Pre-sleep alpha brain entrainment by audio or visual stimulation for chronic widespread pain and sleep disturbance: A randomised crossover feasibility trial

Running title: Alpha entrainment for chronic pain crossover trial

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Abstract

Home-based neuromodulation is a potentially scalable option to assist with management of chronic widespread pain. Since sleep disturbance is closely interrelated with chronic pain, especially in conditions such as fibromyalgia, targeting symptoms pre-sleep could enhance treatment efficacy. Alpha entrainment is a neuromodulatory technique to improve pain which can be applied via a smartphone programme using 10 Hz stimulation through flickering light or binaural beats. The aim of this study was to assess feasibility, mechanistic effects on

alpha spectral power during pre-sleep entrainment and indicate the potential effect on symptoms. Adults with fibromyalgia participated in two weeks of active and sham stimulation at home pre-sleep in a randomised, balanced sequence, with a one-week washout, in a two-period crossover design. Sham stimulation was non-rhythmic but otherwise perceptually similar, and participants and experimenters were masked to sequence. Effect of stimulation was assessed with daily symptom and sleep diary, nightly wearable EEG monitoring (Dreem 3 headband) and actigraphy. Alpha spectral power was enhanced during active compared to sham stimulation, substantiating the entrainment effect under pre-sleep, home based conditions. Pain at night (0–10 scale) decreased with active stimulation compared to sham: difference -0.53 (95% CI -0.81 to -0.25, P<0.001). Sleep quality (0–5 scale) improved with active stimulation compared to sham: difference +0.39 (95% CI 0.15 to 0.64, P=0.002). Pre-sleep sensory alpha entrainment with home-based EEG monitoring in fibromyalgia is feasible with potentially helpful effects on pain and sleep without significant unwanted effects. Longer duration study in larger trials is warranted.

ClinicalTrials.gov registration ID: NCT05699837

Perspective

This study applies a non-invasive pre-sleep neuromodulatory technique in individuals with fibromyalgia. It demonstrates the feasibility of the approach, verifies the mechanism of sensory alpha entrainment in this real-life environment and indicates self-reported improvements to pain and sleep quality compared to a sham stimulation. These findings can help refine interventions and design larger trials.

Key words

Entrainment, Neuromodulation, Fibromyalgia, Alpha power, Nociplastic pain

Introduction

Widespread chronic pain syndromes such as fibromyalgia are particularly poorly responsive to conventional treatments for pain. Improved management strategies are urgently needed, given the high prevalence of fibromyalgia of around 2% of the general population (and approximately 4% of women) [1,2]. Scalability is therefore a highly desirable characteristic for novel effective interventions, which ideally requires them to be low risk, home-based and under the control of the user without requiring intensive healthcare professional input.

Neuromodulation is one potential avenue of investigation to meet this need. Options for achieving this non-invasively include transcranial electric or magnetic stimulation, both of which have been recently reviewed as potential treatments in fibromyalgia [3,4]. Neuromodulation via sensory stimulation has the advantages of being lower risk, lower cost, easier for the user, and more acceptable. Alpha entrainment is one mode of neuromodulation which can be achieved with sensory stimulation. Entrainment refers to enhancement of cortical oscillations in a chosen frequency band by repetitive external stimulation at that same frequency, in this case the alpha band (8–13 Hz) [5]. Alpha entrainment is a promising avenue given the emerging evidence for the role of alpha in modulating the pain experience. Alpha activity is reduced with pain and the expectation of pain, and increased with pain relief and expectation of pain relief [6]. Furthermore, sensory stimulation in the alpha frequency band does successfully entrain alpha (optimally at 10Hz), with a reduction in intensity of experimentally induced pain compared to control stimulation [7,8] and reduction in intensity of clinical chronic pain, which is correlated with the degree of entrainment [9,10].

Alpha entrainment may therefore provide an immediate and short-term pain reduction, but how best to apply this clinically remains undefined. The rationale to target the pre-sleep

period is that pain reduction at this point may allow enhanced sleep quality and thereby leverage a larger overall benefit in symptoms. Sleep disturbance is ubiquitous in fibromyalgia [11] and the relationship between the symptoms has long been observed to be mutually reinforcing [12]. Perhaps unexpectedly, the relationship is stronger in the direction of sleep acting on pain [13,14]. Sleep may even be mechanistically implicated in symptom generation in fibromyalgia. The sleep disturbance seen in fibromyalgia is characterised by fragmentation [15], experimentally shown to impair descending pain inhibition [16], which is known to be deficient in fibromyalgia in particular [17]. This correlates with the experience of individuals, who describe sleep and pain problems interacting in a cycle [18]. Therefore, targeting pre-sleep pain may offer amplified benefits via a virtuous cycle involving both symptoms.

An open loop 10 Hz audio or visual stimulation system called ‘home-based Brain Entrainment Technology’ (hBET) was developed to investigate the clinical utility of alpha entrainment [19,20]. ‘Open loop’ refers to the fact that the stimulation settings are set in advance and fixed, whereas in ‘closed loop’ systems there is feedback from real time monitoring which dynamically modifies the stimulus. A previous open label feasibility study identified that the use of hBET pre-sleep in people with chronic pain and sleep disturbance is acceptable and felt to have symptomatic benefits [18,21]. The current study was designed to extend this with the addition of a sham control and home-based EEG monitoring. The aims were to assess the feasibility and acceptability of using hBET with a home-based EEG monitoring tool and a masked, sham control condition; to characterise the alpha entrainment effect of open-loop stimulation delivered in the home environment before sleep; and to give an indication of the potential clinical impact of alpha stimulation on pain, sleep and related patient reported outcomes.

Materials and methods

A randomised crossover design was chosen to meet the study objectives, taking advantage of the chronicity of the condition to allow within participant comparison and mitigate between-

participant variability. The study was registered at ClinicalTrials.gov (NCT05699837), received ethical approval from the UK Health Research Authority (Yorkshire & The Humber - Sheffield Research Ethics Committee Approval Number: 19/YH/0313) and was conducted in accordance with the Declaration of Helsinki.

Participants

Participants were adults with fibromyalgia, recruited from NHS chronic pain and rheumatology services in two large cities in the north of England (Leeds and Manchester), and via online publicity materials. Inclusion criteria were: having a previous diagnosis of fibromyalgia made by a doctor; currently meeting the 2016 American College of Rheumatology diagnostic criteria for fibromyalgia; having nocturnal pain (≥4/10 on a numerical rating scale); and having self-reported sleep difficulties (defined as at least one of: trouble falling asleep, difficulty staying asleep, waking up too early, or waking up unrefreshed 3 or more nights per week during the past month). Exclusion criteria were: having cancer related pain; seizure disorder; photosensitivity; hearing or vision problems causing inability to use audio or visual stimulation; cognitive or mental health problems causing inability to consent; night shift work; and having a known primary sleep disorder such as obstructive sleep apnoea. Participants continued their normal medications and did not start or stop any medications during the study period. As this was a feasibility study, sample size was not derived from a power calculation, but 15-20 participants were expected to meet the study aims which included estimating the variance, recruitment and dropout rates which would inform planning for future effectiveness trials.

Procedures

Largely remote procedures were used as these had been found to be effective in previous work during the Covid-19 pandemic [21] and were convenient for participants over a wide geographic area. Informed written consent was taken from each participant. Participants were familiarised with the procedures and equipment in a face-to-face or videoconference meeting. Participants used the sleep monitoring devices for one night before the start of the

baseline week as a habituation night. Each participant underwent a one-week baseline period followed by randomised allocation on a 1:1 basis to receive either rhythmic stimulation for two weeks then sham non-rhythmic stimulation for two weeks, or the reverse order. There was a one-week washout period between the two stimulation periods which was chosen based on the short lived neurophysiological effect of entrainment [22]. The study duration was therefore six weeks in total. The hBET application can provide either audio or visual stimulation (not both simultaneously) and participants selected at the outset which they preferred to use, and were required to keep to that modality throughout the study period. This choice was available as it was found to aid acceptability in a previous open-label study [21]. The procedure participants followed on a given study night was to apply the sleep monitoring equipment and hBET equipment (described below) at night when they had completed their evening routine and were ready to turn lights off and settle down to sleep. They were instructed to commence the hBET programme and sleep monitoring in close succession, then begin trying to get to sleep. The hBET application interface allowed participants to select the correct stimulation programme by simply clicking a ‘go’ button corresponding to the week of the study they were currently in. Participants were aware that the stimulation would differ across these blocks, but not primed to expect some weeks to be ‘active’ and some to be ‘sham’. Randomisation was performed by creating a series of versions of the application, one for each participant, which were all identical except for the order of the active and sham stimulation periods which were determined using a random number generator in Microsoft Excel. This procedure was performed by one investigator (LX) who had no contact with participants and released the key as to which participant received which order of intervention to other investigators only after data collection was complete. Therefore, both the participants and the investigator directly interacting with them were masked as to their allocation during data collection, but the investigators were not masked during data analysis.

Interventions

The hBET programme is a smartphone application designed to provide repetitive sensory stimulation at 10 Hz for investigation of the management of chronic pain. Its at-home use in an open label feasibility study in a similar population [21], user co-design [23] and qualitative user feedback [18] have previously been described. The choice of 10 Hz stimulation is because this lies at the centre of the distribution of individual alpha peak frequency across individuals [24] and was previously found to be the optimal alpha frequency for analgesia [7]. The hBET programme provides open-loop stimulation at 10 Hz using either visual or auditory modes. In visual mode the screen alternates between black and white at 10 Hz and a virtual reality headset is used to hold the phone in front of the user's eyes and block external light sources. The user is asked to have their eyes closed during stimulation. Screen brightness is pre-set at mid-range but can be adjusted by the user. The smartphone's blue light filter was applied in view of the melatonin suppressing effect of blue light [25]. The auditory mode uses binaural beats (different frequencies presented to each ear, with the binaural beat frequency being the difference between them) [26] to create 10 Hz stimulation using pure tones at 400 and 410 Hz. Headphones must therefore be used. A wireless sleep headband with integrated headphones was provided for comfortable use lying down (model PT28, Perytong, Shenzhen, China). Participants could use their own headphones if they preferred, since comfort was deemed to be important for this pre-sleep intervention. The production of pure tones at the mid-range frequencies used here (400 – 410 Hz) does not require specialist headphones, and since volume was under the user's control for comfort, using specific headphones for reasons of intensity standardisation was not a relevant consideration. Technical modification of the application to include a sham condition has been reported [20]. The visual sham mode presents non-rhythmic (jittered) screen flicker with instantaneous frequencies in the range 5–15Hz, whilst the audio sham mode presents tones of 400 and 400.01 Hz, which is a binaural frequency (0.01Hz) below the range of neuronal oscillations. Therefore, each sham mode is experientially similar for the user to the active

stimulation but is designed to not cause entrainment. Both the active and sham modes present stimulation for 30 minutes and then stop. The application includes a usage logger which records the timing of each start and stop of either active or sham stimulation, providing accurate timings of stimulation use for analysis.

Outcome measures

The outcome measures used reflect the three aims of this study: to assess feasibility, to provide mechanistic clarity and to provide an indication of clinical effect. Feasibility was assessed regarding data completeness, data quality, intervention adherence, and study completion rates. The mechanistic question is addressed by directly measuring the alpha entrainment effect of active stimulation, defined as alpha spectral power (that is, the total magnitude of activity within the alpha range) during active stimulation use pre-sleep, compared with that during sham stimulation and that during the pre-sleep period in the nights of the baseline week. Effect on clinically relevant factors was explored with measures of sleep (participant reported and instrumented), pain and related symptoms as described below.

Demographic, medical and pain history, including medication use, was collected based on participant's own report with a paper questionnaire at baseline. Pain was assessed with a daily diary reporting a 0–10 numerical rating scale of average pain over 24 hours and night pain, and with the Brief Pain Inventory, completed at baseline and weekly throughout the study period. Sleep was evaluated using an electroencephalographic headband, the Dreem 3 (Dreem, Paris), which has five dry electrodes corresponding to the International 10-20 system as positions Fp2 (ground), F7, F8, O1 and O2 measuring EEG signal at 250Hz. From these the Dreem derives five bipolar channels: F7-O1 (Channel 1), F8-O2 (Channel 2), F8-F7 (Channel 3), F8-O1 (Channel 4) and F7-O2 (Channel 5). These signals, along with 3D accelerometry, generate sleep architecture and continuity metrics using the Dreem automatic sleep staging classification system, which has been validated against gold

standard polysomnography with 84% overall accuracy [27]. These sleep metrics were downloaded for each night of recording and had to pass two quality checks before being accepted into the dataset, in accordance with the manufacturer's guidance. These criteria were that the device was detected as being on the user's head for at least 95% of the recording period, and secondly a record quality of 85% or greater, which refers to the proportion of epochs which were considered scorable by the algorithm. The raw EEG data from the Dreem headband were used to compute the alpha power, as described below.

Sleep was also monitored with nightly actigraphy using a Motionwatch 8 (CamnTech Ltd, Cambridge, UK) device, and with a daily sleep diary with wording according to the consensus sleep diary [28]. The diary additionally allowed participants to report on their impression of sleep quality and how refreshed they felt every morning, each using a 0–5 numerical rating scale. Standardised questionnaires were used to assess fatigue (Multidimensional Fatigue Inventory), depression and anxiety (Hospital Anxiety and Depression Scale), and health related quality of life (EQ-5D-5L), each completed at baseline and at the end of each intervention period in reference to the preceding two weeks. Patient global impression of change (a seven-point scale ranging from 'very much worse' to 'very much improved') for the active and sham stimulation periods separately was administered during a videoconference debriefing with each participant at the point they completed the final week. Side effects were proactively enquired about during this meeting and could also be reported to the investigator at any point during the study.

EEG analysis

Raw EEG data were downloaded for each night of Dreem recording for the purpose of analysing the alpha entrainment effect. Although stimulation was at 10 Hz (mid alpha) for all participants, the spectral power change of interest was across the whole alpha band (8–13Hz), for the reason that endogenous alpha at surrounding frequencies may also be entrained, as has been suggested based on the underlying neural mechanisms [22] and mathematical modelling [29]. The period of interest was when the participant was trying to get

to sleep (whilst using hBET, in the active and sham stimulation periods), for a maximum of 30 minutes (the full duration of the hBET programme) or until the point when they transitioned into sleep, if this occurred in less than 30 minutes. This was to avoid the confounding effect of the natural spectral power changes in the alpha range which are known to occur at sleep onset and subsequent transition into stage 2 sleep [30]. These periods of interest ranged from 1 to 30 minutes in length (median 14 minutes, IQR 8–24 minutes). Short periods resulted from the participant quickly falling to sleep, whereas 30 minutes equates to the stimulation programme's full length.

EEG signals were pre-processed as follows: a Q=10 Butterworth notch filter was applied to remove 50 Hz powerline noise, a first order Butterworth low-pass filter at 50 Hz to remove high-frequency noise and first order Butterworth high-pass filter at 0.16 Hz to remove the direct current offset. The pre-processed EEG data was imported into the MATLAB EEGLAB toolbox (MATLAB version: R2023a; EEGLAB version: v2023.1). Artefact Subspace Reconstruction (ASR), as implemented in the "pop_clean_rawdata()" function of EEGLAB, was used for artefact control. This is a suitable artifact removal technique for low channel counts [31]. Parameters of the ASR method were set as follows: the automatic artifact identification threshold was set to 10, based on previous work optimizing ASR parameters for low channel counts [32]; window length was set to 2 seconds; the settings for additional removal of bad data windows were retained at default (length 1 second with 66% overlap, window criterion tolerances range [-Inf,7]).

The Power Spectral Density was computed using the Welch method (MATLAB 'pwelch' function) with a 2-second Hamming-tapered sliding window, applied without overlap, and a 2^{15} points Fast Fourier Transform (FFT). The oscillatory component of the EEG power spectrum was then extracted using the Fitting Oscillations and one Over f (FOOOF) method [33] (implemented using the Python implementation from https://fooof-tools.github.io/fooof/, called into Matlab using the Matlab-Python interface) using a model fit threshold of $R^2 > 0.9$ for data to be retained. The resultant oscillatory component of the signal was subsequently

integrated across the alpha band range (8–13 Hz) with the MATLAB 'trapz' function, log transformed and multiplied by 20 to give a value in decibels (dB). The EEG processing code is publicly available at https://doi.org/10.48420/27619353.

Statistical analysis

Statistical analysis was performed in STATA (StataCorp 2023, Release 18, Texas, United States). A small proportion (1.4%) of alpha power results were marked as outliers more than three standard deviations from the mean and these were removed. Exploration of the effect of the intervention on daily reported clinical measures of pain and sleep, the effect of the intervention on alpha power, and the impact of alpha power on clinical measures were all evaluated using multilevel mixed effects linear regression. This model took sequence, period and intervention (active or sham) as covariates, and participants as random effects to reflect the repeated measures within each person. Day of treatment was added as an interaction term to explore whether effects accrued or dissipated over time. The restricted maximum likelihood (REML) fit method and the Kenward-Roger method for degrees of freedom estimation were selected based on the small number of individual participants. The paper-based questionnaires completed at just one or two time points in each condition were analysed with Wilcoxon sign-rank tests.

Results

Nineteen participants were enrolled between September 2022 and June 2023. Patient flow through the study is shown in Figure 1.

The clinical and demographic profile of participants is shown in Table 1. This compares the participants randomised to each sequence of active and sham stimulation, and all participants receive both in this crossover design.

Intervention use and adherence

Regarding the feasibility of procedures and acceptability of the intervention, there was a noticeable drop-out rate, as illustrated in Figure 1. Two individuals were randomised but changed their minds and chose to discontinue participation in the study prior to ever using the stimulation equipment. A further four individuals (two from each arm) withdrew during the study after experiencing the intervention and sleep monitoring procedures. Importantly, three of these were at least partly for reasons associated with the difficulty of managing the study equipment and procedures alongside their chronic symptoms.

In terms of frequency of intervention use for those who did complete the study (n=13), the intervention (including both active stimulation and sham stimulation modes) was used for 321 nights which represents 88% of the total available nights in the protocol. Eleven of the 13 participants missed 3 or fewer of the 28 available uses of the hBET programme, whereas two participants had much lower adherence, missing 10 and 14 nights. Only one participant used the visual stimulation programme, whilst 12 used the audio stimulation option. A sensitivity analysis removing the one participant who used visual stimulation resulted in no significant change to the main clinical outcomes (supplementary table 1).

Participants were asked if they could tell the difference between the first and second stimulation periods. The majority could not tell any difference, and those who did described subtle differences in the character of the stimulation but approached both periods as potentially active.

Assessing feasibility of the home-based EEG headband was a study aim. Of 13 participants, one did not successfully use the Dreem headband at all. Sufficient quality of data for inclusion in the spectral power analysis during the pre-sleep period of interest were acquired for 399 nights, from 12 participants. With respect to a theoretical maximum across 13 participants of 546 nights, this represents 73% completeness. Algorithmically derived sleep architecture metrics were included when the whole recording met the manufacturers data

quality recommendations. This resulted in 264 nights of sleep data available for inclusion in the analysis, from 9 participants, which represents 48% completeness.

Adverse effects

There were no significant adverse effects. Two (15%) of participants reported minor side effects; one noticed some headaches which they related to use of the headband with integrated Bluetooth speakers, and which resolved when they switched to using different earphones. One further participant reported an increase in pre-existing visual perceptions of patterns behind their closed eyelids described as a “web of lights” as they were falling asleep. This was a participant using audio stimulation, did not result in discontinuing use and occurred with both active and sham stimulation. Six participants mentioned issues with the electrodes of the Dreem headband of minor discomfort or marks left on their skin which persisted for up to a day.

Alpha entrainment

As outlined above in *Outcome Measures,* the Dreem headband produces five bipolar EEG channels. Four of these are fronto-occipital, whilst one is frontal (F8-F7). For the analysis of effect of stimulation on alpha spectral power the four fronto-occipital channels were modelled as a joint multivariate outcome, since they were found to be highly correlated and represent global alpha effects, which are the focus of this study. Details of the correlation and individual channel results are shown in supplementary table 2–4. Fronto-occipital alpha power was first descriptively inspected with a comparison to baseline using a linear mixed model with sequence and period as fixed effects and participant as a random effect. Secondly, in the main randomised analysis of the effect of hBET on alpha power, active stimulation was compared to sham stimulation using the same linear mixed model. The results of both analyses are shown in Table 2 and visualised in Figure 2.

Inspecting the alpha power in a participant-by-participant manner revealed two clear outlying cases where minimal alpha seemed to be generated or detected under any condition. A post hoc analysis leaving out these two participants resulted in a strengthening of the effect of stimulation on alpha power, with an active – sham difference estimate of 0.52 dB (95% CI 0.12 to 0.92, P=0.011) and a larger effect size of Cohen's d 0.39. The justification for an analysis leaving these out is that baseline alpha characteristics could easily be screened for as part of patient selection in a clinical setting. This serves to provide a more meaningful estimate of the effect size in the majority of participants who do generate alpha as detected with this method. Detail on the participant-by-participant inspection is provided in supplementary figure 1.

Adding day of the intervention period as an interaction term in the linear mixed model revealed a significant interaction between day and effect of active stimulation on alpha power in one of the five EEG channels (F7-O1) (P=0.046), indicating there may be a trend for alpha power to cumulatively increase over the two-week intervention period, but this was not a significant effect in the other channels or when fronto-occipital channels were modelled as a joint multivariate outcome.

Daily clinical measures of pain and sleep

Pain at night and sleep quality scores were both improved whilst using active stimulation compared to baseline and compared to when using sham stimulation. The direct comparison of active to sham stimulation showed a significant improvement which was of small clinical magnitude; half of one point on the 0-10 numerical rating scale for pain and just under half of one point on the 0-5 scale for sleep quality. Four participants reached an improvement level of at least 30% or at least 2 points on the pain at night numerical rating scale with active stimulation, whilst only one reached this level of improvement with sham stimulation. The daily measures of pain and sleep in each condition with randomised direct comparison of active and sham stimulation are shown in Table 3. These results for key patient-reported pain and sleep measures are illustrated in Figure 3 (panel A showing pain at night, panel B

showing pain over 24 hours, panel C showing sleep quality score and panel D showing refreshed score).

Total sleep time measured by both the Dreem headband and actigraphy was longer in active compared to sham stimulation periods. However, these were both shorter than in baseline. The longer total sleep time in active stimulation represented increased duration of N2 sleep, as this differed significantly by +19 minutes compared to sham, whilst durations and proportions of N1, N3 and REM sleep were unchanged as measured by the Dreem headband (full results provided in supplementary table 5).

Adding day of the intervention period as an interaction term in the linear mixed model revealed that there was no evidence that the effect of active stimulation on pain at night either accumulated or dissipated over the two-weeks of use (P=0.880). The day-by-day trend of pain at night in each experimental condition is available in supplementary figure 2. There was a significant interaction between day of the intervention period and effect on sleep quality score (P=0.029) indicating that sleep quality improves cumulatively over the two-weeks of use.

Questionnaire measures

The results of questionnaire-based measures at baseline and after active and sham stimulation periods are shown in Table 4. Sleep quality as measured by the Pittsburgh Sleep Quality Index was very poor at baseline, with an average of score of 15.2 (scores above 5 out of maximum 21 indicate poor sleep). The average scores improved to 11.8 after active stimulation, which was a statistically significant change with a large effect size (r) of 0.82. This is greater than the 3 point ‘response’ criteria suggested by Buysee and colleagues in a chronic insomnia population [34]. PSQI score also improved, although to a lesser extent, after sham stimulation, to 13.1. The difference in PSQI between active and sham stimulation was not statistically significant. Similarly, the Pain Interference score of the Brief Pain Inventory

showed an improvement from baseline with active stimulation which was statistically significant and of large effect size (r = 0.74) but only of borderline clinical significance (less than 1.0 points on the 11 point NRS), and again this change was not significantly different to the improvement also seen with sham stimulation. Questionnaire measures of fatigue, anxiety, depression and health related quality of life did not change significantly.

Patient Global Impression of Change was assessed for each stimulation period during the final debriefing meeting (with both participant and interviewer masked to allocation sequence). Six participants reported they felt much or very much improved in the active stimulation period whilst only two reported this of the sham stimulation period. Three felt unchanged in both periods and one felt minimally improved in with sham and unchanged with active stimulation.

Discussion

In this randomised crossover study, pre-sleep use of hBET and study procedures including home-based EEG were feasible, and key symptoms of pain at night and sleep quality were significantly better after nights of using active stimulation compared to sham stimulation, in people with fibromyalgia. Moreover, the mechanism of active stimulation enhancing the power of alpha band oscillatory activity over and above an experientially similar control was substantiated. This represents the first demonstration of successful alpha entrainment via open loop 10 Hz sensory stimulation delivered at home in a population with fibromyalgia. Notably, when asked at the completion of the study, participants did not know which period was active and which was sham, and they interacted with both as potential treatments, likely controlling placebo effect effectively. The magnitude of the additional benefit of active over sham stimulation was clinically small, at around half a point on the 0–10 numerical rating

scale for pain at group average. However, this is after just two weeks of intervention use, in a cohort who had experienced an average of 10 years of pain. Four participants (31%) experienced an improvement in pain at night reaching the established threshold for a clinically important change: a reduction of 2 points or 30% [35]. To put this in context, use of the Federal Drug Administration approved drug pregabalin in fibromyalgia has a number needed to treat to achieve a 30% improvement in pain of seven, equating to just 14% of individuals achieving this response [36]. Establishing effectiveness is not an aim of this feasibility study, but these results are judged to be sufficient to motivate further study of this intervention.

An important feasibility finding is the attrition rate in the participant flow through this study. Usable data were yielded from 13 out of 19 randomised participants. By comparison, the prevalence of dropout across randomised trials of exercise in fibromyalgia was estimated at 19% in a meta-analysis [37]. The attrition rate reflects a protocol requiring daily engagement from participants over several weeks, including change to their bedtime routine and use of the EEG monitoring headband, which is a moderately complex wearable device. The data completeness this yielded for spectral power analysis (73%) and for overnight sleep architecture (48%) is indicative of the trade-off which exists when taking advanced monitoring out of laboratory conditions. Sleep laboratory or technician-applied home sleep monitoring would not be feasible over such a long period or provide the same level of ecological validity. Furthermore, it is reasonable to expect a relatively high attrition when working with individuals with a condition which is known to cause severely debilitating symptoms which are fluctuant and unpredictable. This should be factored into the design of larger studies, whilst also taking steps to promote inclusion through flexibility and provision of technical support to meet individual's needs. Despite these challenges, for participants who completed this study the intervention was used on 88% of the total available nights in the protocol, indicating there is clear feasibility in carrying out such an investigation.

No significant differences in questionnaire measures of clinical outcomes such as sleep quality and pain interference were seen between active and sham stimulation. The average baseline scores and the significant degree of improvement from baseline in these measures are similar to those seen in a previous non-controlled study of this intervention [21] but here improvement was also seen after sham periods. This may reflect a shared placebo effect, but also lack of responsiveness of these questionnaire measures of longstanding symptoms over the short stimulation and washout periods used here. Furthermore, this feasibility was not designed for sufficient statistical power to discern change in these measures, which do not benefit from the statistical efficiency afforded by the repeated measures of the daily reported outcomes.

The significant interaction with day of treatment on sleep quality, and lack of an equivalent interaction effect on pain, is consistent with the direct effect of stimulation on pain being an immediate one, with sleep improvement subsequently improving over time, in line with expectations. The small numbers in this study preclude firm conclusions, but it may be that longer intervention periods would allow greater degree of sleep improvement, and that in turn unlock further pain relief over time. This would be consistent with prior evidence not only of the predictive power of sleep quality on subsequent pain level [13,14], but with the finding that therapeutic effect on sleep also improves pain [38]. Complicating the interpretation of how alpha entrainment exerts its effect is the possibility that there may be a direct action on sleep, not via a pain mechanism. From a cognitive perspective it is conceivable that sleep onset could benefit from increased alpha power, based on the hyperarousal model of insomnia [39]. This implicates cognitive arousal such as pre-sleep rumination, represented by higher frequency cortical activity (beta and gamma), which may be ameliorated if replaced with alpha. This is not the mechanism motivating the development of hBET, but highlights important questions about how neuromodulation might incorporate or sit alongside other management options, such as Cognitive Behavioural Therapy for Insomnia.

An interesting finding is that sham stimulation resulted in a significant increase in alpha power compared to baseline, albeit to a lesser degree than active stimulation. The sham intervention is not acting via the phenomenon of entrainment so an alternative mechanism is presumably at play. This could be the expectation of pain relief, which is itself associated with increased alpha activity [40], or the effect of attending to a sensory stimulus, which is also associated with modulation of alpha activity in complex ways [41]. This highlights the need to control against an experientially similar condition for mechanistic clarity in clinical studies, but in real life use the summative benefit of attention, placebo and active entrainment would be available to the user.

Two participants were seen to have markedly lower alpha power across all conditions and entrainment was more successful in the remaining participants who displayed a higher level of alpha power throughout. This has potential implications for further development of this technology. It is possible that the failure to detect the expected level of global alpha power in two participants is due to insensitivity of the reduced-montage, user-positioned EEG system used here, or variation in how precisely participants adhered to the protocol (e.g. eyes open instead of closed). For open loop stimulation the EEG is solely a research tool, and real-life use without the discomfort of the EEG headband may allow greater clinical improvement. However, if future development sought to employ closed loop stimulation, then the reliability of the EEG positioning and signal quality would need to be optimised. Alternatively, the finding may represent a real distinction of alpha power profiles with the implication that potential end-users could be screened for their alpha characteristics before entrainment is deemed a suitable approach.

A limitation of this study is the small number of participants which constrains the precision of any estimates of the clinical effect in a wider patient population, and the findings should be interpreted with a level of caution consistent with the exploratory feasibility stage of this study. The gender composition of the sample, being 85% women, was in keeping with classical descriptions of the demography of fibromyalgia [42] but given that the gender ratio is

closer to 2:1 when using recent diagnostic criteria (which omit tender point examination) [43] it is likely that this is an overrepresentation of women. Interpretation is also limited by the brief intervention period of two weeks in each mode, and lack of any long-term outcome measures.

Here, the aim was to study an ecologically valid situation of individuals in their own environments over several weeks, which is a strength in terms of the applicability of the findings to complex real-life situations. This inevitably gives rise to a restriction in how much control the researchers had over how the tools were used day by day. Also, concurrent drug use was not standardised, which is a further reflection of the pragmatic, 'real life' focus of the design. This includes use of drugs which are known to affect sleep, such as tricyclic antidepressants. The crossover design does go some way to control for this, in that each participant acts as their own baseline, and participants did not alter medications during the study period.

In conclusion, this study found the pre-sleep use of a neuromodulation strategy using sensory stimulation and associated research processes including home-based night long EEG to be feasible. It demonstrates that entrainment of alpha activity can be achieved with sensory stimulation in this real-world context. Establishing clinical efficacy was beyond the scope of this feasibility study, but the indication of a symptomatic improvement in pain and sleep domains compared against a well-controlled sham should motivate further study with larger scale trials. If found to be efficacious, this type of non-pharmacological intervention could represent a significant advance in scalable and cost-effective treatment option for this common and disabling clinical condition.

Disclosures

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CRediT authorship contribution statement

SH: conceptualisation, methodology, project administration, investigation, analysis, visualisation and writing – original draft. LX: software, analysis. DCG: analysis, visualisation, review and editing. NKYT: methodology, review and editing. NJTB methodology, analysis, review and editing. CB conceptualisation, methodology, review and editing. AKPJ conceptualisation, supervision, review and editing. RJO'C: supervision, review and editing. AJC: methodology, software, analysis, validation, visualisation, review and editing. MS: conceptualisation, supervision, methodology, analysis, review and editing.

Data Availability

Data will be made available on reasonable request.

Figure legends

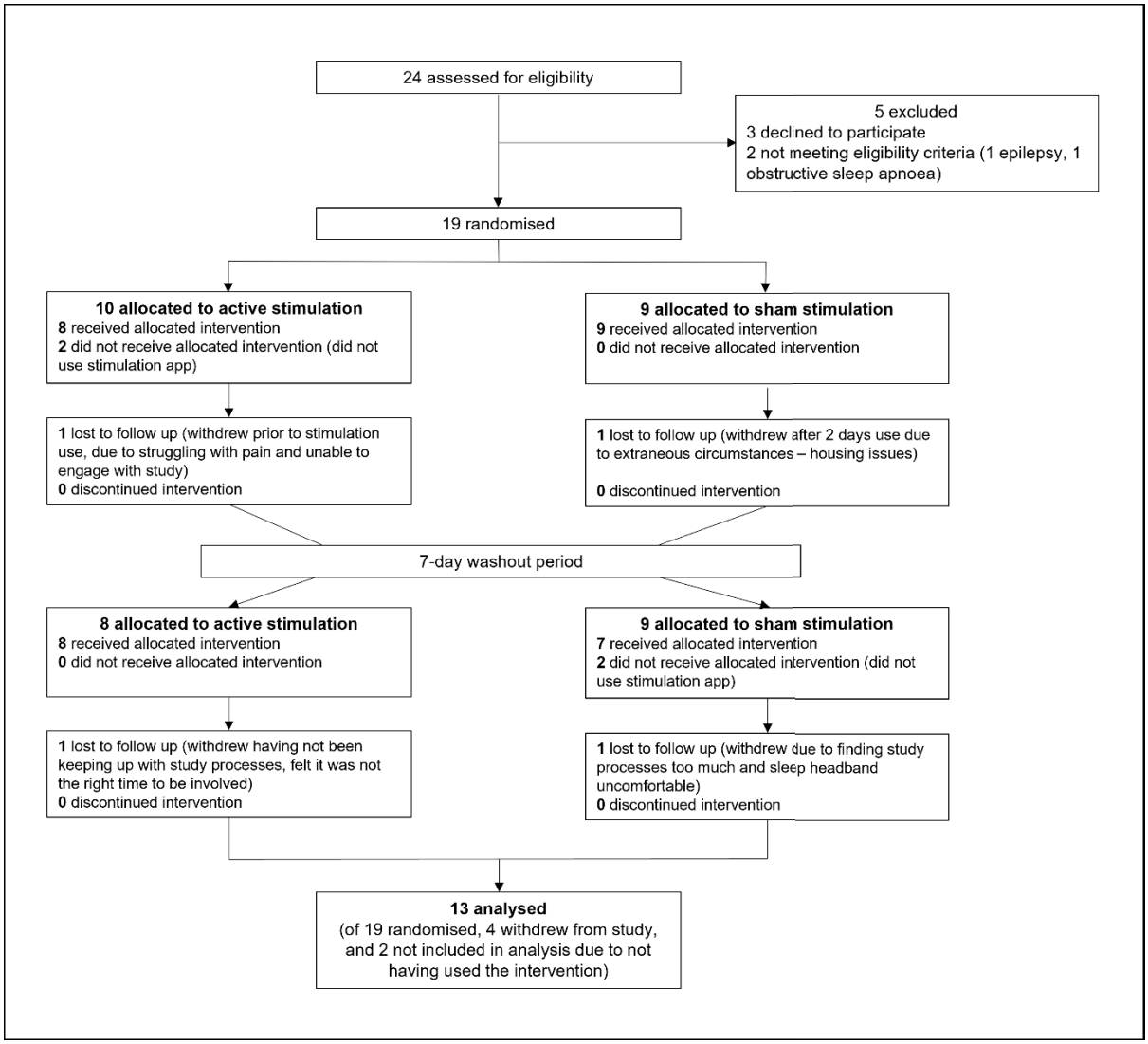

Figure 1. Participant flow through the study

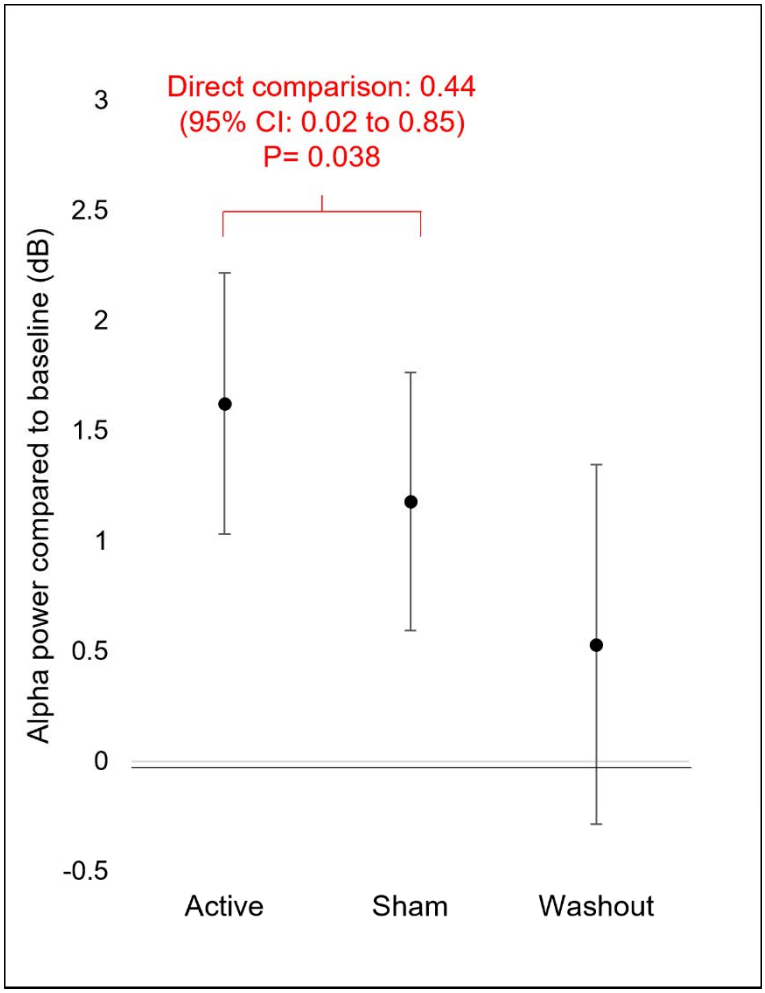

Figure 2. Effect of stimulation on alpha power, showing point estimate and 95% confidence intervals for each comparison to baseline, with direct active – sham comparison.

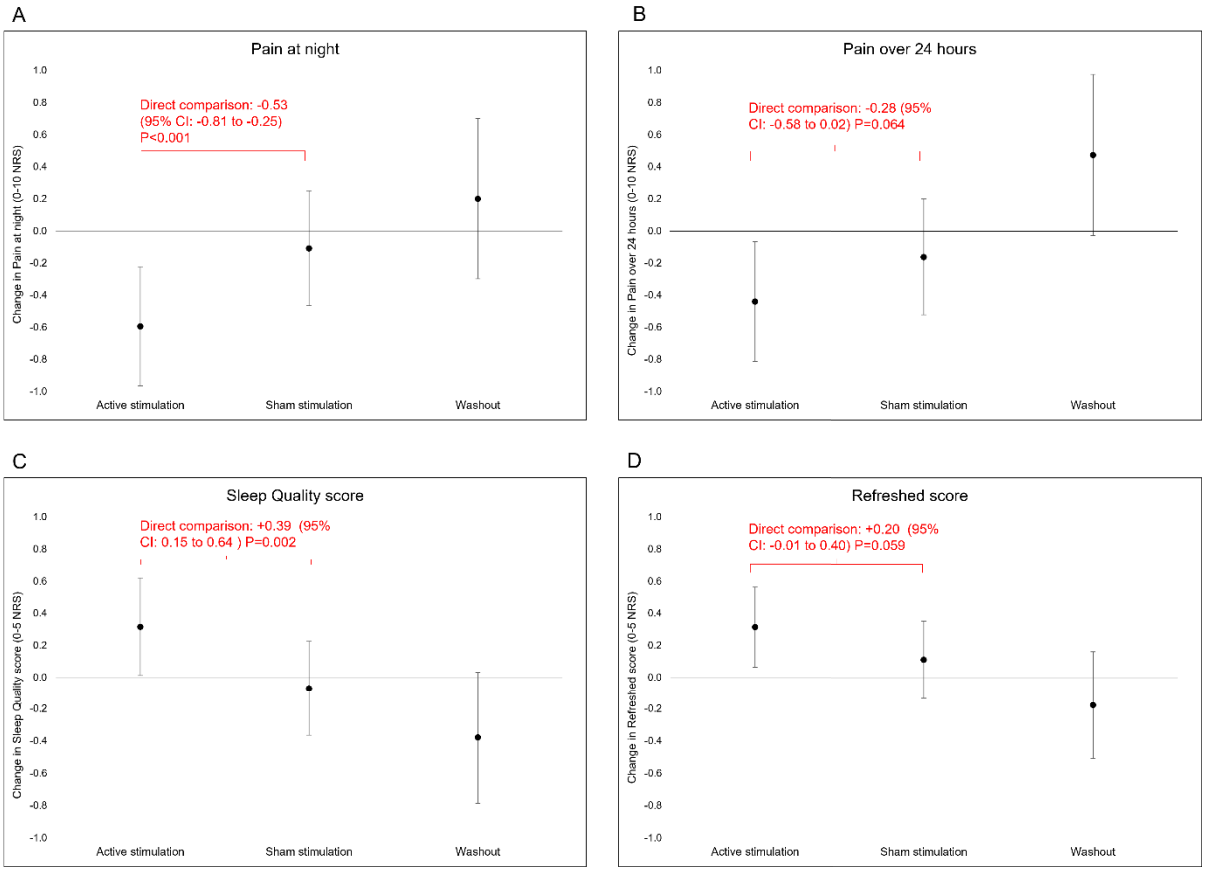

Figure 3. Difference (and 95% confidence interval) in active stimulation, sham stimulation and washout periods compared to baseline for daily diary report of A) Pain at night B) Pain over 24 hours C) Sleep quality score and D) Refreshed score. Also displaying result of the direct active – sham comparison. NRS, numerical rating scale.

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	Allocated to receive Active stimulation first, then Sham (6)	Allocated to receive Sham stimulation first, then Active (7)
Age (mean, years)	48 (range 34–53)	47 (range 26–58)
Gender (self-reported)	5 women, 1 man	6 women, 1 man
In employment	2 Yes, 4 No	4 Yes, 3 No
Duration of pain (years)	8	13
Duration of sleep problems (years)	9	18
Time since FM diagnosis (years)	2	4
Coexistent depression/anxiety	5 Yes, 1 No	4 Yes, 3 No

Median number of pain medications	2.5	3
Currently taking:		
Opioid	3 Yes, 3 No	5 Yes, 2 No
SNRI	3 Yes, 3 No	1 Yes, 6 No
Gabapentinoid	3 Yes, 3 No	3 Yes, 4 No
TCA	1 Yes, 5 No	3 Yes, 4 No
2016 ACR diagnostic criteria scores:		
Widespread Pain Index (0–19)	15	15
Symptom Severity Score (0–12)	10	10

Table 1. Clinical profile of participants, by allocation. ACR, American College of Rheumatology. FM, fibromyalgia. SNRI, serotonin and noradrenaline reuptake inhibitor. TCA, tricyclic antidepressant. Medical history obtained from patient report.

A. Comparison to baseline

Active stimulation			Sham stimulation			Washout		
Estimate	95% CI	P	Estimate	95% CI	P	Estimate	95% CI	P
1.62	(1.03 to 2.22)	<0.001	1.18	(0.59 to 1.76)	<0.001	0.53	(-0.29 to 1.35)	0.203
	(Cohen's d = 0.64)			(Cohen's d = 0.47)				

B. Active vs Sham stimulation

Estimate	95% CI	P	Cohen's d
0.44	(0.02 to 0.85)	0.038	0.17

Table 2. Effect of stimulation on fronto-occipital alpha power, in decibels: A) active, sham and washout periods compared to baseline and B) direct comparison of active and sham stimulation (n=12)

	Baseline		Sham stimulation		Active stimulation		Comparison of Active - Sham simulation (95% CI)		P value
	Mean (SD)		Mean (SD)		Mean (SD)				
Daily measures of pain and sleep quality (n=13)									
Pain at night (0-10 NRS)	6.9	(2.2)	6.6	(2.4)	6.1	(2.4)	-0.53	(-0.81 to -0.25)	<0.001
Pain over 24 hours (0-10 NRS)	7.2	(1.8)	6.8	(2.0)	6.4	(1.8)	-0.28	(-0.58 to 0.02)	0.064
Sleep quality score (0-5 NRS)	2.2	(1.5)	2.2	(1.4)	2.6	(1.2)	0.39	(0.15 to 0.64)	0.002
Refreshed score (0-5 NRS)	1.3	(1.3)	1.6	(1.4)	1.8	(1.2)	0.2	(-0.01 to 0.40)	0.059
Sleep diary (n=13)									
Total sleep time (minutes)	404.0	(128.5)	394.7	(134.1)	378.6	(113.8)	-7.7	(-34.0 to 18.6)	0.564
Sleep onset latency (minutes)	37.2	(38.6)	36.8	(32.4)	30.1	(20.1)	-7.4	(-12.9 to -1.8)	0.010
Sleep efficiency (%)	78.7	(15.9)	77.9	(14.3)	77.4	(15.5)	0.98	(-2.1 to 4.0)	0.529
Wake after sleep onset (minutes)	19.0	(29.8)	15.4	(27.3)	10.9	(15.3)	-3.4	(-8.5 to 1.8)	0.199
Dreem headband sleep measures (n=9)									
Total sleep time (minutes)	429.5	(77.6)	399.8	(88.1)	419.7	(79.0)	23.8	(1.4 to 46.2)	0.037
Sleep onset latency (minutes)	23.8	(25.8)	19.4	(20.5)	18.6	(15.6)	-2.4	(-7.6 to 2.8)	0.358
Sleep efficiency (%)	88.0	(9.4)	89.5	(7.8)	90.2	(6.6)	1.7	(-0.1 to 3.5)	0.072
Wake after sleep onset (minutes)	26.0	(24.5)	22.9	(26.5)	23.1	(25.3)	-2.9	(-9.6 to 3.8)	0.394
Actigraphy sleep measures (n=13)									
Total sleep time (minutes)	401.1	(98.2)	373.9	(99.2)	387.8	(101.8)	23.6	(0.7 to 46.5)	0.044
Sleep onset latency (minutes)	19.6	(31.3)	9.7	(14.6)	10.4	(19.1)	-0.8	(-5.1 to 3.5)	0.715
Sleep efficiency (%)	84.7	(8.2)	87.3	(7.8)	86.5	(6.5)	1.2	(-0.2 to 2.6)	0.081
Wake after sleep onset (minutes)	49.5	(30.2)	38.3	(19.6)	46.4	(27.4)	3.2	(-1.0 to 7.3)	0.132

Table 3. Daily clinical measures of pain and sleep (NRS, numerical rating scale)

	Baseline	Sham stimulation	Active stimulation	P-value Active vs Baseline	P-value Active vs Sham	P-value Sham vs Baseline
Pittsburgh Sleep Quality Index	15.2	13.1	11.8	0.005	0.341	0.012
BPI Pain Interference	7.7	7.0	6.9	0.007	0.985	0.054
BPI Pain Severity	7.0	6.8	6.4	0.125	0.330	0.520
MFI	82.2	83.0	81.1	0.641	0.688	0.547
HADS Anxiety	13.0	11.9	11.9	0.406	0.992	0.484
HADS Depression	10.7	10.9	11.2	0.424	0.746	0.801
EQ-5D VAS	33.2	36.2	38.6	0.322	0.706	0.617
EQ-5D Index value	0.19	0.19	0.21	0.910	0.664	0.945

Table 4. Questionnaire measures and results of Wilcoxon sign rank tests. BPI, Brief Pain Inventory. MFI, Multidimensional Fatigue Inventory. HADS, Hospital Anxiety and Depression Scale. EQ-5D, Euroqol 5 dimensions health related quality of life measure. VAS, visual analogue scale.

Highlights

- Non-invasive neuromodulation could be a scalable management option for chronic pain
- Sensory stimulation can be used to modulate alpha band cortical activity
- Alpha entrainment delivered pre-sleep was feasible alongside home EEG monitoring
- Users demonstrated an increase in alpha activity compared to sham stimulation
- The improvement in pain and sleep quality should be further evaluated in future studies