Research Paper

Infralow neurofeedback in the treatment of substance use disorders: a randomized controlled trial

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Background: Infralow neurofeedback (ILF-NF) was recently developed as a subtype of traditional, frequency-based neurofeedback that targets cerebral rhythmic activity below 0.5 Hz and improves brain self-regulation. The efficacy of ILF-NF in the treatment of substance use disorder has not yet been evaluated, but clinical evidence suggests that it may prevent relapse by improving functioning in various life domains. The current study aimed to fill this research gap and extend empirical evidence related to this issue. **Methods:** Ninety-three patients with substance use disorders at an outpatient unit in Norway were randomized to receive 20 sessions (30 minutes each) of ILF-NF training combined with treatment as usual (TAU), or TAU alone. The primary outcome was quality of life post-treatment as an overall measure of functioning. We analyzed between-group differences using Student *t* tests. **Results:** We found no significant differences in quality of life between groups. We found similar nonsignificant results for most of the secondary outcome measures, including drug use, sleep, anxiety and depression. Compared to TAU, the ILF-NF + TAU group reported significantly lower restlessness scores post-treatment (mean difference –1.8, 95% confidence interval –3.1 to –0.5; $p = 0.006$). **Limitations:** This study was limited by broad inclusion criteria and a lack of placebo control (sham neurofeedback treatment). **Conclusion:** ILF-NF offered limited additional benefit when combined with TAU, except in the area of restlessness. Future studies could further investigate the relationship between ILF-NF, restlessness and substance use in targeted subpopulations to illuminate relapse mechanisms. **Clinical trial registration:** ClinicalTrials.gov: NCT03356210

Introduction

Neurofeedback is a psychophysiological training procedure in which brain activity is digitized and fed back to the trainee in sensory form for self-regulation via surface electrodes attached to the scalp.[1] Since its introduction in the 1970s, this approach has been used increasingly as an intervention for substance use disorders because of its potential to change psychopathological abnormalities by enhancing self-regulatory systems in the brain.[2]

Sparked by encouraging early studies from Peniston and colleagues,[3] the impact of neurofeedback on electroencephalographic (EEG) topography and clinical symptomatology in patients with substance use disorders has been investigated frequently over the past 30 years.[4–6] However, reports have been somewhat mixed. Although previous work has demonstrated that neurofeedback can prolong treatment retention,[2] improve clinical outcomes by inducing long-lasting changes in neurophysiological brain activity and improve regulatory capabilities and executive function,[7,8] other studies have shown no significant effect of neurofeedback on addictive behaviours.[2,9]

In recent years, neurofeedback has been applied successfully in diverse populations of patients with substance use disorders, such as those with disorders related to various substance classes,[10–12] common comorbidities (including craving, abstinence rates and attention deficits) and psychopathologies (such as trauma and depression).[9,13–15] Based on these findings, several systematic reviews have concluded that neurofeedback appears to be a promising tool for modulating brain activity related to cognitive and emotional impairment in patients with substance use disorder.[4–6] Since 2002, neurofeedback has been listed as a level 4 intervention (i.e., "probably efficacious") for substance use disorders in the guidelines for evaluation of clinical efficacy of psychophysiological interventions.[16]

Traditional neurofeedback protocols incorporate principles of operant conditioning, in which select EEG frequencies within the conventional EEG spectrum of 0.5 to 40 Hz are differentially reinforced. A newer form of neurofeedback is infralow frequency neurofeedback (ILF-NF), which extends the conventional frequency-based training to the lower frequency range, with modulation targets below 0.5 Hz.[17] It is claimed

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that by impinging on the functional connectivity of the intrinsic connectivity networks, ILF-NF optimizes communication between and within neuronal networks. This seems to have a calming effect on the nervous system and the acute fight-or-flight response prevalent in the early recovery of patients with addiction,[17,18] providing a crucial buffer against relapse.

Leong and colleagues[19] conducted the first randomized, double-blind, placebo-controlled study to evaluate the effects of ILF-NF on addictive conditions. They found a significant decrease in different dimensions of state food craving in women with food addiction, a decrease that was thought to be related to accompanying increases in infralow activity in the posterior cingulate cortex, which is central to the brain's reward system.

By addressing the integration of networks responsible for functions such as memory, affective response, autonomic regulation and attention, ILF-NF may lead to an even larger reduction in symptom severity than traditional frequency training and alleviate withdrawal-related stress in patients with substance use disorders. However, to the best of our knowledge, no systematic study has investigated the use of ILF-NF in this patient group. We aimed to fill this research gap by investigating whether the physiologic effects of ILF-NF could help to counteract the negative emotional states (e.g., mental distress, restlessness, obsessive thinking) that are thought to be crucial in relapse prevention.[20] We also investigated whether these effects could be captured by changes in a multidimensional construct that included physical, mental and social domains, such as quality of life.

Laudet and colleagues[21] pointed out that recovery consists of abstinence plus improved quality of life. Thus, enhanced quality of life post-treatment is an important factor in remission. The reasoning is that higher life satisfaction may "increase the price" of future substance use. As such, quality of life is not merely the end goal of recovery, but can also serve as protection against relapse and enhance the likelihood of sustained remission. Following this argument, we chose to regard substance use as a secondary outcome.

Based on previous findings,[10,11,19] we hypothesized that patients allocated to an ILF-NF program of 20 sessions combined with traditional substance use disorder treatment would report significantly higher quality of life scores post-treatment than patients who underwent traditional treatment only. Similarly, we hypothesized that we would find a significant change in related physical and psychological variables in patients who received ILF-NF.

Methods

Study design and setting

This study was a randomized controlled trial; for a CONSORT checklist, see Appendix 1, available at www.jpn.ca/lookup/doi/10.1503/jpn.210202/tab-related-content.

The Norwegian specialized addiction treatment system is largely financed publicly; outpatient services are provided for a minimal deductible. Patients can be referred to treatment by general practitioners, social services or other units in the hospital.

Participants in the present study were recruited from an outpatient clinic at the Addiction Unit of Sørlandet Hospital in Kristiansand, Norway, over a period of 2.5 years from September 2017 to March 2020. This institution serves mainly Agder, the southernmost county in Norway (population 310 000).

Inclusion and exclusion criteria

Patients were eligible for the study if they had been enrolled in the outpatient program for at least 1 month. Patients were ineligible if they had a severe psychiatric disorder (e.g., psychosis) that had not been stabilized with medication, or if they had severe cognitive impairment or language deficiencies that made the patient unable to converse during interviews or understand instructions. Patients enrolled in the clinic's opioid maintenance programs (methadone, buprenorphine) were excluded to prevent possible cross-effects from pharmacological treatment regimens. The clinicians at the unit informed potential candidates about the study and carried out initial patient selection based on the established eligibility criteria. In some cases, specialist neurofeedback therapists were asked to provide additional information.

After providing informed consent, participants completed the inventory described below. The study was conducted in accordance with the Helsinki Declaration and was approved by the Norwegian Regional Committee of Ethics of the South-East region.[22]

Randomization and assessment

To ensure a balanced sample across the 2 groups over time and avoid predictability, we applied mixed blocked randomization with random variation in block sizes.[23] An external researcher with no direct contact with the participants carried out the randomization procedure and prepared the group allocation notes in sealed, opaque envelopes.

Patients were assessed at baseline and after they completed the intervention (either 20 sessions ILF-NF + TAU or approximately 5 months of TAU). A research assistant who was blinded to patients' assignments conducted the post-treatment interviews. Participants received 250 Norwegian kroner per interview.

Intervention

TAU

Patients in the TAU group received traditional substance use disorder treatment in the form of cognitive behavioural techniques, psychosocial approaches and motivational interviews according to the patient's needs and the therapist's preference.

ILF-NF + TAU

Patients in the ILF-NF + TAU group received traditional substance use disorder treatment plus 20 sessions of ILF-NF training over a period of 5 ± 3.2 months (mean ± standard deviation [SD]) using Cygnet software from EEG Info. Each

session lasted 30 minutes of active training time. Three experienced therapists with a minimum of 5 years' experience in neurofeedback training conducted the sessions.

ILF-NF was administered with participants sitting in a comfortable reclining chair in front of a computer screen. The skin at the relevant points on the scalp was prepared with an abrasive to lower impedance. The 4 electrodes were positioned according to the 10–20 system, an international standard for electrode placement used in studies on topography and source analysis of spontaneous and evoked EEG activity.[24] The impedance of the active electrodes was kept below 5 kΩ. Standard placement sites were used, with active electrodes on T4–P4, T3–T4, T4–FP2 and T3–FP1, according to individual needs and symptom presentation. Active electrodes were placed on primary sites and referenced to the Cz or FPz areas. Ground electrodes were positioned at the mastoids.

The patient's brain activity was displayed as raw data on the therapist's monitor, and as a visual image or video game with sound effects on the patient's monitor. Tactile feedback was given through a stuffed animal connected to the computer setup. The feedback threshold was kept at the factory standard; for 90% of the time, sound effects were played and the video game progressed smoothly when the participant's cerebral activity met the infralow threshold.

Participants were advised to relax and pay attention to the computer game on the video screen without making conscious attempts to influence it directly. No other specific instructions were given.

Instruments and outcomes

We used the Mini International Neuropsychiatric Interview (MINI) version 6.0 at baseline to confirm diagnosis of a substance use disorder.[25] We used the European version of the semistructured Addiction Severity Index (EuropASI) interview to collect data on patient demographics, life context and treatment history.[26]

We measured the primary study outcome — quality of life — using the QoL-5 instrument. Based on an integrative theory of the quality-of-life concept and considered useful as a disease-nonspecific instrument, the QoL-5 instrument has been described as valid for measuring quality of life in general population samples as well as across different illness categories.[27,28] QoL-5 consists of 5 subjective quality-of-life statements: 2 related to health (physical and mental); 2 about the quality of relationships with important others (partner and friends); and 1 about existential quality of life (relationship with oneself). Responses are scored on 5-step ordinal scales ranging from 1 (very good) to 5 (very poor). Scores were then reversed and transposed onto a decimal scale from 0.1 to 0.9, where 0.9 was the highest or best score and 0.1 was the lowest or worst.[29] We calculated mean scores for the 3 domains (health, relationships and existential quality of life) and based total quality of life on the mean of these 3 subscores. Normative data from a general population sample indicated a mean quality of life score of 0.69, and we used this as our reference.[27,30] It has been suggested that the cut-off for a markedly low quality of life is approximately −0.15 below the general population (less than 0.55); a score of less than 0.4 is considered to be extremely low.[30] A minimal clinically relevant improvement and between-group difference is 0.10.[31]

Secondary outcomes included substance use, perceived mental distress, restlessness and obsessive thinking, sleep quality and perceived functioning.

We measured substance use with the EuropASI.[26] Data on drug and alcohol use in the 30 days before the interview yielded composite scores ranging from 0 (no problem) to 1 (severe problem).

We measured perceived mental distress using the Hopkins Symptom Check List 10 (SCL-10), a 10-item index that maps anxiety (4 items) and depression (6 items).[32] Responses were scored on a 4-point scale. The global severity index constitutes the average of all items; the highest score indicates the highest distress. A total mean score greater than 1.85 is considered to be pathological. This scale is a valid indicator of mental distress and has been validated in a Norwegian setting.[33]

We measured restlessness and obsessive thinking using a visual analogue scale (VAS) on which the respondents were asked to rate their level of uneasiness from "none" to "very high" on an unmarked 10 cm horizontal line.[34] Similarly, we used an inverted VAS scale ranging from "poor" to "good" to measure sleep quality. We determined VAS scores by measuring the distance in centimetres from the end of the line on the left to the point that the patient had marked.

We measured perceived functioning using the Outcome Rating Scale (ORS), a brief outcome measure consisting of 4 subscales that assess functioning on a personal level, in interpersonal relationships (friends and family), in general social interactions, and a more global measure of overall functioning.[35] These items were scored on VAS scales similar to those described above, and results were summed to obtain a final score. The total score ranged from 0 to 40, and higher scores indicated better functioning. The clinical cut-off is 25, and clinically meaningful improvement is represented by a change of 5 points or greater from the pretreatment score.[36]

Sample size

We based our sample size calculation on a previous study in a similar population, in which patients had a mean ± SD quality of life score of 0.57 ± 0.17.[37] A sample size of 40 in each group had 80% power to detect a 0.10 difference between means with a 2-tailed significance level (α) of 0.05. We expected a 20% attrition rate post-treatment; therefore, we planned for 50 patients in each group. The power calculation was carried out in StatMate version 2.0 (GraphPad Software, Inc.).

Statistical analysis

We provided descriptive statistics for all variables. We used independent sample *t* tests to compare post-treatment scores in the ILF-NF + TAU and TAU groups for the primary outcome measure (quality of life), and for the secondary outcome measures. We performed all statistical analyses using SPSS version 26 (IBM).

Results

Participants

The 93 patients we recruited ranged in age from 19 to 66 years (mean ± SD 38 ± 11.7 years; Table 1). Most participants were male (66%), native Norwegians or European-born, and had a long history of problematic substance use (mean approximately 10 years). All participants met the criteria for substance use disorder according to the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10).[25] Half of the sample were living alone. The education level among participants was relatively low: 45% had only the minimum 10 years of mandatory education. Almost all participants relied on some form of welfare benefits. Patients in the TAU group received 10.8 ± 6.8 TAU sessions (mean ± SD). Patients in the ILF-NF + TAU group received 14.4 ± 7.4 ILF-NF sessions plus 7.0 ± 5.8 TAU sessions.

For the sample as a whole, we found a low baseline score for substance use (< 0.20 for alcohol use and < 0.10 for substance use). We found no significant differences between groups at baseline, indicating that the randomization procedures worked as intended. We reached 73 patients post-treatment, but 6 did not provide quality-of-life scores. Thus, our analysis was based on 67 participants (72% of the initial sample; Figure 1).

Attrition analysis showed no significant differences between those who were assessed and those who were lost to follow-up post-treatment.

Table 1: Participant baseline characteristics

Variable	ILF-NF + TAU* *n* = 46	TAU only* *n* = 47
Age, yr	39.6 ± 12.6	36 ± 11.8
Male	30 (65)	31 (66)
Education level		
Primary school or less	18 (39)	24 (51)
High school	21 (46)	16 (34)
Bachelor's degree or higher	5 (11)	5 (11)
Living alone	22 (48)	24 (51)
Problematic substance use, yr†	9.2 ± 8.2	9.9 ± 8.7
Working days in the past 30 d	3.5 ± 6.8	3.7 ± 9.2
EuropASI score‡		
Alcohol use	0.15 ± 0.19	0.14 ± 0.19
Drug use	0.04 ± 0.1	0.04 ± 0.1
Mental distress§	2.39 ± 0.52	2.47 ± 0.67
Sleep quality¶	4.1 ± 2.3	3.9 ± 3.0
Restlessness¶	5.5 ± 2.2	6.4 ± 1.8
Obsessive thinking¶	6.6 ± 2.3	6.7 ± 2.8
Perceived functioning**	20.0 ± 8.4	19.2 ± 8.8
QoL-5 score††	0.51 ± 0.13	0.50 ± 0.16

EuropASI = Addiction Severity Index, European version; ILF-NF = infralow frequency neurofeedback; TAU = treatment as usual.
*Data are presented as *n* (%) or mean ± standard deviation.
†Problematic use of major drug(s) of abuse, as defined in EuropASI, was the consumption of 5 or more standard drinks at least 3 times weekly, or binge drinking on 2 consecutive days to a level that afflicted daily functioning.
‡Measures substance use severity using a composite score of 0 (no problem) to 1 (severe problem).
§Measured using the Hopkins Symptom Check List 10 (SCL-10). Responses are scored on a 4-point scale of 1 to 4 and averaged to a global severity index; a higher score indicates higher distress.
¶Measured using 10 cm visual analogue scales. The sleep quality scale ranged from "poor" to "good," and the restlessness and obsessive thinking scales ranged from "none" to "very high."
**Measured using the Outcome Rating Scale; scores range from 0 to 40, and higher scores indicate better functioning.
††Measured using the QoL-5 scale, ranging from 0.1 to 0.9, where 0.9 is the highest or best score.

Primary outcome measure

Independent-sample *t* tests showed no significant difference between groups for the primary outcome measure (Table 2). Considering the sample as a whole, we found a significant but modest improvement in quality of life from baseline to post-treatment (mean improvement 0.06, 95% confidence interval 0.03 to 0.09; $p < 0.001$, paired-sample *t* test).

Other outcome measures

For outcome measures related to substance use, we found no significant difference between groups for alcohol and drug use post-treatment (Table 2). We found similar results for most of the other secondary outcome measures, including mental distress, sleep quality, perceived functioning and obsessive thinking. Both groups showed improvement in perceived functioning, but only the TAU group had a clinically significant improvement (≥ 5-point improvement from baseline to post-treatment on the ORS). Post-treatment scores on the restlessness scale were significantly lower for the ILF-NF + TAU group than in the TAU group (mean difference –1.8, 95% confidence interval –3.1 to –0.5; $p = 0.006$).

Discussion

The key finding in this study was that, compared to patients who received TAU only, patients who received ILF-NF + TAU did not have better post-treatment quality of life, the study's primary outcome. Similar null results emerged for most of the secondary outcomes, including drug use, sleep quality, anxiety and depression. Compared to TAU, ILF-NF + TAU resulted in a significantly lower post-treatment restlessness score.

The present study yielded disappointing results for the primary outcome and did not appear to contribute more than TAU to most of the secondary outcomes. This contradicted early optimistic findings related to neurofeedback in the field of substance use disorder treatment. Neurofeedback has been generally accepted for its clinical utility as an adjunct treatment to other interventions for substance use disorders,[4–6,8] but comparing studies and drawing conclusions about its effectiveness is difficult because of its diverse applications in terms of equipment used, populations trained, treatment protocols used and outcome measures employed.

Two recent studies measured quality of life to assess the usefulness and effects of neurofeedback in patients with substance use disorder. In contrast to the present study,

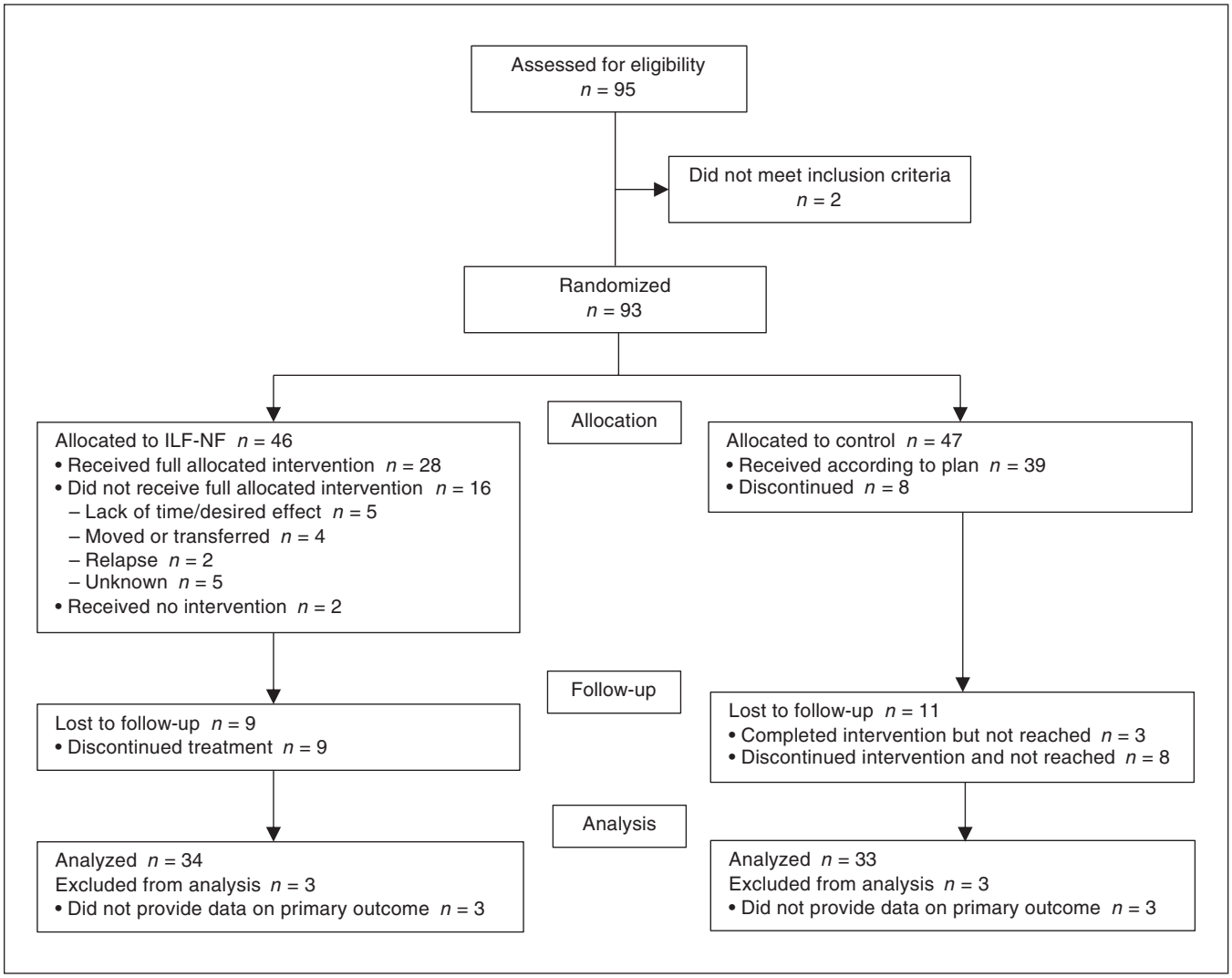

Figure 1: Study flow chart of participant selection, randomization and completion. ILF-NF = infralow frequency neurofeedback.

Table 2: Participant outcomes post-treatment

Outcome	ILF-NF + TAU* $n = 34$	TAU* $n = 33$	Mean difference (95% CI)	p value
Primary outcome				
Quality of life†	0.54 ± 0.17	0.58 ± 0.16	–0.04 (–0.13 to 0.04)	0.28
Secondary outcomes				
Alcohol use‡	0.13 ± 0.18	0.11 ± 0.18	0.02 (–0.07 to 0.11)	0.65
Drug use‡	0.04 ± 0.07	0.04 ± 0.08	0.00 (–0.04 to 0.04)	0.94
Mental distress§	2.08 ± 0.55	2.06 ± 0.64	0.02 (–0.27 to 0.32)	0.89
Sleep quality¶	5.2 ± 2.7	5.3 ± 3.2	–0.1 (–1.5 to 1.3)	0.89
Restlessness¶	4.1 ± 2.5	5.9 ± 2.8	–1.8 (–3.1 to –0.5)	0.006
Obsessive thinking¶	5.7 ± 2.3	5.5 ± 3.0	0.2 (–1.1 to 1.5)	0.76
Perceived functioning**	23.0 ± 9.6	25.8 ± 8.9	–2.8 (–7.3 to 1.7)	0.22

CI = confidence interval; EuropASI = Addiction Severity Index, European version; ILF-NF = infralow frequency neurofeedback; TAU = treatment as usual.
*Data are reported as mean ± standard deviation.
†Measured using the QoL-5 scale, ranging from 0.1 to 0.9, where 0.9 is the highest or best score.
‡Measured using the EuropASI, which uses a composite score of 0 (no problem) to 1 (severe problem).
§Measured using the Hopkins Symptom Check List 10 (SCL-10). Responses are scored on a 4-point scale of 1 to 4 and averaged to a global severity index; a higher score indicates higher distress.
¶Measured using 10 cm visual analogue scales. The sleep quality scale ranged from "poor" to "good," and the restlessness and obsessive thinking scales ranged from "none" to "very high."
**Measured using the Outcome Rating Scale; scores range from 0 to 40, and higher scores indicate better functioning.

Rostami and colleagues[11] found significant improvements in quality of life in patients who used crystal methamphetamine after they underwent 20 sessions of neurofeedback compared to a waitlist control group. Dehghani-Arani and colleagues[10] reported similar results when they investigated neurofeedback as an alternative to pharmacological treatment in opioid users. Both of these studies used conventional frequency training modelled after the Scott–Kaiser modification of the Peniston protocol, which incorporated sensory motor rhythm, and β and α/θ protocols, rather than the ILF-NF protocol used in the present study. Rostami and colleagues[11] used waitlisted patients as a reference group and found that neurofeedback was superior to no treatment.

When it comes to the utility of ILF-NF, little research has been published. Leong and colleagues[19] used ILF-NF in participants with eating disorders and found that it produced significant increases in infralow activity and infralow–β nesting in brain areas involved in cravings and reward, accompanied by a significant decrease in different dimensions of state food craving compared to baseline and placebo. Because addictions to food and chemical substances are thought to share some common neurobiological mechanisms, it is conceivable that this finding is transferable to populations with substance use disorders. It may also help to explain the positive effect on the restlessness variable reported by the neurofeedback group in the current study.

Closely tied to the concept of cravings, restlessness may be viewed as a triggering factor for substance use relapse. It is one of the most frequently endorsed sensations in drug cue–related experiences, comprising both general arousal and specific interoceptive responses as described in patients' self-reports.[38,39] This type of negative emotionality may lead to compromised self-control and increase a person's vulnerability to relapse.[40,41] By lowering their level of restlessness and increasing their capacity for self-regulation, neurofeedback training may reduce a patient's need for chemical regulation and contribute to the prevention of relapse.

Based on dual-process theories, Dousset categorized the relapse mechanism into 2 subcomponents: a fast, intuitive, affect-driven process (bottom–up) versus slower, more deliberative reasoning (top–down).[6] That is, the user experiences a conflict between increased impulses to consume addictive substances and disrupted prefrontal control over urges. Leong's findings may indicate that ILF-NF targets the underlying urge to use drugs (i.e., the craving mechanism), to which restlessness may be a contributing factor, as well as the ability to control these impulses.[19,42,43]

Previous studies have shown positive results from neurofeedback in individuals with attention-deficit/hyperactivity disorder and attentional deficits.[44] Whereas our sample was drawn from an unselected drug-using population, other studies have focused more narrowly on selected subpopulations of substance users and, therefore, had a more homogeneous patient sample. This difference may account for some of our observations. For example, a study found a 30% prevalence of childhood attention-deficit/hyperactivity disorder in methamphetamine users,[45] which might indicate that a subpopulation with more hyperactivity traits such as restlessness could have yielded more conclusive results in the present study, as well as for other outcomes.

Although the present study did not yield significantly better results for most of the study outcomes in the ILF-NF + TAU group, our positive findings can still contribute to guiding clinical practice and future research. Lessons learned from the study include an appreciation of the challenges posed by patient recruitment during a pandemic such as COVID-19. Moreover, as a global instrument, QoL-5 seemed to lack the sensitivity to detect the more specific effects that may be experienced with neurofeedback in this patient group. Instruments that were effective in detecting differences from baseline to post-treatment (e.g., mental distress) could be considered as an alternative primary outcome. To obtain more conclusive results, further research might benefit from a more homogeneous study sample and a better matching strategy between targeted symptoms or populations, as well as more specific outcome measures.

Clinically, studies such as the present one can play a role in identifying responders at an early stage to ensure more precise targeting of efforts and resources. Identifying predictors of neurofeedback learning may be one of the most pertinent topics for future research in the field. For example, some clinicians will argue that most responders show an effect within the first 4 to 5 sessions. In clinical practice, this could be translated to the benefit of a "trial period" to determine response, as well as patient adherence, before a longer, costlier treatment regimen is attempted.

The number and frequency of training sessions may also be important. We were unable to reach our goal of 1 to 2 sessions per week for all patients. Because neurofeedback is thought of as a learning process and therefore governed by general learning principles, more frequent training sessions may be preferred for new learning to occur.

Limitations

Study limitations included the lack of a placebo control group (i.e., a group that received sham treatment). A control group with an alternative active ingredient (e.g., a computer-guided relaxation program) could have helped us determine whether the positive effect we observed on the restlessness scale could be attributed to the additional number of treatment sessions provided to the ILF-NF + TAU group. A longer-term post-treatment follow-up would also have been desirable. Because the patients were in "real-world" conditions (i.e., an outpatient setting) and not in a controlled environment, we considered a 5-month time frame to be a reasonable study period. Because of the clinical preselection of potential candidates, it was difficult to determine the total number of patients eligible for the study. Following the outbreak of the COVID-19 pandemic in March 2020, we discontinued the inclusion of participants before we reached the target sample size of 100 patients.

Conclusion

The findings of this study have increased our understanding of the potential and limitations of ILF-NF in a population with substance use disorder. The study failed to show effectiveness for ILF-NF in improving quality of life when used in a heterogeneous population of substance users.

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Competing interests: None declared.

Contributors: K. Gabrielsen, S. Hollup and J. Vederhus designed the study. K. Gabrielsen acquired the data, which K. Gabrielsen, T. Clausen, S. Haugland and J. Vederhus analyzed. K. Gabrielsen and J. Vederhus wrote the article, which all authors reviewed. All authors approved the final version to be published and can certify that no other individuals not listed as authors have made substantial contributions to the paper.

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