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

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Resting-State EEG and MEG Correlates of Auditory Hallucinations in Adults With Schizophrenia: A Systematic Review

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Abstract

Auditory hallucinations (AH) are reported by 60–75% of people diagnosed with schizophrenia. They have been linked to a range of cortical structural and functional changes. We systematically reviewed electroencephalogram (EEG) and magnetoencephalography (MEG) resting-state studies of adults with schizophrenia experiencing auditory hallucinations (verbal and/or nonverbal). After searching for relevant studies using the PubMed and Web of Science databases, we applied the PRISMA method to exclude duplicates and studies not matching our inclusion criteria. The selection process yielded 16 studies (8 EEG, 5 MEG, 2 qEEG-LORETA, and 1 EEG-fMRI). Results suggest that both EEG frequency changes and altered intra- and interhemispheric coherence play a role in the generation or perception of AH. Also, while overactivity of the auditory cortex and disruption of normal activity in speech-related areas have been proposed, MEG research suggests that distinct symptoms in schizophrenia may be related to different types of brain alterations and also that different cortical regions may be involved in different types of AH. More research in younger populations is needed and follow up studies should evaluate the effects of targeted interventions during the occurrence of hallucinatory episodes.

Keywords: auditory hallucinations; EEG; MEG; resting-state schizophrenia

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Introduction

The clinical profile of schizophrenia includes positive (e.g., hallucinations, delusions), negative (e.g., apathy, thought, and speech impairment), cognitive (e.g., attention and memory deficits), affective (e.g., depression) and psychomotor (e.g., catatonia) symptoms. Although auditory hallucinations (AH; the perception of sounds in the absence of auditory stimuli) also occur in both other diagnoses and individuals with no psychiatric history (McCarthy-Jones, 2012, 2017), they are reported by 60–75% of people diagnosed with schizophrenia (Lecrubier et al., 2007; Shinn et al., 2012).

Accumulating evidence indicates that distinct symptoms of schizophrenia are associated with both structural and functional neural changes, as detected by a variety of noninvasive imaging techniques (Hu et al., 2017). These studies challenge the idea of a single specific underlying biological mechanism involved in the manifestation of psychotic symptoms, while generally supporting the hypothesis of schizophrenia and related psychotic diagnoses as disconnection syndromes (Andreasen, 1997; Friston, 1999; McGuire & Frith, 1996). According to this hypothesis, the symptomatology of people diagnosed with schizophrenia is strongly associated with altered structural and/or functional communication between distant groups of brain regions that synergistically work as networks. As connectivity between the brain networks regulating resting state have been widely found to be altered in people diagnosed with

schizophrenia (Li et al., 2015; Zhou et al., 2015), the investigation of functional changes associated with spontaneously generated symptoms may shed light on their aetiology. Indeed, people diagnosed with schizophrenia who experience AH have several alterations to the resting state of their brain (Alderson-Day et al., 2016).

Methods such as electroencephalography (EEG) and magnetoencephalography (MEG) have been employed in attempts to identify the physiological processes closely associated with the experience of AH. Relative to other neuroimaging techniques, both EEG and MEG offer excellent temporal resolution (on a millisecond timescale) and allow for tracking brain activity through the scalp, with EEG measuring the electrical signals produced by groups of neurons, and MEG the associated magnetic field. MEG offers greater spatial resolution than EEG as magnetic fields are not significantly distorted, while the propagation of electrical signals related to neuronal activity is affected by the skull (Cohen & Cuffin, 1983). On the other hand, EEG is more accessible to a large number of investigators given its relatively lower cost and can easily be combined with functional magnetic resonance imaging (fMRI), in the attempt of revealing the binding mechanisms between different resting-state networks (Jann et al., 2010; Laufs et al., 2006; Mantini et al., 2007).

EEG studies have produced a significant amount of data and uncovered a range of electrophysiological changes associated with AH (Ford et al., 2012), which might reflect or provide information on the spatial characteristics of the neuronal networks involved (Uhlhaas et al., 2008), in line with the functional dysconnectivity hypothesis of schizophrenia (Andreasen et al., 1998; Friston, 1999).

In an attempt to identify more specific EEG patterns reflecting the perception of AH and a more consistent relationship between hallucinatory episodes and brain topography, a number of studies have also investigated resting-state EEG microstates (Kindler et al., 2011), subsecond time epochs with quasi-stable field topography that are thought to reflect transiently stable distributed neural networks. Microstates are separated by rapid changes of scalp field topography and, since different scalp fields are likely to reflect the unique activation of a neural network, it has been proposed that different microstates correspond to different brain functions (Lehmann et al., 2010). In this context, a specific class of microstates with a fronto-central distribution has been found to be consistently shorter in patients with schizophrenia when compared to healthy controls (Kikuchi et al., 2007; Koenig et al., 1999).

Finally, a significant contribution to the exploration of the underlying neural generators of abnormal EEG activity in schizophrenia is offered by low-resolution electromagnetic tomography (LORETA) EEG studies. In drug-naive symptomatic people diagnosed with schizophrenia, LORETA studies have revealed increased delta activity in the fronto-temporal region and decreased theta/alpha activity in the fronto-temporo-limbic area when compared with normal controls (Mientus et al., 2002; Pascual-Marqui et al., 1999). Beta frequency bands, however, have shown inconsistent differences in schizophrenia. For example, while Pascual-Marqui et al. (1999) reported increased beta activity mainly in right temporal areas, Mientus et al. (2002) found a trend for decreased beta activity.

In this context, the aim of the present systematic review was to discuss the main findings in resting-state EEG (including EEG-fMRI studies) and MEG research in people diagnosed with schizophrenia reporting AH and/or auditory verbal hallucinations (AVH), in an effort to offer an overview of the main frequency-specific changes that have been shown to be closely linked to such experiences. In particular, we sought to determine (a) whether the generation or perception of AH is linked to a specific pattern of altered frequency band oscillations; and (b) whether different types of AH (i.e., acousmata vs. AVH) reflect distinct EEG change patterns and/or originate in separate brain regions. The results will be discussed within the framework of the dysconnectivity hypothesis of schizophrenia, attempting to integrate different methods of investigation and data analysis.

Methods

A search was carried out in the PubMed and Web of Science online databases without date restrictions for English-language articles containing the terms: “(eeg OR qeeg OR electroencephalogram OR eegfmri OR eeg-fmri OR meg OR magnetoencephalogram OR megfmri OR meg-fmri) AND (auditory verbal hallucinat* OR auditory hallucinat* OR verbal hallucinat* OR (hear* voice*) OR (hallucinat* AND voice*)) AND (schizophr* OR psychosis)”.

We looked for EEG, MEG, and EEG/MEG-fMRI studies in adults diagnosed with schizophrenia-spectrum disorders, who experienced AH, during

resting state. We excluded reviews, book chapters, meeting and conference abstracts, editorial material, and publications in languages other than English. We also excluded studies where AH were not specifically mentioned.

The search was originally concluded on January 20, 2021, and then updated on September 20, 2022. The updated search returned 236 results from PubMed and 252 from Web of Science. We then applied the PRISMA method to exclude duplicates and studies not matching our inclusion criteria (Figure 1). The selection process yielded 16 articles. Of these, 12 studies employed EEG only, 8 MEG only, 2 qEEG-LORETA, and 1 EEG-fMRI. A descriptive summary of the papers included is presented in Table 1.

Figure 1. *PRISMA Flow Diagram for Systematic Review.*

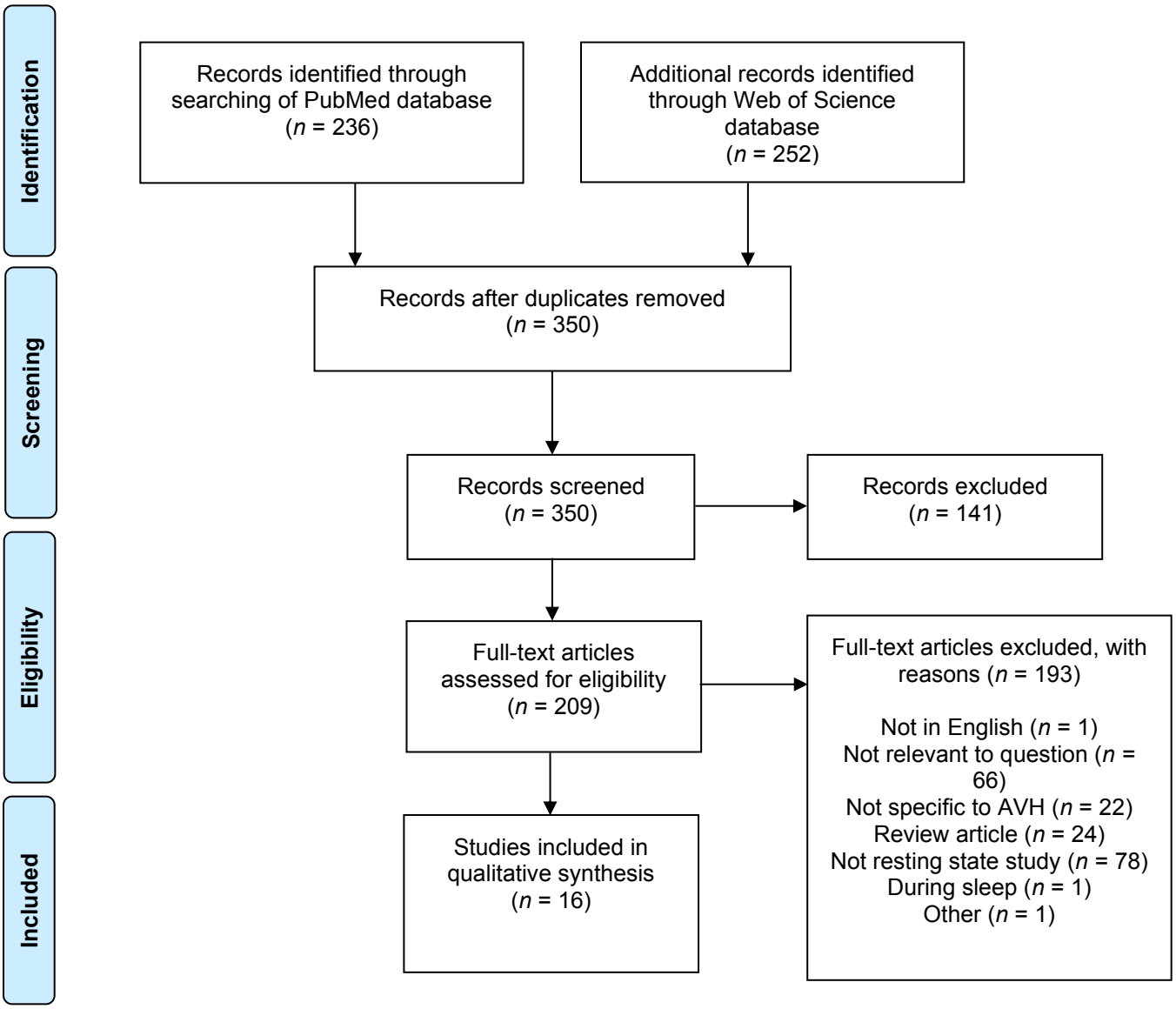

Table 1
Summary of the Reviewed Studies

Study	Population	Methods	Design	Results
EEG Studies				
Arora et al., 2021	SZ with AH (*n* = 12; 8 males, mean age = 44.25 years, *SE* = 3.16 years). SZ without AH (*n* = 12; 10 males, mean age = 45.67 years, *SE* = 3.16 years). HC (*n* = 12; 6 males, mean age = 39.75 years, *SE* = 3.16 years).	Spontaneous EEG.	Between-groups cross-sectional design.	Alpha activity was lower in patients with SZ and AH compared to patients with SZ and no AH in frontal areas bilaterally. Beta activity was lower in patients with SZ and AH when compared to patients with SZ and no AH. AH severity negatively correlated with alpha activity at F3, F4, P3, and P4. AH severity also negatively correlated with beta activity in the parietal area bilaterally.
Kindler et al., 2011	SZ with AH (*n* = 9; 6 males; mean age = 35.2 ± 11.7 years).	EEG (resting state/patients were asked to listen and attend to the voices and indicate the beginnings and endings by a button press).	Within-subjects design; experience of AH signaled by button press.	AVH were associated with shortening of Class D microstate.
Ahn et al., 2019	SZ with AH (*n* = 8).	qEEG measured during resting state, before/after transcranial alternating current stimulation.	tACS delivered and ΔEEG related to ΔAH.	Decrease of AH was associated with an increase in alpha-oscillation power in the left temporoparietal/frontal region.
Sritharan et al., 2005	SZ with AH (*n* = 7; 3 males, mean age = 31.9 years, *SD* = 4.9 years).	Spontaneous EEG.	Within-subjects design; experience of AH signaled by button press.	Increase in coherence between the left and right superior temporal cortices during AH vs. non-AH states.
Lee et al., 2008	SZ with AH (*n* = 25; 11 males, mean age = 39.2 years, *SD* = 6.8 years). SZ without AH (*n* = 23; 10 males, mean age = 38.5 years, *SD* = 7.1 years).	Spontaneous EEG.	Between-groups cross-sectional design.	SZ with AH patients had increased gamma frequency D2 in Fp2 (right prefrontal cortex) and decreased beta frequency D2 in the left parietal region.

Table 1
Summary of the Reviewed Studies

Study	Population	Methods	Design	Results
Angelopoulos et al., 2011	SZ with AH (*n* = 8; 4 males, mean age = 36 years, *SD* = 7 years). SZ without AH (*n* = 7; 3 males, mean age = 30 years, *SD* = 9 years). HC (*n* = 16; 8 males, mean age = 31 years, *SD* = 6 years).	Spontaneous EEG.	Mixed design. Between group cross-sectional analysis and within-subject design; experience of AH signaled by button press.	Increased phase-coupling of alpha band in patients with SZ and AH, distributed intra- and interhemispherically in the anterior brain areas. Increase of alpha-band synchrony in SZ patients with AH, compared to both SZ patients without AH and HC at the T7–T8 electrode pair interhemispherically.
Van Lutterveld, Koops, et al., 2012	SZ with AH (*n* = 24; 17 males, mean age = 41 years, *SD* = 14 years).	Spontaneous EEG.	rTMS delivered and ΔEEG related to ΔAH.	No correlations between changes in whole-head alpha-band or theta-band power and changes in AH.
Zheng et al., 2017	SZ with AH - medicated (*n* = 20; 12 males, mean age = 21.75 years, *SD* = 4.7 years). SZ with AH – unmedicated (*n* = 12; mean age = 21.21 years, *SD* = 6.72 years). HC (*n* = 22; 7 males, mean age = 22.91 years, *SD* = 6.91 years).	EEG (eyes focusing on a white cross on a black background on a computer screen).	Between groups cross-sectional design.	When the two SZ groups were compared, greater activities were found in RMFG (alpha and beta band) and LSTG (alpha and beta band) in the nonmedicated group when compared with the medicated group.
MEG Studies				
Ishii et al., 2000	SZ with AH (*n* = 1; one male, age 28 years).	Spontaneous MEG recordings.	Within-subjects design; experience of AH signaled by button press.	Increase in theta-band activity during experiences of AH. When AH reduced at follow-up, significant theta-band activity in the left superior temporal cortex was no longer detected.
Ropohl et al., 2004	SZ with AH (*n* = 1; male, age 33 years). HC (*n* = 13; all male, mean age = 31.3 ± 4.7 years).	Spontaneous MEG recordings.	Between groups cross-sectional design.	Increase of fast activity (12.5–30 Hz) in the left superior temporal cortex during AH in patients, relative to HC.

Table 1
Summary of the Reviewed Studies

Study	Population	Methods	Design	Results
Reulbach et al., 2007	SZ (*n* = 16; 9 males, mean age = 33 years, *SD* = 2.8 years) of whom 8 had AH. HC (*n* = 8; 4 males, mean age = 35 years, *SD* = 8.2 years).	Spontaneous MEG recordings.	Between groups cross-sectional design; experience of AH signaled by button press.	Greater number of dipoles in the fast frequency range (12.5–30 Hz) in SZ patients with AH when compared with SZ patients without AH. AH per se were associated with a concentration in dipoles on the left superior temporal gyrus and parts of the dorsolateral prefrontal cortex. AH involving commands were associated with a concentration of dipoles in parts of the left dorsolateral prefrontal cortex.
Sperling et al., 1996	SZ with AH (*n* = 3; 2 males). HC (*n* = 3; 2 males).	Spontaneous MEG recordings.	Between groups cross-sectional design.	Slow activity dipoles (2–6 Hz) were not increased in patients with SZ and AH over both hemispheres compared with HC. Patients with SZ and AH had greater fast frequency (12.5–30 Hz) activity in the temporal region of the left and right hemispheres.
Van Lutterveld, Hillebrand, et al., 2012	SZ with AH (*n* = 12; 8 males, age range 26–62 years).	Spontaneous MEG recordings.	Within-subjects design; experience of AH signaled by button press.	Experience of AH was associated with a decrease in beta-band power in the left temporal cortex and a decrease in alpha-band power in the right inferior frontal gyrus. The onset of AH was associated with a reduced theta-band power in the right hippocampus.
qEEG-LORETA Studies				
Lee et al., 2006	SZ with AH (*n* = 25; 11 males, mean age = 39.2 years, *SD* = 6.8 years). SZ without AH (*n* = 23; 10 males, mean age = 38.5 years, *SD* = 7.1 years).	qEEG/LORETA (eyes closed/eyes open).	Between groups cross-sectional design.	Gamma (30–50 Hz) and beta (2 and 3) frequencies were correlated in SZ with AH, but not in SZ without AH. Patients with SZ and AH had significant increase of beta 1 (13–18 Hz) power in the left inferior parietal lobule and in beta 2 power (19–21 Hz) in the left medial frontal gyrus when compared with patients with SZ and no AH.

Table 1
Summary of the Reviewed Studies

Study	Population	Methods	Design	Results
Horacek et al., 2007	SZ with AH (*n* = 12; 7 males, mean age = 34.4 years, *SD* = 9.1 years).	LORETA (eyes closed).	Within-subjects design; rTMS delivered and ΔEEG related to ΔAH.	Symptom improvement was associated with bilateral increase of current density in the delta power (anterior cingulate cortex), beta 1 and beta 3 power (temporal lobe) as well as beta 2 power (middle temporal and inferior parietal lobule).
EEG-fMRI Studies				
Hare et al., 2017	SZ with AH but no VH (*n* = 42; 32 males, mean age = 37.8 years, *SD* = 11.9 years). SZ with AH and VH (*n* = 40; 30 males, mean age = 37.2 years, *SD* =11.3 years). SZ with no hallucinations (*n* = 61; 44 males, mean age = 40.2 years, *SD* = 11.8 years). HC (*n* = 155; 110 males, mean age = 37.8 years, *SD* = 11.3 years).	Simultaneous EEG/fMRI.	Between-groups cross-sectional design.	Some evidence that AH were associated with decreased mean amplitude of low-frequency fluctuations (ALFF) across the posterior brain regions (cuneus and lingual gyrus). Also, ALFF was increased in the right inferior frontal gyrus and in part of the inferior temporal lobe.

Note. AH = auditory hallucinations; D2 = correlation dimension; EEG = electroencephalogram; fMRI = functional magnetic resonance imaging; HC = healthy controls; LORETA = low-resolution brain electromagnetic tomography; MEG = magnetoeletroencelography; qEEG = quantitative electroencephalogram; rTMS = repetitive transcranial magnetic stimulation; SZ = schizophrenia; tACS = transcranial alternating current stimulation; VH = visual hallucinations.

Results

The studies reviewed included a range of designs. Three studies compared people with schizophrenia with AH to healthy controls (Sperling et al., 1996; Reulbach et al., 2007; Ropohl et al., 2004). It is not possible to determine from such designs what activity is specific to AH and what is either related to schizophrenia per se or the use of medications.

Comparing People With Schizophrenia With and Without AH

Two studies compared people with schizophrenia with and without AH (Lee et al., 2008; Lee et al., 2006). Assuming that these patient groups do not differ on any factors except the presence of AH (a questionable assumption), such designs have the potential to identify neural activity associated with trait AH specifically. The most recent of these studies found that AH were associated with increased (more chaotic) gamma frequency correlation dimension in the right prefrontal cortex (Fp2) and decreased (less chaotic) beta frequency correlation dimension in the left parietal cortex (P3) region (Lee et al., 2008). The authors speculate that the more chaotic integration of gamma frequency information in the prefrontal cortex could represent difficulties differentiating internally and externally

generated sensory inputs, hence representing a misattribution process. In an earlier study, Lee et al. (2006) found that trait AH were associated with increased beta 1 and beta 2 frequency amplitude in the left inferior parietal lobule and the left medial frontal gyrus.

Comparing Healthy Controls and Schizophrenia Patients With and Without AH

Four studies compared neural activity between three groups: people with schizophrenia with and without AH, as well as healthy controls (Angelopoulos et al., 2011; Arora et al., 2021; Hare et al., 2017; Zheng et al., 2017). The study by Arora et al. (2021) found decreased beta-band activity to be associated with trait AH. This finding mirrored that of Lee et al. (2006) noted above. Arora et al. (2021) also examined correlations between AH severity and EEG activity, reporting that higher AH severity was associated with lower parietal beta activity. Arora et al. (2021) also reported that alpha activity was lower in people with schizophrenia with AH compared to those without AH in frontal areas bilaterally. Again, severity of AH was negatively correlated with alpha activity at frontal and parietal sites. Although Zheng et al. (2017) reported findings that could be interpreted as an increase in alpha-band activity being associated with AH, because these findings involved comparing a medicated and unmedicated group of patients such a conclusion may be unreliable. Angelopoulos et al. (2011) reported increased alpha-band phase-coupling to be associated with AH, both intra- and interhemispherically in the anterior brain areas, as well as an increase in alpha-band synchrony at the T7–T8 electrode pair interhemispherically.

Finally, in a multisite EEG-fMRI study that was able to differentiate between neural activity associated with auditory and visual hallucinations in schizophrenia, Hare et al. (2017) found some evidence that AH were associated with decreased mean amplitude of low-frequency fluctuations (ALFF) across posterior brain regions (cuneus and lingual regions) as well as increased ALFF in the right inferior frontal gyrus and part of the inferior temporal lobe.

State Experiences of AH

Five studies examined neural activity associated with state experiences of AH (Ishii et al., 2000; Kindler et al., 2011; Reulbach et al., 2007; Sritharan et al., 2005; Van Lutterveld, Hillebrand et al., 2012). These studies asked patients to press a button to signal experiences of AH and compared the activity during the presence of AH to periods when no AH were present.

Kindler et al. (2011) found AH to be associated with a shorter duration of Class D microstates in a fronto-central location. In terms of coherence, Sritharan et al. (2005) found increased coherence in the alpha frequency band between the left and right superior temporal cortices during AH. In terms of power, Van Lutterveld, Hillebrand, et al. (2012) found that experiencing AH was associated with (a) a decrease in alpha-band power in the right inferior frontal gyrus, (b) a decrease in beta-band power in the left temporal cortex, and (c) reduced theta-band power in the right hippocampus. In contrast, to this finding of reduced theta band, Ishii et al. (2000) found that experiences of AH were associated with increased theta-band activity during experiences of AH. When AH reduced at follow-up, significant theta-band activity in left superior temporal cortex was no longer detected, suggesting a causal role for increased theta-band activity in AH. Finally, Reulbach et al. (2007) reported that experiences of AH were associated with elevations of dipoles and dipole density maxima in the beta frequency range.

EEG Changes Related to AH Changes After Neurostimulation

Three studies examined how changes in EEG resulting from neurostimulation treatments correlated with changes in AH (Ahn et al., 2019; Horacek et al., 2007; Van Lutterveld, Koops, et al., 2012). The earliest of these studies found that improvements in AH resulting from rTMS were associated with bilateral increase of current density in the delta band (anterior cingulate cortex), beta 1 and beta 3 bands (temporal lobe) as well as the beta 2 band (middle temporal and in the inferior parietal lobule; Horacek et al., 2007). In contrast, Van Lutterveld, Koops, et al. (2012) found no correlations between changes in whole-brain alpha-band or theta-band power and changes in AH after rTMS. Finally, Ahn et al. (2019) found that a decrease in AH after transcranial alternating current stimulation (tACS) was associated with an increase in alpha power.

Discussion

Due to the use of a wide range of designs and forms of EEG analysis (e.g., power, coherence, microstates), there are very few reliable well-replicated findings in this area. The first takeaway from this review is hence the need for the creation of well-powered replicated studies that create a clearer picture of the nature of EEG changes associated with AH. Nevertheless, the disparate range of

findings do appear to often point in the same direction, particularly when we consider how the findings from intervention studies align with the findings from cross-sectional studies.

In terms of alpha-band power, the work of Arora et al. (2021) has provided evidence of lower alpha activity in frontal areas bilaterally being associated with both trait and state AH. Similarly, Van Lutterveld, Hillebrand, et al. (2012) found state experiences of AH were associated with a decrease in alpha-band power (specifically in the right inferior frontal gyrus). This suggests that improvement in AH should be associated with increased alpha power, which is what Ahn et al. (2019) found using tACS. However, it was notable that other studies had not found such changes in alpha-band power to be associated with neurostimulation-induced AH improvements (Horacek et al., 2007; Van Lutterveld, Koops, et al., 2012). The evidence of increased phase-coupling of alpha-band activity distributed intra- and interhemispherically, along with the finding indicating an increase in the frequency of AVH during an eyes-closed versus eyes-open task (Angelopoulos et al., 2011) also supports the assumption of an alpha-oscillation role in AVH generation.

Such findings are consistent with antipsychotic-related improvements in people diagnosed with schizophrenia being associated with enhancement of alpha oscillations (Jin et al., 1995). The meaning of such alpha-band changes is not clear. Although alpha oscillations have been shown to reflect idling (Pfurtscheller et al., 1996) or the active inhibition of task-unspecific brain circuits (Busch & Herrmann, 2003), there is also evidence for a positive correlation of the alpha amplitude with short-term memory and working-memory load (Jensen et al., 2002), as well as task difficulty (Sauseng et al., 2005). Notably though, Ahn et al. (2019) suggest an important “organizing role of alpha oscillations, which, when enhanced by stimulation, enable improvement of other, impaired network dynamics in other frequency bands” (p. 134).

In terms of beta activity, two studies found decreased beta-band activity to be associated with trait AH (Arora et al., 2021; Lee et al., 2006). Decreased beta-band activity was also associated with more severe AVH (Arora et al., 2021) and experience of AH (Van Lutterveld, Hillebrand, et al., 2012). Lee et al. (2008) also point to less chaotic beta frequency correlation dimension in the left parietal cortex region as associated with AH. Consistent with these findings, improvements in AH resulting from rTMS were associated with increases in beta-band activity in a range of temporal and parietal sites (Horacek et al., 2007). Another interesting finding was that the beta frequency power D2 in the left parietal brain region was lower in patients with AH when compared with nonhallucinating patients. It is known that beta oscillations follow periods of synchronous gamma activity (Kopell et al., 2000; Traub et al., 1999). Similarly, transitions from gamma to beta oscillations can be detected following the presentation of novel auditory stimuli (Haenschel et al., 2000), suggesting that beta oscillations might reflect the encoding of auditory stimuli.

In terms of the meaning or role of these beta-band alterations, beta oscillations are argued to be involved in signalling the novelty or salience of a stimulus (see Van Lutterveld, Hillebrand, et al., 2012). Alternatively, the link between decreased beta-band power and AH has been proposed to result from impaired corollary discharge signalling between frontal and temporal regions (see Van Lutterveld, Hillebrand, et al., 2012). There is hence the need to better establish the precise role of such alterations in beta-frequency power in AH.

Although, Van Lutterveld, Hillebrand, et al. (2012) found experiencing AH was associated with reduced theta-band power (in the right hippocampus), Ishii et al. (2000) found that experiences of AH were associated with increased theta-band activity. Other studies have failed to find alterations of theta power to be associated with AH, finding such changes to relate to schizophrenia per se instead (Arora et al., 2021). There is hence a need for a clearer picture of the role (if any) of theta-band changes in relation to AH.

There is also evidence for a direct association between phase synchronization or EEG signal coherence in frontal, temporal, central with parietal brain regions, and positive/negative symptoms of schizophrenia (Bob et al., 2008). Of note is the research suggesting that functional changes in left fronto-temporo-parietal resting-state language processing and speech monitoring networks, could be associated with the generation of AVHs (Wolf et al., 2011). Other resting-state EEG research, however, has revealed both decreases and increases in coherence associated with schizophrenia (Jalili et al., 2007) and the data analysis method used (i.e., multivariate synchronization analysis) should be further explored.

A potentially important finding is that the gamma frequency D2 in the right prefrontal cortex is higher in patients with AH. Gamma oscillations (30–50 Hz) are thought to play an important role in high-level cognitive processing (Tallon-Baudry & Bertrand, 1999). It has also been proposed that gamma activity is related to or reflects coherent object representations, perhaps mediating internally driven representations and memory storage (Allen et al., 2005). Previous research also indicates that the prefrontal cortex is implicated in the processes that allow a healthy person to distinguish between endogenous sensations from those induced by external influences (Frith, 1996). Thus, it is possible that a chaotic integration of gamma frequency information in the prefrontal cortex in patients with AH reflects the reduced ability to discriminate internal from external sensory inputs. In this context, Kindler et al. (2011) suggest that the reduction of specific microstate duration in schizophrenia may impair the correction of an erroneous misattribution of self-generated inner speech to external sources. However, it is also possible that increased D2 in the right prefrontal region of the brain is only a consequence of emotion processing during the perception of AH (George et al., 1996), which typically bear a derogatory and hostile tone.

Clearly, EEG studies pointing at alterations in the temporal lobe are consistent with the wider research literature on the localization of neural changes associated with AH (Jardri et al., 2011). Similarly, treatment studies aimed at reducing neural activity in the left superior temporal gyrus, through neurofeedback training (Orlov et al., 2018) and neurostimulation (Giesel et al., 2012) have reported reductions in AVH, although larger studies are needed to establish if genuine therapeutic effects are present (Guttesen et al., 2021). Understanding the specific type of activity associated with the presence of AH in this region could inform the future design of such studies.

Some of the studies reported here suggest the importance of distinguishing between AH and specifically AVH. In their MEG study on patients with both acousmata (unspecific noises) and AVH, Reulbach et al. (2007) identified the left superior temporal lobe and the left dorsolateral prefrontal cortex as the neural correlates of increased activity in the fast frequency range. However, within this population, patients hearing acousmata showed only a concentration of dipoles in the left superior temporal gyrus, while patients with AVH showed combined and confluent localization of dipole maxima in the left superior temporal gyrus and parts of the left dorsolateral prefrontal cortex. These results suggest a differential role of separate regions in the generation or perception of different types of AH (cf. Jones, 2010) and might also add to previous findings relating subsyndromes of symptoms to distinct cerebral flow patterns (Liddle et al., 1992) and metabolic changes (Cleghorn et al., 1992). They might also support and extend previous multimodal research, including MEG and MRI studies, suggesting the differential roles of the dorsolateral prefrontal cortex and superior temporal gyrus in AH (e.g., Kawaguchi et al., 2005; Shergill et al., 2000)

All the studies included in the present review were carried out in adult participants. Longitudinal studies in younger populations indicate that differential structural or functional and neurochemical changes take place at different stages of the illness, from the prodromal phase to the phase when the first psychotic episodes start to manifest (Keefe, 2014; Pantelis et al., 2005; Wood et al., 2011). This suggests that the profile for the abnormalities discussed in the present review could vary considerably during the illness progression and that the evidence gathered from investigations in adults should stimulate similar investigations with younger populations.

Also, most of the studies reviewed here included medicated patients, which raises the question of whether and to what extent the changes in the parameters reported were genuine consequences of the illness, drug effects, or a mixture of both (Koch et al., 2016). The differences found by Zheng et al. (2017) between nonmedicated and medicated patients suggest that more EEG research should investigate AH-related changes in first episode or drug naïve participants, with follow-up studies evaluating the effects of therapeutic interventions on selected measures. In this context, studies involving the administration of antipsychotic drugs and also other nonpharmacological interventions (e.g., neurofeedback training) should be considered.

In conclusion, at rest, frequency-specific changes in EEG activity may differentially contribute to the experience of AH in people diagnosed with schizophrenia. Whilst the results of studies in relation to alpha- and beta-band activity appear to line up well, there is still the need for large, well-powered and replicated studies in this area. Such work should take into account the potential to identify separate neural correlates for unspecific noises (acousmata) versus AVH, recruit participants at a range of stages of illness, and make use of both longitudinal and intervention studies.

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Declaration of Interest

All authors declare no conflicts of interest.

Author Contribution

Dr. Amico and Dr. McCarthy-Jones undertook the systematic review process. All authors contributed to the writing of the manuscript.

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NeuroRegulation

ISNR INTERNATIONAL SOCIETY FOR NEUROREGULATION & RESEARCH

Proceedings of the 2022 ISNR Annual Conference: Keynote and Plenary Presentations

Selected Abstracts of Conference Keynote and Plenary Presentations at the 2022 International Society for Neuroregulation and Research (ISNR) 30th Annual Conference, Orlando, Florida, USA

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KEYNOTE PRESENTATIONS

The New Psychiatry: Functional Medicine and HYLANE Technology

Robert Hedaya
Whole Psychiatry & Brain Recovery Center, Bethesda, Maryland, USA

The current paradigms underlying the treatment of most chronic or recurrent psychiatric disorders, and most neurodegenerative conditions, has been exposed as largely inadequate. Dr. Abraham Hoffer's pioneering work was extended by Dr. Hedaya through the formalized use of Functional Medicine which demonstrated full recovery in 100% of treatment resistant depression patients (retrospective analysis) in 2004. This is in stark contrast to the STAR-D trial which, using psychotherapy and polypharmacy, demonstrated a 25% long-term remission rate. In 2019, Dr. Hedaya discovered through the use of quantitative EEG, that even after substantial improvement in clinical symptoms with the use of a comprehensive functional medicine treatment, most neuropsychiatric patients continue to have abnormalities in cortical and network functions, which he has learned to correct using a combination of technologies (HYLANE). This has resulted in striking changes (e.g., the reversal of acquired prosopagnosia, MCI and temporal lobe absence seizures, partial reversal of moderate aphasia, reversal of facial distortion in paranoid schizophrenia, and reversal of cognitive decline in early vascular dementia [e.g., restoration of verbal memory from 66th to 95th percentile]. In this talk Dr. Hedaya will provide an overview of functional medicine, its efficacy and limits in neuropsychiatric patients, and the use of HYLANE technology as an effective augmentation strategy.

Multimodal Brain Music Interfaces to Promote Entrainment and Connection

Grace Leslie
Georgia Tech, Atlanta, Georgia, USA

Music is an important and universal means of communication. The feelings of connection and well-being that music creates are supported by a process in the brain and body called entrainment, in which our natural rhythms (speaking, walking, heartbeats, breathing, and even brain waves) synchronize with the rhythms we hear. The research activities I supervise at the Brain Music Lab at Georgia Tech expand on this powerful process by building software and hardware that translates brain and body rhythms into music and sound. I will review several music technologies that invite beneficial brain and body rhythms within and between listeners, and I will introduce the musical performance and composition practice I've developed in concert with these technologies. For researchers, doctors, and caretakers, this work has the potential to expand our scientific understanding of music's beneficial effects on the brain and body and may lead to new music-based interventions for adults, children, and infants.

The Connectome the Treatment of Behavioral Disorders Psychosurgery, Neuromodulation, Psychedelics, and HBOT

Joseph Maroon
University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

The human brain is a magnificent tapestry of billions of neurons, trillions of synaptic connections with axons woven into a network of nodes and thousands of fiber tracks or edges. Together, these structures constitute the connectome or "the wiring diagram" of the brain. How the "wiring" occurs is dependent upon neuroplasticity, genetic and epigenetic factors: transgenerational experiences, environment

exposure at all ages, diet, drugs, stress, and physical activity. Thus, our feelings, thoughts, memories, fears, behavior, and who we are are all imprinted in this incredibly complex 3-lb, gelatinous network of neuroplastic nervous tissue.

Traditionally, abnormal behavior or psychiatric disorders have been characterized by symptoms and clinical observations; hence, the *Diagnostic and Statistical Manual of Psychiatric Disorders* (DSM-5). Although diagnostic labels create the illusion of an explanation, they are scientifically meaningless, have no relationship to the actual structure or function of the brain, and can create stigma and prejudice. We now know dysfunction (depression, mania, PTSD, suicide) arises when functional alterations (miswirings) occur between large-scale neural networks. Thus, psychiatric disorders are actually "disconnection syndromes" primarily of the executive, default mode and salience networks.

Therapeutic attempts to structurally rewire or alter the functional connectivity of the brain began with frontal lobotomy (Egas Moniz, Nobel Prize). With elucidation of the limbic or emotional system of the brain, selective ablation of more specific targets and presently deep brain stimulation have evolved. More recently, various energy sources like magnetism (transcranial magnetic stimulation [TMS]) electricity (direct and alternating current stimulation [tDCS, tACS]) and light (photobiomodulation) are currently used to alter brain networks transcutaneously. These techniques selectively inhibit or disinhibit specific synaptic function in networks, which are either hyperactive or under active, and are proving effective for treatment resistant depression, anxiety, and even enhancing memory and cognition.

And now, with enhanced knowledge of the psychopharmacology of psychedelic drugs, LSD, MDMA, and psilocybin with their neuroplasticity and synaptic-altering effects are used in enhanced psychotherapy to modulate the connectome and human behavior. Hyperbaric oxygen therapy also is assuming a major role in the treatment of PTSD, postconcussion syndrome, and stroke. An overview of how understanding of the connectome and network neuroscience is revolutionizing neural circuit-guided treatment of disorders of behavior such as depression, anxiety, PTSD, schizophrenia, autism, and more will be presented.

EEG Connectivity in ADHD Compared to a Normative Database: A Cohort Analysis of 120 Subjects from the ICAN Study

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Introduction/Background. This study explores how EEG connectivity measures in a group of 120 children with ADHD ages 7–10 inclusive differ from an age-matched nonclinical database. We aimed to differentiate connectivity in specific networks, Brodmann area connectivity pairs, and frequencies.

Methods. Subjects were in the International Collaborative ADHD Neurofeedback (ICAN) randomized clinical trial, which explored neurofeedback (NFB) for ADHD. Inclusion criteria were mainly rigorously diagnosed ADHD and an EEG theta/beta power ratio (TBR) of at least 4.5. Pretreatment EEGs records were cleaned for analysis. Using statistical and machine learning algorithms, connectivity values were extracted in coherence, phase, and lag coherence at all Brodmann areas (BA) within the attention dorsal, attention ventral, default mode, executive and salience networks, and many subcortical and cerebellar locations in these same networks in each of the main EEG frequency bands. These values were then compared with a normative database and validated with Monte Carlo simulations.

Results. Compared to the normative database, the ADHD children had a higher rate of dysregulation (> ±1.97 *SD*), in some cases as much as 75%, of the Brodmann pairs observed in coherence and phase between areas 7, 10, and 11 with secondary connections to BAs 21, 30, 35, 37, 39, and 40. BAs 10 and 11 (L and R) are highly represented with dysregulated connections to each other.

Conclusion: The three most dysregulated BAs in ADHD are 7, 10, and 11 relevant to ADHD executive-function deficits (prefrontal dysfunction) and provide an important consideration when developing interventions for children with ADHD.

Addressing Ongoing Trauma Among Middle Eastern Journalists: When There Is No "Post" to Trauma Stress Disorders

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As a trauma consultant based in Beirut, I worked between 2016 and 2022 with dozens of journalists covering war and violence in the Middle East and

North Africa. Psychotherapeutic interventions, which came as part of regional and international programs supporting Arab journalists, took place remotely in the midst of local and regional conflict.

During the course of my work, I found that notions such as PTSD and vicarious trauma fall short of explaining the particular experience of my patients. Revolving largely around the reprocessing of past memories (e.g., PTSD) or the management of expected dangers (e.g., general anxiety disorders, hypervigilance), these terms, as we traditionally understand them, may not reflect the case of reporters trapped indefinitely in a social trauma in their homelands, even when off duty.

During conventional psychotherapy, sessions often take place in somewhat stable conditions, or at least in a context where traumatic stressors can be isolated. The local journalists I worked with were not only stuck in the battlefield, but they were also emotionally bound to it. The pain they reported every day was their own. Unable to distance themselves physically from the field, even when at home, journalists faced ongoing dangers as our sessions progressed.

During my presentation, I will propose the concept of ongoing trauma and discuss the creative promises of biofeedback in this context. Defined as a life-changing, terror-inducing, and highly stressful stretch of time, ongoing trauma often leads to a destabilized nervous system and eventually to mental disorders and relational tensions. In the case of ongoing trauma, the danger would still be real at the time of the psychosocial intervention, and the person would still fear for their life, unable to escape harm or to stop it.

During the talk, I will discuss the data accumulated during 400+ sessions with Arab journalists over the last six years, as well as the results of a trauma screening survey administered separately to 240 reporters in the region. I will present an overview of the key stressors and symptoms journalists in the Middle East faced and continue to face and will then address the challenges of therapy—especially of remote therapy—under these conditions.

More specifically, I will talk about the biofeedback approaches I have devised over time and in response to the extraordinary circumstances during which therapy took place; most journalist sessions were done remotely via Zoom, whereby journalists talked to me from home or from the office. No neurofeedback or biofeedback tools were available to them. Most importantly, many cases presented exposure to severe ongoing trauma, including recurrent violence and war, during the sessions.

In response to these challenges, I had to find creative approaches to biofeedback, improvising tools or exercises to help alleviate these cases remotely (e.g., using diaphragmatic breathing, body scans, body mapping, and tapping/EFT among others). As I shall explain, interventions adopted a multilayered combination of approaches:

- Grounding the body (mindfulness, grounding exercises, sensorimotor)
- Addressing self-appraisal (building agency through self-acceptance, self-efficacy)
- Addressing environmental challenges (finding “a way out” through problem-solving, building social support, career development)

PLENARY SESSION PRESENTATIONS

Freeze! You're Under Too Much Stress: Utilizing Neurofeedback for the Mitigation of Law Enforcement Stressors

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Throughout their careers, law enforcement officers will encounter a variety of hostile and trauma-related situations. Experiences such as assault (Kaminski et al., 2003), interactions with adverse citizens (Violanti & Patton, 1999), and altercations with perpetrators (Arnetz et al., 2009) relate to common stressors officers face. Although recent literature explores the relationship between these stressors with intrapersonal factors (Abdollahi, 2002), research on law enforcement stress is largely categorized within two groups; occupational and organizational (Symonds, 1970). Occupational stressors encompass the range of experiences faced in the field, while organizational stressors involve the internal hierarchical structure of the law enforcement vocation. Unfortunately, these career factors often have psychological and physical consequences (Carlan & Nored, 2008; Kop et al., 1999). The onset and development of stress, anxiety, anger, depression, and posttraumatic stress disorder (PTSD) are not uncommon with this population (Rajaratnam et al., 2011). Also, researchers continue to see neurobiological dysregulation and brain structural differences associated with PTSD and continued exposure to traumatic situations (Bremner et al., 1999; Kimble & Kaufman, 2004; Shucard et al., 2012). Moreover, several studies on occupational and

organizational stressors reveal a correlation with both career burnout and poor decision-making while on the job (Kohan & Mazmanian, 2003). With recent legislation identifying the need for mental health interventions among law enforcement officers (163 U.S.C. § 867, 2017), counselors have the unique opportunity to provide services to these professionals. Because the law enforcement occupation traditionally maintains engrained, protective stigmas and stereotypes regarding mental health (Loftus, 2010; Wester et al., 2010), counseling professionals must also consider these factors in conjunction with physical and psychological concerns when developing treatment plans. In this presentation, we propose the concept of integrating neurofeedback alongside a trauma-informed framework when assisting law enforcement officers. Through this lens, we consider multiple facets specific to this profession as well as counselor implications. Furthermore, this article aims to provide meaningful content promoting both career retention, mental health services, and future studies that advocate for law enforcement individuals.

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Determining the Effectiveness of Bioregulation Therapy/Pulsed Magnetic Frequency on the Reduction of Anxiety Symptoms

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Pulsed electromagnetic frequency (PEMF) was approved by the Food and Drug Administration (FDA) in 1979 and has been used to treat various illnesses for many decades. While there are many studies speaking to the benefits of PEMF on various physiological ailments, recent studies are emerging examining the effectiveness of this technology in the treatment of mental illness. This study aims to determine the effectiveness of combined bioregulation therapy and PEMF using the Nesta Bioreg device on symptoms of anxiety when compared to control. This is a single-blind study. A sham device will be used to control for a placebo effect. Adults between 18–65 years of age with a primary diagnosis of anxiety will be randomly assigned to the experimental or control group (n = 30, N = 60). Participants in the control group will go through the same procedural protocol as the experimental group apart from receiving active current. All participants will complete self-report measures at baseline, the beginning of each study week, study completion, and 3-month post completion. The HAM-A, BAI, SCL-90, and GAD-7 will evaluate the participants' level of anxiety and quality of life. When participants complete the baselines measures, they will complete one 30-min session of bioregulation therapy general foundation protocol for acclimation. Participants will receive either active or sham therapy twice weekly for 9 weeks to total 18 therapy sessions of specific anxiety protocols as crated by the manufacturer. Each session lasting around one hour, with protocol times ranging from 40–60 minutes. During therapy sessions, the participants will be asked to turn off electronic devices and remove electronic watches to reduce the electromagnetic interference produced by devices other than the Bioreg device. After completing data collection pretest–posttest scores will be analyzed to make between-group comparisons. Based on previous studies, it is hypothesized the active group will demonstrate

improvement in anxiety symptoms compared to the control group. After study completion, the control group will be offered complimentary active therapy and these results will be further analyzed for effect.

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Treating Acute COVID-19 with Photobiomodulation—Clinical Trial Results and Implications for Long Haul

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Although the concern for the COVID-19 has attenuated at this time, it is widely believed that it will not be eliminated. There is the ongoing concern that variants will continue to emerge, including the possibility of contagious and dangerous ones. While pharmaceutical manufacturers continue to develop vaccines as well as antibodies, there is still a large population that prefers a nonpharmaceutical option if available. In this respect, a randomized clinical trial (RCT) using a photobiomodulation (PBM) device to treat acute COVID-19 is completed with findings to show this potential.

Literature has shown that PBM is antiviral (Liu et al., 2003), anti-inflammatory (Hamblin, 2017), and accelerates the healing of lesions and sepsis (Costa et al., 2017); all are important factors in COVID-19 morbidity. These properties are supported by reports of rapid recovery in several severe hospitalization cases (Soheilifar et al., 2020). These are just a few cases, but the positive outcomes had warranted this RCT.

In this RCT, the patients self-treated at home, electronically uploaded answers to a set of questions daily, and were monitored remotely. The main outcome was the measure of time to recovery from moderate to severe sickness. The Kaplan-Meier method along with the Cox Proportional Hazards model were used.

The study enrolled 294 patients. For the primary outcome, patients who had symptoms for 0–5 days at baseline, the median for recovery in the treatment group was 18 days (95% CI, 13–20) versus the control group of 21 days (95% CI, 15–28), p = .05. Groups with symptoms for 6–10 days or 0–10 days did not show significant difference. The hazard ratio was 1.495 (95% CI, 0.996–2.243), p = .052 for the group with 0–5 days of symptoms.

For secondary outcomes, significant time to recovery were observed in many symptoms. None of the patients in the treatment group suffered death or a severe adverse event (SAE), while there was one death and three SAEs that required hospitalization in the control group. The results showed that the treatment group produced significantly faster time to recovery than the control group in patients with moderate to severe COVID-19 symptoms for 0–8 days before enrollment. When measured for severity of the respiratory symptoms over 30 days, a variety of symptoms also responded significantly better with treatment. There was also no significant worsening of symptoms in the treatment group.

The attention on the pandemic is shifting towards the long-term debilitating sequelae of chronic fatigue, depression, posttraumatic stress disorder (PTSD) on

the survivors, who are commonly known as "long haulers." Literature suggests that PBM has the underlying bases for neuroregulation to potentially address these.

This presentation will present the underlying mechanisms of PBM that lead to an effective treatment for COVID-19 and other coronavirus infections, and how the thoughtful selection of parameters can bring efficacy. It will present more details that includes those for secondary outcomes. The potential of PBM to treat long haulers will also be discussed, particularly the prospect of a new clinical trial that covers mental conditions.

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Neurophysiological Psychological and Social Assessment to Define an Integrative Treatment of Neurofeedback and Psychotherapy

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This presentation focuses on an integration of neurofeedback and CBT/schema therapy as treating clients as well as combining qEEG and CBT as assessment for the treatment.

The CBT Assessment (Sanavio) is an evaluation of the problem reported by the patient in order to conceptualize and understand the process or mechanism to explain the problem, define the therapy goal, and the treatment strategy. The hypothesis and measurements will be compared in baseline, midpoint, and the end of therapy. The assessment data are collected through three distinct source indices: 1) Subjective Index as recorded by patient counseling, family table, and self-reports test. The patient request of intervention is explained through the life story, measured with standardized test and questionnaire; 2) Behavioral Index reached by observation, role playing, diary; 3) Neurophysiology Index reached by biofeedback instrumentation and qEEG recording.

Conceptualization cases and its interventions are being presented according to these three distinct sources. 1) In the Subjective Index the data is compared to normative population, being evaluated by the schema therapy emotional unmet need and defense modes (Young, Arntz). The family table shows the patient representation of relationships, early maladaptive schemas and modes. 2) The Behavioral Index will be described by a therapy diary and clinical observation would show behavior modification and mode flexibility. 3) The Neurophysiology Index will be measured by qEEG, neurofeedback, and biofeedback.

Treatment is a tailored combination of top-down as for schema therapy and CBT, and bottom-up as for neurofeedback and biofeedback. While the Neurophysiology Index drives the neurofeedback intervention and the Subjective Index is chosen to explain and work with the cognitive parts and the schemas, the Behavioral Index would show the driving process.

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Bang, Bottoms Up: The Complexities of Comorbid Trauma and Substance Abuse

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Recent epidemiological research has revealed that around 57% of individuals with chronic posttraumatic stress disorder (PTSD) also struggle with chronic drug and/or alcohol abuse (Simpson et al., 2021). Rates of substance-related overdoses recently hit a record high of 81,000 deaths in the 12 months leading up to May 2020 (Centers for Disease Control and Prevention, 2020). PTSD and substance use disorders each involve a complex array of physical, cognitive, emotional, behavioral, and social challenges; this combination can make treatment especially challenging (American Psychiatric Association, 2013). As such, traditional substance abuse interventions, such as 12-step programs and psychotherapy, have shown high relapse rates of 65–70% within less than a year (Kadam et al., 2017). Considering these high rates of comorbidity and risk, it is important that neurotherapy practitioners take a comprehensive, integrative approach to give their clients the best chance at success.

Traumatic stress, especially during developmental years, is one of the primary suspects for predisposition toward substance abuse, both in terms of neurophysiological changes as well social and lifestyle variables. Preliminary evidence has also shown associations between adverse childhood experiences and dysregulation with the neuroendocrine, gastrointestinal, and immune systems, all of which have been associated with increased risk of addiction (Horn et al., 2018; Salavrakos et al., 2021). These can further exacerbate mental health symptoms and impair frontal regions required for healthy reward and inhibition, thus further propelling the cycle of substance abuse (Le et al., 2021).

Advances in neuroimaging technology have provided the opportunity to further examine neurophysiological factors associated with substance abuse. For example, increased susceptibility for addiction, whether due to genetic factors, psychosocial variables, or substance use, has been linked to reduced connectivity within frontostriatal networks. Hypoconnectivity of these networks can weaken goal-directed decision-making and control over habitual behaviors (Ersche et al., 2020). Chronic substance abuse can lead to prefrontal cortical disengagement, thus impairing stress regulation and reward processing, and ultimately exacerbating PTSD symptoms while reinforcing addictive behaviors (Le et al., 2021).

Neurotherapy interventions, such as neurofeedback and neurostimulation, have shown promise in their ability to balance dysfunctional brain regions, networks, and activation patterns associated with addiction and posttraumatic stress (Bari et al., 2018). This presentation will aim to summarize the current state of evidence for neuromodulation modalities as an intervention for comorbid PTSD and substance use disorders. We will also discuss the challenges of working with clients who are actively using substances, the effects of common substances on brain regions and activation patterns, and practical methods for effectively helping these clients achieve optimal wellness. Furthermore, we will explore future directions around how such modalities might be used to ease the process of quitting the substance,

reducing cravings, decreasing risk of relapse, and promoting more complete, lasting recovery. Due to the systemic effects of both stress and substance use, we will additionally provide education and recommendations for balancing other body systems. through an integrative neurotherapy approach to promote more complete, lasting healing.

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Is Artificial Intelligence the Answer to More Accessible Neurotherapy? Automating Individualized Care to Meet the Current Mental Health Crisis

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Although mental health issues and other behavioral disturbances do not always rise to the level of medical diagnostic criteria, the qEEG and neurofeedback community has demonstrated that multiple symptoms and behaviors in both clinical and nonclinical populations can be improved by EEG biofeedback. Neurophysiological changes and EEG abnormalities are often nonspecific to symptoms and expressed behaviors due to known confounds such as genetics, life experience, health status, brain injury, and now pandemic-related psychosocial stressors and neurological tissue damage from SARS-CoV2 infection. The traumatic brain injury field is familiar with this problem, widely acknowledging that “no two TBIs are alike.”

Neurofeedback offers compelling potential to improve psychosocial and cognitive-affective functioning for millions who are suffering, without the use of medications, and the need has never been greater. However, despite a half-century of development in the field, neurotherapy has not expanded beyond its status as a “boutique practice,” with only about 7,500 practitioners in the United States at present. A lack of consensus regarding evaluations and protocol development has created confusion and mistrust in the scientific community and the public. Potential practitioners must navigate a steep learning curve and invest significant time and money in training, equipment, and continuing education. Current models are often dependent on complex clinical decision-making to determine which metrics are included in the feedback process. These decisions are in turn dependent on clinician training, equipment capabilities, and experience.

Experienced clinicians continue to debate which “failure mode” in the brain should determine the feedback protocols used on any given subject. Within the last decade the complexity of protocol determination has exponentially increased as new modalities introduced various forms of external stimulation to drive brain processes or interrupt habitual circuit behaviors. Conventional models for assessing the effect of neurofeedback protocols have been insufficient to evaluate the constellation of outcomes reflecting changes in both homeostatic (internal) and allostatic (responses to external stimuli) processes, as can be demonstrated in a recent publication. Many interventions have not adequately appreciated and accounted for the complexity of the systems involved in producing any one component of EEG signal or in allowing for adequate response from a wide range of brain “failure modes.”

A new model of delivery is emerging which can provide affordable, accessible, effective neurotherapy. This presentation will describe an

artificial intelligence-driven approach that can individualize therapy on a large scale. We will discuss the evolution of prior neurofeedback paradigms and review recently published data that support the efficacy and rationale for using an integrated model of allodynamic, multinetwork neurofeedback training. These data will demonstrate that it is possible, using an algorithm-driven systemic paradigm, to individualize results within a heterogenous population of neurophysiologically dysfunctional brains.

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PMS Dysphoria Syndrome: qEEG Correlates and sLORETA Default Mode Network and Implications for Trauma

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Background. Women suffering from premenstrual dysphoria disorder (PMDD) often experience instability in emotions, compromised mental and physical health, and stressed interpersonal relationships, which influence work productivity and, subsequently, financial stability. The present study was the first to utilize archival premenstrual brain data to scientifically examine the differences in ROIs in the default mode network's (DMN) activity in broadband qEEG frequency bands across the follicular and luteal phase in PMDD/Dysphoric premenstrual syndrome (PMS) as compared to asymptomatic women.

Method. DMN neuroanatomical structures, Brodmann areas, hubs, and underlying cortical areas were established based on a review of the literature and the International 10–20 system. Brain activation patterns were measured by metrics of qEEG and standardized low-resolution electromagnetic tomographic analyses (sLORETA). A total of 157 women were classified by symptom category to include Asymptomatic/Control (70 women, M = 34.4, SD = 7.8) and PMDD/Dysphoric PMS (87 women, M = 35.0, SD = 5.4) where the categories depict the presence of heightened symptomatology. Asymptomatic women reported no or very mild premenstrual symptoms; PMDD women reported moderate to severe emotional and physical symptoms in the premenstrual phase.

Results. Statistical ANOVA and Median Tests using a minimum of $p < .02$ was used to determine significant findings. Significant differences in brain activation patterns were evidenced in key regions of interest on the DMN. Asymptomatic/Control women showed significant changes in the cingulate gyrus and the insula and showed changes in the percent of voxels from the follicular to luteal phase in the anterior cingulate, cingulate gyrus, insula, and the precuneus. Significant differences in the luteal phase mean-*z* (medians) between the PMDD group and the Asymptomatic group were reported in the subcallosal gyrus. Further analysis of the percentage of abnormal voxels revealed PMDD women with 19% abnormal

voxels as compared to 4% abnormal voxels for the Asymptomatic/Controls.

Discussion. Abnormal brain activity in PMDD women may implicate imbalanced neuronal activation patterns and the recruitment ability within specific DMN regions responsible for or intended to support affective processing and emotion regulation occurring with hormonal changes. These findings provide further insight into aberrant neural activation patterns within the DMN that can develop potentially from forms of trauma in the population of PMDD. Future research should address the psychophysiological interventions available to ameliorate dysregulated aberrant neural activation patterns in PMDD women. The findings will also be discussed in the context of prior analyses looking at the role of trauma in these subjects and the implications of trauma on neural receptor sensitivities and DMN functional reorganization.

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Frontal Gamma Microstates in Addiction and Recovery

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This report describes the basis for using sLORETA frontal gamma activation images in conjunction with automated clustering to identify microstates in a case of addiction and withdrawal. The gamma for ipsative validation using electroencephalography (GIVE) process accesses asymmetric gamma wave bursts in the prefrontal cortex to validate the underlying preconscious decisions behind these self-report responses at the very moment of decision-making. The process uses asymmetric wave analysis resulting from stimulus to validate the underlying mental decisions behind these reported responses, at the very moment of decision-making, thus exposing the true thoughts behind the responses and documenting potential abnormalities between their preassessments and their actual brain activity. This process provides evidence that an evoked emotionally laden response results in corresponding brain activity and documents both the intensity of human emotional responses and the directionality of the response.

We have also applied *k*-means clustering to EEG data gathered during test conditions, using the sLORETA-derived gamma (35–45 Hz) current source density magnitude as a metric. We chose Brodmann's areas 11 and 46, left and right, as indicators for relevant cortical processing. We chose $n = 16$ for the clusters, and watched for clusters that appeared to be repeats, or overlaps, as evidence that this number was sufficient.

We have demonstrated that the use of brain microstate analysis can be used to identify and quantify individual responses to material that has emotional or contextual meaning. We have described a model for human brain microstates that extends the concept of microstates from resting states to states associated with emotions and decision-making. It is shown that the instantaneous processing of words presented on a screen produces a stereotypical response that can be captured in sLORETA gamma activation measures taken 8 per second, for 1.5 s following the stimulus. This provides a promising

avenue for the study of individual responses to emotionally charged material.

The method of measuring instantaneous magnitudes and applying *k*-means clustering to the resulting distributions appears to be a useful and robust method for assessing the states that exist, and their relationships in time.

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QEEG Individualized Protocols for the Treatment of Alcohol Use Disorder

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Throughout United States history, alcohol use disorder (AUD) continues to be a national health concern. Within the last few years, pandemic stressors may also increase the potential for relapse in individuals struggling with AUD (Da et al., 2020). Medical professionals are imploring helping professionals to stay aware of this rising concern and to enhance AUD treatment options. Whereas treatments such as psychotherapy and pharmacology can be efficacious for AUD, there are also limitations to these types of interventions. AUD affects brain wave activity; while the prior mentioned treatments do not directly target brain activity, one treatment that does is neurofeedback. Neurofeedback is well documented for helping individuals with AUD, and other addiction concerns, to reach an enhanced state of regulation (Sokhadze et al., 2008).

After IRB approval and participant recruitment, my supervisor and I created qEEG individualized protocols while also considering Peniston and Kulkosky's (1989, 1990) seminal neurofeedback studies that recommend certain brain wave parameters for AUD protocols. In addition, we also referred to the Scott-Kaiser modification (Scott & Kaiser, 1998) of the Peniston Protocol. The Peniston Protocol uses alpha/theta training and seeks to reduce states of stress and anxiety, while the Scott-Kaiser modification (e.g., SMR-beta modulation) aims to reduce impulsivity tendencies by remedying cognitive issues (Dousset et al., 2020). Participants were asked to complete pre and post qEEG and heart rate variability (HRV) measures along with self-report assessments of pre, post, and follow-up measures of the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993), and repeated measures of a craving desire assessment after every neurofeedback session. Also, participants were asked to attend twice-weekly neurofeedback sessions for 6 weeks or at least twelve 10- to 25-minute sessions. University student clinicians and neurofeedback clinicians administered the neurofeedback sessions. Due to the pandemic and subsequent limiting factors (i.e., COVID concerns or lack of money for transportation), participants were allowed remote neurofeedback. Only one participant asked to utilize remote services.

The primary purpose of this study was to determine if qEEG individualized neurofeedback protocols helped participants regulate their brain activity and reduce AUD cravings. Secondary purposes included comparing physiological data to self-report data and exploring neurofeedback session-to-session changes with a single-subject approach. This poster presentation will include pre and post qEEG *z*-score comparisons from NeuroGuide and pre and post HRV comparisons from BioTrace. Further, I will explore individual changes over time according to participants' neurofeedback protocols using single-case research design methods and participants' individual craving desire changes. The presentation will also entail implications for future research.

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Comparison Between Audiovisual and Visual Beta Neurofeedback for Attention Enhancement

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EEG neurofeedback therapy (EEG-NFT) allows modulation of brain signals by either inhibiting or enhancing them and, consequently, improving the cognitive domain. One such domain is attention or peak performance, which is targeted by enhancing the beta frequency. The adult attention span has a duration of 20 minutes on average (Chaney, 2005). In Pakistan, inattention and hyperactivity among medical students shows 29.6% prevalence (Hamid et al., 2020). Most neurofeedback studies check efficacy for attention by visual feedback (Jurewicz et al., 2018). Visual and motor protocols are effective for task-based attention (Thomas et al., 2013) and auditory EEG-NFT, for meditation (Hunkin et al., 2021). No such comparison between the audiovisual and visual stimuli for attention enhancement exists, hereby creating a need for such study. We anticipated that beta EEG-NFT leads to changes in cognitive behavior. The objective is to compare the impacts of visual and audiovisual feedback on the subjects' behavioral, psychometric, and neurological aspects of attention. We have conducted a pilot study for attention enhancement with two groups: audiovisual NFT (10 subjects) and visual NFT (2 subjects) targeting the beta band (15–22 Hz). Six neurofeedback sessions, with five blocks per session, have been conducted on alternate days. This study has shown an increase in the mean beta power post-NFT followed by the psychometric and behavioral scores. The audiovisual feedback exhibited an increase of 36.15% mean beta power on average, while visual feedback showed an increase of 35.88%. This increase in beta power indicates an increase in attention. The proposed study is an extension of our pilot study to further validate the effect of EEG-NFT for improving attention with increased number of sessions. It consists of a pre-NFT qEEG recording in eyes-opened and eyes-closed conditions, for 2 min each, using a Mistar NVX52 DC amplifier, with 40 channels. ELAS and MAAS questionnaires and Stroop Test are conducted for pre-NFT and post-NFT. The EEG-NFT sessions are initiated with a baseline recording of 2 min in eyes-opened condition, using an EMOTIV EPOC+ 14-channel device. This baseline determines the threshold value for the feedback which, in this study, is set to be 10% of the baseline. The active feedback electrode is FC5, covering the right frontal and central region of the brain. The feedback mechanism works by video pausing itself when the beta power fails to cross the threshold value. The results of pilot study show a significant difference between the mean beta powers at the time prebaseline was recorded and during the NFT sessions ($p < .001$). Increase in prebaseline of all the subjects was evident from regression results. There was a significant difference between the pre-NFT and the post-NFT Stroop test response times ($p = .04828$). The results show successful attention enhancement. A reference for the experiments has yet to be set to find out whether audio plays a vital role along with the visual feedback and if the visual feedback on its own is sustainable enough to enhance the attention. The limitation of the ongoing study is the smaller number of participants and sessions.

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Dynamics of the Psycho-Emotional State and fMRI Neuroimaging During Biofeedback Training Course

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Background and hypotheses. Functional magnetic resonance imaging (fMRI) allows development of new insights about biofeedback mechanisms. The study was aimed at investigation of the specifics of the central processes during the game-based autonomic biofeedback and analysis of the psycho-emotional state of a trainee in the process of mastering the skills of self-regulation. Research hypotheses predicted that (a) the psycho-emotional state changes during biofeedback training will be featured by lower anxiety, decreased neuropsychic tension and the general improvement of emotional state, and (b) the fMRI data will allow to visualize the underlying cerebral network as a set of voxels in the areas of activation (AA).

Materials and methods. The study was conducted on 20 healthy volunteers aged 18 to 30 years, with high personality and situational anxiety and high scores on the neurotic scale (based on Eysenck, Spielberger-Khanin, SHAS, Taylor, and Zung Self-Rating Depression questionnaires). Training course included 10 sessions of heart rate biofeedback using the “BOS-Pulse” system “Vira!” game. Pre- and post-training course, 12 subjects participated in the fMRI-study of biofeedback effects.

Results. By the end of the training the ability for long-term volitional efforts, working capacity, and self-regulation skills increased. As a result of the training the level of neuro-psychic tension decreased significantly ($p < .001$). The situational anxiety decreased after the biofeedback training ($p < .001$) and scores on the scale of subdepression and depressed mood also significantly decreased ($p < .01$). The analysis of the dynamics of autonomic indices during biofeedback matched to the fMRI data allowed visualization of the underlying cerebral network as a set of voxels in the AA. It was shown that the “epicenters” of the AAs were prone to shift into the cerebellum and the brainstem during optimal cognitive strategy used by subjects. The growth of the AAs volume indicated the successive involvement of several networks. The architectonic areas of the cortex included the 37 Brodmann areas (BA) during the first stage, and BA 2, 7, 39, and 44, with the second and the third stages characterized by further involvement of the cortical structures of BA 6, 9, 19, 22, and 40. During the subsequent stages, the activation volumes declined, and AAs were maintained in the BA 6, 7, 37, and 40.

Conclusion. The course of heart rate biofeedback helps to reduce situational anxiety, improve mood, reduce neuropsychic stress, and increase the activity of mental activity (i.e., positively affects the general mental state). The integrative brain activity related to the course of the biofeedback media training points to the fact that developing of the skills of physiological functions self-regulation is accompanied by the activation of the sensory and associative (prefrontal and parietal) cortical areas, subcortical regions (the cerebellum) and is not limited to the cerebral structures that are traditionally considered as cognitive ones. During the learning to self-regulate the heart-rate AAs shifted to the sensory brain areas.

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Real-Time fMRI-EEG Neurofeedback for Stroke Rehabilitation

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In this study poststroke patients performed motor-imagery task and received feedback signal based on mu-rhythm desynchronization and functional activation in supplementary motor area (SMA) and dorsal premotor cortex (PreM) in the 6-session fMRI-EEG neurofeedback treatment course. The patients were enrolled within the period of 1.5–24 weeks from the stroke onset. The inclusion criteria were (a) right-handedness patients aged over 45 years; (b) verified stroke-related hand function impairment; (c) ability to tolerate tests in the MRI; scanner and lie still within the training sessions; (d) mild cognitive impairment allowing them to understand instructions; and (e) while featuring no other severe condition. An ischemic stroke was verified with neuroimaging and other clinical criteria (i.e., MoCA scores, Ashworth scale scores, lower and upper limbs paresis scores, etc.). The study aimed to test the effectiveness of fMRI-EEG neurofeedback. Both control and experimental group patients were admitted to the hospital for 2–3 weeks and were subject to standard medical rehabilitation procedures. At the beginning and end of the treatment course, diagnostic fMRI-EEG sessions were recorded, including structural MR-tomography, resting-state condition, motor-execution and motor-imagery tasks. Patients from the experimental group have participated in six neurofeedback sessions, consisted of two 10-min runs with eight regulation blocks. Each block began with a 20-s rest, then the patients were given 40 s for a motor imagery trial, and then feedback on a scale of 0 to 100 demonstrated for 10 s. SMA and PreM contralateral to the injured hand were chosen as fMRI targets, and desynchronization in mu (8–13 Hz) and beta (18–26 Hz) frequency band for C3 and C4 electrodes as EEG targets. OpenNFT software was used for collecting, preprocessing, and modelling of real-time fMRI data. In the EEG case, data were cleaned of scanner and cardioballistic artifacts using RecView (Brain Products) software. The fMRI-EEG data have been collected for eight patients of the experimental group (five – left, two – right hemiparesis, one was excluded later due to artifacts) and six of the control group (three left and right). In the experimental group on average significant ($p < .05$) positive percent signal change of fMRI signal in PreM is revealed for 45% of neurofeedback sessions and 51% in SMA. Despite a positive linear trend in total fMRI-EEG feedback scores for four patients from seven over the treatment course, there is no group differences in this value between sessions. There were (a) significant interaction between time and group factor on the Kinesthetic and Visual Imagery Questionnaire (KVIQ) scale ($F = 5.849$, $p = .034$) using a repeated measures ANOVA with 2x2 design, and (b) significant Spearman correlation coefficient of session number with box-n-blocks test dynamic in the experimental group ($r = 0.986$, $p < .001$). More patients are required for the better statistical results. In addition, dynamic causal modelling is needed for investigation of effective connectivity before and after intervention.

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Braingomo: An Innovative Smartphone-Based Neurofeedback Platform

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Neurofeedback is the brain training during which individuals learn to regulate the brain activity voluntarily for the side effect free treatment of many neurological and psychological conditions (Marzbani et al., 2016). For example, a large body of clinical research, including meta-analyses, has consistently shown that neurofeedback serves as an effective treatment for attention-deficit/hyperactivity disorder (ADHD) with its standard training protocols and long-term treatment outcomes (Arns et al., 2014; Cortese et al., 2016; Van Doren et al., 2018). Considering the continuously increasing acceptance of neurofeedback and its profound treatment outcomes, we aim to further contribute to the field by developing the Braingomo platform. The Braingomo platform is an innovative smartphone-based neurofeedback platform that provides home-based brain training under the supervision of a clinician, thus bringing neurofeedback to anyone, anywhere, and anytime. Braingomo is composed of a mobile EEG system with dry electrodes as the hardware, and a smartphone app and a web server as the software. We acknowledge that good brain training needs good data quality. Accordingly, the main part of the Braingomo innovation comes from our self-designed and self-manufactured dry electrodes that provide high-quality data. We have developed copper and conductive polymer-based electrodes that both have high electrical conductivity based on the microvolt range of human brain waves (Chen et al., 2014). The copper electrodes have good conductivity throughout the scalp (e.g., occipital region), due to the diagonal pins that pass through any amount of hair, thus recording brain activity from any scalp region. The polymer-based electrodes have softer pins, thus suitable for sensitive skins. Both electrodes have a high life span and a high signal-to-noise ratio but low production costs. Moreover, they are compatible with any standard cable due to their connections through standard snap buttons. The prototypes have shown promising results with a high potential to be improved further by coatings as well as better design and production path. We also acknowledge that treatment outcomes depend on several neurofeedback parameters such as training intensity and repetition as well as psychological factors including individualization of the training and coaching that further affect the motivation and adherence to the training (Kadosh & Staunton, 2019). Accordingly, as another innovation, we implement all these parameters into the Braingomo platform by combining the software's smartphone app and web server. Smartphone app receives brain activity and analyses it in real time for brain training anywhere and anytime, thus providing flexibility in training time and place. Moreover, it has many appealing game options with a reward system, thus increasing the motivation and adherence to the training. The connection between the smartphone app and the web server provides supervision and control by clinicians over training sessions and training reports, thus providing supervised and individualized training outside of clinics. We consider that the Braingomo platform offers a novel neurofeedback approach that has a high potential to decrease the accessibility limit of neurofeedback, thus contributing further to the widening of the neurofeedback applications, acceptance, and treatment outcomes (Bussalb et al., 2019).

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QEEG-Guided sLORETA Neurofeedback Effects on Event-Related Potentials and Cognitive Performance on a Stroke Sufferer: A Case Study

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Cognitive and motor impairments are highly prevalent and persistent in stroke survivors. Network disruptions caused by a stroke event on brain regions implicated in the different aspects of cognition can significantly impact the quality of life. Accordingly, targeting both focal cortical tissue damage and nonfocal global changes in brain function should be considered when developing therapeutic strategies to improve brain dysregulation, recovery rate, and cognitive performance of brain injury survivors. In this regard, the use of standardized low-resolution electromagnetic tomography analysis (sLORETA) *Z*-Score neurofeedback (sLZNFB) is a promising approach to target dysregulation in networks on deep cortical locations. The present study aimed to explore the effects of sLZNFB on brain electrophysiology and cognitive performance for a 67-year-old male who suffered a stroke in the left hemisphere (speech difficulty and right hemiparesis were presented at intake). The study used a pre-experimental design with pre–post comparison. To this end, sLZNFB (surfaces plus coherence training) was applied to affected brain areas for 15 sessions. An eyes-open training approach was conducted as the patient showed low engagement/arousal at the initial stages of recovery. Baseline and post measurements were made on qEEG metrics, event-related potentials at Pz (oddball paradigm), attention, memory, executive function, reaction time, and cognitive flexibility. Clinical improvements were found in attention, memory, and reaction time after 15 sessions of sLZNFB on computerized cognitive tasks. QEEG Z-score maps show positive changes on frontal high frequencies and left posterior delta. Improvement in connectivity variables was observed across all frequencies. Greater discrimination and less latency for auditory stimulus were also found on P300 ERP component analysis at Pz after the intervention. In addition, significantly improved speech and motor function were also observed at session #8. These findings suggest the potential effectiveness of sLZNFB on cognitive performance improvement among stroke sufferers. Further studies with a larger number of patients and control groups may be required to evaluate the full potential of this type of training in stroke patients.

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Effect of TMS on EEG Biomarker in a Patient with PTSD Performance on a Stroke Sufferer: A Case Study

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Background. A large majority of the United States population will experience at least one traumatic event in their lifetime, and 5–10% will go on to develop posttraumatic stress disorder (PTSD; Yehuda et al., 2015). Trauma-focused therapy is the recommended treatment for PTSD, but 30–50% of patients do not respond (Jonas et al., 2013). There is significant interest in using focal neuromodulation, such as transcranial magnetic stimulation (TMS), to induce functional brain changes as a potential treatment for psychiatric disorders (Zandvakili et al., 2019). Quantifying TMS's functional and neurophysiological effects and their link to symptom severity change is essential to understanding TMS's neural mechanisms and developing more effective and individualized TMS therapies. This study

explores an electrophysiological biomarker by comparing electroencephalography (EEG) signals before and after 10 days of TMS in patients with PTSD symptoms.

Method. Four female patients (age 36.5 ± 16.3) with PTSD symptoms underwent our TMS study procedures consisting of 20 sessions (1800 pulses each) of 1 Hz to the right dorsolateral prefrontal cortex (DLPFC). We assessed the patient's PTSD symptom severity using the PTSD checklist for DSM-5 (PCL-5) before and after the 10-day treatment. Additionally, we recorded EEG signals using a 14-channel wireless EEG headset (Emotiv, San Francisco, CA) with a 128 Hz sampling rate for 6 min at these time points. The 14 channels include AF3, AF4, F3, F4, F7, F8, FC5, FC6, T7, T8, P7, P8, O1, and O2 (Duvinage et al., 2013). We segmented each session of EEG signal into 5-s nonoverlapping epochs. Next, for each epoch, we extracted spectral power features including theta (5–8 Hz), alpha (9–12 Hz), and beta (13–30 Hz) of both pre- and post-TMS for each contact. We trained a five-fold nested cross-validation logistic regression (LR) with elastic net regularization (ENR) to classify pre- and posttreatment states based on the spectral power feature of each contact separately. The receiver operating characteristic (ROC) of the cross-validation and area under the curve (AUC) was used to measure the classifier performance (Sendi et al., 2021). Finally, we used ENR as a feature learning method to find the feature with the most contribution in the classification.

Results. In this study, we only analyzed data from one patient who showed a 40% reduction in PTSD symptom severity after a 20-session TMS treatment. We found that frontal contact, including AF3 and F3, were the top two contacts separating the pre- and posttreatment conditions with an AUC value of 0.78 ± 0.09 and 0.68 ± 0.13, respectively. Additionally, we found that the AF3 beta and F3 theta power have the highest contribution in classifying pretreatment and posttreatment conditions ($p < .001$).

Conclusions. This $N = 1$ study shows that frontal contacts significantly separate pre- and post-TMS conditions and change in PTSD symptoms, suggesting its relevance for TMS response biomarker in PTSD. Data collection and analysis is ongoing and future study is needed to explore other EEG features across multiple patient data.

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Loreta *Z*-Score Neurofeedback in Nine Clients with Anxiety and Posterior Cingulated Deviations

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Loreta *Z*-score neurofeedback training (LZNFB) is an individualized method of neurofeedback. This method trains specific brain hubs and networks towards $Z = 0$, which are the most deviant for each individual client and the most likely linked to their symptomatology. Studies investigating the efficacy of LZNFB are promising in that they often show a significant decrease in symptoms. However, too few studies report qEEG changes among their outcome measures. The aim of this pilot study is to bridge this gap in LZNFB research, investigating results in a subgroup of clients with anxiety and posterior cingulate gyrus abnormalities.

Participants. Nine adult clients (five men, four women, age $M = 32.72$, $SD = 10.73$) with mental health complaints filled in the Brief Symptom

Inventory (BSI-53) before and after their neurofeedback therapy. They all reported anxiety as a main symptom and had significant deviation in the posterior cingulate gyrus before LZNFB.

Method. All clients started with an intake and qEEG assessment, guiding their LZNFB protocol. Before the first training session patients filled out the BSI-53 in order to clarify symptoms related to the physiological profile. Each LZNFB session lasted between 30 and 40 minutes. The training protocols were designed to target a neural network, that has a significant role in the client's symptomatology and includes the posterior cingulate gyrus. Since this study was made in a clinical setting, each client did a number of sessions limited to their financial possibilities. After their last session, they filled the BSI-53 again.

Results. The participants did 16 sessions on average (*SD* = 3.87). On average, the global BSI-53 scores before neurofeedback (*M* = 3.96, *SE* = 0.73) were higher than after neurofeedback (*M* = 0.78, *SE* = 0.35). This difference, 3.18, was significant, *t*(8) = 4.02, *p* < .01, and represented a very large effect size of *d* = 2.45. The scores on the anxiety scale of the BSI-53 was also better after neurofeedback (*M* = 0.76, *SE* = 0.46) than before neurofeedback (*M* = 4.25, *SE* = 0.62). This difference, 3.49, was significant, *t*(8) = 4.49, *p* < .01, and also represented a very large effect size of *d* = 3.35. The average standard deviation (across all frequencies left and right) in Brodmann area (BA) 31 decreased from a mean of 0.83 (*SE* = 0.08) before neurofeedback to a mean of 0.60 (*SE* = 0.74) after neurofeedback. This difference, 0.23, was significant, *t*(8) = 3.17, *p* = .01, and also represented a large effect size of *d* = 1.05. The only noticeable side effect was fatigue, which subsided within a day after each session. Interestingly, there was a significant correlation (*r* = 0.71, *p* = .03) between difference in anxiety scores and difference in BA31 deviation.

Conclusion. LZNFB shows promise to improve anxiety in a subgroup of patients with posterior cingulate gyrus abnormalities. The more the posterior cingulate gyrus normalized through LZNFB, the more the anxiety score decreased. This could confirm both the working mechanism of LZNFB (bringing subjective progress through changes in brain activation patterns), and the role of the posterior cingulate gyrus in anxiety symptoms. These findings and the conclusions that it could bring, remain to be confirmed in a larger sample.

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The Application of Biofeedback and Neurofeedback in Underserved Children and Adolescents in Pediatric Neurology

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Mental health issues represent a major global economic burden and affect 21% of adults in the U.S. each year. According to the Centers for Disease Control and Prevention, 1 in 5 children living below the United States federal poverty line has a mental, behavioral, or developmental disorder.

As underserved communities lack resources and access to medical and mental health care, their social and environmental difficulties, as well as their cultural, systematic, and individual barriers, are magnified. The need for a comprehensive approach to reduce disruptive mental disorders in children from minority populations is therefore imperative. Despite the wide avenue of treatments available, these children and families are less likely to seek and receive such services. Biofeedback therapy and electroencephalography (EEG) biofeedback are noninvasive therapeutic techniques that have been shown to regulate brain activity and improve clinical symptomology of neurological conditions including depression, anxiety, and migraine. Although there is indeed a wealth of studies that regard strong evidence of the therapeutic effects of biofeedback training on mental health problems, nationally representative evidence on minority individuals in these studies remains scarce. To date, the biofeedback framework has been built without enough appreciation of pertinent factors such as race, ethnicity, and culture and their underlying determinants of health. This is especially true for children and adolescents living in underserved communities which represent a high-risk population aggravated by network inadequacy in healthcare. Therefore, it is imperative and a growing urgency to study the effectiveness of these therapies in children living in historically marginalized communities. While there are only a handful of studies that have tried to shed light on this knowledge gap, most of them were performed and carried out in nonclinical settings. Our ongoing study aims to investigate the application of biofeedback and neurofeedback in underserved children and adolescents, ages 7 to 21, treated at an outpatient site at the Vanderbilt Clinic in New York-Presbyterian Hospital at Columbia University. We will present a thorough analysis of results and demographics gathered from approximately 50 underserved patients, primarily Hispanic and Black, during intervention sessions. Patients initially presented negative symptoms associated with either anxiety, depression, or migraine. An intervention treatment plan of biofeedback or neurofeedback was tailored for each patient prior to the commencement of the first session. Our preliminary data suggest clinically significant improvement in most of the symptom-related outcome variables. We will discuss thoroughly the limitations and challenges of the current study. To our knowledge, this is the first research study exploring the implementation of biofeedback and neurofeedback in ethnic minority groups in the United States, especially children and adolescents. This study will highlight the meaningful incorporation of biofeedback and neurofeedback services in pediatric neurology practices to provide underrepresented populations access to this health service, who would otherwise not receive it. We understand the significance of bridging this gap for health equity in clinical practice and biomedical research representation, and we aim to encourage others to join these efforts.

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Power Spectrum Analysis in a SMR/Theta Neurofeedback Protocol Using Different Behavioral Strategies

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The literature reports that it is possible to modify the pattern of electroencephalographic (EEG) activity from neurofeedback techniques; however, such findings continue to have limitations. One of the most widely used clinical protocols consists of increasing sensorimotor rhythm (SMR) and simultaneously decreasing theta activity with the aim of increasing attentional performance and reducing hyperactive and impulsive behaviors. The SMR band is characterized by a frequency of 12–15 Hz and is the expression of synchronized oscillatory activity, reflected in the sensory motor cortex; it is associated with body movement and the ability to concentrate (Gruzelier et al., 2010). SMR neurogenesis emanates from the ventrobasal nucleus of the thalamus which is generally related to the conduction of somatosensory information (Gruzelier et al., 2010). The protocols that train SMR/theta report the use of different behavioral strategies to favor the production of trained rhythms; however, there is no consensus regarding the use of which strategies are more effective. On the other hand, there are SMR/theta protocols that are not combined with any behavioral strategy, and participants are successful in the protocol. (Binsch et al., 2017; Crivelli et al., 2019; Dessy et al., 2020; Gonçalves et al., 2018; Jirayucharoensak et al., 2019; Lee et al., 2019; Shtark et al., 2018; Skottnik et al., 2019; Pei et al., 2018; Wood, Brickwedde, et al., 2019).

The objective is to analyze the effect of the following behavioral strategies: guided imagery, mindfulness, or heart rate variability (HRV) during a neurofeedback protocol on absolute SMR/theta power in healthy volunteer participants. In this study, 25 healthy volunteer participants between 21 and 50 years old were assigned to four groups: (a) Comparison group: NRA, n = 8; (b) Intervention group 1: NRA + HRV, n = 6; (c) Intervention group 2: NRA + guided imagination, n = 5; and (d) Intervention group 3: NRA + mindfulness, n = 6. The absolute power of each of the frequency bands was analyzed with the continuous wavelet transform. Likewise, the contribution factor of the area under the curve of each brain frequency was compared. The nonparametric Spearman's Rho test was performed to assess the degree of correlation between the contribution factor of the SMR/theta frequency bands and the number of training sessions.

The behaviors observed both in the contribution factor and in the power indicate that the behavioral strategies used to train the SMR/theta rhythms differ in their effect, so it is important to standardize the strategies proposed in the SMR/theta protocols.

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Effect of Transcutaneous Electrical Nerve Stimulation of the Auricular Branch of the Vagus Nerve for the Treatment of Anxiety

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Background. Vagus nerve stimulation is a known technique to modulate autonomic function (Clancy et al., 2014) and is FDA approved for the treatment of certain diseases like depression and epilepsy. However, traditional stimulation methods are invasive, require an implant, and are reserved for

severe or drug-resistant cases and approval for use in anxiety-related diseases has yet to be achieved.

Objective. The purpose of this study was to assess the safety and efficacy of transcutaneous auricular vagus nerve stimulation (taVNS) compared to a sham taVNS in patients with anxiety using a novel neurostimulation device.

Methods. A randomized, sham-controlled approach was used to investigate the effects of active or sham taVNS on state-anxiety in 24 participants as scored by the State-Trait Anxiety Inventory (STAI). Participants completed a stress-inducing task before and after using a sham or active neurostimulation device at a target site over the proximal lateral cervical region containing the auricular vagus nerve. The STAI was used to measure anxiety before and after each stress-inducing task was completed. Upon completion of the tasks and treatment, the safety and tolerability of the device were assessed. EEG and physiological measures were recorded throughout the study tasks. Results were examined to compare the change in anxiety levels, EEG, physiology, task performance, and safety and tolerability measures before and after treatment with the P57 ONE (sham vs. active).

Results. A Fisher's Exact Test was used to quantify the relationship between immediately after and 24 hours after safety reports (yes or no) of discomfort, dizziness, blurred vision, headache, skin irritation, relaxation, and distraction from the stimulation protocols (sham vs. stimulation). An unpaired *t*-test was used to compare average levels (1–10) of comfort, discomfort, dizziness, blurred vision, headache, skin irritation, relaxation, and distraction ratings immediately after stimulation and at least 24 hours after stimulation between each protocol group. An unpaired two-tailed *t*-test was used to compare the difference (post and pre) in state-anxiety, EEG, physiology, and task performance between active and sham stimulation groups. Analyses for safety and tolerability ratings found no significant differences between active and sham users immediately after or 24 hours after stimulation. Compared to the sham group, the active treatment group reported the experience as relaxing more frequently (p = .001) and a greater level of relaxation (p = .002). Analysis of STAI, EEG, physiology, and performance data is ongoing; these results will be presented during the poster session.

Conclusion. This study provides preliminary evidence in support of using taVNS to elicit a beneficial effect on relative anxiety via increased relaxation. Stimulation of the target site with a novel neurostimulation device was found to be both safe and tolerable. Analysis of STAI, EEG, physiology, and performance data will be presented to address efficacy aims. This technique of noninvasive stimulation could be a new effective method to quickly reduce anxiety without having to resort to pharmaceutical or invasive intervention.

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