand, hyposynchronization of theta frequencies from executive processing regions (areas 8 and 9) to linguistic integration regions (area 21), alpha frequencies from sensorimotor reception and expression areas (3 and 4) to fusiform gyrus (area 37) linguistic/semantic regions, and beta frequencies from DL-PFC (area 10) to somatosensory association cortex (area 7), and from somatosensory association cortex (area 7) to middle temporal gyrus (area 21) word-meaning and language processing areas could well indicate complex linguistic difficulties for our concussed patients during the cognitive/attentional challenge. Figure 2 presents an swLORETA neuroimage of the TOVA cognitive challenge for significant concussed minus neurotypical delta phase differences.

Figure 2. *ANI NaviStat swLORETA NeuroImage of TOVA Cognitive Challenge Concussed Minus Neurotypical Significant Delta Phase Differences, Posterior Head View*.



Note. Purple spheres represent center voxels of Brodmann areas referred to in text. Colored bars represent the significance of connectivity pathways among Brodmann areas. Colored scales reflect significance levels of differences (red end of color bar → difference p = .0000). Note the significance of left somatosensory and motor areas and corresponding bilateral cerebellar regions in the processing and activation of this cognitive and motor challenge.

Discussion

Because of the relative availability of patients having chronic head injuries, most qEEG studies to date, indeed most studies in general, of TBI have involved chronic TBI patients. It is well documented that chronic TBI symptomatology is contaminated by multiple comorbidities (particularly chronic PTSD), a history of pharmaceutical and other treatments, and sociocultural lifestyle adaptations (Logan et al., 2013; Marshall et al., 2012; Merritt, 2023; Slobounov et al., 2012; Swanson et al., 2017; Thatcher et al., 2001; Thatcher et al., 1989). As noted earlier, very few studies over the past 2 decades have examined the acute (within 48 hr) head injury population, and even fewer of these investigations utilized full International 10-20 recordings of cortical power and connectivity. Indeed, compromises in diffuse cortical connectivity require a more complete assessment of electrical activity in the brain. Additionally, acute concussion patients are more likely to be free of comorbidities and other medications and treatments which could directly impact brain functioning. Consequently, this study is one of the first comprehensive qEEG investigations to examine concussion/mTBI in its purer, nascent state.

The outcomes of this study in some ways contradicted the established lore of TBI neurocognitive effects. Early EEG studies have suggested predominant elevated slow-wave power and increased amplitude asymmetries. It is important to note that our study did not support salient acute effects in these indices. Our outcomes, on the contrary, indicated scant anomalies in these power measures and remarkable and significant impairments in neurological connectivity measures, consistent with salient effects of neuronal shearing

in white and gray-matter conduction pathways across the cortex. Indeed, our consistent, particularly theta, hypocoherence anomalies across eyes-closed, *d* prime, and neurocognitive/attentional challenge conditions were quite extensive across frontotemporal, central, parietal, and even reaching into occipital regions of the cortex. Phase angle differences likewise revealed diffuse hyperconnectivity in slow-wave delta frequencies, particularly in the more cognitively demanding TOVA challenge, while showing some scattered largely hypoconnectivity in faster theta and alpha bands, the latter particularly in the eyes-closed condition. These connectivity anomalies for our acute concussion patients are largely consistent with connectivity anomalies found with more long-term TBI effects for chronic head injury patients, supporting the predominant role of neurological connectivity impairments in TBI and highlighting the catastrophic acute effects of neuronal shearing even in mild head injury (Popa et al., 2020; Thatcher et al., 1998; Thatcher et al., 1986; Thatcher et al., 2001; Thatcher et al., 1989).

Corresponding functional effects were seen in Brodmann areas involved in executive decision-making, working memory, and sensorimotor control, spatial and visuomotor coordination, and self-referential, empathic, and semantic processing and expression. These functional connectivity impairments are consistent with the TOVA deficits found in attentional, reaction time, and stimulus discrimination deficits quite similar to those of diagnosed ADHD patients. An inclusion of a cognitive/attentional measure in our study was important to the assessment of lifestyle characteristics of our sample of college students at a major southwestern United States university and endeavored to assess more pervasive deficits that would be problematic to their daily functioning. It was somewhat surprising that our concussion sample did not show more impulsivity problems on the TOVA nor more remarkable attentional problems as assessed by the *d* prime measure. However, our sample of acute concussion patients did show corresponding psychological difficulties in overall emotional distress on the BSI subsequent to their head injury. Additionally, our concussed participants did report significantly more frequent alcohol use and trends toward greater marijuana and antidepressant use than our controls. These differences could reflect greater risk-taking tendencies on the part of young college students who are more prone to accidents in general.

This was one of only two studies that we have found in our concussion literature review that matched acute concussion patients to similar neurotypical controls. Doing so allowed for a relatively small number of participants but with sizeable power to comfortably reject our null hypothesis. An additional advantage of this design has to do with managing an observed limitation of the study discussed below, that being occasional rather noisy concussion EEGs. By matching carefully artifacted but still somewhat noisy concussion EEGs to similarly noisy controls effectively allowed a further subtraction of noise from the data and a cleaner, more artifact-free overall dataset. We recommend a similar matching of concussion participants in future studies where possible.

Another advantage of this design had to do with the assessment of participants across three conditions, eyes closed, eyes open, and relevant challenge conditions. Conducting identical assessments across two conditions, eyes closed and eyes open, allowed for a quasireplication of the study within one setting. And obtaining nearly identical outcomes, with very large effect sizes on both, across these two conditions provides some support for the validity of these outcomes.

An important implication of this study is that with qEEG we have quantified a serious, potentially severely debilitating, and critical prognostic consequence of traumatic brain injury, that being diffuse axonal injury or axonal shearing, which with repetitive injury could well lead to the tragedy of chronic traumatic encephalopathy. Indeed, the qEEG connectivity metrics of coherence and phase difference could well become important diagnostic, prognostic, and specific localization indicators of “hard” neurological damage from head injuries. We also offer the suggestion that the impacts of co-occurring coup-contrecoup contusions could be reflected in the recorded metrics of elevated low frequency spectral power and amplitude asymmetries. If subsequent studies confirm and extend our findings, then qEEG could offer an added treatment for TBI in targeted neurotherapies to operantly condition damaged neural networks back to normative functioning.

A recent nonstatistical review by the American Clinical Neurophysiology Society (ACNS) of nine selected studies published since 1996 has criticized the current research qEEG literature as not supportive of qEEG in the diagnosis of mTBI, nor in the differentiation of TBI from other neuropsychiatric diagnoses, such as clinical depression, nor from effects of neuropsychiatric medications (Tenney et al., 2021). This ACNS review, while presently

discouraging the diagnostic utility of qEEG, takes pains to offer ways to improve on the research literature and to conduct meaningful and more definitive studies of the effects of this potentially powerful technology in the differential diagnosis of acute C/mTBI. These authors recommend that future research involve (a) use of healthy controls rather than just normative databases, (b) control for other comorbid neuropsychiatric disorders, (c) control for effects of central nervous system medications, (d) control for the effects of drowsiness by recording during an alert and drowsy state, (e) statistical corrections for multiple comparisons, (f) use of standardized and conventional neurophysiological recording technologies and electrode impedance testing, (g) EEG data collection by a qualified EEG technician and review and noise artifacting of raw EEG data by a qualified electroencephalographer, (h) use of accepted, standardized, "gold-standard" criteria for the identification of TBI samples, (i) clear, accepted criteria for identification of qEEG abnormality, (j) analysis of multiple qEEG measures reflecting varied neurophysiological states, (k) development of predictive as well as explanatory models, and (l) blinded qEEG interpretation regarding the clinical status of participants. The present investigation meets 11 of these 12 criteria; we hope that with replications with a larger sample, we can develop more predictive as well as explanatory models for the diagnosis of concussion/mTBI utilizing qEEG.

Limitations. Neuroscientists nearly always lament the size of their samples, for their assessment and intervention measures are so often very resource- and response-intensive. Such was the case for this study, as the number of coauthors and the nature of the assessment devices suggests. As noted above, the matching of participants helped increase our statistical power. But a larger sample could well have allowed us to conduct the desired regression and discriminant analyses to develop further predictive models for the diagnosis and prognosis of concussion/mTBI.

A problem that emerged early on in the conduct of this study was that acute concussion patients, sometimes within hours of their injury, entered the recording session quite physically and cognitively compromised, nearly always with head pain and significant muscle tension, often confused, sometimes aphasic, and generally irritable. This participant status rendered the recording of artifact-free EEGs quite challenging at times and required some clinical skills to reduce head muscle tension. Our careful and painstaking artifacting procedures improved on this condition considerably, but still some records had to be accepted with some artifacts. The matching of concussed EEGs with neurotypical EEGs by quality of recording allowed for a further reduction of these artifacts. Despite this unavoidable handicap, we feel that our analyzed EEG traces were quite free of noise artifacts and reflect valid EEG data.

The homogeneity of our patient and control samples represented both an advantage, as discussed above, but also a disadvantage. While the age, gender, and other characteristics of our sample are quite similar to those of young military personnel and may well generalize to that population, that homogeneity likewise limits the generalization of our outcomes to other more disparate populations. Of course, replication of this study with other populations will improve the predictive capabilities of our outcomes.

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Exploring Effect of Chamber Restricted Environmental Stimulation Therapy on Salivary Cortisol and Information Overload in Young Adults

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Abstract

Environmental challenges like noise, light exposure, and information overload impact young adults' overall health, reducing time for self-care. Restricted environmental stimulation therapy (REST), specifically chamber REST, offers a cost-effective intervention for stress management. In our study, 49 participants in chamber REST (N = 35) and a control group (N = 14) were compared. Measures, including cortisol, information overload, anxiety, stress, rumination, and obsessive-compulsive symptoms, were assessed before and after treatment, and selected at 1 week follow-up. Results showed no cortisol concentration differences, but at the 1 week follow-up, the chamber REST group reported significantly lower information overload, $t(45) = -3.04$, $p = .004$, $\eta^2 = .17$ and obsessive-compulsive symptoms, $t(46) = -2.1$, $p = .042$, than the control group. Correlational analysis revealed a calming effect in the chamber REST ($r = .421$, $p = 0.015$) but not in the control condition ($r = -.096$, $p = 0.744$). In conclusion, chamber REST seems to foster adaptive self-reflection, aiding coping, and resilience against information overload and obsessive-compulsive symptoms in young adults, suggesting its potential as an effective preventative intervention.

Keywords: restricted environmental stimulation therapy; cortisol; information overload; self-reflection; young adults

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Introduction

Environmental and Societal Challenges

A recent study analyzing the interplay of macroenvironmental physical and socioeconomic factors found a link between different urban environmental profiles and specific negative mental health symptoms (Xu et al., 2023). According to Ventriglio et al. (2021) environmental pollutants are exponentially increasing since industrialization processes and technology are being developed worldwide. Although, environmental factors seem to pose a greater risk for urban than rural communities (Sánchez-Rodríguez et al., 2006). In particular, noise represents the most frequent stressor and is caused by work environment and household appliances, planes, and city traffic. Young adults specifically have shown a positive attitude to noise, a passion for loud music, and lack of knowledge of the consequences of noise damage (Keppler et al., 2015). Prolonged noise exposure can lead to annoyance and sleep disruptions, triggering heightened activity in the hypothalamic-pituitary-adrenal (HPA) axis, elevating stress hormones like cortisol (Münzel et al., 2014). The HPA axis is a key endocrine system in psychological stress response (Ulrich-Lai & Herman, 2009), and cortisol, its primary output, profoundly influences stress-sensitive psychobiological processes, impacting immunity, learning, memory, and overall health (DeMorrow, 2018; Rohleder, 2012; Wolf, 2017).

Light pollution is another significant factor (Ventriglio et al., 2021). Life on Earth has evolved to align with

the 24-hr solar day, synchronizing behavioral and biological processes (Bedrosian & Nelson, 2017). In their systematic review of 42 studies, Brautsch et al. (2023) found associations between bedtime or nighttime screen use of mobile phone to poor sleep outcomes and daytime tiredness in samples of young people aged 16–25 years. The human circadian system is highly sensitive to blue light, affecting melatonin and cortisol, key circadian mediators (Jung et al., 2010; Lewy et al., 1980). Contemporary lifestyles often clash with our natural rhythms, causing challenges for our circadian system (Schroeder & Colwell, 2013).

Last, but not least, need for work performance, attention and decision-making requirements, time pressure, and time restrictions often lead to information overload (Misuraca & Teuscher, 2013; Scheibehenne et al., 2010). This occurs when decision-makers face more information than they can process effectively, leading to decreased decision-making performance (Shields, 1980), reduced attention (Li & Sun, 2014), and lower judgment accuracy (Pennington & Kelton, 2016). Information overload also leads to decreased participation in social communities (Zha et al., 2018), demotivation (Baldacchino et al., 2002), and increased stress (Ledzińska & Postek, 2017). It can adversely affect mental, emotional, and physical well-being, often prompting irrational behavior like excessive engagement on social media instead of prioritizing self-care (Roetzel, 2019). Additionally, it reduces time for contemplative activities (Misra & Stokols, 2012). Individuals, mainly in the age group of 18–25, reported the highest levels of information overload, with less time to reflect or absorb them, compared to other age groups (Benselin & Ragsdell, 2016). Moreover, a large cross-sectional study (*N* = 4.731) comparing three generational cohorts of university students (pre-2004, pre-COVID, and post-COVID), found a gradual decline in coping skills (measured by self-regulation subsystem scale of Psychological Immune Competence Inventory), suggesting preventative programs and interventions aimed at improving their mental health and resilience (Takács et al., 2021).

Restricted Environmental Stimulation Approach

Excessive stimuli in modern-day age constitutes a major source of stress, and taking breaks from this bombardment can help to reduce and cope with it (Suedfeld & Kristeller, 1982). Restricted environmental stimulation therapy (REST) is an emerging intervention that shows promise in improving mental and physical well-being. It significantly reduces environmental information and stimulation influx. There are two main methods: chamber REST and flotation REST. In chamber REST, subjects spend up to 24 hours in a dark, sound-reduced room. Essentials like food, water, and toilets are accessible, and assistance is available via an intercom. In flotation REST, sessions last about 45 min in a quiet, dark environment with a pool or covered tank. The flotation medium, a warm mixture of water and Epsom salts, allows for safe and comfortable floating (Suedfeld & Bow, 1999).

Experience of REST and Its Effects on Physiology

Turner and Fine (1983) investigated the impact of repeated flotation REST on hormone levels in healthy subjects. Six participants received eight 35–min sessions. The results indicated a slight decrease in adrenocorticotropic hormone (ACTH) and a significant 20% decrease in noon plasma cortisol across sessions in the REST group compared to the control group. This supports the verbal reports of REST subjects who found the experience to be "very relaxing." In a follow-up study, same authors (Turner & Fine, 1991) explored the impact of repeated brief flotation REST on plasma cortisol levels with a larger sample size. The REST group (*N* = 15) underwent eight sessions over 3 weeks. The REST group exhibited a significant decrease in both the concentration and variability of cortisol in plasma (mean plasma cortisol decreased by 21.6%), while no changes were observed in the control group. This suggests a beneficial effect of flotation REST on cortisol regulation.

There were no decreases in cortisol concentration after a single flotation REST session (Broderick et al., 2019; Schulz & Kaspar, 1994). The psychological effects, such as increased subjective levels of sedation and euphoria, were more prominent than the neuroendocrine changes associated with relaxation. The authors suggest that the relaxation induced by flotation REST may be linked to sedation, reduced central nervous system arousal, or mediated through muscle relaxation (Schulz & Kaspar, 1994). Another positive effect of REST was seen in reduction of subjective pain in 40 subjects diagnosed with chronic tension headache (Wallbaum et al., 1991). This effect was confirmed also in 37 chronic pain patients after receiving nine flotation REST sessions, with significantly lower levels of noradrenaline metabolite (3-methoxy-4-hydroxyphenylethyleneglycol; Kjellgren et al., 2001). Chamber REST sessions also positively influenced physiology of four patients suffering from essential hypertension. Completion of a 24-hr chamber REST

combined with relaxation training led to a partial immediate but gradually more pronounced decrease in blood pressure at 1-month follow-up, measured during ongoing examinations by a cardiologist. Authors further attribute long-term effects of chamber REST to improved stress-management and health-related behaviors (Suedfeld et al., 1982). Unfortunately, to date, there have been no studies aimed at evaluating neurohormonal changes in relation to chamber REST.

In Flux et al.'s (2022) study, 37 anxious participants underwent a single 90-min session of flotation REST. This significantly reduced systolic and diastolic blood pressure, as well as breathing rate, compared to a nature documentary-watching control. Lower blood pressure correlated with reduced anxiety and increased serenity. These effects were unique to flotation REST. Additionally, it induced a relaxation response in heart rate variability, with lower sympathetic output (LF) and higher parasympathetic modulation (HF). The findings suggest consistent physiological benefits irrespective of anxiety level. Similar tendencies of cardiovascular reactivity was also found in chamber REST (Vytykáčová et al., 2022).

In their meta-analysis, van Dierendonck and Nijenhuis (2005) examined 25 articles from 1983 to 2002 involving 449 participants. They found positive effects of REST on physiology, well-being, and performance, with an overall pre–post mean effect size of d = 1.02. In randomized control groups, the effect size was d = 0.73. REST outperformed other stress reduction techniques like relaxation exercises and biofeedback. Long-term studies suggested that repeated exposure to REST amplified its effects, indicating improved integration and benefits over time.

The Current Study

Given the limited number of studies on physiological measures in this field, particularly cortisol measurement, which has yielded somewhat inconsistent results, our focus extended to this variable. Our review predominantly centers around flotation REST, with chamber REST research in physiology notably sparse (except for a few studies). Interestingly, post-1990s, researchers predominantly directed their attention towards flotation REST, largely overlooking chamber REST. Objectively, chamber REST, in contrast to flotation REST, is easier to implement, less demanding, and doesn't necessitate special preparations or hygienic procedures, making it more convenient for participants. In this study, using flotation REST as a reference due to its similar intervention essence, we honed in on the impact of a single brief chamber REST session on pre–post salivary cortisol changes—a marker of stress-sensitive psychobiological processes. Our aim was also to explore potential interactions of chamber REST with pre–post information overload and stress symptomatology in young adults. Our hypothesis is that a single session of brief chamber REST will induce a higher pre–post reduction in salivary cortisol concentrations compared to the control group. We also raise questions about the relationships between chamber REST, information overload, and interactions with other relevant psychological variables.

Materials and Methods

Participants

Our research sample consisted of 49 participants (40 women, 9 men; Age: mean = 23.69, SD = 4.68), healthy Caucasian young adults. Eligibility criteria of participants was based on no previously diagnosed psychiatric disorder, substance abuse, neuroendocrinological functional defects, or ongoing medication treatment. At first, participants were recruited for experimental group (chamber REST, N = 35), then for control group, but due to time constraints which coincided with the COVID-19 pandemic, included fewer subjects (N = 14).

Instruments

Cortisol Assessment. Cortisol assessment involved the use of synthetic-fiber absorbent rolls (e.g., Salivette Cortisol; Sarstedt, Nümbrecht, Germany). Participants placed the rolls in their mouths for approximately 2 min, gradually infusing them with saliva. Two samples (15 min apart) were collected before and after treatment, immediately stored at −20 ºC until laboratory testing. Notably, the samples were unlikely to be influenced by the cortisol awakening response (CAR) as the study occurred at least 1 hr after participants woke up for morning measurements.

Information Overload. Visual Analog Scale (VAS) was used for measuring information overload (1 = *not at all*, 10 = *completely*), before treatment, and at 1-week follow-up, “To what extent do you perceive that you are overloaded with stimuli and information during the last week?”

Obsessive-Compulsive Symptoms (OCS). We used a 10-question scale from The Symptom Checklist-90 (Derogatis et al., 1973). Participants rated on Likert scale (0 = *not at all*, 4 = *extremely*),

how often they experience these symptoms. Cronbach's α of scale for our sample α = .79.

The Perceived Stress Scale (PSS). We used 10 question scale version (Cohen et al., 1983), to measure perceived stress in the last week (Likert scale: 0 = *never*, 4 = *very often*). Cronbach's α of scale in our sample was α = 0.84.

Rumination-Reflection Questionnaire (RRQ). RRQ is a 12-item scale for measuring compulsively focused attention on the symptoms of one's own distress, its possible causes and consequences, as opposed to solutions (Trapnell & Campbell, 1999). Participants rated (1 = *strongly disagree*, 5 = *strongly agree*), how much they agree with the occurrence of item in the last week. Cronbach's α = .90.

State-Trait Anxiety Inventory (STAI). STAI is a 20-item questionnaire for measuring state anxiety (Spielberger, 1989). Participants evaluated how they feel in the present moment on 4-point Likert scale (1 = *not at all*, 4 = *very*). Cronbach's α = .90.

The Stress Adjective Checklist (SACL). SACL measures individual's phenomenological awareness of bodily processes and assesses the behavioral and cognitive components of reaction (Mackay et al., 1978). The scale is divided into two dimensions each comprising of two counterparts and five items: (a) Stress (active-negative: α = .85) / Calm (passive-positive: α = .86) and (b) Fatigue (passive-negative: α = .77) / Arousal (active-positive: α = .85). Participants were asked to rate how they feel in the moment on 4-point Likert scale (1 = *not at all*, 4 = *extremely*).

Chamber REST. The room provides conditions of limited environmental stimulation (darkness—complete absence of light stimuli, partial acoustic isolation, social isolation). There was comfortable chair, bed, pad for exercise, fully equipped bathroom. Food and drinks were provided according to the needs of the participant. There was an SOS device accessible to participants in case of any emergencies.

Control Group. The control group participants were placed into a fully lit room, without sound attenuation in laboratory premises, containing table and chairs, they were instructed to engage in an ordinary activity (which simulated exposure to "normal" levels of sensory and information stimulation); for example, reading, writing homework, working on computer, mobile phone, etc.

Procedure

In our study we used factorial design, where time assessments before and after the treatment session constituted the within-subject factor. Control and experimental (chamber REST) group constituted the between-subject factor. Participants in both groups were given option to assign for measurements in the morning (8:15–13:00) or in the afternoon (13:45–18:30), while respecting the need for equal distribution – [experimental: morning (*n* = 16), afternoon (*n* = 18); control: morning (*n* = 8), afternoon (*n* = 6)]. All procedures performed were in accordance with the ethical standards of the Faculty of Arts, Comenius University institutional research committee [Project code: EK/02/2020] and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All participants in the study signed an informed consent and received detailed instructions in advance, which allowed for coordinated measurements with little intrusion from experimenter. Testing was divided into several phases:

1) Data collection took place 2 days before the treatment in form of online questionnaires (completed between 16:00–22:00) and included demographics and additional information, Perceived Stress Scale (PSS), Rumination-Reflection Questionnaire (RRQ), obsessive-compulsive symptoms (OCS).
2) Data collection took place immediately before treatment on the premises of the laboratory, where pretreatment included two measures of salivary cortisol at Time 1 (0 min) and Time 2 (15 min), State-Trait Anxiety Inventory (STAI), The Stress Adjective Checklist (SACL), information overload.
3) Data collection took place immediately after a 3-hr (180 min) stay in chamber REST (or control condition) on the premises of the laboratory, where posttreatment included two measures of salivary cortisol at Time 3 (195 min) and after 15 min at Time 4 (210 min), State-Trait Anxiety Inventory (STAI), The Stress Adjective Checklist (SACL).
4) Data collection was followed up 1 week after the treatment in the form of online questionnaires (completed between 16:00–22:00), including Perceived Stress Scale (PSS), Rumination-Reflection Questionnaire (RRQ), obsessive-compulsive symptoms (OCS), information overload.

Results

Statistical analysis was conducted in IBM SPSS statistics (version 24) and JASP (version 0.18.1). All data were checked for normality distribution, and transformation has been recommended in psychoneuroendocrine research (Miller & Plessow, 2013). For the current analyses, we used a log transformation of the salivary cortisol concentration values.

Cortisol Analysis

In our analysis we utilized several cortisol indices as summarized by Khoury et. al. (2015). Overall cortisol reactivity (RT) is defined as change in cortisol between the baseline and last measured values (computed as last value minus baseline value). AUC_G (area under the curve with respect to ground) and AUC_I (area under the curve with respect to increase/decrease) represent the two most often used indices that capture cortisol levels across repeated measures. AUC_G measures total cortisol output, capturing both intensity (overall distance of cortisol samples from the ground) and sensitivity (difference between individual cortisol samples), whereas AUC_I measures change in cortisol over repeated samples, regardless of prechallenge cortisol concentrations (Fekedulegn et al., 2007; Pruessner et al., 2003).

Based on Pruessner et al. (2003) we computed AUC_G, according to following equation (with variable times between cortisol measurements):

$$AUC_G = \sum_{i=1}^{n-1} \frac{(m_{(i+1)} + m_i) \cdot t_i}{2}$$

And AUC_I was computed as follows:

$$AUC_I = \left(\sum_{i=1}^{n-1} \frac{(m_{(i+1)} + m_i) \cdot t_i}{2} \right) - \left(m_r \sum_{i=1}^{n-1} t_i \right)$$

For cortisol data analysis there was totally N = 46 (out of N = 49) participants (experimental = 33, control = 13), because of incomplete data from three subjects. Table 1 contains raw cortisol data for both groups, and according to Mann-Whitney U test, there were no significant differences between groups in raw cortisol indices at any measurement phase.

Table 1
Descriptive Statistics for Raw Cortisol Values

		Pre		Post	
Cortisol index	Group	Time 1	Time 2	Time 3	Time 4
Mean cortisol (nmol/l)	Experimental	6.43 (4.66)	4.94 (3.6)	2.80 (2.86)	2.79 (2.64)
	Control	6.55 (6.99)	5.05 (3.7)	2.07 (1.53)	1.63 (0.87)
AUC_G	Experimental	824.65 (520.46)			
	Control	755.97 (462.81)			
AUC_I	Experimental	−525.77 (688.02)			
	Control	−620.97 (1046.19)			
RT	Experimental	−3.63 (4.95)			
	Control	−4.92 (6.76)			

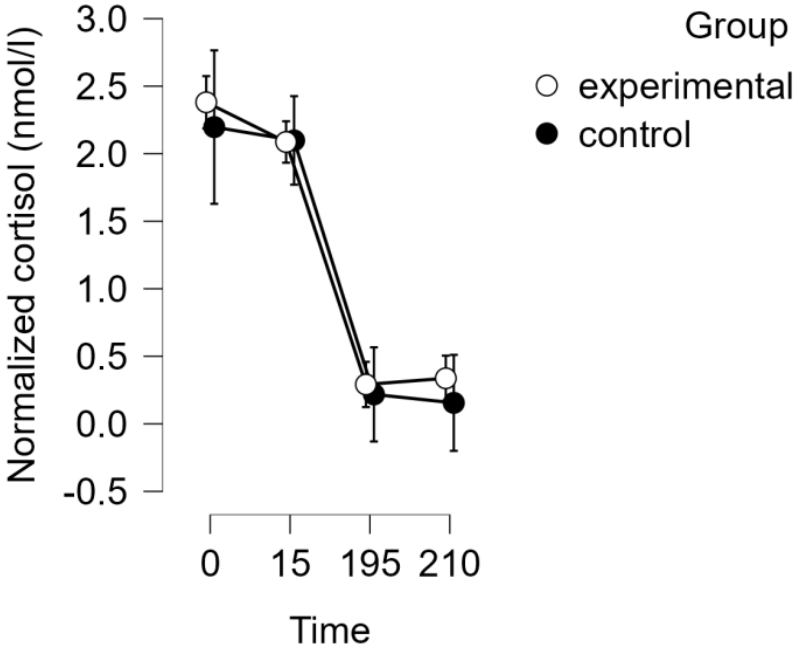
Note. Mean (standard deviation); Preintervention - Time 1 at 0 min, Time 2 at 15 min; Postintervention - Time 3 at 195 min, Time 4 at 210 min; AUC_G = area under the curve with respect to ground; AUC_I = area under the curve with respect to increase/decrease; RT = reactivity.

Cortisol – Repeated Measures Analysis

A two-way repeated measures ANOVA was conducted to compare normalized mean values of salivary cortisol at four different time points: preintervention - Time 1 at 0 min, Time 2 at 15 min; postintervention - Time 3 at 195 min, Time 4 at 210 min, for experimental and control groups (Figures 1–3). There was a significant within-subject effect for time Wilks' Lambda = .171, $F(3, 42) = 67.76$, $p < .001$, effect size was large (multivariate partial

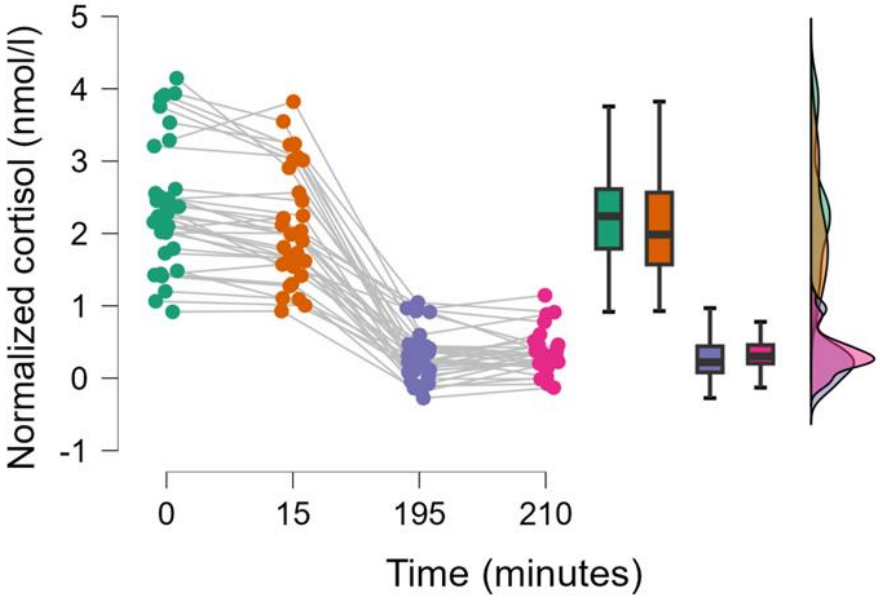
η^2 = .829) for participants in both groups. Post hoc test revealed significant differences between Time 2 and Time 3 (pre-post) values $F(3, 42) = 1.84$, $p < .001$, partial $\eta^2 = .823$. Between-subject analysis showed nonsignificant difference between groups $F(1, 44) = 0.421$, $p = .520$, partial $\eta^2 = .009$).

Figure 1. *Graphic Representation of Normalized Cortisol Changes Across Repeated Measures*.



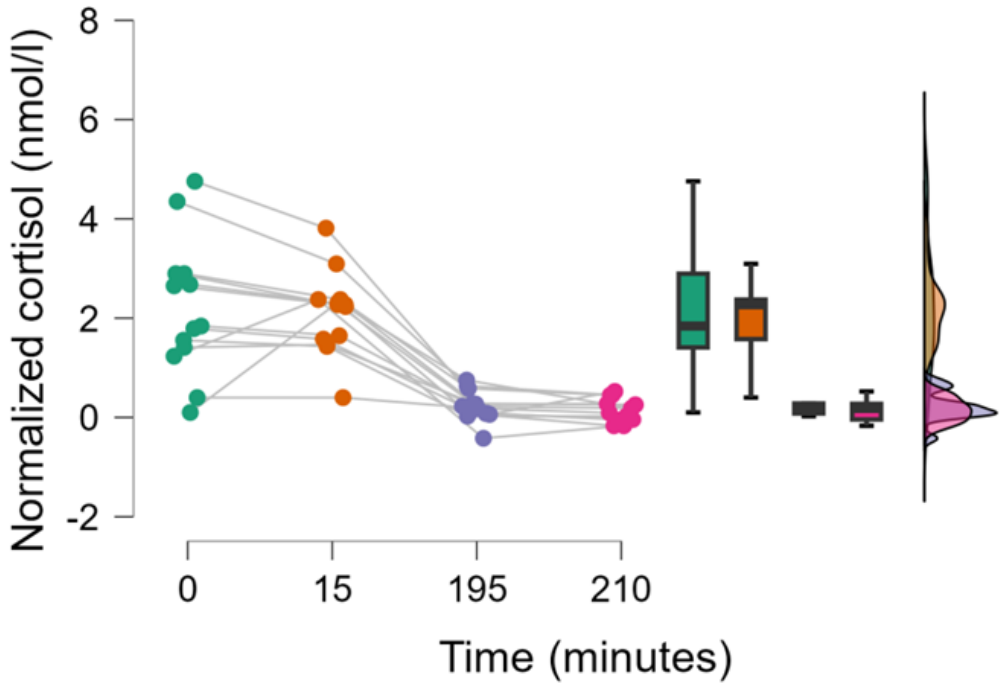
Note. Pre and posttreatment at time: 0 min, 15 min, 195 min, 210 min, for experimental and control group; [CI = 95%].

Figure 2. *Raincloud Plot of Normalized Cortisol Changes Across Repeated Measures*.



Note. Pre and posttreatment at time: 0 min, 15 min, 195 min, 210 min, for experimental group (N = 33).

Figure 3. *Raincloud Plot of Normalized Cortisol Changes Across Repeated Measures*.



Note. Pre and posttreatment at time: 0 min, 15 min, 195 min, 210 min, for control group (*N* = 13).

Cortisol – Individual Differences

On the individual level, we looked at raw AUC_I values for each participant and identified different overall cortisol reactivity patterns, based on direction of AUC_I change (increase/decrease) throughout repeated measures. In experimental group (*N* = 33, chamber REST), 26 (78.79%) participants exhibited a positive response (a decrease in salivary cortisol), 5 (15.15%) participants negative reaction (an increase in salivary cortisol), 2 (6.06%) neutral response (fairly unchanged cortisol levels). In control group (*N* = 13), 9 (69.23%) exhibited positive response, 3 (23.08%) negative response, 1 (7.69%) neutral (Table 2). However, based on one-way ANOVA, different responses in both groups did not significantly differ in levels of perceived stress (SACL), or anxiety (STAI) after treatment. A chi square test revealed that difference in distribution of responses between experimental and control groups was not statistically significant (X^2 = 0.487, *p* = 0.784).

Comparison and Correlation Analysis of Self-Report Measures of Whole Sample and Individual Groups

For information overload analysis there was *N* = 47 (out of *N* = 49) participants (experimental = 33, control = 14)—missing data from two subjects. Also at 1-week follow-up, for measures of PSS, RRQ, OCS there was *N* = 48 participants (experimental = 34, control = 14)—missing data from one subject.

Table 2

Number of Participants who Exhibited Positive/Negative/Neutral Responses According to AUC_I Changes Throughout Repeated Measures for Experimental and Control Conditions

	Experimental group (*N* = 33)	Control group (*N* = 13)
Positive response	26 (78.79 %)	9 (69.23 %)
Negative response	5 (15.15 %)	3 (23.08 %)
Neutral response	2 (6.06 %)	1 (7.69 %)

Measurement of information overload with VAS in our sample, was as shown appropriately chosen, because of significant Pearson correlation with PSS (at 1-week follow-up; *r* = .410, *n* = 47, *p* = .004) the higher subjective information overload, the higher perceived stress.

An independent-samples *t*-test was conducted to compare pre–post treatment information overload VAS scores for experimental and control groups. Pretreatment, there were no significant differences in information overload for experimental (M = 7, SD = 2.3) and control group (M = 6.57, SD = 1.78), $t(45) = 0.62$, $p = .538$. At 1-week follow-up posttreatment, we found significantly lower information overload in experimental (M = 5.69, SD = 2) than in control group (M = 7.64, SD = 1.82) week after treatment, $t(45) = -3.04$, $p = .004$. The magnitude of the differences in the means was large ($\eta^2 = .17$; Table 3).

An independent-samples *t*-test was conducted to compare pre–post treatment obsessive-compulsive symptoms (SCL 90) for experimental and control group. Pretreatment, there was no significant difference in obsessive-compulsive symptoms between experimental (M = 23.22, SD = 9.48) and control group (M = 26.71, SD = 6.5), $t(47) = -1.26$, $p = .215$. At 1-week follow-up, we found significantly lower level of obsessive-compulsive symptoms in experimental (M = 22.44, SD = 8.16), compared to control group (M = 27.78, SD = 7.67), $t(46) = -2.1$, $p = .042$ (Table 3).

Using correlation analysis, we found significant positive relationship between information overload and obsessive-compulsive symptoms at 1-week follow-up ($r = .354$, $n = 47$, $p = .015$).

Pearson correlation analysis also showed significant relationship between information overload pretreatment and scores on SACL dimension—feeling calm, measured after exposure to experimental condition ($r = .421$, $n = 33$, $p = .015$), but not for control condition ($r = -.096$, $n = 14$, $p = .744$).

Table 3

Descriptive and Independent Samples T-test Statistics for Experimental and Control Group Pre–Post (1-Week Follow-up) Intervention.

		Pre (week prior)				Post (1-week follow-up)			
	Group	Mean (*SD*)	*t*(df)	CI = 95%		Mean (*SD*)	*t*(df)	CI = 95%	
				Lower	Upper			Lower	Upper
PSS	Experimental	17.8 (7.38)	*t*(47) = −.257 *p* = .798	−4.920	3.806	15.58 (7.08)	*t*(46) = −947 *p* = .348	−6.581	2.265
	Control	18.35 (5.22)				17.64 (6.14)			
RRQ	Experimental	39.25 (13.63)	*t*(47) = −.958 *p* = .343	−11.384	4.042	37.67 (10.6)	*t*(46) = −1.3 *p* = .199	−10.807	2.526
	Control	42.92 (6.7)				41.92 (9.39)			
OCS	Experimental	23.22 (9.48)	*t*(47) = −1.25 *p* = .215	−9.058	2.0874	22.44 (8.16)	*t*(46) = −2.1 *p* = .042*	−10.718	−0.3681
	Control	26.71 (6.5)				27.78 (7.67)			
Information overload	Experimental	7.00 (2.3)	*t*(45) = 0.62 *p* = .538	−0.963	1.821	5.69 (2.06)	*t*(45) = −3.04 *p* = .004**	−3.231	−0.660
	Control	6.57 (1.78)				7.64 (1.82)			

Note. **$p < .01$; *$p < .05$; PSS = Perceived Stress Scale; RRQ = Rumination-Reflection Questionnaire; OCS = obsessive-compulsive symptoms (SCL 90).

Discussion

In our hypothesis we suggested that single chamber REST condition would elicit higher reduction in salivary cortisol concentration compared to control condition. Results showed that raw cortisol indices RT, AUC_G, and AUC_I did not significantly differ between groups, meaning that overall reactivity (increase/decrease) and concentration of cortisol were at similar levels. Both groups also achieved analogous normalized cortisol concentration values during observed period of time; therefore, our hypothesis was not confirmed. Chamber REST intervention did not provoke greater cortisol reduction, as seen compared to control group, both showed similar pattern. Based on mean gradual cortisol reduction in the control group, we can conclude that chamber REST condition also simply followed similar cortisol diurnal rhythm seen in healthy individuals (Oster et al., 2017). Onset of our

morning measurements (at least 1 hr after awakening of participants) started after beginning of CAR decline, with slow continuation until the evening. There was significant reduction in cortisol concentration between Time 2 and Time 3 (pre–post treatment) for both groups, but measurements being so far apart (3 hr) only suggests leap over gradual cortisol diurnal decline.

On the individual level, as measured by AUC_I, we identified that not all participants manifested decreases in cortisol levels. In total of five participants (15.15%), chamber REST induced "negative response" as seen by an increase in cortisol concentrations over measurement phases. Individual reports suggest that for few individuals, adaptation to complete darkness and absence of stimuli was more challenging than for others. However, positive and negative response individuals did not significantly differ in the levels of perceived anxiety (STAI) and stress (SACL), with only minor indication. In control group, three participants (23.08%) exhibited negative response with elevated cortisol, which is comprehensible with regards to characteristics of condition (engagement in work duties, writing homework or staying at laboratory over time can be perceived as frustrating for someone). For others, not engaging in such burdensome activities during observed time, was perceived as more plausible (positive response). Similarly, there was not significant difference in perceived anxiety and stress in control group. Problematic association between cortisol and self-report anxiety was noted previously (Leininger & Skeel, 2012). Nevertheless, results showed that higher information overload week before treatment significantly correlated with feeling calm (SACL) after chamber REST session. In other words, the higher experienced information overload, the better calming effect chamber REST facilitated. An effect of rapid deafferentation from normal or excessive stimuli could be perceived as challenging for some individuals, yet beneficial in whole. This relationship was not observed in control condition. Our results regarding cortisol changes and psychological effects are more in line with explanation of Schulz and Kaspar (1994), such as, that perceived subjective levels of comfort after treatment (feeling calm), were more notable than the neuroendocrine changes associated with relaxation.

A notable result is that chamber REST group achieved significantly lower subjective information overload at 1-week follow-up, compared to control group. The core of the explanation could be in the process of directing one's attention during the course of these conditions, which was in the control group focused outwards and in chamber REST attention directed inwards, which is a major difference. Based on closer analysis of individual reports from the REST session, we have identified several emerging themes of "activities", such as contemplating/meditating/self-reflecting; reviewing own personality traits/relationships and reactions to close people; processing previous experiences; planning/time managing upcoming duties and free time; catching up on sleep deficit/regenerating/relaxing; and pausing from screen time (mobile phone). Mediated effect of processing of these themes was also emphasized at 1-week follow-up by majority of participants. Added value of chamber REST, based on Dishon et al. (2017), could be for both: individuals with higher levels of trait self-awareness who are more predisposed to engage in self-reflective reasoning, and also others, for whom suitable environmental conditions might act as the catalyst for self-reflection. As for the diminished subjective information overload in chamber REST group, possible explanation could be found in current models of self-reflection. They propose that engaging in self-reflection regarding the management of everyday stressors, and extracting coping strategies from these reflections (insights), could serve as means to fine-tune and fortify one's resilience capabilities, which in turn heightens the probability of achieving psychologically resilient outcomes (Crane et al., 2019)—such as greater tolerance of information influx or improvement in processing capacity (sufficiently attended residual or avoided sensations and experiences can unburdened cognitive capacities for new processing). It is further important to stress that adaptive (healthy) self-reflection is associated with perceived resilience and well-being indirectly, via insight. This component is missing in general self-reflection (Bucknell et al., 2022). Based on our results, a possible sign that adaptive self-reflection is occurring in chamber REST session could be the outcome of declined rumination score, although nonsignificant, and significantly lower obsessive-compulsive symptoms at 1-week follow-up compared to control group. Chamber REST facilitating adaptive self-reflection could be emphasized in comparison to general self-reflection, which has been found to predict rumination (Takano & Tanno, 2009), and its associations with higher prevalence of obsessive-compulsive symptoms (Raines et al., 2017).

It is noteworthy that single chamber REST session seems to facilitate processes (contemplation,

adaptive self-reflection) observed particularly in meditation (Dorjee, 2016) and achieve similar effects, but without prolonged practice or systematic training. Life needs periods of rest and introspection, especially in the period of identity development. Results of our study could be beneficial not only for personal life resolution and optimal functioning of young adults, but also in corporate environment, where the term *information overload* is used frequently. Arnold et al. (2023) in their latest review of 87 studies, including the fields of medicine, production and management, listed number of recommendations in dealing with information overload and technostress, including various types of skill training and coping strategies. Among five identified levels through which the information is mediated and processed, this intervention could be applicable on the personal level, for development of healthy coping measures, ensuring sufficient work-life balance and prevention of burnout. Actually, flotation REST has already been utilized as health care measure for corporate employees (Kjellgren & Westman, 2014). However, this is the first study to date, to explicitly associate actual reductions in subjective information overload following REST.

Limitations

The main limitation of our study is unequal distribution of participants in experimental and control group, in addition, majority of participants consisted of women. Also, participants themselves in both groups chose a preferable time for their measurements (morning to afternoon). Another widely emphasized issue is self-report character of psychological variable measures. The degree and accuracy of self-reflection are presumably variable among participants. Measurements of cortisol variations only before and after single chamber REST could not have fully capture individual characteristics of cortisol concentration changes. For the future research, an individual cortisol diurnal profile acquired through several days of measurements, before and after single chamber REST session would shed better light on possible changes in cortisol values.

Conclusion

Our study explored effect of single brief chamber REST on cortisol reactivity and information overload in sample of young adults. Preliminary results indicate that chamber REST in this condition does not have significant effect on secretion of cortisol. It seems that REST in greater extent affects psychological functioning of an individual. As shown, the higher information overload before treatment the better calming effect (measured by SACL) chamber REST exhibited. Moreover, REST seems to facilitate adaptive self-reflection, leading to healthier coping and resilience with significantly less subjectively perceived information overload and obsessive-compulsive symptoms at 1-week follow-up as compared to control condition.

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Evidence-Based Interventions for Improved Psychosocial Outcomes in Harmful Alcohol Use: A Scoping Review

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Abstract

Background. Harmful alcohol use is defined as a drinking pattern that lasts at least one month or has occurred often during the preceding 12 months and that negatively impacts multiple facets of life. It has a high recurrence rate and a poor prognosis, despite the availability of cognitive-behavioral and psychosocial therapy. Emerging neuromodulation techniques for treating harmful alcohol use are gaining traction in the field of psychotherapy, but knowing their efficacy in terms of psychosocial outcomes necessitates an adjuvant approach. This scoping review aims to investigate the existing evidence on the effectiveness of various psychosocial interventions that improve quality of life (QoL) dimensions in conjunction with neurotherapies for individuals with harmful alcohol use. **Methods**. The review utilized a five-stage technique to search for research papers from 2000 to 2022. After screening and reviewing 41 full-text papers, 29 were found to meet the inclusion criteria. **Conclusion**. The articles highlighted the advantages of integrated therapeutic interventions such as motivation enhancement therapy, cognitive behavior therapy, neurotherapy, multimodal therapy, supportive therapy, and 12-step facilitation programs. However, limited studies have explored the effectiveness of combining neurotherapy with psychosocial interventions. **Implications**. Future research should focus on the efficacy of combining neurofeedback with psychosocial therapies to improve QoL for individuals with harmful alcohol use.

Keywords: quality of life (QoL); psychosocial outcomes; harmful alcohol use; EEG neurofeedback; psychosocial intervention

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Background

Harmful alcohol consumption is a global mental health concern, as it has a wide range of negative life consequences in the physical, psychological, social, and environmental domains (Ugochukwu et al., 2013). There are 3 million annual deaths attributed to alcohol consumption, and several cases of disability and illness. The negative effects of alcohol consumption account for 5.1% of the global disease burden (World Health Organization [WHO], 2018).

Many unfavorable outcomes have been associated with alcohol usage beginning in adolescence (Adger & Saha, 2013) or early adulthood (Englund et al., 2018). Risky drinking habits are categorized as psychosocial phenomena in the biopsychosocial framework (Gopiram & Kishore, 2014) and its intake is known as a typical stress-reduction coping strategy. In young adults harmful alcohol use has been traced back to early life or chronic exposure to psychosocial stresses (supported by “sensitivity to the effects of alcohol” or negative affectivity paradigm). It was found to be associated with negative life consequences, such as deterioration in physical health, intrapersonal, interpersonal (peers, family), social, difficulties at work or school, spiritual, and legal issues (Dhananjay & Prabhuswami, 2022; Foster, Peters, et al., 2000; Linskiy et al., 2022; Luk et al., 2022), and psychological impairment contributing to poor quality of life (QoL; Shiji et al., 2020). Research studies revealed that these psychosocial risk factors might intensify unhealthy drinking patterns, which can have a range of detrimental psychological and physical

repercussions, including the ability to exacerbate the effects of stress (Anthenelli & Grandison, 2012). A high stress threshold, along with a propensity for alcohol misuse, has been shown in the literature to alleviate the risk of retorting to addictive behavior (for more, see the stress coping model; Wagner et al., 1999).

Yet another study found that life stress influences treatment outcomes and relapse rates in substance addiction (Brady & Stone, 1999; Sinha, 2008). Even after accounting for other factors like income, socioeconomic status, comorbidities, marital status, and place of residence, it was still found to be independently associated with a lower QoL score (Callaghan & Tottenham, 2016). This could be because alcoholics believe they have little to no control over their drinking when faced with adversity. Stress cues and cognitive priming have been consistently linked to relapse. Advocates of a harm reduction approach recognize that while abstinence is the ideal outcome, not every individual is able to achieve it. For some individuals, controlled drinking may be a more realistic goal for reducing the risks associated with alcohol use. Research studies suggest that a small but significant proportion of patients may be able to resume normal or controlled drinking (Armor et al., 1976; Polich et al., 1980). However, this remains a controversial area that requires further evidence-based intervention research.

Numerous psychosocial interventions have been employed to treat harmful alcohol use either in conjunction with pharmacotherapy or as a standalone treatment. The most commonly utilized interventions include motivational interviewing (MI; Miller & Rose, 2009), cognitive behavioral therapy (CBT), screening and brief interventions (SBI), 12-step facilitation programs, cue exposure treatment, social network therapy, and multimodal therapy. Research has demonstrated that individuals who undergo detoxification and treatment without alcohol are more susceptible to relapse (Foster, Marshall, et al., 2000).

However, there is evidence to suggest that the effectiveness of many psychosocial interventions has been overestimated and that their limitations have been overlooked. Furthermore, the results of these interventions are difficult to generalize (McCambridge & Saitz, 2017).

The review seeks to comprehensively analyze and fill the gaps in research on various evidence-based practices used in conjunction with adjuvant therapies. This will involve considering factors such as therapeutic duration or intensity (brief or extended), setting (primary care-based or inpatient), mode of delivery (group, individual, or web-based), and treatment goals (abstinence-oriented or harm reduction) in enhancing different domains of QoL (as defined by The Whoqol Group, 1998) for individuals exhibiting harmful alcohol use behavior.

Methods

With the use of a systematic search, a scoping review was conducted. Scoping reviews have been increasingly popular in the last few years, especially in the area of health care research (Daudt et al., 2013). This is because a systematic review is a suitable method to employ in fields with either inadequate prior research or where the results and conclusions of the most recent studies appear to be contradictory to one another. First, this scoping review examines the scope, depth, and nature of published research on different evidence-based psychosocial and allied interventions in the domain of alcohol use. The review does not necessarily assess study quality. Second, study gaps were identified and communicating the research findings in some specific domain was prioritized. Knowledge gaps in the Discussion section may prompt further research. Since there is limited knowledge summary on integrated intervention and effectiveness of psychosocial outcomes in conjunction to adjuvant therapeutic, this form of wide mapping is suited for enabling an overview of the knowledge status in this domain.

Articles using the terms “quality of life,” “psychosocial intervention,” “alcohol use,” “harmful alcohol use,” “integrated intervention,” and “EEG Neurofeedback” were searched in PUBMED, SCOPUS, Google Scholar, Science Direct, Proquest, the ETOH archival database of the National Institute on Alcohol Abuse and Alcoholism, EBSCO, and MEDLINE from 2000 to 2020, to define the psychosocial interventions used for people with harmful alcohol use who have been diagnosed with or are undergoing treatment using a variety of tools thought to be reflected in patients' QoL outcomes. Based on the results of this search, it appears that there is a lack of research on psychosocial intervention in conjunction to neurotherapy (integrated intervention). In order to create a more complete literature map, it was decided that papers presenting psychosocial outcome from several angles (standalone or adjuvant interventions) would be included. Statistically significant relationships with QoL domains such as physical, psychological,

interpersonal, intrapersonal, social (i.e., at the 95% confidence level) were also extracted. The review followed the five-stage methodological framework created by Arksey and O'Malley (2005), which was guided by the strategy for conducting systematic scoping reviews by Levac et al. (2010).

Identifying Research Question

This scoping study was driven by the following question:

> What is known from the literature about the use of evidence-based interventions in relation to improved psychosocial outcomes in harmful alcohol use?

Identifying Relevant Studies

Following the initial search in PUBMED, SCOPUS, the ETOH archive database of the National Institute on Alcohol Abuse and Alcoholism, EBSCO, and MEDLINE, with the most recent searches conducted on March 11, 2020, no time constraints were imposed. The search approach incorporated context (harmful alcohol use, alcohol use disorder) and concept specifications (psychosocial outcome, QoL, psychosocial intervention; Peters et al., 2015). A more precise identification of the search phrases was then made. Combinations of the terms “alcohol use disorder,” “substance use,” and “harmful alcohol use” were used in reference to a person's psychosocial outcome. Psychosocial intervention were the major themes of the overarching idea term.

Study Selection

***Inclusion Criteria*.** Full-length, original, quantitative, qualitative case study research papers that have been peer-reviewed were considered. The research papers were found through a manual search of key references and references known by coauthors. For this reason, we did not include study protocols or conference papers whose findings had not been published in peer-reviewed journals, even if they were relevant to our overarching goal of summarizing the current state of knowledge. Moreover, papers given in languages other than English were not considered due to time and resource constraints. Non-peer-reviewed empirical publications and studies were also eliminated.

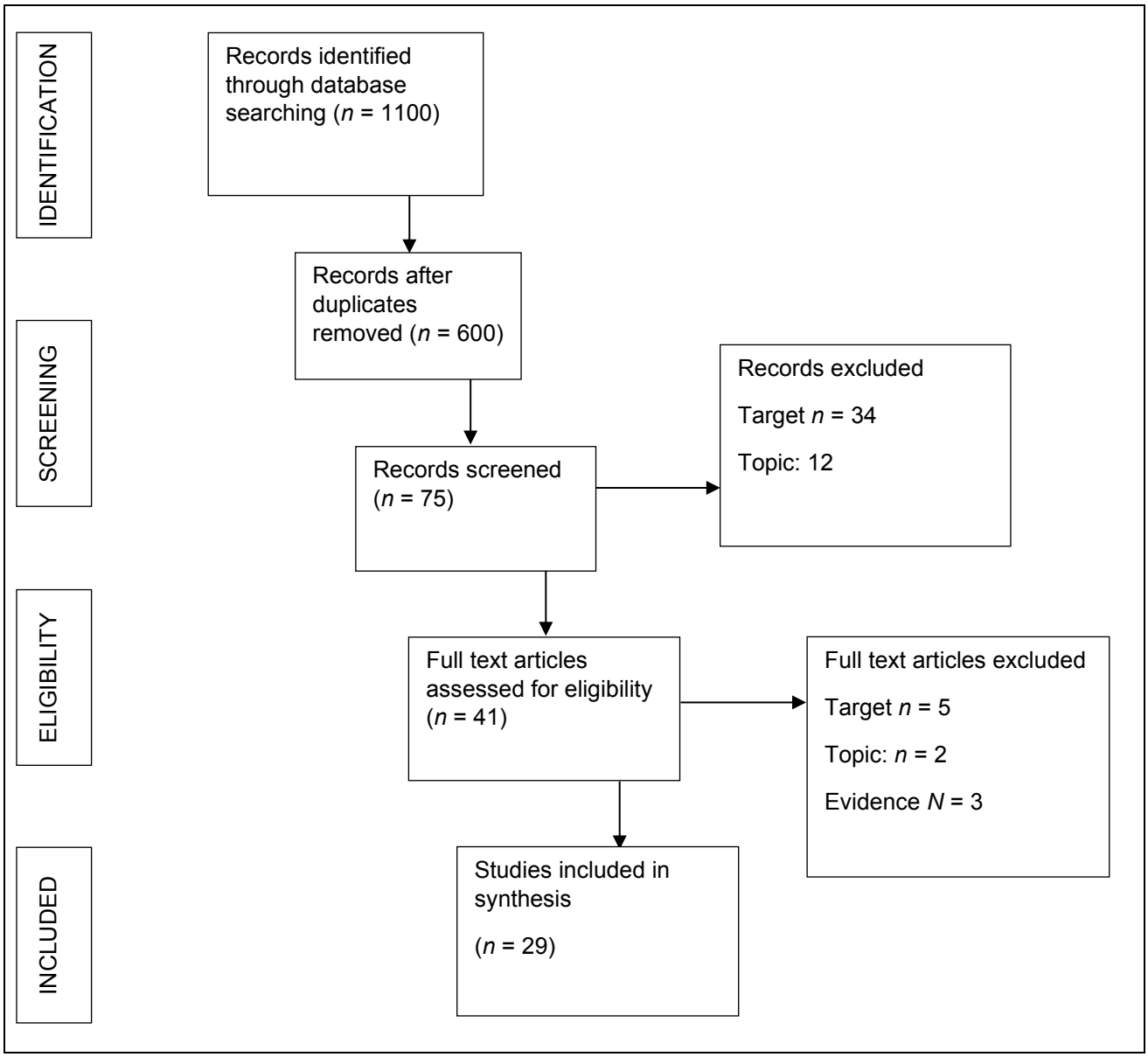
Participants. Everyone who met the criteria was taken into account, including people who had been previously diagnosed with an alcohol use disorder. Psychosocial therapies with QoL and psychosocial outcome studies completed on a subset of the population were included in the literature mapping.

Concept. The best way to define psychosocial interventions is as "psychologically-based interventions aimed at reducing habitual alcohol consumption behavior or alcohol-related problems" (Kaner et al., 2018). Evidence-based psychosocial interventions reportedly used in conjunction to pharmacological and allied treatments have been discussed below. The primary concept discussed in the review was the psychosocial outcome, which refers to an individual's perception of their physical, psychological, social, intrapersonal, interpersonal, and environmental aspects of life. Studies that only focused on the relationship between alcohol use and comorbidities were excluded.

Context. All of these studies had one thing in common: alcohol use disorder. The studies' settings varied from clinical to nonclinical, but all of them measured patients' psychosocial outcomes.

Search Strategy. There was a total of 1,100 records found after applying the search method across all four databases. Data was transferred to EndNoteX8 from other sources. Four entries were found using other methods like a manual search of key references and input from coauthors. After eliminating duplicates, we had 600 records from which to select the titles and abstracts to review. Each author screened records individually, comparing titles and abstracts to the inclusion criteria, and settled on 75 abstracts screened and 41 papers reviewed as potentially relevant studies to do a full-text screening on. Twelve of the full-text articles that were checked had to be disqualified with reasons given. Most of these studies weren't included because their subjects didn't accurately represent the target population (those with alcohol use disorder and with comorbidities). This was also true for the qualitative case study articles that were not included, the majority of which had an emphasis on intangible indicators of subjective well-being or life satisfaction. The inclusion of articles that deviated too much from the psychological domains was restricted. Twenty-nine papers were included in the final analysis (Figure 1).

Figure 1. *Flowchart of the Evidence Selection Process*.



Charting the Data. The three main stages of qualitative content analysis were employed by the authors to carry out their research on how evidence-based interventions enhanced psychosocial outcomes in harmful alcohol use: data collecting, data organization, and data presentation (Elo & Kyngäs, 2008). A tool for working with structured data was employed for this purpose. Further study characteristics were gathered by the authors, reviewed, and then incorporated into the consensus. As this constituted a scoping review, each study was not evaluated for its quality (e.g., risks of bias or study strength; Arksey & O'Malley, 2005). The review's screening process is depicted in the flow chart (Figure 1), illustrating the number of studies at each stage and the reasons for their exclusion. This methodical approach helps uphold transparency and rigor in the review process by systematically organizing and categorizing the issues arising from the research results included in the evaluation.

Collating, Summarizing, and Reporting the Results. Publication dates were used to categorize the studies. Research articles from the same year were divided into sections based on the surnames of their original authors. Several interventions have

been devised to improve different psychosocial domains of functioning in relation to harmful alcohol use. Various psychosocial interventions have been developed to ameliorate the harmful effects of alcohol consumption. Outcomes related to complementary treatments used such as CBT including relapse prevention (RP), contingency management (CM), CBT/psychoeducation MI/ motivation enhancement therapy (MET), SBI, 12-step facilitation programs, social network therapy, and EEG neurofeedback are obtained and discussed below.

Psychoeducation and Brief Motivational Interview. It has been found that the combination of psychoeducation and brief MI is more effective in reducing alcohol intake than psychoeducation alone. Studies conducted by Hulse and Trait (2002) and Kraemer et al. (2002) have shown significant improvements in the physical domain as a result of this approach. Additionally, MI has been found to produce neural changes in various areas of the brain, including the central, postcentral, and superior temporal gyrus, as well as the orbitofrontal cortex (OFC), nucleus accumbens, insula, caudate, and putamen, which impact gustatory cue reactivity in patients with alcohol use disorder (Feldstein Ewing et al., 2011).

Broad-Spectrum Treatment, 12-Step Facilitation Program, and MET. The combined use of broad-spectrum treatment, a 12-step facilitation program, and MET has demonstrated greater efficacy in treating individuals with alcohol use disorder when integrated with pharmacotherapy. The broad-spectrum treatment strategy, which is encompassed by cognitive behavior coping skill therapy, emphasizes various aspects of life that are linked to relapse and drinking (Davidson et al., 2007). This approach involves identifying the triggers of negative emotions that may lead to increased drinking. Other forms of cognitive behavior coping skill therapy, such as the community network approach or behavioral self-control training, as well as relaxation training, including neurofeedback, can also be employed. Research has shown that neurofeedback intervention, particularly through deep relaxation training, can enhance mentalization capacity by strengthening connections in the default mode network (Imperatori et al., 2017). Studies have also suggested that stress can exacerbate alcohol use and potentially lead to relapse, as evidenced by impaired function in the hypothalamic-pituitary-adrenal (HPA) axis during the initial 6 months of abstinence (Burtscheidt et al., 2001; Dunne & Ivers, 2023). Therefore, further investigation of neurofeedback as an adjunct therapy alongside the aforementioned treatments is warranted.

MET and Social Behavior and Social Network Therapy (SBNT). The relationship between alcohol consumption and treatment for alcohol-related issues can be moderated by the presence of a social network, as per the findings of Mowbray (2013). The research indicates that MET and social behavior and social network therapy (SBNT), which are measured by the social network index, can lead to a reduction in alcohol intake and an improvement in mental health conditions over a period of 12 months (UKATT Research Team, 2005). Furthermore, studies have revealed that dysregulation in the salience network during resting state can adversely affect social, inhibitory, and emotional processing, with activation in the bilateral anterior insula playing a role in the response to alcohol cues (Padula et al., 2011).

CBT and 12-Step Facilitation Program. The integration of CBT and a 12-step facilitation program has been found to be significantly efficacious, as it targets negative affect, dysfunctional behavior, and maladaptive cognitions while simultaneously instilling adaptive cognitive processes (Easton et al., 2007).

CBT, MI, Supportive Therapy. A cognitive-behavioral MI approach, accompanied by guided self-change and both social and natural support, has demonstrated positive results in altering the drinking behavior of individuals with alcohol addiction (Sobell et al., 2000). The integration of CBT, supportive therapy, and psychoeducation has shown favorable outcomes in both physical and interpersonal domains (Addolorato et al., 2013). Numerous studies have reported altered activation in the prefrontal cortex and other limbic regions following integrated behavior therapy (Devito et al., 2012) and CBT (Yuan et al., 2022).

Discussion

Research concentrating on both psychosocial interventions in alcohol consumption and psychosocial consequences is becoming more popular, as evidenced by the fact that most of the studies included in the scoping review were done after 2000 and were from a wide range of western countries. There were two case study designs. When analyzing outcomes based on a pre-post test design, which is often based on randomized control trials, most research employed well-established clinical and psychosocial tools and methodologies.

However, since these tools are based on a range of psychological dimensions and the interventions are aimed at enhancing a specific element of the outcome, results cannot be consistently compared between research. Numerous research papers also employed diverse comparison groups in clinical contexts and a range of study designs, such as a one-group posttest-only design or an experimental and control group design, indicating a variability among studies.

Alcohol Dependence Scale (ADS; Skinner & Horn, 1984), Inventory of Drinking Situations (IDS; Annis et al., 1982), Michigan Alcoholism Screening Test (Selzer, 1971), Structured Clinical Interview SCID for DSM-III-R (Spitzer et al., 1992), and Addiction Severity Index (McLellan et al., 1992) were the instruments utilized as screening measures. Two further widely utilized measures for evaluating drinking patterns were the Timeline Followback Scale (TLFB; Sobell et al., 1996) for alcohol intake and the Drinker Inventory of Consequences (DrInC; Miller et al., 1995).

Baseline assessments, pretests, and posttests employed psychosocial measures, such as the Short Form 36-item (SF-36; Hays et al., 1993) for the physical domain, the Health Survey, the Patient Health Questionnaire (PHQ-9; Kroenke et al., 2001), and the model of end-stage liver disease (MELD) scores (Kamath et al., 2001).

The Mini-Mental State Examination (MMSE; Folstein et al., 1975), Hopkins Verbal Learning Test (Brandt, 1991), Trail Making Test (Partington & Leiter, 1949), Letter-Number Sequencing Test from the Wechsler Memory Scale-III (Wechsler, 1997), Mentalization Questionnaire (MZQ; Hausberg et al., 2012), Barrat Impulsivity Scale (BIS-11; Patton et al., 1995), and Thought Control Ability Questionnaire (Wells & Davies, 1994) were the main tools used to assess the cognitive and psychological domain.

The interpersonal domain evaluation consists of the family environment scale, work functioning, family functioning (Family Evaluation Device; Epstein et al., 1984), and spouse partner functioning (Dyadic Adjustment Scale; Spanier, 1976). The Alcohol Abstinence Self-Efficacy Scale (AASE; DiClemente et al., 1994), Treatment Self-Regulation Questionnaire (Ryan & Connell, 1989), MMPI-2, The Inventory of Clinical Personality Accentuation (Andresen, 2006), the NEO-Five-Factor Inventory (Costa & McCrae, 2008), and the Coping Strategies Scale (CSS; Folkman & Lazarus, 1980) were used to assess intrapersonal domains. The Readiness to Change Questionnaire (RTCQ; Rollnick et al., 1992) was used to measure motivation for change based on the Transtheoretical Stages Change Approach (Prochaska et al., 2004).

Psychosocial Interventions and Adjuvant Therapy Outcomes

Alcohol consumption has been found to be significantly predicted by drinking motives. Likewise, changes in behavior related to alcohol consumption can be predicted by the level of readiness to change (RTC). Ambivalence towards alcohol misuse, for example, may influence commencement and hence an individual's motivational construct (Moustafa et al., 2023). Subjective standards may aid in the reduction of evaluative tension (Priester & Petty, 2001; subjective norms may influence behavioral intention and future behavior in which ambivalence moderate the relationship between subjective norms and behavioral intentions). Individuals with ambivalent opinions would feel more evaluative tension, pushing them to act on relevant groups' subjective criteria (Hohman et al., 2014). In the absence of particular information, people seek advice (Festinger, 1954; Suls & Wheeler, 2008). One method which can facilitate awareness is psychoeducation. Resistance to change is a symptom of ambivalence toward change, not an inherent trait. Confrontational tactics in therapy raise resistance and tension. A nonjudgmental and sympathetic approach is required to determine the client transformation action stage (Miller & Rose, 2015). The scoping review also facilitates researchers to focus on understanding, if intrinsic motivation in the action stage of change predicts improved QoL in alcohol misuse. Through psychoeducation on how to reorganize their social networks to be more conducive to abstinence and less conducive to drinking, network support therapy has been shown to be successful in strengthening the motivational construct (Litt et al., 2016). Therefore, network support therapy, psychoeducation, and motivational enhancement techniques may be helpful adjuvant or complementary treatment modalities in subsequent studies.

Intervention should focus on improving other domains (such as spiritual domain through mindful mediation techniques in conjunction to neurotherapy; Ghosh et al., 2014), facilitating abstinence or instilling social, behavioral, and cognitive skills and should establish a holistic approach to treatment module and follow-up care. To date, only physical and mental health outcomes have been carefully explored, while relatively little is

known about other critical areas of functioning such as sociocultural outcomes (Basheer et al., 2015; Sudhinaraset et al., 2015).

The inability to deal with stress and alcohol stimuli contributes to the continuation of excessive drinking and a relapse into drinking after unsuccessful attempts to quit (Becker, 2008). In addition, CBT includes the utilization of coping skills training to target and improve cognitive and behavioral coping deficiencies (McHugh et al., 2010). Prior studies reviewed above mostly found that both CBT and alternative treatment were equally effective in increasing alcohol-specific coping consistent with prior findings (Jones et al., 1982; McHugh et al., 2010; Monti et al., 1993). Other studies have reported similar findings comparing CBT and 12-step therapy (Carrol et al., 1999; Finney et al., 1998, 2007; Wells et al., 1994).

Research on the efficacy of CBT as a standalone treatment for alcohol dependence has mixed results, with low to moderate efficacy in some cases. Negative findings may be due to methodological flaws or sample population limitations (Hofmann et al., 2012; Powers et al., 2008). Assessing literacy levels is crucial for effective CBT self-help booklet (CBT-SHB) interventions. Studies have consistently reported that coping measures are associated with relapse. An alternative explanation could be that the inability to cope does not reflect a lack of behavioral repertoire, but a lack of motivation to engage in healthy behavior. To improve the methodological rigor of studies on the effects of CBT, four areas must be addressed: measures, treatment, design, and populations. There is a need to improve strategies for measuring CBT mediators. For example, future studies should test treatments that are based on functional analysis of individual patients and are long enough to ensure adequacy of coping skills.

Interpersonal and 12-step programs were shown to purportedly improve avoidance methods as well as stronger interpersonal skills facilitating social support and prevent relapse (Donovan et al., 2013; Easton et al., 2007; Finney et al., 1998; Getter et al., 1992; Kelly et al., 2020). The behavioral skills necessary to manage unpleasant feelings and other drinking-related triggers are not improved by these methods. Since alcoholics typically have a poor perception of their QoL, those who use avoidance as a coping mechanism are more likely to experience stress from emotions of guilt, failure, and discontentment. People often lack social judgment, are impulsive, struggle to deal with change and interpersonal issues, lack planning insight, and have poor long-term psychological adjustment because they are oblivious of their problems (Karlsson et al., 2021).

Modulating brain rhythmic activity is yet another area of investigation by scientists and medical professionals as a possible treatment for alcoholism-related alterations in brain electrophysiology (Fielenbach et al., 2018; Jurado-Barba et al., 2020; Porjesz & Begleiter, 2003; Rangaswamy et al., 2002, 2003; Zhang et al., 2023). Treatment possibilities aimed at regulating brain activity, as explored by Vukadinovic et al. (2024), Dalkner et al. (2017), and Cox et al., (2016) hold potential in altering experiences and behaviors associated with alcohol-related concerns. By combining CBT-facilitated mind-training with neurofeedback techniques (Chiu et al., 2024, including stress management (via the Peniston-Kulkosky alpha-theta protocol) or cognitive enhancement training (using the Scott-Kaiser Modification Beta-SMR), a balanced integration of biological, psychological, and social dimensions in addressing the disorder may be achieved. Ros et al. (2014) found that this approach enhances long-term brain plasticity, enabling intentional control over brain oscillations. Employing these techniques collectively could potentially enhance memory, focus, emotional control, stress-coping skills and self-regulation (Ko & Park, 2018).

Consistency management for drug use and combined psychosocial treatments (e.g., CBT + cue exposure) for alcohol use have been shown to have the maximum treatment results in treatment trials in case of male patients (Monti et al., 1993). When comparing different CBT or RP strategies, there was some indication that CM approaches had more evidence-based support (Rawson et al., 2002). Meeting short-term objectives for abstinence was possible with the majority of evidence-based therapies.

Behavioral couple therapy (BCT) is a specialized approach planned to address issues with alcohol use, resulting in notable decreases in alcohol intake and enhancements in conjugal prosperity. (Epstein & McCrady, 1998). BCT as a standalone treatment, without CBT, was linked to a high rate of treatment retention (Stanton & Shadish, 1997). This may be because the patient's desired support network and home environment were successfully included into the treatment plan.

By conducting this scoping review, we filled in a potential area of future research on QoL and its importance to even consider preventive measures in

nonclinical populations by employing an adjuvant approach to psychotherapy.

Preventative measures, education on the importance of self-monitoring, and access to counselling services are key to enhancing psychosocial aspects for those with hazardous alcohol use outside of a clinical context.

Harmful alcohol use is classified not only by observable drinking patterns, but also by the user's emotional, physical, spiritual, social, and behavioral responses to its effects. These effects span numerous areas that could be carefully investigated in the future by means of a comprehensive assessment of the psychosocial domains (Dutra et al., 2008). Hence, the evaluation of QoL can serve as both an evaluation and a diagnostic tool, with each purpose employing a unique set of outcome characteristics to identify modifications in pattern of behavior (such as gagging motivation as an outcome measure in different stages of change, attitude change, knowledge of consequences, self-efficacy, perceived social support).

Conclusion

Based on the findings and discussion, it was determined that individuals with harmful alcohol use have poor coping mechanisms and experience detrimental psychological effects. In addition, there is a decreased motivation to sustain the behavioral modifications that lead to sobriety and a higher likelihood of relapse. The underlying evidence on combined psychotherapeutic techniques intended to achieve short-term treatment goals are reported in this review paper. In order to achieve long-term objectives, it is recommended that future study consider potential synergistic effects and make use of research findings regarding the most effective combinations of psychotherapy. Furthermore, the understanding of the methodological foundations of neurofeedback and its potential behavioral benefits in both experimental and clinical settings, particularly when used in conjunction with psychoeducation (PE), motivational enhancement therapy (MET), and other relevant psychotherapeutic approaches, remains limited. It is highly advised to incorporate neurofeedback training into comprehensive alcohol treatment plans in future studies. To support individual's assimilation of the changes derived from neurofeedback training, this approach involves introducing them to neurofeedback, elucidating the arousal model, conducting assessments, and closely overseeing and adjusting protocols.

Strength and Limitations

Comprehensive search criteria were used, and a substantial number of relevant studies were found. In a methodical and thorough manner, the authors screened the titles and abstracts. The authors took extra precautions to prevent the loss of significant studies by screening the full texts of publications, as well as using reference lists and holding discussion meetings. Unfortunately, some potentially important records may have been missing since studies published in languages other than English were not included. There were nine databases used in the search, thus it is likely that more were missed. However, experienced academic librarians provided guidance on the databases to use and the search terms to use in order to get the widest possible coverage of the population, concept, and context.

Author Disclosure

The authors affirm that there are no conflicts of interest regarding the research, authorship, and publication of this article. Furthermore, there are no financial interests or benefits associated with this research.

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Understanding Migraine: Epidemiology, EEG Abnormalities, and the Potential of Neurofeedback Training

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Abstract

Introduction. Migraine is a prevalent neurovascular disorder with a significant impact on individuals' quality of life. In this paper, we focus particularly on electroencephalogram (EEG) studies, and the ability of that modality to detect abnormalities in brain waves and provide insights into migraine pathophysiology. Neurofeedback training (NFT) as a potential therapeutic approach for migraine management is also explored. **Methods**. The manuscript provides a review of relevant literature on the epidemiology, classification, pathophysiology, and measurement techniques related to migraine. **Results**. Epidemiological studies highlight the high prevalence of migraine. EEG studies demonstrate delta and beta wave variations in people who experience migraine. Functional connectivity studies using EEG and functional magnetic resonance imaging (fMRI) suggest involvement of specific brain regions, including the prefrontal cortex, anterior cingulate cortex, amygdala, and insular cortex, in migraine pathophysiology. NFT studies indicate promising outcomes in reducing migraine frequency and severity. **Conclusion**. Migraine is a complex disorder with multiple subtypes and triggers. Advances in understanding its pathophysiology suggest the involvement of cortical and brainstem mechanisms, as well as cortical spreading depression. EEG abnormalities provide valuable insights into the neurobiological dysfunctions associated with migraine. NFT shows promise as a noninvasive and personalized treatment option. Future research should further investigate the mechanisms underlying EEG abnormalities and continue to develop effective interventions for migraine management.

Keywords: migraine; electroencephalogram (EEG); neurofeedback training (NFT); functional connectivity; brain waves; EEG abnormalities

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Epidemiology of Migraine

Migraine is a neurovascular disorder and a leading cause of disability, affecting more than one billion people worldwide (Ashina et al., 2021). The percentage of Americans experiencing migraine is estimated at about 15% (Peters, 2019). Head pain or headache was cited as the fifth leading cause of emergency department (ED) visits in the United States (Smitherman et al., 2013). Sudden or severe headache accounts for 3.5 million ED visits per year in the United States (Yang et al., 2022). Migraine significantly impairs many individuals' quality of life and ability to participate in social, work, and family activities (Peters, 2019).

Age, gender, and ethnicity are nonmodifiable risk factors associated with migraine occurrence. As opposed to most other chronic conditions, migraine tends to affect relatively healthy individuals that are young or middle-aged. Migraine prevalence was found to be highest among those between 18 to 44 and lower as people age (Peters, 2019). Women are more prone to self-reporting migraine or severe headache. In 2015, the rates were highest among American Indians and Alaskan Natives, when

compared with Whites, Hispanics, or Blacks. High prevalence was also found among people who are unemployed, individuals with family income below the poverty line, older adults, and people with disabilities (Burch et al., 2018). Migraine is linked to increased risk for other physical and psychological comorbidities, and this risk increases with headache frequency and severity. Migraine and severe headache are a major public health issue.

Introduction to Migraine

Migraine is a complex neurological disorder characterized by episodes of moderate to severe headache. It is mostly unilateral and tends to be associated with light and sound sensitivity, in addition to nausea (Pescador Ruschel & De Jesus, 2022). Migraine has a strong genetic influence, but a pattern of inheritance has yet to be identified. It is uncertain which genes and loci are implicated in migraine pathogenesis (Pescador Ruschel & De Jesus, 2022). The complex genetic component likely interacts with environmental factors to influence susceptibility and symptoms of the disease in affected individuals.

Migraine can be subdivided into multiple classifications. The first is migraine without aura, which is the most prevalent type. These occur in about 75% of migraine cases, consisting of a recurrent headache attack lasting a few hours or days (Pescador Ruschel & De Jesus, 2022). Aura is a group of sensory, motor, and speech symptoms that tend to signal warnings that a migraine attack is about to occur (Shankar Kikkeri & Nagalli, 2022). These symptoms are reversible and include seeing bright lights or blind spots, numbing, or tingling of the skin, changing of speech, smell, or taste, and ringing of the ears (Pescador Ruschel & De Jesus, 2022). Migraine with aura consists of recurrent and fully reversible attacks lasting minutes, with multiple unilateral symptoms (Shankar Kikkeri & Nagalli, 2022). Chronic migraine is another subtype, characterized by a headache that occurs at least 8 or more days in a month for more than 3 months (Pescador Ruschel & De Jesus, 2022).

Triggers are common in the development of migraine headaches. Stress is the most probable factor, followed by hormonal changes in women, skipped meals, lack of sleep, odors, and exposure to light (Park et al., 2016).

For a long time, migraine was considered to be a vascular disorder. The throbbing, pulsating quality associated with headaches was thought to be caused by mechanical changes in vessels (Mason & Russo, 2018). Aura was said to be produced by vasoconstriction and headache by vasodilation (Pescador Ruschel & De Jesus, 2022). This theory is no longer considered viable. Currently, a new explanation for the pathophysiology of migraine is being offered, which suggests that multiple primary neuronal impairments lead to the intracranial and extracranial changes that produce migraines (Pescador Ruschel & De Jesus, 2022).

One postulated mechanism is cortical spreading depression (CSD), an electrophysiological phenomenon characterized by a slowly propagating wave of altered brain activity, involving dramatic changes in neuronal, vascular, and glial function (Charles & Baca, 2013). CSD is now widely thought to be the mechanism by which migraine with aura occurs (Cozzolino et al., 2018). In migraine without aura, it is hypothesized that CSD occurs in areas like the cerebellum, where depolarization is not consciously perceived (Takano & Nedergaard, 2009).

There is significant imaging and clinical evidence for changes in cortical activity among migraineurs (people who experience migraine; Charles & Brennan, 2010). For instance, visual changes tied to migraine aura likely rise from altered function of the occipital lobe, corresponding with the primary visual cortex. Migraineurs may additionally undergo cortical sensory, language, motor, or other cognitive dysfunction (Dai et al., 2021). There is also strong support for the brainstem's role in the pathophysiology of migraine (Goadsby et al., 2017). Autonomic symptoms, along with nausea and vertigo, may be due to changes in the signaling of the brainstem. The brainstem is a key region that receives input from the trigeminal nerve, which carries pain signals from the head and face. During a migraine attack, there is evidence to suggest that the brainstem's pain-modulating circuits may malfunction, leading to an amplification of pain signals and a decreased ability to inhibit pain (Charles & Brennan, 2010). This dysfunction may contribute to the severe and debilitating headache experienced in migraines.

The sequence of activation of different brain areas in migraine continues to remain uncertain. One hypothesis is that cortical activation precedes brainstem activation, due to the typical occurrence of migraine aura before migraine headache (Charles & Brennan, 2010). Brainstem activation has also been shown to evoke changes in cortical blood flow, which raises the possibility for the opposite

sequence. It is also possible for both brain regions to be activated at the same time. This is supported by clinical observations in people who experience symptoms without any clearly defined order. Regardless of the order of activation, there is significant evidence to suggest that cortical and brainstem mechanisms are involved in the development of different kinds of migraine (Charles & Brennan, 2010).

Measurement Techniques

Multiple approaches have been taken to explore the various aspects of migraine pathophysiology, including musculoskeletal impairments, neuroendocrine signaling, and neurological measurements. Physical examination tests focusing on the cervical musculoskeletal system have been used to differentiate between migraine, secondary headaches, and asymptomatic individuals (Anarte-Lazo et al., 2021). These tests encompassed measures such as range of motion, muscular strength and endurance, tenderness palpation, proprioceptive measures, and balance assessment. Such examinations can help rule out other underlying conditions that mimic migraine symptoms.

Neuroendocrine signaling has also been investigated in relation to migraine pathophysiology. Insulin, glucagon, and leptin, which play roles in appetite and glucose regulation, have been found to influence trigeminovascular nociceptive processing and neural activity in the trigeminocervical complex and hypothalamus. These peptides have the potential to modulate specific neural networks relevant to migraine and contribute to the development of migraine attacks (Goadsby et al., 2017).

Functional magnetic resonance imaging (fMRI) has frequently been used to investigate the neural mechanisms of migraine (Shi et al., 2020). Resting-state fMRI is used to explore the functional connectivity between brain regions. This is measured by fluctuations of blood-oxygenation-level-dependent (BOLD) signals (Chong et al., 2019). Previous research has heavily focused on using fMRI measurements to show that migraine and headache disorders are associated with abnormal functional connectivity of many brain regions. These include regions associated with pain processing, along with many core resting-state networks, such as attention, salience, sensorimotor, executive, visual, limbic, and default mode networks (Chong et al., 2019). Functional MRI studies have so far enhanced our understanding of hypersensitivities in migraine, including the identification of brain regions and networks which are associated with abnormal processing of sensory stimuli. This kind of sensory processing is a key feature of migraine, in which individuals are exposed to olfactory, visual, and auditory stimuli that trigger migraine attacks. Most fMRI studies are focused on the interictal phase, which is the period between migraine attacks. These studies have shown consistently abnormal brain responses in the interictal phase to sensory stimuli, absence of normal habituating response, and atypical functional connectivity of the main sensory processing regions among migraineurs (Schwedt et al., 2015). Since migraine is mainly a disorder of brain function, fMRI studies continue to remain useful in studying the underlying mechanisms of migraine. The remainder of this review will focus on another promising method of measuring brain functional connectivity in headache disorders, specifically the use of electroencephalograms (EEGs).

Historically, EEG changes have been a subject of interest in studying migraineurs, with varying reports of definitively abnormal EEG rhythms (Sand, 1991). While some studies have indicated normal EEG findings in individuals with migraines, others have observed slight excesses of different EEG rhythms. These discrepancies in findings could be attributed to differences in patient populations, methodology, and the timing of EEG recordings in relation to migraine attacks. Modern approaches utilizing EEG frequency analysis and topographic brain mapping have proven valuable in exploring these abnormalities (Sand, 1991).

During visual aura, specific EEG changes have been noted in some migraine cases, including slow-wave activity across all cortical areas and a decrease in background activity amplitude (Bjørk et al., 2009) Nonetheless, it is essential to acknowledge that not all migraineurs experience these EEG abnormalities during aura, and normal EEGs have been reported in other cases (Bjørk et al., 2009). Among the most consistent EEG abnormalities recorded in migraineurs are the presence of unilateral or bilateral delta activity during attacks of migraine with disturbed consciousness and hemiplegic migraine (Sand, 1991). This abnormal delta activity, characterized by slow waves in the EEG, may offer valuable insights into the underlying mechanisms of these specific types of migraines. Additionally, EEG frequency analysis studies have consistently demonstrated significant and consistent variability in delta and beta waves among migraineurs (Sand,

1991). Delta waves, associated with slow-wave sleep, have been linked to abnormal brain activity and neuronal synchronization in migraineurs. Meanwhile, the variability observed in beta waves, which are associated with alertness and active cognition, potentially reflects changes in brain excitability and sensory processing in individuals with migraines.

While EEGs may not be the most specific tool for diagnosing migraines, they serve as a valuable platform for studying brain wave patterns and abnormalities that can enhance our understanding of migraine pathophysiology and explore potential treatment options, particularly for chronic migraine and headache patients (de Tommaso, 2019). EEG recordings can help identify abnormal brain wave patterns, such as slow waves, sharp waves, and excessive high-frequency beta activity, which may be associated with migraines. By analyzing EEG data, researchers can gain insights into the functional connectivity and network abnormalities in the brain regions involved in migraine. In addition, it is much more accessible, portable, and requires fewer resources than MRI. In line with observed EEG abnormalities, EEG-based neurofeedback training (NFT) has emerged as a potential therapeutic approach to modulate brain activity and potentially reduce the frequency and severity of migraines (Martic-Biocina et al., 2017). This approach aims to target and regulate specific abnormal brain wave patterns associated with migraines, providing a means for people to learn to self-regulate brain activity and potentially alleviate symptoms.

Experimental Studies

EEG changes have frequently been noted among migraineurs. Such changes include generalized slowing of activity, along with sharp and spike waves (Bjørk et al., 2009). Despite the practically equal number of reports indicating normal and abnormal findings, EEG frequency analyses in common and classic migraine patients continue to receive more and more attention (Bjørk et al., 2009). Neufeld et al. (1991) studied the EEGs of otherwise healthy participants, 18–28 years of age. This was divided among patients with common migraine, classic migraine, and age-matched controls. EEG findings in all three groups indicated mild nonspecific slowing (Neufeld et al., 1991). Sowndhariya and Anandan (2017) conducted another study to investigate abnormalities in the electroencephalography of migraineurs. Participants were 100 migraineurs, 10–40 years of age. About 29% of those studied were found to have EEG abnormalities. When comparing migraine with aura and migraine without aura, those exhibiting the former had a higher percentage (~15%) of EEG abnormalities. Migraine with aura showed changes in the frontal and occipital regions. Migraine without aura patients showed changes in the frontal, occipital, and temporal regions. The most common abnormality was slow waves followed by sharp wave changes (Sowndhariya & Anandan, 2017). It also showed a higher prevalence of migraine without aura, compared to migraine with aura (Sowndhariya & Anandan, 2017).

Rho et al. (2020) conducted a retrospective analysis which reviewed the medical records of 259 pediatric patients with headaches that underwent EEGs over a time span of 3 years. Their methods involved comparing the EEG abnormalities by type of headache and characteristics of wave findings, along with a comparison of the clinical observations between those with normal versus abnormal EEGs. EEG was recorded when the physical examination or medical history of a patient revealed signs of a suspected seizure, such as visual or brainstem auras, continued headaches, or lack of response to medical treatment. Those with history of epilepsy, seizures, significant abnormal brain imaging, or cognitive impairment were excluded from the study. Of the 259 participants, only about 12% showed EEG abnormalities. The Pediatric Migraine Disability Assessment score, used in this study to evaluate the severity of headaches, was significantly higher in the abnormal EEG group, when compared to the normal group. Migraines with aura were found to exhibit more EEG abnormalities than the other types of headaches (including migraine without aura, probable migraine, tension-type headache, and probable tension-type headache). These findings suggest that people with migraines with aura might have overlapping pathophysiologic mechanisms with other neurologic disorders, such as epilepsy. The authors indicate that these people may benefit from electroencephalography in distinguishing between different headache types (Rho et al., 2020).

Exploring Brain Localizations and Connectivity

The specific brain areas that account for the functional abnormality of migraine have yet to be fully elucidated (Rho et al., 2020). Rather than a replacement for traditional fMRIs, EEGs can be used as a supplemental tool in understanding which areas are most involved in the pathophysiology of migraine.

Frequent migraine attacks may be associated with abnormalities in certain brain regions involved in pain processing. Increased functional connectivity has been cited in cerebral areas such as the prefrontal cortex and right rostral anterior cingulate cortex (Ong et al., 2019). Researchers cited stronger connections between the medial prefrontal cortex and both the posterior cingulate cortex and bilateral insula (Taylor et al., 2009).

The anterior cingulate cortex (ACC) is a key structure in the pain processing network. It is involved in descending pain modulation, emotional dimensions of pain, and attention to pain, and it has been implicated in the functional abnormalities of pain-related disorders, including severe headaches and migraine (Edes et al., 2019). A pilot study published in 2019 found that increased sensitivity of the right pregenual ACC (pgACC) to increased serotonin levels in the brain is linked to recurring headaches, along with increased stress sensitivity and emotional aspects of pain. This suggests that pgACC activation might increase during migraine attacks, which may contribute to the suffering element of pain associated with migraine (Edes et al., 2019).

The amygdala is involved in nociceptive processing and emotional responses. Researchers have suggested that functional or structural abnormalities here might contribute to the worsening of pain and mood that occurs in those who suffer from migraine (Huang et al., 2021). They concluded that people with migraine without aura showed decreased connectivity from right amygdala to the right and left superior temporal gyrus and the right precentral gyrus. Effective connectivity between these regions is associated with lesser disease duration (Huang et al., 2021). This might explain the amygdala's role in pain modulation, processing, and duration of migraine. The prefrontal cortex is another region that is important in pain modulation and has been implicated in migraine disorders (Ong et al., 2019).

Another study showed increased functional connectivity between the insular cortex and the default mode network, along with frontoparietal regions (Yuan et al., 2012). The authors remarked on the need for reproducibility of these findings in additional studies. Only by doing so, can these studies be placed in a broader context of understanding functional abnormalities that contribute to migraine and other trigeminal pain disorders.

Neurofeedback Training

Biomedical treatments are not always fully effective in managing the symptoms of chronic pain, including migraine. NFT is one therapy method of targeting the physiological brain abnormalities associated with pain processing (Marzbani et al., 2016). NFT is a noninvasive therapy that aids in regulating brain activity (Marzbani et al., 2016). It is a form of biofeedback that provides users with real-time information regarding their brain activity, allowing them to learn ways to directly change this activity and improve their experience of health and comfort (Roy et al., 2020). The user starts by wearing small electrodes on the scalp that monitor brain activity during the training session. Generally, users will engage by playing a game or watching a video. Measured changes in brain activity are fed back to the user, and every time the targeted brain regions exhibit EEG abnormalities, the game or video will stop. Through this process, the brain gradually learns to change its electrical activity to reduce interruptions and obtain a more cohesive perceptual experience. The objective is to cancel out specific functional abnormalities as the brain recruits new resources, ultimately reducing associated disturbances, such as those involved in pain processing (Roy et al., 2020).

NFT can be performed either by using brain activity measured through EEG or fMRI (Marzbani et al., 2016). Empirical studies have utilized both EEG and fMRI technology to examine the use of NFT in relation to pain. Most of these studies used EEG-based neurofeedback training, due to its lower cost and easier accessibility. A wide range of NFT methods have been used to increase, decrease, or moderate brain activity in specific areas associated with pain (Roy et al., 2020). In a recent systematic review, Roy et al. found an overall positive outcome for this approach (Roy et al. 2020). They concluded that NFT has the potential for reducing pain and improving other behavioral and cognitive outcomes in individuals experiencing chronic pain (Roy et al., 2020). More research is needed however to recommend protocols or methods of therapy that may be most effective.

Martic-Biocina et al. (2017) reported a successful case of biofeedback training, including neurofeedback, in treating a 25-year-old woman with painful migraines. The treatment consisted of 25 sessions using three forms of biofeedback therapy. Administered protocols consisted of the following: inhibition of theta waves (4–9 Hz), enhancement of low beta waves (12–15 Hz), and inhibition of high

beta waves (22–30 Hz). The woman experienced a gradual reduction in pain severity and migraine frequency over 4 months, and she no longer required analgesics (Martic-Biocina et al., 2017). While this case highlights the positive potential of biofeedback therapies for migraine, further research with larger sample sizes and different protocols is needed to establish the best treatment method (Martic-Biocina et al., 2017).

Walker et al. (2011) conducted a study comparing NFT and drug therapy outcomes in 71 people with recurrent migraine without aura. Upon quantitative electroencephalogram (qEEG) screening procedure, all results showed excessive high-frequency beta activity in one to four cortical regions (Walker, 2011). About a third of the participants chose to undergo drug therapy, whereas the remaining selected to participate in NFT. NFT consisted of decreasing high-frequency beta activity in the 21–30 Hz range and increasing 10 Hz activity, over five sessions for each affected region. Among the NFT group, 54% experienced complete cessation of migraine headaches. Thirty-nine percent experienced a decrease in migraine frequency of more than 50%. Four percent experienced a decrease in headache frequency of more than 50%. Only one person did not experience a reduction in migraine frequency. Meanwhile, in those who chose drug therapy, 65% experienced no change in migraine frequency. Twenty percent of this group experienced a reduction of less than 50%, and 8% reported a reduction of greater than 50%. This study seems to provide promise for the efficacy of qEEG-guided neurofeedback in reducing or abolishing headache frequency in those with recurring migraine. However, one alternative explanation is that the self-selecting, nonrandomized allocation to groups confounds the results, whereby those who chose the “experimental” treatment were more sensitive to placebo effects.

Conclusion and Future Directions

In conclusion, migraine is a complex neurological disorder with a significant impact on individuals worldwide. While its exact pathophysiology remains unclear, advancements in research have shed light on various aspects of the condition. Epidemiological studies have revealed the high prevalence of migraine, particularly among specific demographics. This highlights the need for further investigation into understanding the underlying mechanisms and developing effective interventions.

In terms of measurement, EEG has emerged as a valuable tool in studying migraine. EEG abnormalities, such as delta and beta wave variations, have been observed in migraineurs. These findings provide insights into the neurological dysfunctions associated with migraine, particularly during attacks and specific migraine subtypes. Additionally, the identification of brain areas, including the cortical, brainstem, and sensory processing regions has enhanced our understanding of the neurobiological basis of migraine.

Furthermore, NFT shows promise as a potential intervention for migraine. By targeting abnormal brain activity through real-time feedback, neurofeedback has demonstrated positive outcomes in reducing migraine frequency and severity. This approach holds potential for personalized and noninvasive treatment options, emphasizing the importance of further research in this area.

To advance our knowledge of migraine, future studies should focus on investigating the specific mechanisms underlying the observed EEG abnormalities and their relationship to clinical manifestations. Additionally, exploring the potential of neuroendocrine function and musculoskeletal assessments could provide a comprehensive understanding of migraine's multifaceted nature.

In summary, the integration of epidemiological data, EEG analysis, and the identification of key brain areas in migraine research presents a valuable framework for unraveling the pathophysiology of this complex disorder. With ongoing advancements in technology and treatment modalities like NFT, there is optimism for improving the management and quality of life for individuals affected by migraine.

Author Disclosure

M. Keane is Director of the Actualise Psychological Services Clinic which provides NFT services. L. Abdurrahman is a Medical Student who served an internship at the Actualise Clinic.

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The Confluence of Genetic Factors and Neurotransmitter Dysregulation in Schizophrenia: A Comprehensive Review

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Abstract

Schizophrenia is a psychiatric condition characterized by a profound mental illness that impairs an individual's capacity to function in both social and cognitive domains. Individuals diagnosed with schizophrenia display psychopathological symptoms that are categorized as positive, negative, and cognitive. According to some estimates, nearly 98% of people with schizophrenia have cognitive deficits and perform below their expected cognitive capacity, which depends on their premorbid intelligence and parental educational attainment. Schizophrenia affects approximately 24 million individuals worldwide, which translates to a prevalence rate of 0.32%, or 1 in 300 people. In the interim, the prevalence of the condition among adults is 0.45% or 1 in 222 individuals. The heritability of schizophrenia is widely recognized to be significant, ranging from 60% to 90%. As a result, identifying specific risk genes is crucial for comprehending this disorder's underlying causes and physiological mechanisms. The pathophysiology of schizophrenia involves the dysregulation of various neurotransmitters and their pathways; various environmental factors, and heredity are also associated with it. Dopamine and other neurotransmitters linked with it, like serotonin and glutamine, have been the main drug targets of schizophrenia. The purpose of this review is to offer a comprehensive understanding of the etiology, pathophysiological mechanisms, and manifestations of schizophrenia. Overall, there is still insufficient evidence to prove the underlying cause of the pathogenesis of schizophrenia. Nonetheless, it is important to recognize the unknown and unidentified reasons underlying schizophrenia.

Keywords: schizophrenia; mental disorder; psychosis; the genesis of schizophrenia

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Introduction

History and Epidemiology

Schizophrenia is a psychiatric condition with a debilitating mental illness that affects one's ability to operate in both the social and mental spheres. In 1896 Emil Kraepelin elucidated this mental disorder as *dementia praecox*. Later in 1911, Eugen Bleuler redefined it as the term *schizophrenia*. Bleuler, a Swiss psychiatrist, first used the word schizophrenia in 1908 (Hany et al., 2024). This disease was defined as a set of symptoms that, in Bleuler's perspective, were linked to a fundamental shift in how people perceived reality. Dementia praecox was a term used frequently before Bleuler's research and was believed to be early-onset dementia. Since the time of Bleuler's discovery, schizophrenia has undergone a tremendous change (Uno & Coyle, 2019). After release of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) in the year 1952, schizophrenia was officially established as a separate diagnostic category. Moreover, at present *The International Classification of Diseases, Eleventh Edition* (ICD-11) and the *Diagnostic and Statistical Manual of Mental*

Disorders, Fifth Edition, (DSM-5) outline the current diagnostic criteria for schizophrenia.

According to ICD-11 (World Health Organization [WHO], 2022) "schizophrenia is characterized by disturbances in multiple mental modalities, including thinking (e.g., delusions, disorganization in the form of thought), perception (e.g., hallucinations), self-experience (e.g., the experience that one's thoughts or behavior are under the control of an external force), cognition (e.g., impaired attention), volition (e.g., loss of motivation), affect (e.g., blunted emotional expression), and behavior (e.g., bizarre behavior)" (Gaebel et al., 2020). The characteristics of schizophrenia are moreover the main criteria of diagnosis, as per ICD-11 for 1 month any two of the above-mentioned symptoms must be experienced the majority of the time. Similarly, the publication of DSM-5-TR (American Psychiatric Association, 2022) defined current criteria for diagnosing schizophrenia, which require the presence of a minimum of a pair of the symptoms that follow: delusions, hallucinations, disordered thinking (speech), disorganized/catatonic behavior, or negative symptoms. Furthermore, these symptoms need to be actively present for about or more than just 1 month, and the significant impairment in functioning for about 6 months. DSM-5-TR also states that these symptoms shall not be a result of substance abuse or any medical conditions (Biedermann & Fleischhacker, 2016).

Symptoms, Causes, and Risk Factors

Schizophrenia is a psychiatric condition that disrupts an individual's cognitive processes, emotional responses, behavioral patterns, and perception of reality (Rahman & Lauriello, 2016). People with schizophrenia exhibit psychopathological symptoms classified as positive, negative, and cognitive (Table 1).

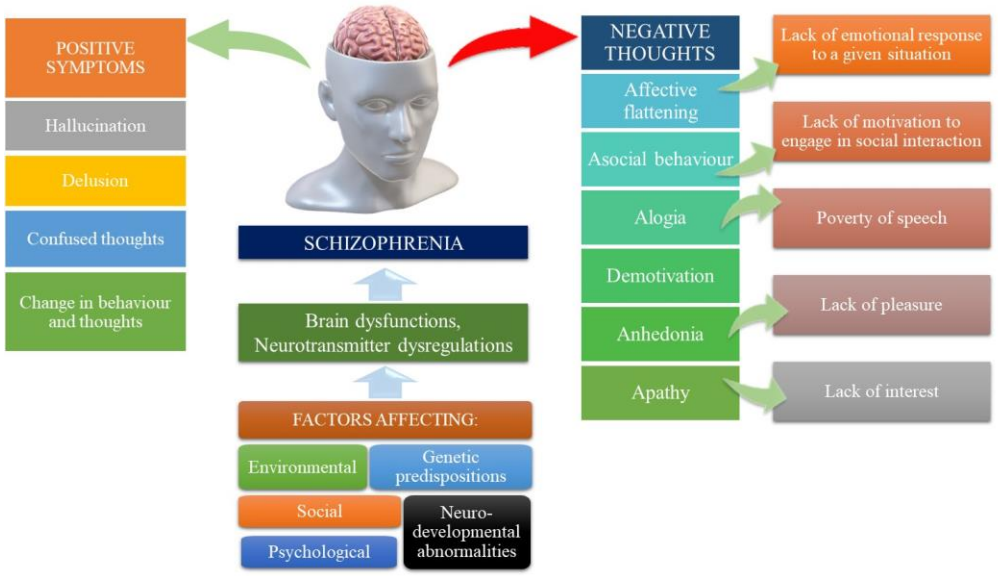
Table 1

Classification of the Symptoms of Schizophrenia

Category	Symptom	Characteristics	Reference
Positive	Hallucinations (e.g., auditory, visual)	Presence of abnormal experiences or perceptions	(Andreasen et al., 1994)
	Delusions (e.g., paranoid, grandiose)	Belief in false, irrational ideas or beliefs	
	Disorganized thinking and speech	Incoherent or illogical thought patterns	
Negative	Heightened emotions (inappropriate affect)	Expressing emotions not congruent with the situation	(Correll & Schooler, 2020; Mosolov & Yaltonskaya, 2022)
	Affective flattening (reduced emotional expression)	Restricted emotional range and lack of facial expressions	
	Alogia (poverty of speech)	Reduced speech output, minimal responses in conversation	
	Anhedonia (inability to experience pleasure)	Inability to derive pleasure from normally enjoyable activities	
	Avolition (lack of motivation)	Reduced motivation to initiate and sustain purposeful activities	
Cognitive	Social withdrawal and isolation	Avoidance of social interactions and withdrawal from relationships	(McCutcheon et al., 2023)
	Impaired memory and attention	Difficulty in maintaining attention, poor memory.	
	Impaired executive functioning (e.g., planning, organizing)	Difficulty in planning, decision-making, and organizing tasks	
	Impaired reasoning and problem-solving	Difficulty in logical reasoning and problem-solving	

Schizophrenia causes hallucinations that exhibit heterogeneity, encompassing a range of sensory modalities such as auditory, verbal, visual, olfactory, gustatory, and multimodal expressions, with auditory hallucinations being the most commonly reported (Llorca et al., 2016). Conceptually, an anomaly in functioning, such as delusional thoughts, hallucinations, or wildly disorganized thoughts or behavior, is regarded as one of the psychosis' positive symptoms (Khan et al., 2013). John Russell Reynolds described that negative symptoms are caused by the loss of "vital characteristics," which can lead to paralysis, anesthesia, and other abnormalities (Dollfus & Lyne, 2017). Typical negative symptoms include blunted affect, which refers to a reduction in emotional activity, anhedonia, which is characterized by an incapacity to encounter pleasure or joy, avolition (which is a lack of motivation), and apathy (which involves the suppression of emotion; Figure 1). Additionally, alogia (which is defined as a lack of speech) is also a common negative symptom.

Figure 1. *Factors Affecting and Symptoms of Schizophrenia.*



These symptoms are more prevalent than positive psychotic symptoms, vary less over time, and are significantly associated with poor psychosocial functioning. Patients are often seen as sluggish and deliberately disconnected by families and others because it is less evident that negative symptoms are signs of psychiatric disease (Wójciak & Rybakowski, 2018).

Based on premorbid intelligence and parental education levels, some estimates place the prevalence of these impairments in schizophrenia patients at close to 98%, which is below their projected cognitive function (Tripathi et al., 2018). A wide range of symptoms makes up this complex condition marked by mental, cognitive, and emotional stress. Schizophrenia affects approximately 24 million individuals worldwide, which equates to a prevalence rate of 0.32%, or 1 in 300 individuals. Conversely, the prevalence of the condition among adults is estimated to be 0.45% or 1 in 222 individuals (Patel et al., 2014). It is not as common as many other mental illnesses. Schizophrenia is known to be highly heritable (60–90%); therefore, identifying particular risk genes is essential for understanding its etiology and pathophysiology. Schizophrenia typically manifests during the late adolescent or early twenties period, with men experiencing its onset earlier than women. Individuals diagnosed with schizophrenia exhibit a significantly higher mortality rate, ranging from two to three times greater in comparison to the general population (Laursen et al., 2014). Until now, no particular cause has been identified for the progression of schizophrenia; however, researchers claim that multiple factors mentioned in Table 2, including physical, genetic, psychological, and environmental factors, contribute to this condition's development (Figure 1).

Table 2
Causes and Risk Factors Associated With Schizophrenia

Risk Factors	Causes	References
Genetic Factors	Family history of schizophrenia Specific genetic variations or mutations Complex genetic architecture, including common and rare genetic variants	(Trifu et al., 2020)
Neurobiological Factors	Neurotransmitter imbalances (e.g., dopamine, serotonin, glutamate) Structural brain abnormalities (e.g., enlarged ventricles) Altered brain function (e.g., impaired connectivity)	(Ross et al., 2006)
Prenatal and Perinatal Factors	Complications during pregnancy or birth Maternal infections, malnutrition, exposure to toxins, or stress	(Meli et al., 2012)
Psychological and Environmental Stressors	Severe stress or trauma during childhood or adolescence	(Stilo et al., 2011)
Childhood Trauma	Experiences of abuse, neglect, or trauma in childhood	(Popovic et al., 2019)
Cannabis Use	Heavy and frequent cannabis use during adolescence Particularly in genetically predisposed individuals	(Patel et al., 2020)
Infections and Immune Factors	Exposure to certain infections during pregnancy or early childhood Autoimmune conditions affecting the brain	(Benros & Mortensen, 2019)
Substance Abuse	Use of psychoactive substances (e.g., amphetamines, hallucinogens) Potential for triggering psychotic symptoms	(Khokhar et al., 2018)
Social Isolation	Lack of social support and social isolation	(Fulford & Holt, 2023)

Schizophrenia is characterized by widespread abnormalities across the brain. Notably, the inferior parietal lobule, superior temporal gyrus, prefrontal cortical areas, amygdala, medial basal ganglia, temporal lobe, corpus callosum, thalamus, and cerebellum exhibit the most persistent neurological changes (Tripathi et al., 2018). Increased awareness of mental health has facilitated the recognition and acceptance of mental disorders, including schizophrenia. Schizophrenia is a complicated and enigmatic disorder that is often subject to misinterpretation and widespread misconceptions.

Pathophysiology

Schizophrenia's pathophysiology entails the dysregulation of various pathways linked to brain function. The pathway is characterized by deviations in neurotransmission levels, either in the form of excessive or insufficient activity. Schizophrenia is characterized by alterations in the dopaminergic, glutamatergic, and γ-aminobutyric acid (GABA)ergic neurotransmitter systems, and the interactions between these receptors are implicated in the underlying pathophysiology of the disorder (Uher et al., 2019).

It has been observed that stimulants of the central nervous system, including amphetamines, increase dopamine release and induce psychotic symptoms. Similarly, positron emission tomography (PET) results of schizophrenia patients demonstrated enhanced dopamine activity in the striatum and midbrain regions of the brain (Howes & Kapur, 2009; Yang & Tsai, 2017). Studies conducted with the aid of PET imaging have demonstrated that schizophrenic patients manifest an elevated level of subcortical synaptic dopamine content (Kesby et al., 2018). The observation that heightened dopamine release is a fundamental factor contributing to psychotic symptoms has led to the inference that dopaminergic pathways represent the primary etiology of psychosis in individuals with schizophrenia (Stahl, 2018). The emergence of the D2 dopamine receptor (DRD2) gene has garnered attention. DRD2 is a transmembrane receptor that is a member of the G protein-coupled family and elicits intracellular signaling by impeding cyclic adenosine monophosphate (cAMP) synthesis (González-Castro et al., 2016).

Schizophrenia's etiology is believed to entail abnormal brain activity, particularly mesocortical dopamine levels. According to the glutamate theory, an excess in this neurotransmitter might result in motor symptoms that include agitation and restlessness (Egerton et al., 2020). Decreased activity of the dopaminergic system can also cause unpleasant symptoms, including anhedonia and apathy, which can lead to the onset of symptoms. The brain is comprised of four primary dopaminergic pathways, and it is hypothesized that schizophrenia's functional symptoms may be linked to reduced levels of mesocortical dopamine (Taylor et al., 2021).

Studies have demonstrated that individuals with heightened schizophrenia symptoms exhibit a greater likelihood of possessing mutations in genes associated with energy metabolism, such as the catechol-O-methyltransferase (COMT) gene (Wawrzczak-Bargieła et al., 2023). Schizophrenia is also linked to mitochondrial dysfunction and changes in how glial cells express themselves (Ni & Chung, 2020). It's been suggested that the absence of the schizophrenia gene in the brain may influence the emergence of symptoms and cognitive difficulties. Postmortem brains from persons with schizophrenia have been shown to exhibit alterations in glutamate receptors and synaptic plasticity, which may replicate symptoms experienced by those with the condition (Uno & Coyle, 2019).

Dysregulation in Neurotransmitter Pathways

The pathogenesis of schizophrenia is significantly influenced by neurotransmitters, which function as signal transmitters in the brain by communicating with each other through chemical compounds. Chemical synaptic transmission is caused by the release of neurotransmitters from presynaptic neural cells to postsynaptic receptors. Dysfunction in neurotransmitter receptors or imbalances in neurotransmitter concentrations can be a primary etiological factor in a range of neurological conditions, including but not limited to schizophrenia, depression, Alzheimer's disease, and other disorders (Bansal & Chatterjee, 2021). There are numerous primary neurotransmitters (Table 3); for example, epinephrine, norepinephrine, dopamine, and serotonin in the central nervous system for the proper functioning of human behavior, emotions, and the pathophysiology of several disorders (Hany et al., 2024). Along with the neurobiological system of the body, neurotransmitters tend to control blood sugar levels. Dopamine, serotonin, acetylcholine, GABA, glutamate, and norepinephrine are all neurotransmitters implicated in schizophrenia's pathogenesis. Dopamine is the most extensively studied neurotransmitter, garnering the highest degree of attention, followed by glutamate,

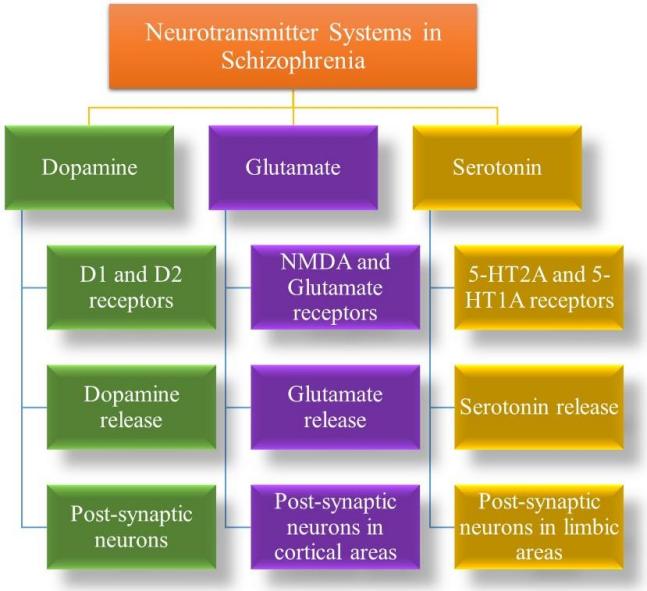
serotonin, GABA, and oxytocin. Schizophrenia has also been said to be linked with abnormalities in neuropeptides including neurotensin and cholecystokinin (Werner & Coveñas, 2010). The reason behind schizophrenia pathogenesis is because of dysfunctions in neurotransmitters like serotonergic alpha-adrenergic hyperactivity and dopaminergic hypoactivity (Figure 2).

Table 3
Neurotransmitters Involved in Schizophrenia

Neurotransmitter	Receptors	Implicated Brain Regions	Reference
Dopamine	DRD1 receptor, DRD2 receptor	Mesolimbic pathway (hyperactivity) and prefrontal cortex (hypoactivity)	(Luykx et al., 2017)
Serotonin	5-HT1A receptor, 5-HT2A receptor	Prefrontal cortex and limbic system	(Eggers, 2013)
Glutamate	NMDA receptor, AMPA receptor	Prefrontal cortex	(Hashimoto, 2011)
Gaba	GABAergic interneurons, GABA-A and GABA-B receptors	Prefrontal cortex	(Schoonover et al., 2020)
Acetylcholine	Muscarinic receptors (e.g., M1, M4) and nicotinic receptors (e.g., A7, α4β2)	Mesocortical pathway or the basal forebrain cholinergic system	(Jones et al., 2011)

It is believed that serotonin and glutamate may affect dopamine release, in the mesolimbic pathway there are dopamine neurons where 5-HT2A receptors are expressed thus by interacting with them serotonin contributes to dopamine activity (Stahl, 2018). Glutamate on the other hand interacts with N-methyl-D-aspartate (NMDA) receptors found on mesolimbic dopamine neurons. There is a chance that NMDA receptor hypofunction's activity is regulated by GABA hypoactivity and reduced glutaminergic activity (Kruse & Bustillo, 2022). Neurotransmitters have a significant impact on the maintenance of mental well-being, including the manifestation of schizophrenia as a mental disorder. Exploring the neurobiology of the neurotransmitter could facilitate the identification of the underlying etiology of schizophrenia and ultimately lead to the development of a viable remedy.

Figure 2. *Important Neurotransmitter Systems and Their Corresponding Receptors Highlight Their Contributions to the Network of Neural Signaling That Has Been Linked to the Development and Phenomenology of Schizophrenia*.



Dopamine

Dopamine's function (to transmit the signal along nerve fibers) makes it an important neurotransmitter, and its involvement in the dopamine hypothesis has become a popular researched theory of schizophrenia pathophysiology. Schizophrenic individuals often suffer from memory loss and thus fail to perform or contribute to the day-to-day chores. These are prominent symptoms of schizophrenia, caused because of disruptions in the dopamine pathway. Imaging studies of schizophrenic individuals' brains have an average of 5.8% increase in D2 receptors, which explains their behavioral hypersensitivity (Seeman, 2013). Since dopamine levels contribute to underlying symptoms, low levels of dopaminergic neurotransmissions in the brain may cause depression (Taylor et al., 2021). The enhanced level of dopaminergic neurotransmission in the mesolimbic pathway however is accountable for the manifestation of positive symptoms that include delusions and hallucinations (Stępnicki et al., 2018). Overactivity in the dopaminergic system can also cause disturbance in sleeping patterns in schizophrenic individuals (Ashton & Jagannath, 2020). Schizophrenic patients exhibit an elevation in the concentration of DRD2 within the striatum. Nevertheless, antipsychotic medications can be employed to manage this area. (Simpson et al., 2021).

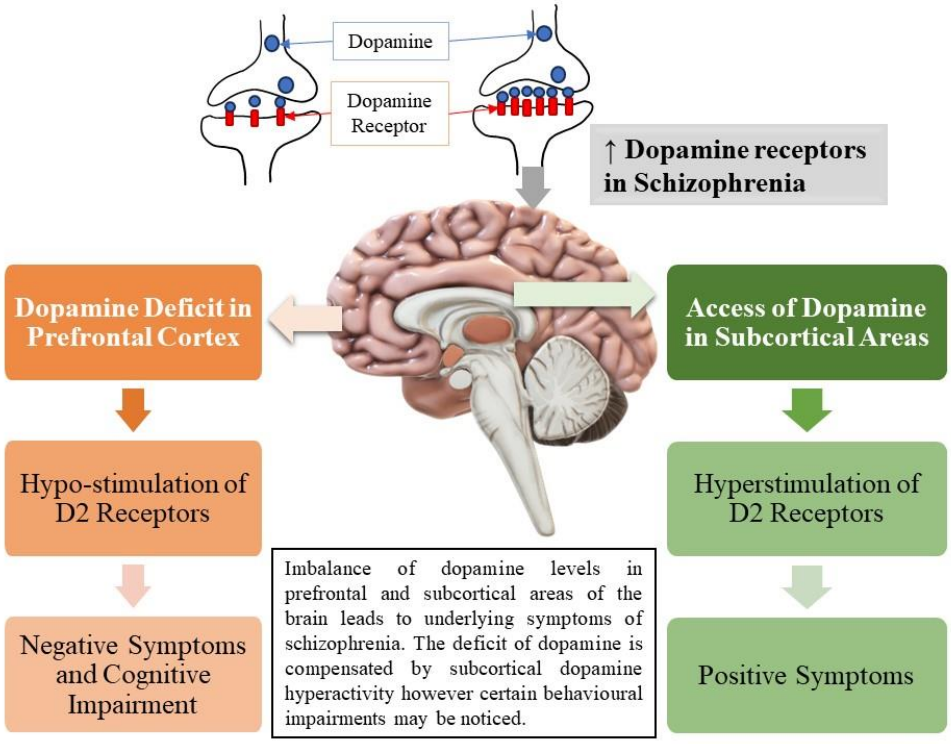
One of the principal treatments of schizophrenia includes antipsychotic medications that target and inhibit D2 receptors in the mesolimbic pathway, meanwhile reducing dopamine-related hyperactivity. In return, these medications tend to reduce the level of positive symptoms of schizophrenia, which gives more evidence for the pathophysiology of the condition (Bruijnzeel et al., 2014). Conversely, D1 receptors have a pivotal function in the regulation of dopaminergic transmission within the prefrontal cortex. Inadequate levels of D1 receptors may result in cognitive dysfunction and negative symptoms in individuals with schizophrenia (Howes & Kapur, 2009). By experimentally inducing striatal dopaminergic transmission, for example, administration of amphetamine can induce psychosis. Amphetamine acts on the dopamine neuron terminals, stimulating the release of higher levels of dopamine. This can elevate the likelihood of psychosis in individuals with schizophrenia, leading to the manifestation of positive symptoms associated with the disorder (Thompson et al., 2020). Enhanced (or imbalanced) transmission of dopamine in the mesolimbic pathway, which originates from the ventral tegmental area is assumed to be the main cause behind positive symptoms, which are supposed to initiate in the nucleus accumbent (Figure 3). Dysregulation of striatal dopamine signaling, which often has far-reaching implications on cortical function, may cause cognitive symptoms in people with dopamine

dysfunction, which are more commonly linked with positive psychotic symptoms (Simpson et al., 2021).

Serotonin

Another known neurotransmitter involved in the etiology of schizophrenia is serotonin (5-hydroxytryptamine or 5-HT). 5-HT surrounds the brain and is known to regulate mood, cognition, and perception. 5-HT in schizophrenia is responsible for causing negative and cognitive symptoms like apathy, anhedonia, and cognitive impairments (Pourhamzeh et al., 2021). There exist two contrasting theories regarding 5-HT regulating dopamine: according to one, serotonin influences dopamine release, while the other states that it may inhibit the release of dopamine in the mesolimbic pathway. Dopamine neuron activity in the striatum, which is involved in motor control and reward processing, is influenced by serotonin. Hence, the motor symptoms of schizophrenia may appear because of the disrupted dopamine system caused by serotonin pathway defects (Rogers, 2010). The central nervous system and peripheral tissue exhibit 14 different subtypes of serotonin receptors categorized as 5-HTx. A known 5-HT receptor, 5-HT2A, is widely known to contribute to the neurobiology of schizophrenia (Kantrowitz, 2020). In the postmortem study of schizophrenic patients, it was observed that along with 5-HT activity, there were 5-HT receptors and serotonin transporter (SERT) expressions as well (Pourhamzeh et al., 2021). 5-HT2A is well found in pyramidal neurons, while some of the 5-HT2A has NMDA glutamate receptors in colocalized form (Meltzer et al., 2003). In schizophrenic patients, the cortical 5-HT2A receptor is often at decreased levels while the 5-HT1A receptor is at increased levels (Meltzer et al., 2003). In schizophrenic individuals, the binding of serotonin to 5-HT2A in the prefrontal cortex regions is quite strong compared to healthy individuals. Because of this strong binding, this interaction may contribute to some distressing symptoms and cognitive deficits in schizophrenia (Quednow et al., 2020). Despite numerous studies, the current state of evidence is inadequate to substantiate the contribution of serotonin to schizophrenia's pathophysiology. However, it is noteworthy that certain 5-HT receptors, specifically 5-HT3 and 5-HT6, may serve as promising therapeutic targets for ameliorating the cognitive deficits and negative symptoms linked with this disorder (Liu et al., 2020).

Figure 3. *Schizophrenic Patients Exhibit Imbalanced Levels of Dopamine Neurotransmitters and Increased Expression of Receptors, Which Are Linked to a Range of Symptoms*.



Glutamate

One of the popular excitatory neurotransmitters present in the brain is known as glutamate. Its action is known to be mediated through receptors such as kainite, amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), and NMDA (Negrete-Díaz et al., 2022). The glutamate pathway starts from its synthesis by neurons, after synthesis, it is released into the brain from where glial cells take it up and transform it into glutamine so that it can be delivered back to the neurons for further synthesis (Nedergaard et al., 2002). This glutamate–glutamine cyclic pathway is quite important for maintaining glutamate homeostasis in the brain. While investigating schizophrenia pathophysiology different deviations of the glutamatergic system have been identified such as glutamate level variations, and changes in receptor expression and function. Subsequent decreases in the expression of NMDA receptors (NMDAR) and lower glutamate levels within various brain regions including the prefrontal cortex and hippocampus were reported in the postmortem examinations of schizophrenic sufferers (Padmanabhan & Keshavan, 2014). Decreased NMDAR expression and disrupted glutamate levels are associated with negative symptoms and cognitive deficit which are characteristic symptoms of schizophrenia, these may include apathy and anhedonia. However, positive symptoms like hallucinations and delusions are also expected to be an output of disruption in the glutamate system in schizophrenic individuals (Mei et al., 2018). According to (Homayoun & Moghaddam, 2007) theory, schizophrenia-induced psychosis could be attributed to the hypofunctional NMDAR that are located on GABA interneurons within the cerebral cortex. This hypofunction can result in excessive stimulation of downstream glutamate signaling and an excess of dopamine within the ventral tegmental and ventral striatum via the mesolimbic pathway. It was observed that schizophrenic patients might have high activity of glutamate within some brain areas at the developing stage of schizophrenia while at the progressing stage of schizophrenia, there might not be enough glutamate activity (Stahl, 2018). Some authors believe that if schizophrenia is caused by glutamates, then the dopaminergic system modulates the secretion of glutamate or vice versa, leading to the onset of schizophrenia symptoms. However, the symptoms might be different for example glutamate may cause negative while dopamine can cause positive symptoms (McCutcheon, Marques, et al., 2020).

Role of Neurotransmitter Receptors in Schizophrenia Pathophysiology and Treatment

To develop novel treatment methods to treat schizophrenia, it is crucial to comprehend the various underlying targets. Hyperactivation, disruption, and poor functioning of multiple brain networks, neurotransmitters, receptors, signaling pathways, and proteins may be a reason for the pathophysiology of schizophrenia. Studies indicate that schizophrenia primarily affects the dopaminergic and glutamatergic brain circuits.

Dopamine Receptor Inhibitor

The first antipsychotic drug against schizophrenia is chlorpromazine, discovered by French Navy anesthesiologist Henry Laborit (Sushilkumar et al., 2022). After the breakthrough discovery of chlorpromazine as a therapy for schizophrenia, the mesolimbic dopamine pathway in dopamine dysfunction has been a major focus for researchers (Boyd-Kimball et al., 2018). “Cariprazine, brilaroxazine (RP5063), F17464, lumateperone (ITI-007), brexpiprazole, and lu AF35700 (Table 4) are examples of new novel substances that primarily impact dopaminergic receptors but also have some action on serotonergic receptors” (Lobo et al., 2022). Among these inhibitors, cariprazine functions as dopamine D2 and D3 receptor agonist, exhibiting greater efficacy in addressing negative and cognitive symptoms of schizophrenia due to its heightened affinity for D3 receptors (Laszlovszky et al., 2021). F-17464 is another compound that exhibits a greater binding affinity towards D3 receptors (Cosi et al., 2017). Clozapine, a second-generation schizophrenia treatment, is the best drug because clozapine balances dopamine and serotonin, improving mood, thinking, and behavior (Siskind et al., 2016). All contemporary antipsychotics function by either antagonizing or stabilizing dopaminergic receptors using D2/D3 partial agonists; one such example is aripiprazole (Molitch, 2020; Strange, 2008).

Table 4
Potential Novel Compounds That Modulate the Dopaminergic System

Substance	Targets	Clinical Trial Phase	Reference
Cariprazine	Partial agonist D2 and D3, 5-HT1A, an antagonist at 5-HT2B, 5HT2A, H1, 5HT2C, α1 (low affinity)	Phase 3	(Garnock-Jones, 2017)
Brexpiprazole	5-HT1A, D2, D3 partial agonist, 5-HT2A, 5-HT2B, 5-HT7, α1A, α1B, α1D, α2C antagonist	Phase 3	(Hsu et al., 2017)
Brilaroxazine (RP5063)	D3 antagonist 5-HT1A partial agonist	Phase 2	(Bhat et al., 2018)
F-17464	Partial agonist D2, D3, D4, 5-HT1A and 5-HT2A antagonist 5-HT2B, 5-HT2C, 5-HT6 5-HT7	Phase 2	(Bitter et al., 2017)
Lu AF35700	Antagonist at 5HT2A, 5HT2, D1	Phase 3	(Fellner, 2017)

5-HT Receptor Inhibitors

The serotonin hypothesis is primarily concerned with the interaction of a hallucinogenic chemical LSD (lysergic acid diethylamide) and 5-HT. The psychotogenic effects of LSD, as well as the antipsychotic benefits of serotonin-dopamine inhibitors that include clozapine and risperidone, have piqued researchers' attention in the interplay of these two neurotransmitters as potential pathophysiological targets in schizophrenia (Yang & Tsai, 2017). Cariprazine, as previously stated, is an agonist for both dopamine and 5-HT receptors, as well as a partial agonist for 5-HT1A and an antagonist for 5-HT2B receptors (Citrome, 2016). According to Satiamurthy et al. (2023), tropisetron, ondansetron, and granisetron have been identified as potential adjunctive treatments for cognitive and negative symptoms. Ondansetron, an antagonist of the 5-HT3 receptor, is often prescribed to cancer patients experiencing nausea and vomiting as a result of chemotherapy. It may also be associated with an anti-inflammatory therapy for schizophrenia and has undergone Phase 3 trials for the treatment of schizophrenia's negative symptoms (Tsitsipa et al., 2022). The newly approved antipsychotic lurasidone is a strong antagonist of SERT type 5 (SERT5), which may have therapeutic significance for the affective aspects of psychosis (Citrome, 2011; Yang & Tsai, 2017).

Glycine Type 1 Inhibitors

During the latter half of the 1990s, a growing body of evidence indicated that the hypoactivity of NMDAR could be a cause of schizophrenia pathophysiology (Balu, 2016). The glycine type 1 (GlyT1) receptor is a molecule with a vital role in the central nervous system. The glycine-type transporters have been recognized as pivotal regulators of glycine concentrations, which govern the functioning of NMDAR in collaboration with D-serine. As a result, GlyT1-mediated transport has become a novel target for the treatment of schizophrenia, prompting the development of high-affinity inhibitors (Shahsavar et al., 2021). The purpose of developing a GlyT1 inhibitor is to enhance the NMDAR-mediated neurotransmission in schizophrenia. Two such inhibitor examples, sarcosine (N-methyl glycine) and RG1678 (a high-affinity compound), are being studied in clinical trials. The prototype GlyT1 inhibitor, sarcosine, has exhibited favorable outcomes for negative and positive symptoms among individuals diagnosed with schizophrenia. Biopterin, a selective and noncompetitive GlyT1 inhibitor, has undergone clinical evaluation for treating negative and cognitive symptoms that have been linked with schizophrenia (Umbricht et al., 2014). After the second phase of clinical trials, the result showed that biopterin reduces negative symptoms which were measured by the Positive and Negative Syndrome Scale (PANSS; Pawlak & Zakowicz, 2022). Another GlyT1 inhibitor currently in the CONNEX program of Phase 3 trials for safety and efficacy evaluation that enhances glutamatergic activity and promises to improve cognitive symptoms in schizophrenia is BI 425809 (Rosenbrock et al., 2018). ORG-25935 is another example of a second-generation antipsychotic; it's a synthetic drug with the property of selective inhibition of GlyT1 since it

includes a residue of sarcosine (Castner et al., 2014). The progress toward the development of novel classes of GlyT1 inhibitors that are not derived from sarcosine was because sarcosine-derived GlyT1 inhibitors were exhibiting unwanted side effects, including ataxia (loss of complete control of bodily movements), hypoactivity, and decreased respiration (Peiser-Oliver et al., 2022).

N-methyl-D-aspartate (NMDA) Receptor and Schizophrenia

The pathophysiology of schizophrenia has been observed to involve a substantial role of NMDA neurotransmission hypofunction. The administration of NMDAR blockers, like phencyclidine (PCP) and ketamine, to individuals without schizophrenia has demonstrated the involvement of NMDAR in the pathogenesis of schizophrenia (Gozzi et al., 2007). The usage of antagonists revealed that healthy individuals exhibited negative and psychotic symptoms as well as cognitive impairment resembling schizophrenia symptoms (Adell, 2020). Several enzymes, such as D-amino acid oxidase (DAAO), which are not widely recognized, are important in the development of schizophrenia. As previously stated, D-serine functions as a coagonist at NMDAR, facilitating its catabolism (Cho et al., 2016). The condition of NMDR hypofunction arises due to reduced levels of D-serine in both the blood and cerebrospinal fluid (CSF). As per the findings (MacKay et al., 2019) there is an increase in the level of DAAO among individuals diagnosed with schizophrenia. This suggests that augmenting the levels of D-serine may enhance the functioning of NMDAR, resulting in the inhibition of DAAO. The compounds sodium benzoate and luvadaxistat TAK-831 (Devoe et al., 2019) are two promising novel DAAO inhibitors for alleviating symptoms of schizophrenia (Kuo et al., 2022). Memantine, also known as 1-amino-3, 5-dimethyladamanantate, functions as a noncompetitive partial antagonist of NMDA channel receptors. The administration of memantine has been observed to enhance both negative symptoms and cognitive deficits, with a specific emphasis on the negative symptoms associated with schizophrenia. This suggests that memantine, when used as supplementary therapy in schizophrenia, can effectively alleviate negative symptoms and cognitive deficits (Kikuchi, 2020).

Phosphodiesterase Inhibitors

Some of the novel compounds belonging to phosphodiesterase inhibitors have been studied for their potential in treating schizophrenia. These include BI409306 and phosphodiesterase 10A (PDE10A) inhibitors such as MK-8189, Roflumilast, and TAK-063 (Amin et al., 2021). The study conducted by (Layton et al., 2023), reveals that MK-8189 exhibits strong inhibitory effects on PDE10A and is being investigated as a promising candidate for a new antipsychotic agent. In mammals, PDE10A is strongly expressed and localized in the striatum. DE10A exhibits robust expression and localization within the striatum of mammalian organisms. The inhibition of PDE10A presents a new approach to restoring deficient striatal output, a key factor in the pathophysiology of schizophrenia (Layton et al., 2023). As per Menniti et al. (2007), the inhibition of PDE10A is capable of reducing positive symptoms of schizophrenia, boosting cognition, and addressing a few of the constraints of present medications by augmenting striatal cAMP and cGMP (cyclic guanosine monophosphate) signaling.

Cholinergic Receptors Inhibitors

According to Beck et al. (2015), nicotine, which is the main reinforcing element in tobacco, is believed to show a positive impact on the symptoms of schizophrenia, possibly due to the "self-medication" hypothesis. Alternatively, individuals with schizophrenia may experience increased rewarding effects from nicotine. Novel treatments for schizophrenia are currently under development, with potential targets such as nicotinic and muscarinic acetylcholine receptors (nAChRs and mAChRs). The mAChR M1 and M4 receptors and the 7-nAChR are increasingly being investigated as possible therapeutic targets (Jones et al., 2011). Clinical studies of schizophrenia patients have examined the use of agonists of 7-nAChRs as a supplementary treatment to antipsychotics in humans (Recio-Barbero et al., 2021).

Genetic Control of Neurotransmitter Pathways

There are several underlying factors behind the pathophysiology of schizophrenia which include genetic factors, environmental factors, and hereditary. From the genetics purpose, there is no particular one gene that may be directly responsible for schizophrenia, multiple genes are said to be causing the beginning and development of schizophrenia (Table 5). The central nervous system is majorly affected during schizophrenia, particularly in the regions of the frontal and temporal lobes which in turn affects memory, comprehension, and more. Numerous potential genes, including COMT, DISC1, RGS4, PPP3CC, ZDHHC8, AKT1, neuregulin, dysbindin, G72/G30, TRAR4, and alpha-7 nicotinic receptor genes, have been linked to schizophrenia. They are also involved in the

regulation of dopamine, a neurotransmitter associated with schizophrenia.

DISC1 Gene and Its Involvement in Neurodevelopmental Processes

The disrupted-in-schizophrenia 1 (DISC1) gene has been thoroughly investigated in schizophrenia, and cytogenetic studies conducted 20 years ago demonstrated the association between DISC1 gene deregulation and predisposition to schizophrenia (Blackwood et al., 2001). By disrupting presynaptic dopamine activity, the DISC1 gene seems to increase the likelihood of developing schizophrenia. According to studies, DISC1 changes are linked to enhanced amphetamine-induced dopamine release, which is correlated with amphetamine-induced positive psychotic symptoms seen in schizophrenia. The disruption of presynaptic dopamine control supports a function for DISC1 in modifying dopamine neurotransmission, despite the absence of obvious alterations in dopamine receptors. A meta-analysis of in vivo data in schizophrenia revealed no changes in dopamine D2/D3 receptor modifications, which is also consistent with the lack of observable changes in receptors (Dahoun et al., 2017).

COMT Gene and Its Impact on Dopamine Regulation

The dysregulation of glutamate elicits a compensatory response that triggers a subsequent dysregulation of dopamine. This dysregulation of dopamine leads to an increase in transcript levels of the COMT gene, which is situated at the 22q11 locus. The codon 158 of this particular gene encodes an enzyme that plays a role in the degradation of dopamine. The variability in the codon sequence has been observed to modulate enzyme activity. Specifically, valine has been shown to exhibit heightened activity, while methionine displays reduced activity. Consequently, the presence of valine is thought to be responsible for increased activity, which in further is linked with an elevated susceptibility to schizophrenia and disruptions in cerebral function (Trifu et al., 2020).

Table 5

Genes Involved in Schizophrenia Genesis

Gene Name	Gene ID	Chromosome	Function	Neurotransmitter System	Expression Pattern	Pathogenic Mechanism	References
ZNF804	91752	2q32.1	ZNF804A encodes zinc finger-binding protein.	glutamatergic neurotransmission	prefrontal cortex, hippocampus, and amygdala	Schizophrenia is linked to ZNF804A gene polymorphisms, specifically rs1344706.	(Wang et al., 2019)
PRODH	5625	22q11.2	PRODH encodes proline oxidase, which degrades proline.	glutamatergic neurotransmission	prefrontal cortex, hippocampus, and striatum	Dysregulation of PRODH and proline metabolism may affect synaptic plasticity, neurodevelopment, and oxidative stress, contributing to schizophrenia	(Clelland et al., 2014)
DISC1	27185	1q42.1	Gene regulates cortical and neurite outgrowth	dopamine, serotonin, and glutamate neurotransmission	hippocampus, prefrontal cortex, and striatum	DISC1 dysregulation disrupts neurodevelopmental processes such neuronal migration, synaptic plasticity, and dendritic spine shape, contributing to schizophrenia.	(Liu et al., 2019)
COMT	1312	22q11.21	Catabolizes catecholamine neurotransmitters including dopamine, norepinephrine, and adrenaline.	dopaminergic signalling	prefrontal cortex	Val158Met polymorphism, impacts prefrontal brain dopamine levels and may increase schizophrenia risk and cognitive impairment.	(Horikoshi et al., 2019)

Table 5
Genes Involved in Schizophrenia Genesis

Gene Name	Gene ID	Chromosome	Function	Neurotransmitter System	Expression Pattern	Pathogenic Mechanism	References
NRG1	3084	8p12	NRG1's membrane glycoprotein assists in intercellular communication and organ system development.	glutamatergic and dopaminergic neurotransmission.	prefrontal cortex, hippocampus, and striatum.	Schizophrenia may result from NRG1 signaling dysregulation.	(Vaht et al., 2016)
DTNBP1	84062	6p22.3	Involved in melanosome, platelet dense granule, and lysosome biosynthesis	glutamatergic and dopaminergic neurotransmission	hippocampus, prefrontal cortex, and striatum	DTNBP1 dysregulation impairs synaptic function, brain development, and neuronal connection, perhaps leading to schizophrenia.	(Domschke et al., 2011)
DRD2	1813	11q23.2	Facilitates the functionality of G protein-coupled receptors	dopamine neurotransmission	striatum, prefrontal cortex, and limbic system	Gene's missense mutations induce myoclonus dystonia and schizophrenia.	(Kaur et al., 2019)
5HTR2A	3356	13q14-q21	Codes for serotonin neurotransmitters	serotonin neurotransmission	prefrontal cortex, hippocampus, and striatum	Schizophrenia and OCD are linked to HTR2A gene mutations.	(Massoud et al., 2023)

Neuregulin 1 (NRG1) Gene and Its Role in Glutamatergic Signaling

Any disruption in brain development and neuronal transmission is associated with mental disorders including schizophrenia which is controlled by the gene neuregulin 1 (NRG1; Yang et al., 2020). Schizophrenia has been associated with genetic polymorphisms in the NRG1 gene, mostly in noncoding areas. These variants might control the expression of the NRG1 gene. Studies on the expression of NRG1 in schizophrenia patients' brains have produced inconsistent findings. While other research reveals higher NRG1 expression or greater NRG1 signaling in schizophrenia brains, some report reduced levels of NRG1 isoform 1 alpha. To properly comprehend NRG1's function in schizophrenia, more study is required (Wang et al., 2021).

Proline Dehydrogenase (PRODH)

Located on the 22q11 chromosome, the proline dehydrogenase (PRODH) gene is involved in the metabolism of L-proline, an amino acid thought to be important in glutamatergic neurotransmission. Although the precise mechanisms and connections are still being studied, dysregulation of the PRODH gene, particularly through overexpression of some variations, may affect glutamatergic pathways and contribute to the onset of schizophrenia (Yao & Han, 2022). Furthermore, a study conducted in Iran involving 360 participants has identified three polymorphisms located in the PRODH gene at positions 1766 A/G, 757C/T, and 1852 G/A. These polymorphisms are correlated with an increased chance of schizophrenia (Ghasemvand et al., 2015).

Dystrobrevin-Binding Protein 1 (DTNBP1)

The dystrobrevin-binding protein 1 (DTNBP1) gene, which produces the protein dysbindin-1, is situated on chromosome 6 at location 22.3. There are two coiled-coil domains in this conserved protein, which has about 350 amino acids. Dysbindin-1 comes in three different isoforms: dysbindin-1A, dysbindin-1B, and dysbindin-1C. Postsynaptic densities (PSDs) are the home of dysbindin-1A, synaptic vesicles are the main site of dysbindin-1B, and PSDs and synaptic vesicles are the home of dysbindin-1C. Dysbindin-1 plays a part in the control of the dopaminergic system and synaptic transmission in the hippocampus (Năstase et al., 2022), which is implicated in the pathophysiology of schizophrenia, according to experimental investigations using dysbindin-1 knockdown. Dysbindin-1B and dysbindin-1C levels in the hippocampus are decreased in schizophrenia patients, whereas dysbindin-1A levels are unaltered. Wang et al. (2017) suggest that different isoforms of dysbindin-1

showcase distinct biological functions in the context of schizophrenia.

Other Genes Linked with Schizophrenia

O'Donovan et al. (2008) in their first genome-wide study found a link between schizophrenia and polymorphism at position 804A of the ZNF804 gene that codes for the zinc finger protein. As per Nair et al. (2022) the trace amine receptor 4 (TAAR6) gene at location 6p23.2 is also identified as a candidate associated with schizophrenia. Epsin 4 located on chromosome 5q33 codes for a protein that controls neurotransmitter stability and transport and showed evidence of LD with schizophrenia (Tang et al., 2006). Even though autopsy studies have linked genes to schizophrenia, additional research is necessary to comprehend how genes affect the pathogenesis of the disease. To determine the efficacy of an antipsychotic drug, it is necessary to examine the SNPs (single nucleotide polymorphisms) of schizophrenia-associated risk genes. Future research on these SNPs could enable for more informed decisions regarding the optimal antipsychotic medication for specific patients.

Omics-Based Findings, Potent Therapies, and Drug Targets

The clinical heterogeneity of schizophrenia can now be better understood by researchers using genetic data. They intend to investigate how these genetic factors relate to symptom patterns, the likelihood of treatment response, and the clinical course of the disorder by assessing genetic liability in individuals, such as the number of common risk alleles, copy number variations (CNVs; Degenhardt, 2020), and exonic deleterious variations (Giusti-Rodríguez & Sullivan, 2013). Analysis of proteins and metabolites in schizophrenia sheds light on the intricate interactions between genetic, environmental, and developmental variables. Notably, these investigations demonstrate changed amino acids (glutamate, glutamine) and proteins (NEFL, GNB1, GLUL) in the glutamatergic system, suggesting its function in schizophrenia. Furthermore, schizophrenia has been connected to metabolic dysregulation, which is linked to reduced glucose tolerance and metabolic syndrome, highlighting the importance of altered energy metabolism in the condition (Guan et al., 2021).

Currently, treatments for schizophrenia are more focused on improving the cognitive deficits in the sufferers. Since symptoms of schizophrenia are not specific, according to the prognosis of the disorder, every schizophrenic individual goes through different sets of symptoms which makes it difficult to choose the right drug for treatment. Nevertheless, constant research is being made to develop antipsychotics, combinational therapeutics for the alleviation of schizophrenia. Therefore, there is always a possibility of encountering drawbacks, such as drug rejection, and the emergence of adverse effects such metabolic and cardiovascular issues, weight gain, mobility difficulties, and cognitive impairment as reported by Leucht et al. (2012). These adverse effects are attributed to the administration of antipsychotic medications, which have demonstrated efficacy in the management of schizophrenia. Diabetic patients are susceptible to weight gain due to the propensity of antipsychotic medications such as olanzapine, clozapine, and risperidone to induce weight gain. (Bansal & Chatterjee, 2021). The pharmacological approach along with cognitive remediations are the standard treatments for now. Early diagnosis of cognitive symptoms or any deterioration before it starts affecting lifestyle should be a concern and requires more research (Best & Bowie, 2017). A potential method for treating schizophrenia by modifying the affected neuronal circuits is provided by advanced and novel approaches like noninvasive brain stimulation (Gainsford et al., 2020), such as transcranial magnetic stimulation (TMS; Wu et al., 2022) or transcranial direct current stimulation (tDCS; Mondino et al., 2014). Another noninvasive brain stimulation targeting neuroplasticity—that includes transcranial stimulation electrically or magnetically, or stimulation of the vagus nerve—may be employed to target excitatory/inhibitory imbalance in schizophrenia (Blay et al., 2021; Markiewicz-Gospodarek et al., 2023).

Chronic schizophrenia, that shows no improvement even after medication, may also be managed with therapies with neuroplasticity potential like neurofeedback (NF) based treatments, and rehabilitation therapy with virtual reality and cognitive remediation (Markiewicz-Gospodarek et al., 2023; Surmeli et al., 2012). Although sample heterogeneity, NF training method, specific factors that drive NF outcomes, and experiments that evidently dissociate the different mechanisms that govern these outcomes are still the challenges being investigated, many successful attempts have been made using quantitative electroencephalography (qEEG) and quantitative event-related potentials (qERP; John et al., 1994; John et al., 2007; Surmeli et al., 2012). Other methods of biofeedback (BF) may be galvanic skin response (GSR-BF), electromyography (EMG-BF), and heart rate variability (HRV-BF; Markiewicz-Gospodarek et al.,

2023). These therapies have been successful in treating other neuropsychiatric conditions like thought disorders, personality disorders, behavioral disorders, depression and anxiety, drug-induced disorders, and dementia (Duric et al., 2023; John et al., 2007; Surmeli, 2014; Markiewicz-Gospodarek et al., 2023).

Effective drug targets still need to be researched, and there is a lack of evidence to understand schizophrenia's pathophysiology. For example, the role of serotonin in modulating symptoms of schizophrenia has been explained via dopamine regulation but its specific role is yet to be discovered. "Cariprazine, Brilaroxazine (RP5063), F17464, lumateperone (ITI-007), Brexpiprazole, and Lu AF35700 are a group of newly developed compounds that exhibit some impact on serotonergic receptors while primarily targeting the dopaminergic receptors" (Sparacino et al., 2022). Also, some drug development plans are targeting the NMDAR, as any deficits in this receptor contribute to cognitive impairments associated with schizophrenia. The potential use of memantine, a low-affinity antagonist of the NMDAR, has been identified for the management of positive symptoms and cognitive function (Kikuchi, 2020). The finding is significant because most NMDAR antagonists, together with PCP and ketamine, typically impair both symptoms and cognitive functioning in individuals with schizophrenia. (Frohlich & Van Horn, 2014). The investigation of the potential therapeutic effectiveness of cannabidiol (CBD) in the management of schizophrenia has been a topic of interest. Nevertheless, the findings from various studies have yielded inconclusive outcomes regarding the use of CBD as a treatment option for schizophrenia (White, 2019).

Conclusion

Schizophrenia originated from the Greek word "schizo" and "phren" meaning split mind and is characterized by a disrupted thought process, split personality, and distorted behavior. The precise cause of schizophrenia has been unidentified for over a century since it was first labeled in 1908. However, it appears that schizophrenia is developed because of an amalgam of genetic, environmental, and neurological variables. Currently, different research mentions the imbalance of neurotransmitters, particularly dopamine, serotonin, and glutamate, and their importance for the treatment of cognitive, negative, and positive symptoms. The prefrontal cortex, the hippocampus, and the thalamus are the main affected regions of the brain as neurotransmitters like serotonin, dopamine, and glutamate are respectively involved in there. These regions along with the action of the neurotransmitter play an essential role in a variety of cognitive functions which may include memory, thinking ability, problem-solving, movements, etc. The root cause not being known until now opens the door for more research on the pathophysiology of schizophrenia. Ultimately, schizophrenia is a complex and heterogeneous disorder involving numerous biological, psychological, and social factors. To thoroughly comprehend the mechanism, additional research is required.

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NeuroRegulation

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Implementation Science Application to EEG Neurofeedback Research: A Call to Action

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Abstract

This article is a call to action for implementation research in the field of electroencephalogram (EEG) neurofeedback. While the effectiveness of neurofeedback in improving clinical outcomes has been well established and is continuing to expand into a variety of symptom presentations and mechanisms of action, there is lack of research bridging the gap between the research setting and neurofeedback's implementation in mental health clinics. Our review of the published research to date revealed no articles incorporating the burgeoning utility of implementation science into neurofeedback research to bridge the gap and provide practical information about how to use neurofeedback in real-world settings. Research is urgently needed to explore the feasibility and process of implementing neurofeedback in the clinical setting, without which the applicability and usefulness of outcome studies are called into question.

Keywords: neurofeedback; implementation science; systematic review

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Introduction

Electroencephalogram (EEG) neurofeedback first began to gain popularity in the 1950s and 1960s as an intervention to treat epilepsy and anxiety disorders (Hardt & Kamiya, 1978; Sterman & Friar, 1972). Since this time, the utilization of neurofeedback has branched into a wide variety of symptoms and treatment goals within and outside of the mental health field. A 2016 comprehensive review of the literature by the International Society of Neuroregulation and Research (ISNR, formerly the International Society for Neurofeedback and Research) found over 700 published articles related to the use of neurofeedback to treat a wide range of presenting issues and disorders from attention-deficit/hyperactivity disorder (ADHD) to performance enhancement (Hammond & Novian, 2017). Since the publication of that review, a review of neuromodulation research was published in 2019, which reviewed the ISNR bibliography and highlighted a wide variety of studies across different types of neurofeedback (Perl & Perl, 2019). This review found 314 total studies exploring the effects of neurofeedback. To date, neurofeedback has been found to have sustained effects in the treatment of ADHD (Arnold et al., 2021; Bluschke et al., 2020; Dobrakowski & Łebecka, 2020; Lubar & Shouse, 1976; Purper-Ouakil et al., 2019; van Doren et al., 2019), reduction of symptoms and reduced relapse rates in substance use disorder (Dalkner et al., 2017; Dehghani-Arani et al., 2010, 2013; Goldberg et al., 1976; Horrell et al., 2010; Ko & Park, 2018; Lackner et al., 2016; Lamontagne et al., 1975; Passini et al., 1977; Peniston & Kulkosky, 1989; Saxby & Peniston, 1995; Scott et al., 2005), and a significant decrease in posttraumatic stress disorder (PTSD) symptoms (Fisher et al., 2016; Gapen et al., 2016; Kluetsch et al., 2014; Leem et al., 2021; Nicholson et al., 2020; Noohi et al., 2017; Peniston & Kulkosky, 1991; Rogel et al., 2020), including participants who had not responded well to previous PTSD treatment (Askovic et al., 2020; van der Kolk et al., 2016). After this success in the utilization of neurofeedback to treat PTSD, more recent research has also explored the specific mechanisms of

neurofeedback that are having an impact, including changes to the brain's default mode network, a commonly implicated network in trauma psychopathology (Bluhm et al., 2009; Kluetsch et al., 2014; Lanius et al., 2015; Nicholson et al., 2020). This forward movement in the field of PTSD was also substantiated in 2023 by FDA clearance being granted to a neurofeedback for the treatment of PTSD (GrayMatters Health, 2023).

While a variety of individual studies have illustrated the efficacy of specific types of neurofeedback and neurofeedback protocols in treating the above mentioned mental health conditions, the neurofeedback field has struggled to establish as robust of an evidence-base as other interventions in the mental health field due in part to the wide variety of neurofeedback approaches, inconsistent research design to allow for more across study comparisons and meta-analyses (i.e., lack of controls and debate over the use of sham conditions), and insufficient funding to support more large-scale randomized controlled trials (Fisher et al., 2016; Kuznetsova et al., 2022; Marzbani et al., 2016; Micoulaud-Franchi et al., 2021; Perl & Perl, 2019; Riesco-Matías et al., 2021; Trocki, 2006; van der Kolk et al., 2016). Despite claims regarding neurofeedback's effectiveness comparability with "gold standard" mental health treatments (Nicholson et al., 2020), some within the mental health field question its credibility in part due to its controversial history, which includes significant disagreements and contradictions from key stakeholders in the field (Kuznetsova et al., 2022; Robbins, 2008). Neurofeedback clinicians have questioned why neurofeedback is not more popular in the mental health field based on the results they see in their practices (Robbins, 2008). While some have speculated as to why neurofeedback is not more commonly implemented in mental health settings (i.e., expense, lack of insurance coverage, theoretical differences among practitioners; Marzbani et al., 2016; Robbins, 2008), the field lacks scientific evidence to establish these and other potential factors as implementation barriers.

As any research-aware clinician knows, discovering what interventions work in the laboratory setting is not enough to successfully bring them to the clinical settings (Bauer & Kirchner, 2020). It is not uncommon in the mental health field to find interventions that have been shown to be effective in the literature that are not commonly or correctly utilized in actual clinical practice (Kettlewell, 2004). In a commentary on the topic of dissemination and implementation of evidence-based treatments in the field of mental health, Kettlewell pointed to a gap between science and clinical practice in psychology as a significant problem for the field and that our ability to close this gap "will determine our ability to remain a highly regarded helping profession" (Kettlewell, 2004, p. 190). He went on to state, "We have treatments that work, and most practitioners do not use them" (Kettlewell, 2004, p. 190). As much as 85% of medical research dollars do not impact the public due to what is referred to as "research waste" (Chalmers & Glasziou, 2009). The NIMH has the strategic goal to "speed up the development, adoption, and implementation of effective, evidence-based mental health services to improve the reach and outcomes of these services in diverse communities and populations" (National Institute of Mental Health, 2022). For research to have the desired impact, it is imperative that we identify feasible implementation strategies that minimize the barriers to implementing evidence-based interventions in real-world settings. Therefore, research using implementation science approaches is needed to optimize implementation of evidence-based interventions like neurofeedback.

Implementation science is the scientific study of how evidence-based clinical interventions or research findings are best adopted and integrated into routine practice (Eccles & Mittman, 2006). Recognizing that many evidence-based interventions either never make it into routine care or take many years to do so (Balas & Boren, 2000; Morris et al., 2011), implementation science offers methods to identify factors that influence uptake and sustained use of evidence-based mental health interventions and strategies that support implementation. Clinical implementation is an important step in the translational science spectrum, as it bridges the gap between clinical research findings and integration into routine care for the general public. Because there is strong evidence for the clinical effectiveness of EEG neurofeedback (Markiewcz, 2017), implementation research in mental health care settings is the logical next step.

Approach and Findings

To explore the extent of research on the implementation of neurofeedback in mental health settings, we conducted a systematic literature review. We focused on peer-reviewed articles published since 1995 that explored implementation factors, strategies, and/or outcomes. After several informal searches provided no relevant articles, we partnered with a Health Sciences Informationist at the University of Arkansas for Medical Sciences

(UAMS) to conduct a review of four databases (PubMed, PsycInfo, CINAHL, SocINDEX) using the following search terms: ("neurofeedback" OR "EEG neurofeedback" OR "EEG biofeedback" OR "biofeedback") AND ("Implementation Science research" OR "Implementation Science framework" OR "implementation science" OR "implementation research" OR "knowledge translation"). This search resulted in no articles exploring the use of an implementation science lens to explore the utilization of EEG neurofeedback in mental health treatment.

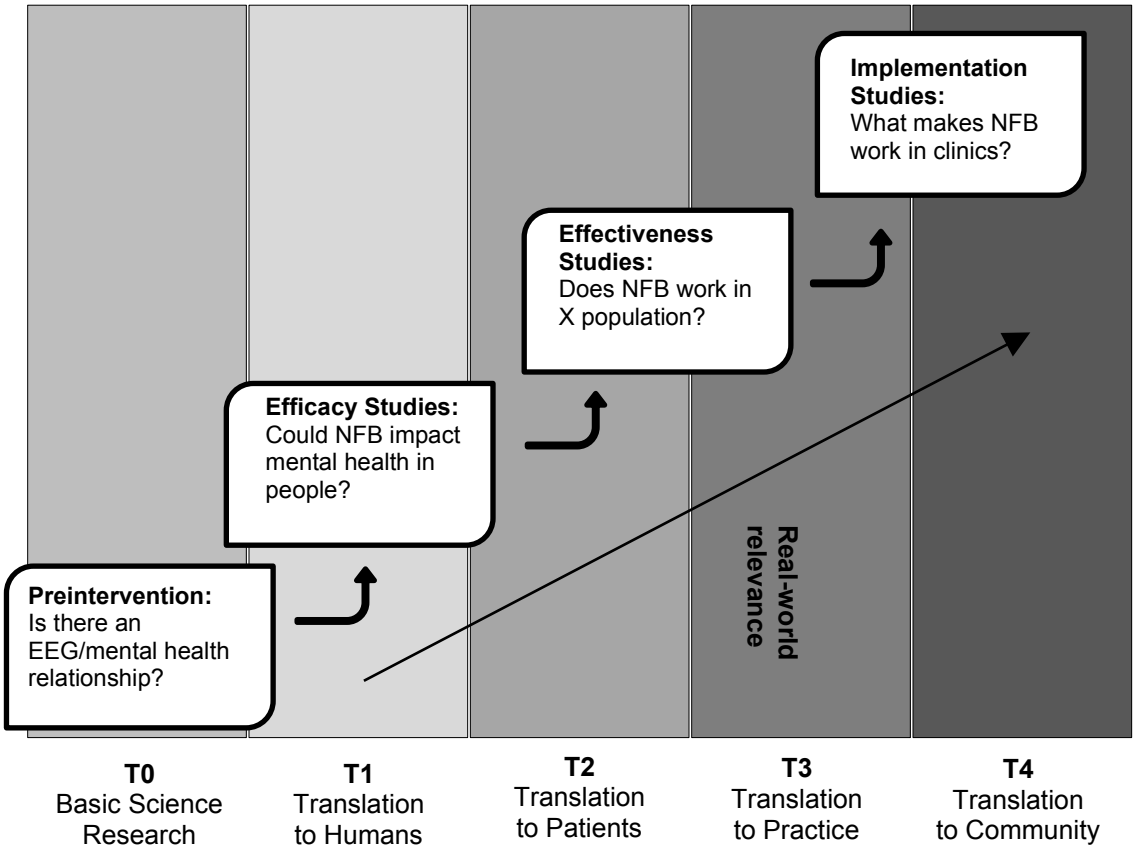
Despite many clinicians' and researchers' support of the use of neurofeedback, our search identified no implementation peer-reviewed research articles to date that specifically or systematically explored the barriers and facilitators of neurofeedback's use in clinical mental health settings or strategies needed to promote uptake or sustain use in these settings. The closest relevant studies found in our informal search were two studies that broadly explored neurofeedback practitioners' perspectives (Larson et al., 2010; Luctkar-Flude et al., 2019) and one that explored the experiences of neurofeedback clients (Aguilar-Prinsloo & Lyle, 2010). Luctkar-Flude et al.'s (2019) study specifically explored neurofeedback clients' and providers' experiences of the results of neurofeedback in a very specific client population—cancer survivors. While this was a well-designed study that provided useful insights, the author's goal was to describe the personal experiences and outcomes of those involved in the neurofeedback treatment, not specifics regarding the barriers and facilitators to its implementation.

Larson and colleagues' (2010) study came a step closer to the implementation research we are suggesting here. While the authors did not approach the study with an implementation science lens, part of their goal was to learn more about neurofeedback providers' beliefs about aspects of the use of neurofeedback, such as advantages, disadvantages, and other components of using neurofeedback in a mental health setting. Larson et al.'s (2010) study resulted in three main findings: the effectiveness of neurofeedback in treating a variety of mental health issues, the need for extensive practitioner commitment due to the complexity of the intervention, and problems related to dissemination and funding of neurofeedback. Though practitioners' beliefs about an intervention are one of many potential determinants of implementation, there are many other potential determinants to explore for a full understanding of implementation factors (Damschroder et al., 2009). Therefore, Larson et al.'s (2010) exploration is only the tip of the iceberg in understanding implementation factors for neurofeedback in mental health settings. Additional research is needed to explore all possible determinants of neurofeedback implementation in order to make this evidence-based intervention more accessible to the public.

Future Research

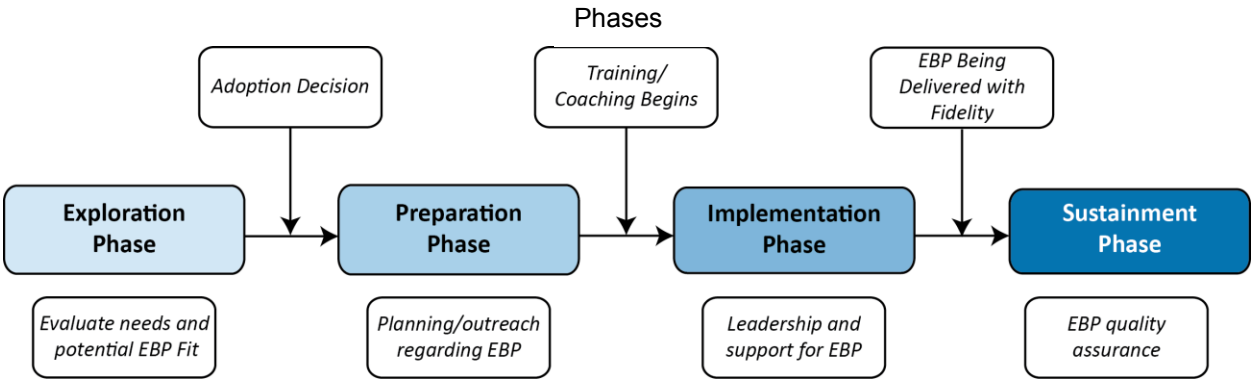
With evidence for the effectiveness of neurofeedback in treating a variety of mental health conditions, the natural next step in the translational research continuum "from bench to bedside" (Drolet & Lorenzi, 2011) is to further study the implementation of neurofeedback to increase its delivery in routine mental health care. Figure 1 illustrates how the translational research continuum applies to research in the neurofeedback field. As mentioned above, the work to date from preintervention studies to studies of efficacy and effectiveness of neurofeedback have shown that neurofeedback can and does impact mental health within a variety of treatment settings and symptoms presentations. However, our larger point here is that this last phase of the research continuum involved in illustrating the real-world relevance of the intervention is lacking and represents the next step in the application of neurofeedback in mental health treatment.

Figure 1. *Translational Research Continuum*.



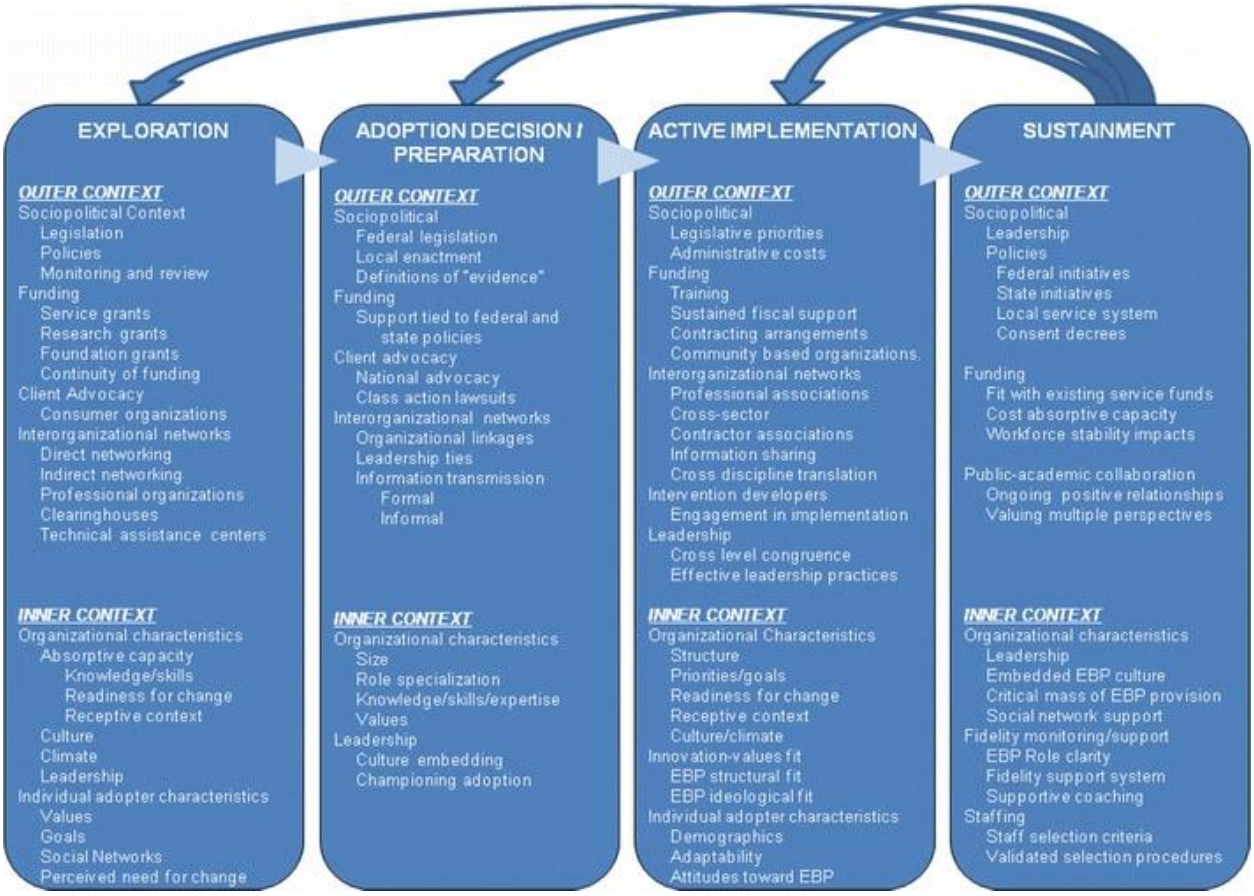
Within the field of implementation science research, there are a wide variety of models, frameworks, and approaches that provide tangible insight into barriers and facilitators to intervention implementation across different settings and from the perspectives of different stakeholders throughout the process (Brownson et al., 2017). The EPIS model is one worthwhile example of a model that can be used to organize and provide specific direction for future neurofeedback implementation research (Aarons et al., 2011).

Figure 2. *The Four Phases of the EPIS Model (EPIS Framework, 2024)*.



The EPIS model describes four phases of the implementation process and specific elements within each of these phases that past research has shown to have an impact on evidence-based practice (EBP) implementation (see Figure 2). These phases are meant to evaluate current needs and evaluate EBP fit before the implementation is adopted (the Exploration phase), planning and outreach regarding the EBP (the Preparation phase), early active implementation of the EBP (the Implementation phase), and finally, sustained implementation and possible adaptation of the EBP over the long term (the Sustainment phase). Each phase includes inner and outer context factors, as well as factors that bridge these contexts. For example, outer context factors in the neurofeedback field could include professional organizations' support for neurofeedback, research funding to support randomized-controlled trials of neurofeedback in mental health settings, or insurance panel advocacy for coverage of neurofeedback as part of routine mental health care (see Figure 3). Inner context factors could include variables such as organization and individual practitioner characteristics, staffing structures of specific mental health clinics, and the perceived need for change or the addition of an intervention like neurofeedback in the clinics' clinical practice offerings.

Figure 3. *Aarons et al. (2011) Conceptual Model of Implementation Phases and Factors Affecting Implementation in Public Service Sectors*.



Due to the scarcity of literature on neurofeedback implementation described above, future neurofeedback implementation research could benefit from focusing on any variety of the specific contextual factors within any of the four EPIS phases. One strategy to discern which of these factors or areas on which to focus would be to learn from experienced neurofeedback practitioners, consultants, and trainers to learn more about their anecdotal observations of the barriers and facilitators of implementation of neurofeedback. Two possible examples are described below:

- An experienced neurofeedback practitioner observes a trend among new neurofeedback providers who, initially, are excited to start using neurofeedback but give up within 6 months. This insight could lead to an exploration of inner and/or outer context factors with the Sustainment phase of the EPIS. The use of longitudinal surveys and/or interviews of newly trained neurofeedback practitioners could provide insight into what specific factors are leading to this failure of implementation, which could lead to tangible changes in the training or early mentoring of neurofeedback practitioners.
- Neurofeedback practitioners may observe a general lack of knowledge within the mental health field of the use of neurofeedback in mental health treatment. This could lead to research within the Exploration phase by surveying individuals, organization leaders, and other stakeholders about their knowledge of neurofeedback and/or the process involved in how they usually learn about new interventions that they may later adopt.

As in the early phases of any new research, the exploration must begin somewhere. The breadth and depth provided by an established field like implementation science allows for the possibility of building a strong foundation that can be built upon for many years to come. Much like the study of the brain, as the field of neurofeedback implementation research blossoms and grows, the answers we find will likely lead to even more questions, which will lead to a deeper and richer understanding that will benefit the field greatly.

Conclusion

In describing the barriers to translating research into practice in critical care, Berenholtz and Pronovost said, “the most cost-effective opportunity to improve patient outcomes will likely come not from discovering new therapies but from discovering how to deliver therapies that are known to be effective” (Berenholtz & Pronovost, 2003, p. 321). We believe that neurofeedback is an ideal intervention to improve patient outcomes in this way. Anecdotally, we have heard that there may be concerns in the field about a lack of public and healthcare community awareness about neurofeedback, the costs associated with neurofeedback to both clinician and client, and other provider- and clinic-level barriers; however, without implementation research to systematically identify these issues, it is unknown which are true barriers and what implementation strategies are needed to overcome them. While the outcome studies are promising, without a clear understanding of how to bring this intervention to these populations, including the barriers and facilitators to doing so, the research will be of little use. It is time for the field of neurofeedback to convert its abundance of successful outcomes research and so many neurofeedback providers’ and clients’ countless “n of 1” experiences (S. Fisher, personal communication, August 10, 2022; Panisch & Hai, 2020) into tangible application through the use of established frameworks, like EPIS, provided by implementation science.

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Reflections on the Increase in Autism, ADHD, Anxiety, and Depression: Part 2 – Exposure to Neurotoxins and Ultraprocessed Foods

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Abstract

Mental health symptoms of attention-deficit/hyperactivity disorder (ADHD), autism, anxiety, and depression have increased over the last 15 years. An additional risk factor that may affect mental and physical health is the foods we eat. Even though our food may look and even taste the same as compared to 50 years ago, it contains herbicide and pesticide residues and often consist of ultraprocessed foods. These foods (low in fiber and high in sugar, animal fats, and additives) are a significant part of the American diet and correlate with higher levels of inattention and hyperactivity in children with ADHD. Due to affluent malnutrition, many children are deficient in essential vitamins and minerals. We recommend that diet and lifestyle are assessed before beginning neurofeedback and behavioral treatments (we call this Grandmother therapy assessment). If the diet appears low in organic foods and vegetable, and high in ultraprocessed foods and drinks, then nutritional deficiencies should be assessed. The next intervention step is to then reduce the nutritional deficiencies and implement diet changes from ultraprocessed foods to organic whole foods. Meta-analysis demonstrates that providing supplements such as vitamin D, reducing simple carbohydrates and sugars, and eating more vegetables, fruits, and healthy fats during regular meals can ameliorate the symptoms and promote health.

Keywords: ADHD; anxiety; depression; mental health; diet; vitamins; malnutrition; pesticides; herbicides

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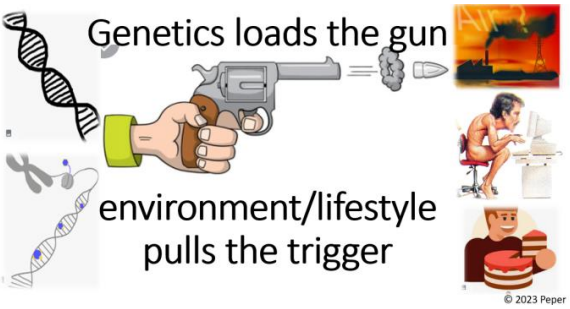
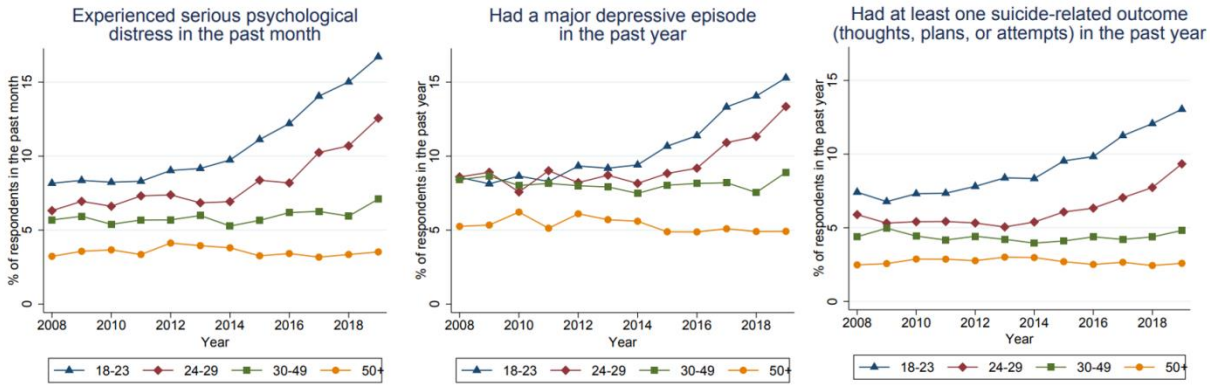
The previous article "Reflections on the Increase in Autism, ADHD, Anxiety, and Depression: Part 1 – Bonding, Screen Time, and Circadian Rhythms" pointed out how the changes in bonding, screen time, and circadian rhythms affected physical and mental health (Peper, 2023). However, there are many additional factors, including genetics, that may contribute to the increase in ADHD, autism, anxiety, depression, allergies, and autoimmune illnesses (Swatzyna et al., 2018). Genetics contribute to the risk of attention-deficit/hyperactivity disorder (ADHD) since family, twin, and adoption studies have reported that ADHD runs in families (Durukan et al., 2018; Faraone & Larsson, 2019). In most cases, genetics is a risk factor that may or may not be expressed. The concept underlying this paper is that genetics loads the gun, while environment or behavior pulls the trigger.

Figure 1. *Interaction Between Genetics and Environment*.



The pandemic only escalated trends that already were occurring. For example, Bommersbach et al. (2023) analyzed the national trends in mental health-related emergency department visits among USA youth, 2011–2021. They observed that, in the United States over the last 10 years, the proportion of pediatric emergency department visits for mental health reasons approximately doubled, including a fivefold increase in suicide-related visits. The mental health-related emergency department visits increased an average of 8% per year, while suicide related visits increased 23.1% per year. Similar trends have been reported by Braghieri et al. (2022) from the National Survey on Drug Use and Health, as shown in Figure 2.

Figure 2. *Mental Health Trends in the United States by Age Group in 2008–2019*.



Note. Data from the National Survey on Drug Use and Health. Reproduced with permission from Braghieri et al. (2022).

The trends reported from this data show an increase in mental health illnesses for young people ages 18–23 and 24–29 and no changes for the older groups which could be correlated with the release of the first iPhone 2G on June 29, 2007. Thus, the COVID-19 pandemic and social isolation were *not* the cause but an escalation of an ongoing trend. For the younger population, the cellphone has become the vehicle for personal communication and social connections. Many young people communicate more with texting than in person and spend hours on screens, which impacts sleep (Peper, 2023). At the same time, there are many other concurrent factors that may contribute to the increase of ADHD, autism, anxiety, depression, allergies, and autoimmune illnesses.

Without ever signing an informed consent form, we all have participated in lifestyle and environmental changes that differ from that evolved through the process of evolutionary natural selection and promoted survival of the human species. Many of those changes in lifestyle are driven by demand for short-term corporate profits over long-term health of the population, as exemplified by the significant increase in vaping in young people as a covert strategy to increase smoking (Centers for Disease Control and Prevention [CDC], 2023) or the marketing of ultraprocessed foods (van Tulleken, 2023).

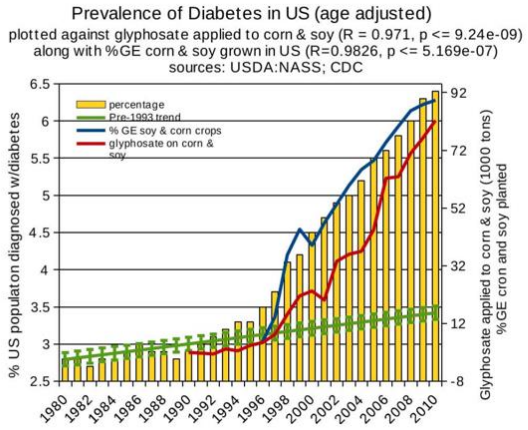
This paper focuses on how pesticides and herbicides (exposure to neurotoxins) and changes in our food negatively affect our health and well-being and may be another contributor to the increased risk for developing ADHD, autism, anxiety, and depression. Although our food may look and even taste the same compared to 50 years ago, it is now different—containing more herbicide and pesticide residues and is often ultraprocessed. It contains lower levels of nutrients and vitamins such as vitamin C, vitamin B2, protein, iron, calcium, and phosphorus than 50 years ago (Davis et al., 2004; Fernandez-Cornejo et al., 2014). Nonorganic foods as compared to organic foods may reduce longevity, fertility, and survival after fasting (Chhabra et al., 2013).

Being Poisoned by Pesticide and Herbicide Residues in Food

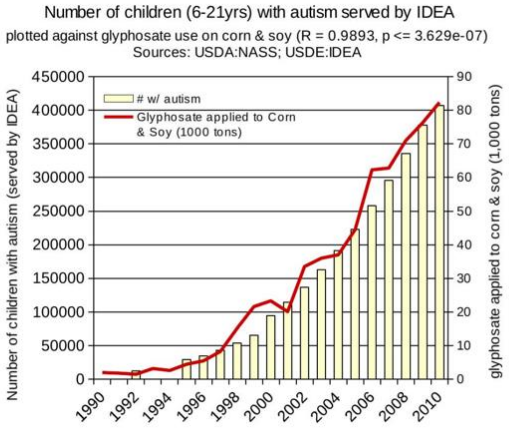
Almost all foods, except those labeled organic, are contaminated with pesticides and herbicides. The United States Department of Agriculture reported that “pesticide use more than tripled between 1960 and 1981. Herbicide use increased more than tenfold (from 35 to 478 million pounds) as more U.S.

farmers began to treat their fields with these chemicals" (Fernandez-Cornejo et al., 2014, p. 11). The increase in herbicides and pesticides is correlated with a significant deterioration of health in the United States (Swanson et al., 2014), as illustrated in the following figures reproduced with permission.

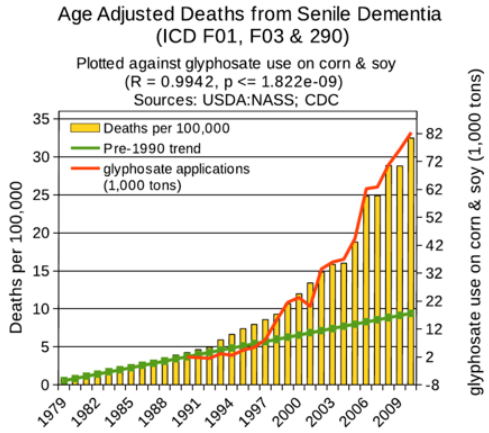
Figure 3. *Correlation Between Disease Prevalence and Glyphosate Applications*.



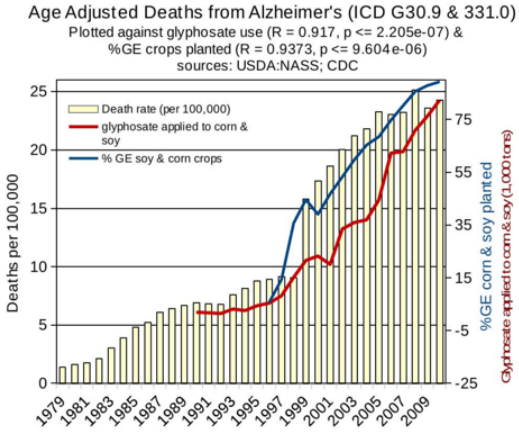
Correlation between age-adjusted diabetes prevalence and glyphosate applications and percentage of US corn and soy crops that are GE. Reproduced from Swanson et al. (2014).



Correlation between children with autism and glyphosate applications. Reproduced from Swanson et al. (2014).



Correlation between age-adjusted dementia deaths and glyphosate applications. Reproduced from Swanson et al. (2014).



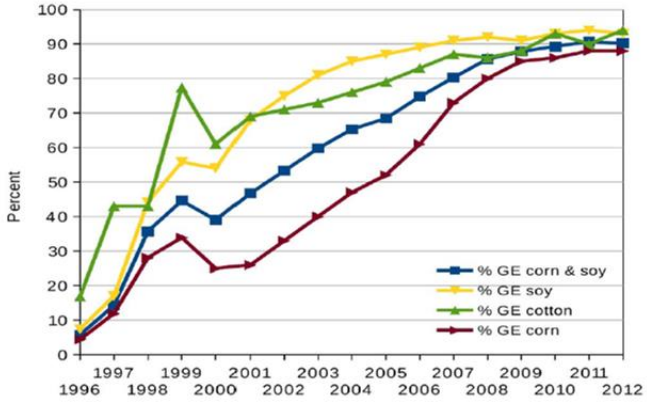
Correlation between age-adjusted Alzheimer's disease deaths and glyphosate applications and percentage of US corn and soy crops that are GE. Reproduced from Swanson, et al. (2014).

Although correlation is not causation, and similar relationships could be plotted by correlating consumption of ultrarefined foods, antibiotic use, decrease in physical activity, increase in computer, cellphone and social media use, etc.; nevertheless, it may suggest a causal relationship. Most pesticides and herbicides are neurotoxins and can accumulate in the person over time, affecting physical and mental health (Arab & Mostaflou, 2022; Bjørling-Poulsen et al., 2008). Even though the United States Environmental Protection Agency (EPA) has determined that the residual concentrations in foods are safe, their long-term safety has not been well established (Leoci & Ruberti, 2021). Other countries—especially those in which agribusiness has less power to affect legislation through lobbying and utilize the research findings from studies not

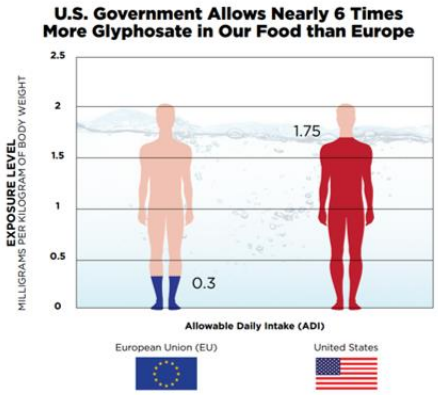
funded by agribusiness—have come to different conclusions.

For example, the USA allows much higher residues of pesticides such as Round-Up, with a toxic ingredient glyphosate (0.7 parts per million), in foods than European countries (0.01 parts per million; European Commission, 2023; EPA, 2023; Wahab et al., 2022), as is graphically illustrated in Figure 4.

Figure 4. *Percent of Crops Sprayed With Glyphosate and Allowable Glyphosate Levels in the USA Versus the EU*.



Adoption of GE crops in US. Reproduced by permission from Swanson et al. (2014).



https://s3.amazonaws.com/media.fooddemocracynow.org/images/FDN_Glyphosate_FoodTesting_Report_p2016.pdf

The USA allows this higher exposure than the European Union even though about half of the human gut microbiota are vulnerable to glyphosate exposure (Puigbò et al., 2022). The negative effects most likely would be more harmful in a rapidly growing infant than in an adult. Most likely, some individuals are more vulnerable than others and are the "canary in the mine." They are the early indicators for possible low-level, long-term harm. Research has shown that fetal exposure from the mother (gestational exposure) is associated with an increase in behaviors related to ADHD and executive function in the child when they are 7 to 12 years old (Sagiv et al., 2021). Also, organophosphate exposure is correlated with ADHD prevalence in children (Bouchard et al., 2010). We hypothesize this exposure is one of the cofactors that have contributed to the decrease in mental health of adults 18 to 29 years.

At the same time as herbicides and pesticides acreage usage has increased, ultraprocessed food has become a major part of the American diet (van Tulleken, 2023). Eating a diet high in ultraprocessed foods, which are low in fiber and high in sugar, animal fats, and additives, has been associated with higher levels of inattention and hyperactivity in children with ADHD; namely, high consumption of sugar, candy, cola beverages, and non-cola soft drinks, and low consumption of fatty fish were also associated with a higher prevalence of ADHD diagnosis (Ríos-Hernández et al., 2017).

In international studies, less nutritional eating behaviors were observed in the ADHD risk group as compared to the normal group (Ryu et al., 2022). Artificial food colors and additives are also a public health issue and appear to increase the risk of hyperactive behavior (Arnold et al., 2012). In a randomized, double-blind, placebo-controlled trial, 3- and 8- to 9-year-old children had an increase in hyperactive behavior for those whose diet included extra additives (McCann et al., 2007). The risk may occur during fetal development since poor prenatal maternal care is a critical factor in the infant's neurodevelopment and is associated with an increased probability of developing ADHD and autism (Li et al., 2016; Zhong et al., 2020).

Poor Nutrition Even Affects Your Unborn Grandchild

Poor nutrition not only affects the mother and the developing fetus through epigenetic changes, it also impacts the developing eggs in the ovary of the fetus that can become the future granddaughter. At birth, the baby has all of her eggs. Thus, there is a scientific basis for the old wives' tale that curses may skip a generation. Providing maternal support is even more important since it affects the newborn and the future grandchild. The risk may even begin a

generation earlier since the grandmother's poor nutrition as well as stress causes epigenetic changes in the fetus eggs. Thus 50% of the chromosomes of the grandchild were impacted epigenetically by the mother's and grandmother's dietary and health status.

Highly Processed Foods

Highly refined foods have been processed to remove many of their nutrients. These foods include white bread, white rice, pasta, sugary drinks, and almost all fast foods and snacks. These foods are low in fiber, vitamins, and minerals and high in sugars, unhealthy fats, and calories. In addition, additives may have been added to maximize taste and mouth feel and implicitly encourage addiction to these foods. A diet high in refined sugars and carbohydrates increases the risk of diabetes and can worsen the symptoms of ADHD, autism, depression, and anxiety and increase metabolic disease and diabetes (Lustig, 2021; van Tulleken, 2023; Woo et al., 2014). Del-Ponte et al. (2019) noted that a diet high in refined sugar and saturated fat increased the risk of symptoms of ADHD; whereas, a healthy diet, characterized by high consumption of fruits and vegetables, would protect against the symptoms.

Most likely, a diet of highly refined foods may cause blood sugar to spike and crash, which can lead to mood swings, irritability, anxiety, depression, and cognitive decline; often labeled as "hangryness" (the combination of anger and hunger; Barr et al., 2019; Gonçalves et al., 2023). At the same time, a Mediterranean diet improves depression significantly more than the befriending control group (Bayles et al., 2022). In addition, refined foods are low in essential vitamins and minerals as well as fiber. Not enough fiber can slow down digestion, affect the human biome, and make it harder for the body to absorb nutrients. This can lead to nutrient deficiencies, which can contribute to the symptoms of ADHD, autism, depression, and anxiety. Foods impact our mental and physical health, as illustrated by foods that tend to reduce depression (LaChance & Ramsey, 2018; MacInerney et al., 2017). By providing appropriate micronutrients such as minerals (iron, magnesium zinc), vitamins (B6, B12, B9, and D), omega-3s (Phosphatidylserine) and changing our diet, ADHD symptoms can be ameliorated.

Many children with ADHD, anxiety, and depression are low on essential vitamins and minerals. For example, low levels of omega-3 fatty acids and vitamin D may be caused by eating ultrarefined foods and fast food and drinking soft drinks. At the same time, children are sitting more indoors in front of the screen and thereby have lower sun exposure than is necessary for vitamin D production.

> Because of lifestyle changes and sunscreen use, about 42% of Americans are deficient in vitamin D. Among children between 1 and 11 years old, an estimated 15% have vitamin D deficiency. And researchers have found that 17% of adolescents and 32% of young adults were deficient in vitamin D (Porto & Abu-Alreesh, 2022).

Reduced sun exposure is even more relevant for people of color and older people, since their darker skin (increased melanin) protects them from ultraviolet light damage but at the same time reduces the skin's production of vitamin D.

Northern Europeans were aware of the link between sun exposure and vitamin D production. To prevent rickets (a disease caused by vitamin D deficiency) and to reduce upper respiratory tract infections, their children were given a tablespoon of cod liver oil to swallow (Linday, 2010). Cod liver oil, although not always liked by children, is more nutritious than taking vitamin D supplements. It is a whole food and a rich source of vitamin A and D as well as contains a variety of omega- 3 fatty acids (eicosapentaenoic acid; U.S. Department of Agriculture [USDA], 2019; US EPA, 2023).

Research studies suggest that ADHD can be ameliorated with nutrients and herbs supplements (Henry & CNS, 2023). Table 1 summarizes some of the nutritional deficits observed and the reduction of ADHD symptoms when nutritional supplements were given (adapted from Henry, 2023; Henry & CNS, 2023).

Table 1
Examples of Vitamin and Mineral Deficiencies Associated With Symptoms of ADHD and Supplementation to Reduction of ADHD Symptoms.

Nutritional deficits observed in people with ADHD	Decrease in ADHD symptoms with nutritional supplements
Vitamin D: In meta-analysis with a total number of 11,324 children, all eight trials reported significantly lower serum concentrations of 25(OH)D in patients diagnosed with ADHD compared to healthy controls. (Kotsi et al., 2019).	After 8 weeks, children receiving vitamin D (50,000 IU/week) plus magnesium (6 mg/kg/day) showed a significant reduction in emotional problems as observed in a randomized, double-blind, placebo-controlled clinical trial (Hemamy et al., 2021).
Iron: In meta-analysis, lower serum ferritin was associated with ADHD in children (Wang et al., 2017) and the mean serum ferritin levels were lower in the children with ADHD than in the controls (Konofal et al., 2004).	After 12 weeks of supplementation with iron (ferrous sulfate) in double-blind, randomized placebo-controlled clinical trials, symptoms in children with ADHD as compared to controls were reduced (Pongpitakdamrong et al., 2022; Tohidi et al., 2021).
Omega-3s: Children with ADHD were more likely to be deficient in omega-3s than children without ADHD (Chang et al., 2017).	Adding omega-3 supplements to their diet resulted in an improvement in hyperactivity, impulsivity, learning, reading, and short-term memory as compared to controls in 16 randomized controlled trials including 1,514 children and young adults with ADHD (Derbyshire, 2017).
Magnesium: In meta-analysis, subjects with ADHD had lower serum magnesium levels compared with to their healthy controls (Effatpahah et al., 2019).	The 8 weeks of supplementation with vitamin D and magnesium caused a significant decrease in children with conduct problems, social problems, and anxiety/shy scores (Hemamy et al., 2020).
Vitamins B2, B6, B9, and B12: Deficiency has been found in many patients with ADHD (Landaas et al., 2016; Unal et al., 2019).	Vitamin therapy appears to reduce symptoms of ADHD and ASD (Poudineh et al., 2023; Unal et al., 2019). The 8 weeks supplementing with vitamin B6 and magnesium decreased hyperactivity and hyperemotivity or aggressiveness. When supplementation was stopped, clinical symptoms of the disease reappeared in a few weeks (Mousain-Bosc et al., 2006).

Supplementation of vitamins and minerals in many cases consisted of more than one single vitamin or mineral. For an in-depth analysis and presentation, see the superb webinar by Henry and CNS (2023): https://divcom-events.webex.com/recordingservice/sites/divcom-events/recording/e29cefcae6c1103bb7f3aa780efee435/playback? (Henry & CNS, 2023).

Whole foods are more than the sum of individual parts (the identified individual constituents/nutrients). The process of digestion is much more complicated than ingesting simple foods with added vitamins or minerals. Digestion is the interaction of many food components (many of which we have not identified) which interact and affect the human biome. A simple added nutrient can help; however, eating whole organic foods is most likely healthier. For example, whole-wheat flour is much more nutritious. Whole wheat is rich in vitamins B1, B3, B5, riboflavin, folate, and fiber. Refined white flour has been bleached and stripped of fiber and nutrients to which some added vitamins and iron are added.

Recommendation

When working with clients, follow Talib's principles as outlined in Part 1 by Peper (2023), which suggest that to improve health first remove the unnatural, which in this case are the ultraprocessed foods, simple carbohydrates, exposure to pesticides, and

herbicides (Taleb, 2014). The approach is beneficial for prevention and treatment. This recommendation to optimize health is both very simple and very challenging. The simple recommendation is to eat only organic foods and as much variety as possible as recommended by Professor Michael Pollan in his books, *Omnivore's Dilemma: A Natural History of Four Meals* and *Food Rules* (Pollan, 2006; Pollan, 2011).

> Look at your hand or your brain and remember that every cell is constructed out the foods you ingested. If you ingested inferior foods (raw materials to be built your physical structure), the structure can only be inferior. If you use superior foods, you have the opportunity to create a superior structure which provides the opportunity for superior functioning. —Erik Peper

Do not eat foods that contain herbicides and pesticide residues or are ultraprocessed. Although organic foods, especially vegetables and fruits, are often much more expensive, you have a choice: You can pay more now to optimize health or pay later to treat disease. Be safe and not sorry. This recommendation is similar to the quote, "Let food be thy medicine and medicine be thy food," that has been attributed falsely since the 1970s to Hippocrates, the Greek founder of western medicine (5th Century, BC; Cardenas, 2013).

There are many factors that interfere with implementing these suggestions, since numerous people live in food deserts (no easy access to healthy unprocessed foods) or food swamps (a plethora of fast-food outlets) and 54 million Americans are food insecure (Ney, 2022). In addition, we and our parents have been programmed by food industry advertising to eat ultraprocessed foods and may no longer know how to prepare healthy foods such as exemplified by a Mediterranean diet. Recent research by Bayles et al. (2022) has shown that eating a Mediterranean diet improves depression significantly more than the befriending control group. In addition, highly processed foods and snacks are omnipresent, often addictive, and more economical.

Remember that clients are individuals and almost all research findings are based upon group averages. Even when the data implies that a certain intervention is highly successful, there are always some participants for whom it is very beneficial and some for whom it is ineffective or even harmful. Thus, interventions need to be individualized for which there is usually only very limited data. In most cases, the original studies did not identify the characteristics of those who were highly successful or those who were unsuccessful. In addition, when working with specific individuals with ADHD, anxiety, and depression, there are multiple possible causes.

Before beginning specific clinical treatment such as neurofeedback or medication, we recommend the following:

1. "Grandmother assessment" that includes an assessment of screen time, physical activity, outdoor sun exposure, and sleep rhythm, as outlined in Part 1 by Peper (2023). Then follow-up with a dietary assessment that investigates the prevalence of organic and nonorganic foods, ingestion of fast foods, ultraprocessed foods, soft drinks, high simple carbohydrate and sugar, salty/sugary/fatty snacks, fruits, vegetables, and eating patterns (eating with family or by themselves in front of screens). Be sure to include an assessment of emotional reactivity and frequency of irritability and "hangryness."
2. If the assessment suggests low levels of organic whole foods and the predominance of ultrarefined foods, it may be possible that the person is deficient in vitamins and minerals. Recommend that the child is tested for vitamin deficiencies. If vitamin deficiencies are identified, recommend supplementing the diet with the necessary vitamins and minerals and encourage eating foods that naturally include these substances (Henry & CNS, 2023).
3. If there is a high level of emotional reactivity and "hangryness," a possible contributing factor could be hypoglycemic rebound from a high simple carbohydrate (sugar) intake or not eating breakfast, combined with hyperventilation (Barr et al., 2019; Engel et al., 1947). Recommend eliminating simple carbohydrate breakfast and fast-food snacks and substitute organic foods that include complex carbohydrates, protein, fats, vegetables, and fruit. Be sure to eat breakfast.
4. Implement "Grandmother Therapy" by having the family and child change their diet to eat a wide variety of organic foods (vegetables, fruits, some fish, meat, and possibly dairy) and eliminate simple carbohydrates and sugars. In time, this diet will reduce nutritional deficits and may eliminate the need for supplements.
5. Concurrent with the stabilization of the physiology, begin psychophysiological treatment strategies such as neurofeedback biofeedback and cognitive behavior therapy.

Author Disclosure

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