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

Francesco Amico[1], Michael Keane[2], Meredith Lee[2], and Simon McCarthy-Jones[1]*

[1]Department of Psychiatry, Trinity Centre for Health Sciences, St. James Hospital, Dublin 8, Ireland
[2]Actualise, Dublin 1, Ireland

Abstract

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

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

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***Address correspondence to**: Dr. Francesco Amico, c/o Dr. Simon McCarthy-Jones, Department of Psychiatry, Trinity Centre for Health Sciences, St. James Hospital, James's Street, Dublin 8, Ireland. Email: amicof@gmail.com

Edited by:
Rex L. Cannon, PhD, Currents, Knoxville, Tennessee, USA

Reviewed by:
Rex L. Cannon, PhD, Currents, Knoxville, Tennessee, USA
Wesley D. Center, PhD, Liberty University, Lynchburg, Virginia, USA

Introduction

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

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

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

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

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

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

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

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

Methods

Recruitment

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

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

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

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

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

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

Participants

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

Table 1

Assessment Scores of Participants.

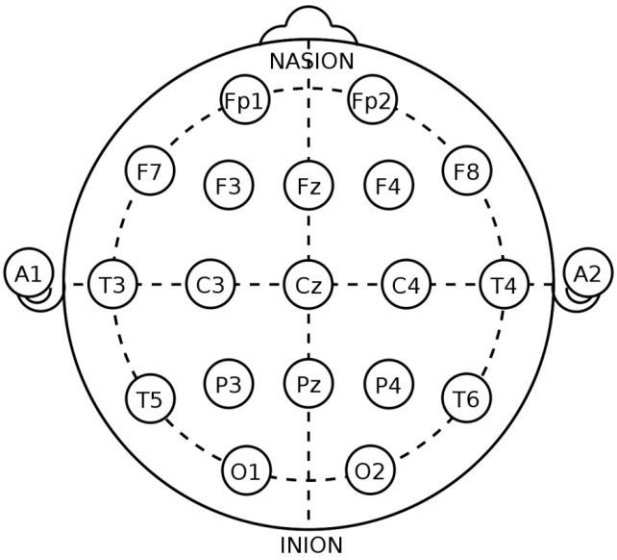
	Patient A 20 sessions		Patient B 11 sessions		Patient C 8 sessions		Patient D 14 sessions	
Study measures	Baseline	End	Baseline	End	Baseline	End	Baseline	End
PSYRATS-AH	21	15	21	28	20	16	23	27
PSYRATS-D	16	11	16	15	*	12	15	15
AHRS	20	24	21	20	15	10	33	31
HADS (anxiety)	10	13	5	13	10	12	10	5
HADS (depression)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

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

EEG Data Aquisition

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

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



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

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

Neurofeedback Training

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

NFT Protocols

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

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

Regions of Interest and Target EEG Measures

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

effects on alpha coherence for the electrode pairs C3-C4, C5-C6, T3-T4, P5-P6, and F7-F8.

qEEG Data Analysis

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

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

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

Results

Feasibility of Recruitment

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

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

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

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

Participants

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

qEEG

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

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

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

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

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

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

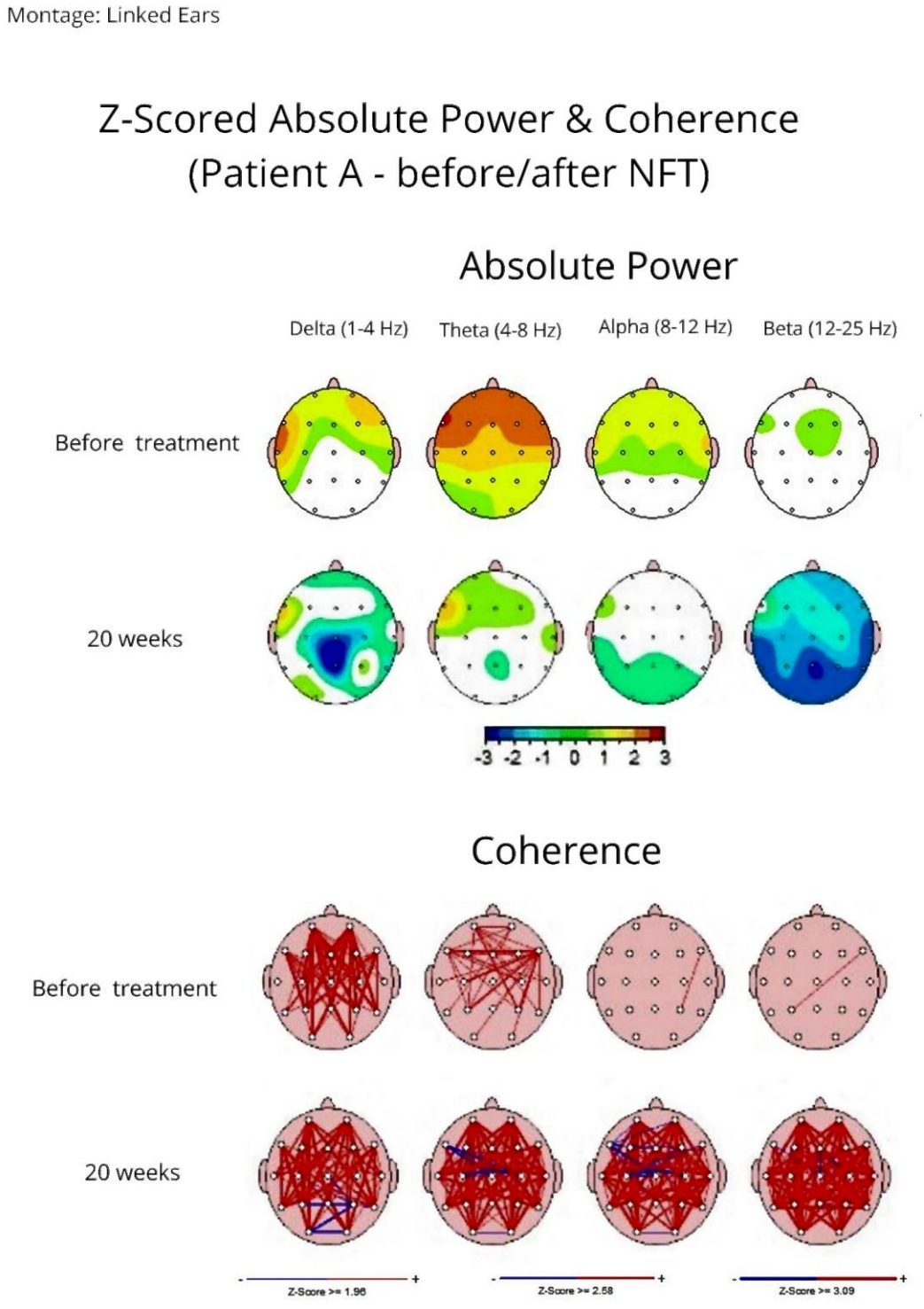
Note. ns = not significant.

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

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

Note. ns = not significant.

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



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

Table 4
Amplitude Asymmetry in the Alpha Frequency Band

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

Note. ns = not significant.

Discussion

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

Feasibility of Recruitment

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

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

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

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

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

Neurofeedback

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

Remarkably, there was marked heterogeneity in the four patients' EEG differences as compared to a normal template at baseline. Two patients showed widespread nonnormative theta power, whereas two others did not. This could represent altered EEG activity associated with specific subtypes of AVH (Jones, 2010). If so, this suggests the importance of personalizing NFT, based on an individual's EEG profile, rather than a one-size-fits-all approach. However, it may be that such differences were not

associated with AVH or other symptoms, but with medication use, as clozapine and other psychotropic medications have been reported to impact EEG readings (Aiyer et al., 2016; Kim et al., 2019). To minimize widespread effects of medication however, we used a Laplacian montage, which does not rely on one single reference point but uses nearby electrodes as a combined reference. As such, this montage is more sensitive to local variations in EEG activity and is recommended when recording from patients regularly treated with psychoactive drugs (Yao et al., 2019).

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

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

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

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