Pre-sleep alpha brain entrainment for chronic pain and sleep disturbance

by

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I confirm that the work submitted is my own, except where work which has formed part of jointly authored publications has been included. My contribution and that of the other authors to this work have been explicitly indicated below. I confirm that appropriate credit has been given within the thesis where reference has been made to the work of others.

Chapter 2 is a jointly authored publication: Halpin, S.J., Casson, A.J., Tang, N.K.Y., Jones, A.K.P., O'Connor, R.J. and Sivan, M. 2023. A feasibility study of pre-sleep audio and visual alpha brain entrainment for people with chronic pain and sleep disturbance. Frontiers in Pain Research. 4, 1096084. doi: 10.3389/fpain.2023.1096084. My contribution was to write the study protocol, obtain ethical and regulatory approvals, assist in intervention development, recruit participants, collect the data, perform the data analysis and draft and edit the manuscript. The contribution of other authors was: AJC led the development of the intervention technology, contributed to devising the study, supervised the project and edited the manuscript. NKYT contributed to study methodology and analysis techniques and edited the manuscript. AKJP conceptualised the study, supervised the project and edited the manuscript. RJO'C supervised the project and edited the manuscript. MS conceptualised the study, helped develop the intervention and methodology, supervised the project and edited the manuscript.

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This thesis has been prepared in the alternative style including published material since these consecutive papers logically form a single coherent body of work. It has been constructed by supplementing the papers with contextualising introductory materials and a discussion section, which offers a critical analysis of the contribution of the papers taken as a unified whole.

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Individual Contributions

This research has been carried out by a team centred around the Human Pain Research Group in the University of Manchester and the Academic Department of Rehabilitation Medicine in the University of Leeds, which has included Professor Manoj Sivan, Professor Rory O'Connor, Professor Anthony Jones, Professor Alex Casson, Dr Le Xing, Professor Nicole Tang, Dr Christopher Brown, Dr Darren Greenwood and Dr Nelson Trujillo-Barreto. My own contributions, fully and explicitly indicated in the thesis, have been that I performed all the practical execution of each study, including ethical and regulatory approvals, all recruitment, all contacts with participants, all data collection and data management. I performed the analysis in Chapters 2 and 3. In Chapter 4 I contributed to the data processing phase of analysis, and performed the subsequent statistical analysis, with guidance. I wrote the manuscripts of each paper, collated edits from co-authors and submitted the papers for publication and wrote the thesis.

The other members of the group and their contributions have been as follows: Manoj Sivan conceptualised the first study, supervised me throughout the project, oversaw ethical and regulatory approvals, assisted in acquiring funding to pursue the work and reviewed the thesis. Rory O'Connor supervised me throughout the project, independently reviewed codes as part of the qualitative analysis in Chapter 3 and reviewed the thesis. Anthony Jones provided guidance and oversight as the named Principal Investigator based in the University of Manchester and reviewed the thesis. Alex Casson provided

supervisory guidance throughout the project, led the software development of all iterations of the hBET application and led on processing the EEG data in Chapter 4. Le Xing developed the software for the sham stimulation and the hBET app used in Chapter 4 and helped undertake the EEG data processing. Nicole Tang provided methodological and analysis guidance regarding assessment of sleep. Christopher Brown and Nelson Trujillo-Barreto each contributed to the design and analysis of the study in Chapter 4. Darren Greenwood provided statistical guidance and example code for the analysis of data in Chapter 4 and contributed to interpretation and presentation of the data. I also acknowledge the work of Dr Nikhil Kurian Jacob PhD for his work developing earlier iterations of the hBET application.

Abstract

Home-based neuromodulation is a potentially scalable option to help address the globally important challenge of chronic pain. Alpha entrainment is a neuromodulatory technique which has emerged as potentially helpful for pain. In this project it has been applied via a smartphone application called hBET which provides repetitive audio or visual stimulation at 10 Hz. The general aim is to study the feasibility and effect of home-based use of hBET delivered pre-sleep for people with chronic pain and sleep disturbance, in a way which helpfully informs future research.

To fulfil this aim three studies are presented. In the first, an uncontrolled feasibility study, participants with chronic pain and disturbed sleep found the use of hBET at home acceptable and beneficial to symptoms. The high adherence rate and improvements in participant-reported measures of pain, sleep, mood and fatigue demonstrates the technique is feasible and clinically promising. The second study, a qualitative investigation into participants' experience of engaging with hBET, contributes detailed learning on how the intended users interact with this technology which informs future development and provides new insights into how pain and sleep interact. The third study progresses the investigation by adding a sham control and real time home-based EEG monitoring, using a crossover randomised design. This trial confirms that hBET entrains alpha and results in an improvement in pain at night and sleep quality, compared to the sham control. It also demonstrates, for the first time in the literature, the feasibility of pre-sleep sensory alpha entrainment in conjunction with home EEG monitoring for individuals with chronic pain.

Taken together, this body of work establishes the potential of sensory alpha entrainment as a management tool for chronic pain and sleep disturbance and informs the technical development of the intervention and future trial design.

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Abbreviations

AASM	American Academy of Sleep Medicine
ACR	American College of Rheumatology
ASR	Artefact Subspace Reconstruction
BPI	Brief Pain Inventory
CBT-I	Cognitive Behavioural Therapy for Insomnia
CDC	Centres for Disease Control and Prevention
CI	Confidence Interval
DNIC	Diffuse Noxious Inhibitory Controls
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalogram
EQ-5D	EuroQol score 5 - dimensions
ERP	Event-Related Potential
FFT	Fast Fourier Transform
FM	Fibromyalgia
FOOOF	Fitting Oscillations and One Over f
GABA	Gamma Amino Butyric Acid
GBD	Global Burden of Disease
GDP	Gross Domestic Product
HADS	Hospital Anxiety and Depression Scale
hBET	Home-based Brain Entrainment Technology
HRA	Health Research Authority
IAF	Individual Alpha Frequency
IASP	International Association for the Study of Pain
ICD	International Classification of Diseases
ICF	International Classification of Function, Disability and Health
ICSD	International Classification of Sleep Disorders
IQR	Interquartile Range
MFI	Multidimensional Fatigue Inventory

NHS	National Health Service
NIHR	National Institute for Health and Care Research
NREM	Non Rapid Eye Movement
NRS	Numerical Rating Scale
PAF	Peak Alpha Frequency
PPIE	Patient and Public Involvement and Engagement
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
RCD	Research Diagnostic Criteria
REM	Rapid Eye Movement
REML	Restricted Maximum Likelihood
SD	Standard Deviation
SE	Sleep Efficiency
SF-36	36-item Short Form health survey
SNRI	Serotonin and Noradrenaline Reuptake Inhibitor
SOL	Sleep Onset Latency
tACS	Transcranial Alternating Current Stimulation
TCA	Tricyclic Antidepressant
tDCS	Transcranial Direct Current Stimulation
TENS	Transcutaneous Electrical Nerve Stimulation
TMS	Transcranial Magnetic Stimulation
TST	Total Sleep Time
VAS	Visual Analogue Scale
WASO	Wake After Sleep Onset
WHO	World Health Organisation
YLD	Years Lived with Disability

Chapter 1 Introduction

1.1 Chronic pain, sleep disturbance and how they are related

The investigations in this thesis address a novel intervention at the point where two large clinical problems intersect. For a full understanding of the context of these health issues, physiologically, clinically and epidemiologically, the following sections will introduce pain and sleep separately, and then explore how they are related. This will lead on to a discussion on the need for better management options in this area and make the case for tackling pain and sleep together in the pursuit of improved treatments.

1.1.1 Pain and chronic pain

1.1.1.1 Function and dysfunction

Pain serves a function essential to survival with clear evolutionary purpose. As is apparent in the definition provided by the International Association for the Study of Pain (IASP), pain is not a simple sensory phenomenon, but something perceived, experienced by the individual: “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage” (Raja et al., 2020). This percept has long been known to be generated through the integration of sensory inputs with affective, motivational and cognitive factors (Melzack and Casey, 1968), which aligns with its primary function of maintaining the organism’s safety and integrity, by dominating attention and urgently motivating the organism to take action.

Overarching models of the neurophysiological basis for pain have evolved since the seminal gate control theory of Melzack and Wall (1965) which represented an influential shift in establishing the concept that the experienced pain is a result of modulation during the ascent of signals from the periphery, chiefly focussing on those occurring in the spinal cord. The theory states that non-nociceptive input to the dorsal horn can inhibit the upward transmission of nociceptive input, explaining the modulating influence of other simultaneous sensory stimuli. Whilst subsequent experimental findings contested the specifics of the mechanism (Mendell, 2014) the theory nevertheless opened the door to a neurophysiological framework to understanding pain as a complex experience capable of being modulated by psychology, experience, expectation, genetics and so on. As experimental evidence grew around and overtook the gate control theory, Melzack elaborated it into the ‘neuromatrix theory of pain’ concept (Melzack, 1989) and more clearly articulated later (Melzack, 2001). This advances further the mechanisms by which cognitive and affective factors contribute to pain. Built on observations in phantom limb

phenomena, it positions pain as the output of a widely distributed neural network in the brain, (in contrast to being the direct result of peripheral noxious stimulation), and that the characteristic activation of this network gives rise to the 'neurosignature' of pain. It proposes that although this is usually activated by sensory inputs it can also be activated independently of them, allowing for the many clinical situations whereby pain seems to be disconnected from actual ongoing tissue damage or threat. As observations from many neuroimaging studies added to knowledge of the structures which are activated when pain is experienced (for example, (Wager et al., 2013)) the neuromatrix evolved to become known as the Pain Matrix and was a dominant concept in the early part of this century. It helpfully emphasised that there was no single pain centre in the brain, and propelled investigation into the functional anatomy serving the integration of the components of pain, for example in distinguishing those regions important in localisation versus the cognitive evaluative component of pain (Kulkarni et al., 2005). However, its characterisation as a 'pain' matrix implies a specificity to pain which it has been argued is not supported by evidence (Iannetti and Mouraux, 2010) and could equally result from non-painful salient sensory inputs. A current overarching conceptualisation of the integration of cognitive, affective and sensorimotor contributions is proposed in the Dynamic Pain Connectome model (Kucyi and Davis, 2015). This draws heavily on studies of attention to pain and emphasises the function of dynamic communication within and between key brain networks to encode pain, implicating the salience network, default mode network, and antinociceptive system as important. In contrast to the earlier models, it centres the temporal element, rather than a static spatial network. The concept is that the dynamic connectivity between elements of the spatial network are what constitutes the pain signature, representing integration of the components of the pain experience. This emphasis means the model integrates well with approaches to pain which draw on modulating oscillatory dynamics of brain activity (Ploner et al., 2017).

Pain, whilst unpleasant, is part of normal human experience and clearly does not always denote any dysfunction. Chronic pain, on the other hand, is an undesirable state which has the potential to become largely disconnected from ongoing threat or damage and therefore ceases to be useful, as shall be later explored. Clinically, chronic pain is defined as that which persists or recurs for more than three months. (Since the term 'chronic' is often misunderstood, 'long-term pain' is preferable for lay audiences, however for the purpose of this thesis 'chronic' will be retained as it is codified in clinical taxonomies of pain). Pain is unusual, spanning classification systems in that it can be both a symptom and a disease in its own right. Its recognition as a disease in its own right is relatively

new, and followed much academic debate (Taylor et al., 2015; Raffaeli and Arnaudo, 2017; Treede et al., 2019), but the latest revision of the International Classification of Diseases (ICD-11) includes new categories on chronic pain (World Health Organization, 2019). For the first time, ICD-11 introduces the category of chronic primary pain, which is distinguished from six categories of chronic secondary pain, such as chronic cancer related pain and chronic secondary visceral pain (Nicholas et al., 2019). In these secondary pain conditions the pain is linked to the other diseases as the underlying cause and, at least initially, can be regarded as a symptom (Treede et al., 2019). When the chronic primary pain classification applies the pain is best thought of as a condition in its own right. The studies in this thesis focus on fibromyalgia, which falls under the category of chronic primary pain. To illustrate how the lineages of chronic primary and secondary pains relate in ICD-11, a schema that includes fibromyalgia is shown in Figure 1.1.

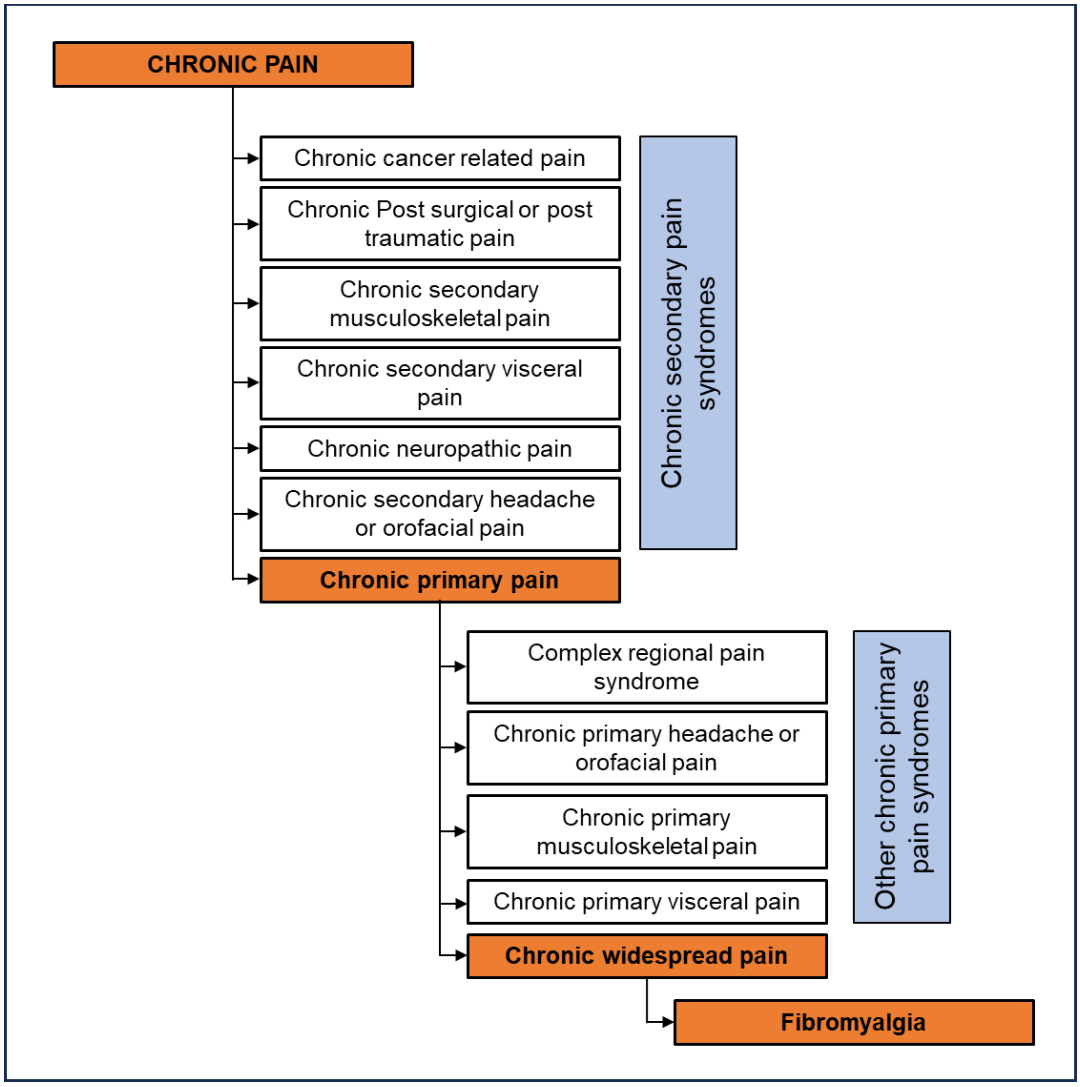

Figure 1.1 The ICD-11 taxonomy of chronic pain (World Health Organization, 2019), showing fibromyalgia in relation to other chronic primary and secondary pain categories

Pain also has mechanistic categories. Classically, neuropathic pain was set in a binary against nociceptive pain, where the former implied causative damage to the nervous system either peripherally or centrally, with the latter being caused by tissue damage or inflammation via the normal function of pain-sensing apparatus. A third category has more recently been proposed alongside these, that of nociplastic pain, which when occurring in isolation can be seen as a mechanistic corollary to the chronic primary pain category. Nociplastic pain is that which results from increased sensitivity due to altered function of pain related pathways in the periphery and central nervous system (Fitzcharles et al., 2021). The term is a portmanteau of 'nociceptive plasticity' to highlight the change in function of pathways in the absence of damage to them. It can occur in isolation, as in chronic primary pain syndromes, or alongside conditions which cause pain via nociceptive or neuropathic mechanisms, as may be the

case later in the time course of chronic secondary pain syndromes. Although it lacks biomarkers, proponents of the term argue that in practical terms for clinical use this is also true for nociceptive or neuropathic pain, and it is necessary for definitions to include the common scenario of pain where no actual or threatened tissue damage is present to initiate normal nociception, and the structural components of the neural system are intact (Kosek et al., 2016). The mechanistic category of nociplastic pain overlaps with the concept of central sensitisation, which is a term describing the neurophysiological basis for how pain is maladaptively amplified in the central nervous system (Harte et al., 2018). Fibromyalgia, a chronic primary pain condition, is usually considered to be maintained by nociplastic mechanisms and has been described as the 'prototypical centralised pain state' (Clauw, 2015).

1.1.1.2 Individual impact

A biopsychosocial framework is required to understand how a health condition relates to impacts for an individual, and this is best provided by the model of the World Health Organization's International Classification of Functioning, Disability and Health (ICF) (World Health Organization, 2001). This is structured around the domains of body functions (the physiological and psychological functions of body systems) and body structure (anatomical parts of the body and their components), activity (the execution of a task by the individual) and participation (involvement in a life situation). Problems with body function and structure are known as impairments, difficulties in activity are known as limitations, and difficulties in the participation domain are known as restrictions. Alongside these domains in the framework are contextual factors, which are divided into environmental and personal factors. Together these factors make up the physical, social and attitudinal environment in which people live. An example of how chronic widespread pain as a health condition may interact with component domains of functioning and contextual factors to give rise to disability in the ICF model is shown in Figure 1.2. For illustrative purposes all the examples of domain specific factors in this figure are taken from the ICF core set for chronic widespread pain (except for personal factors which are not currently classified within the ICF).

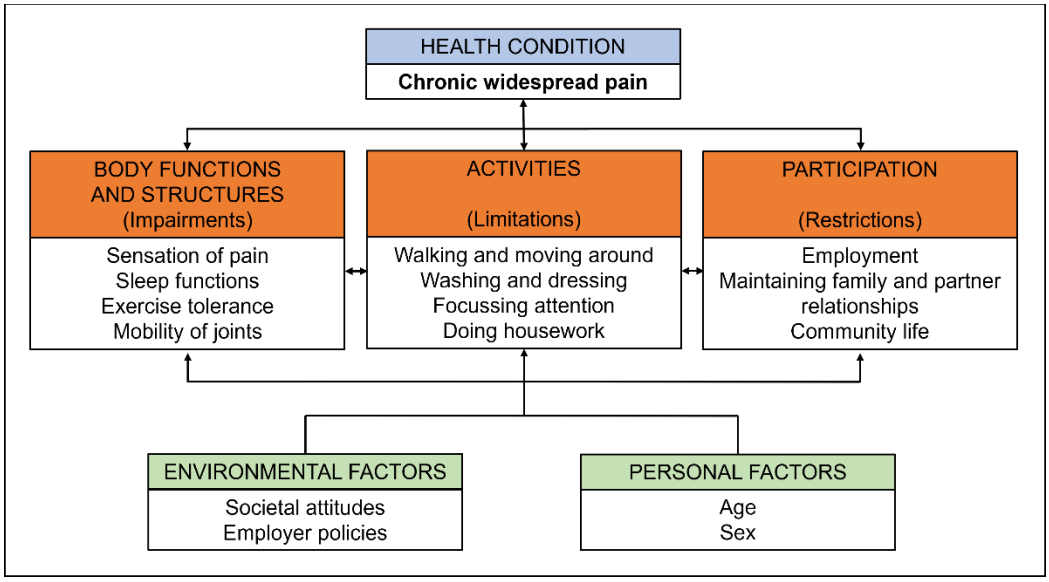

Figure 1.2 Example application of the ICF to illustrate the individual impacts of chronic pain. (Adapted from World Health Organization 2001)

Given these multidimensional problems for the individual, it is unsurprising that chronic pain gives rise to a substantial impact on health-related quality of life. In a UK based, mixed methods study the impact on health-related quality of life was found to be significantly greater in chronic pain than other long term conditions and to span all the domains measured by a widely used instrument (the SF-36) (Hadi et al., 2019). The economic burden referred to in section 1.1.1.3 also has an individual dimension, as it is largely related to inability to work and lost productivity, which equates to lost income for the individual. Almost half of respondents in a large multinational survey study of individuals with chronic pain had lost or changed their job due to pain (Breivik et al., 2006). Direct healthcare costs are also borne by the individual in out-of-pocket expenditure in some health systems.

1.1.1.3 Societal impact

Pain rates among the very largest health burdens globally in terms of morbidity. In the Global Burden of Disease (GBD) studies, low back pain is consistently the single leading cause of Years Lived with Disability (YLDs) globally, and is within the top ten in every country in the world (Global Burden of Disease Study Collaborators, 2015). Figure 1.3 shows a visualisation of this created with an online tool for exploring GBD data in which the contributions to overall global burden from back pain, neck pain, other musculoskeletal conditions, osteoarthritis and headache can all clearly be seen (Institute for Health Metrics and Evaluation (IHME), 2020).

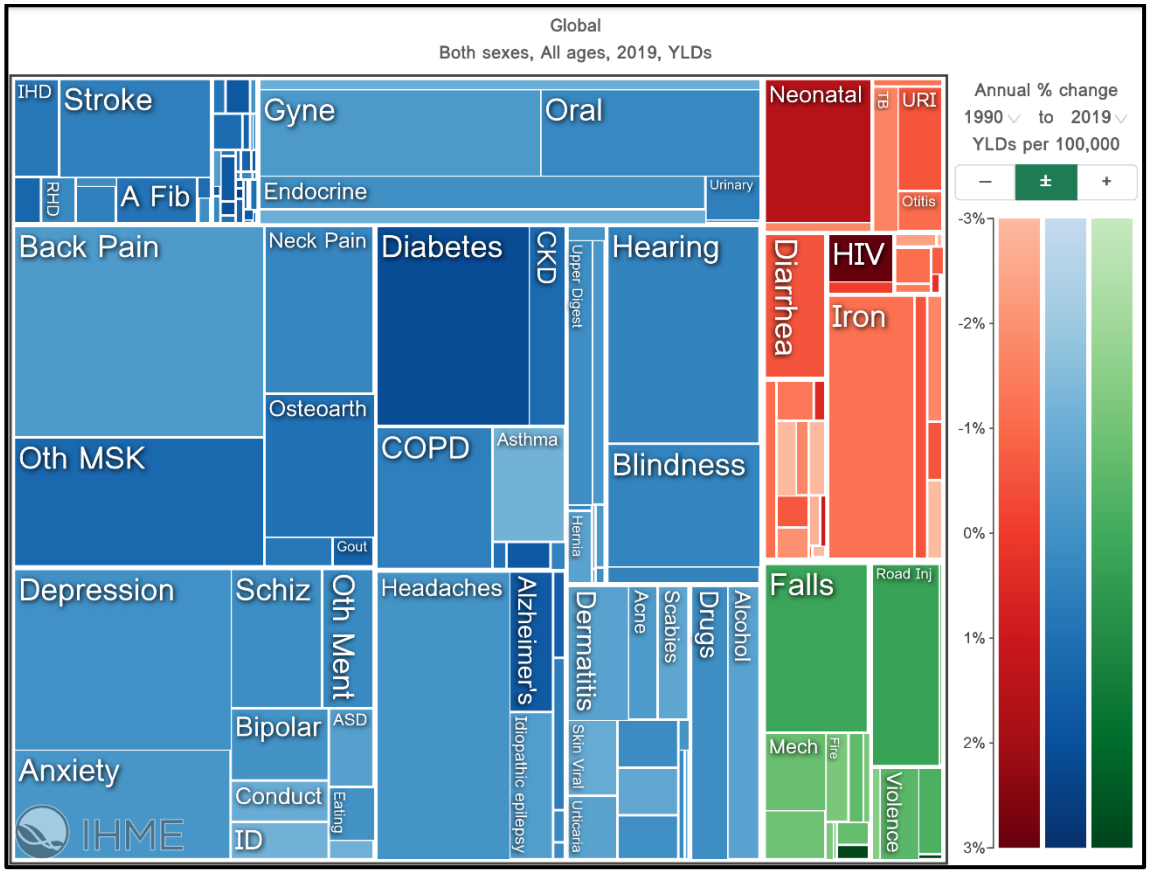

Figure 1.3 A visualisation of causes of Years Lived with Disability from GBD data

The prevalence of chronic pain in England has been estimated in a survey of 8000 adults conducted by Public Health England at 34% of all adults, rising to over half of adults over 75 years (Public Health England, 2020). This astonishingly high prevalence is replicated in other studies in the UK (Fayaz et al., 2016) (35-51%) and across Europe (Leadley et al., 2012) (27%, considering moderate to severe pain only). Those affected experience adverse impacts on daily activities, employment stability and social wellbeing (Breivik et al., 2006). This correlates with substantial economic burden both in direct healthcare costs, and work absenteeism and lost productivity, which has been estimated at up to $635 billion in the United States (Gaskin and Richard, 2012) and across European countries represents 3-10% of a nation's Gross Domestic Product (GDP) (Gustavsson et al., 2012; Raftery et al., 2012; Stubhaug et al., 2024). An estimate for the total economic cost of chronic pain specific to the United Kingdom is not available but twenty five years ago the cost of back pain alone was estimated to be over £10 billion (Maniadakis and Gray, 2000).

Whilst this should place chronic pain at the crux of global health policy, institutional priorities such as in the World Health Organisation (WHO) non-communicable disease strategy rarely mention chronic pain (Rice et al., 2016).

A strong health and economic case has been made to increase the prioritisation of chronic pain (Breivik et al., 2013).

1.1.2 Sleep and sleep disturbance

1.1.2.1 Function and dysfunction

Sleep has been described as a reversible behavioural state of perceptual disengagement from and unresponsiveness to the environment, which is usually accompanied by postural recumbence, behavioural quiescence and closed eyes (Carskadon and Dement, 2011). Although the primordial evolutionary purpose for sleep is unclear (Krueger et al., 2016), it is clear that humans have a profound need for it. Experimental sleep deprivation in healthy people results in significant adverse effects on memory (Newbury et al., 2021), vigilant attention (Hudson et al., 2020), state anxiety levels (Pires et al., 2016), serum markers of inflammation (Irwin et al., 2016), and insulin resistance (Zhu et al., 2019). Thus, sleep serves an array of purposes and is critical for health.

Normal human sleep has a physiological ‘architecture’, characterised by the pattern of transitions between stages of sleep, which themselves are defined by standardised features seen on polysomnography (PSG), the gold standard sleep investigation. The stages reflect the division of sleep into two fundamental states: rapid eye moment (REM) sleep and non-rapid eye movement (NREM) sleep. NREM sleep is further subdivided into stages N1, N2 and N3. Normal sleep architecture sees sleep being entered through NREM, and progresses through sequentially deeper NREM stages, with the first episode of REM being after 80-100 minutes and subsequently cycling between these states with a period of roughly 90 minutes (Carskadon and Dement, 2011). The relative proportions of NREM and REM sleep within each cycle shifts from predominance of deep NREM sleep early in the night towards increased length of REM episodes towards the end of the night. The durations, proportions and latency to each stage can be reported and a graphical summary represented by the hypnogram, which is exemplified in Figure 1.4. On a simpler level, describing the temporal characteristics of a sleep episode only requires distinguishing between periods of sleep and wake. The most common metrics derived are Total Sleep Time (TST, the total amount of actual sleep obtained) Sleep Onset Latency (SOL, the time taken to enter sleep from when the individual started trying to sleep), Wake After Sleep Onset (WASO, the total time spend awake after sleep onset and before the final awakening) and Sleep Efficiency (SE, time asleep as a proportion of the whole sleep opportunity time).

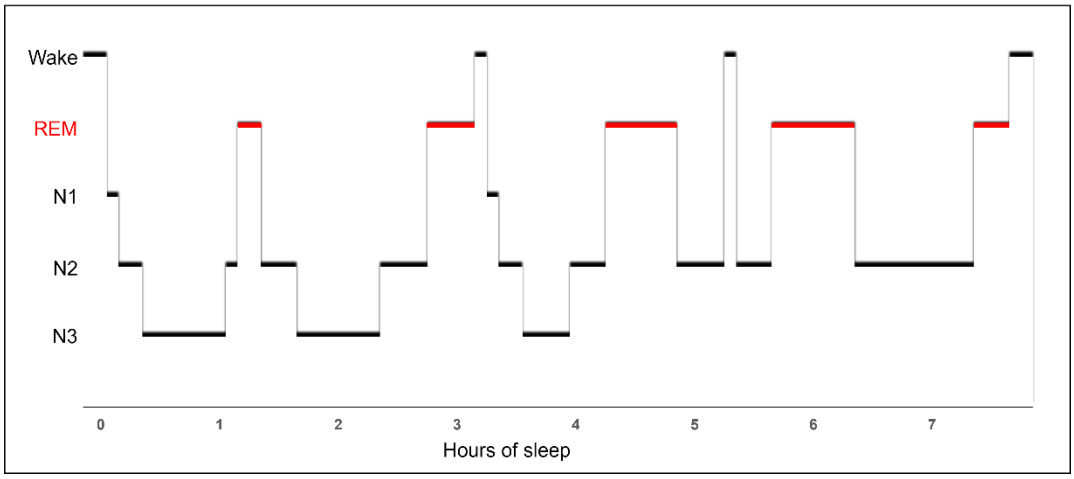

Figure 1.4 A hypnogram illustrating normal human sleep architecture

'Sleep disturbance' is an inclusive, non-clinical term which here is simply taken to mean any disturbance relating to sleep, whether the primary problem is about the temporal characteristics of sleep, problems with daytime function or the individual's evaluation of the sleep quality or adequacy. The closest corollary in terms of clinical sleep disorders is that of insomnia. Sleep disorders have multiple clinical classification systems including the ICD, DSM (the Diagnostic and Statistical Manual of Mental Disorders, now on version 5), ICSD (International Classification of Sleep Disorders, now on version 3) and the RDC (Research Diagnostic Criteria (Edinger et al., 2004)) but they largely converge around the definition of insomnia as being difficulty initiating or maintaining sleep that occurs despite adequate opportunity and circumstances for sleep and that results in general sleep dissatisfaction and some form of daytime impairment. It does not require any instrumented measurement of sleep. Chronic insomnia is when this is frequent and persistent, that is, several nights per week for three months or more.

1.1.2.2 Individual impact

The individual impacts of sleep disturbance or disorders can also be viewed through the biopsychosocial lens of the ICF. The daytime impacts of sleep disorders are often a component of their classification as disorders. As such this necessarily implies limitations in the activity domain (for example, concentrating on a task, driving) and restriction to participation (for example, employment, relationships). Sleep disorders also have unique considerations in the domain of personal contextual factors, as a sleeping partner may be relevant in a number of ways: as a helpful motivator to improve the sleep environment, as the primary

source of the history which identifies the sleep problem, or may even be injured by behaviours due to the disorder, in the case of some parasomnias.

These cross-domain impacts result in diminution of quality of life and employment. Taking chronic insomnia as an example, in a large survey study across three high income countries (United States of America, France, Japan) the health-related quality of life of people with chronic insomnia was found to be significantly lower than that of good sleepers (Léger et al., 2012). This was the case across all eight domains of the instrument used (the SF-36), was similar across the three country settings, with decrements across the domains of magnitudes similar to or greater than those reported by individuals on haemodialysis (Merkus et al., 1997). Insomnia is significantly associated with being unable to work or perform usual daily activities, with one large cohort study finding on average almost 1 day out-of-role per month (Hajak et al., 2011). These serious individual impacts also summate to represent a large health issue across society more broadly.

1.1.2.3 Societal impact

The public health implications of insufficient sleep arise from direct and indirect effects. It is directly implicated in road traffic (Bioulac et al., 2017) and workplace accidents (Brossoit et al., 2019) and indirectly represents a risk factor for other significant health conditions including stroke (Ge and Guo, 2015) and type-2 diabetes (Shan et al., 2015). There is controversy around whether this ultimately leads to an effect on overall mortality. Meta-analyses come to contrasting conclusions (Liu et al., 2017; García-Perdomo et al., 2019) and there is a suggestion that positive findings are a result of failing to control for baseline health (Magee et al., 2013). Whilst the direction of causality may be hard to establish in these cohort studies it nevertheless appears that sleep is a viable target for public health interventions. This is supported by an analysis of data from two waves of a large UK longitudinal survey which demonstrates that positive changes to sleep improve health and wellbeing (Tang et al., 2017).

The economic impacts related to sleep problems arise via ill health and reduced productivity. An analysis from the policy thinktank RAND Europe suggests that the workplace productivity loss associated with employees having insufficient sleep equates to the equivalent of over 200,000 working days lost in the UK per year and has a total economic cost to the country of 1.86% of GDP, or around $50 billion (Hafner et al., 2017).

Given the importance of sleep and the associated individual and societal costs of sleep problems it is not surprising that public and professional interest in sleep has increased in recent years, from the rise of wearable sleep monitors,

increased research funding and a scientific briefing to the UK Parliament (Parliamentary Office of Science and Technology (POST), 2018).

1.1.3 The relationship between chronic pain and sleep disturbance

Here the interrelationship of the two problems described above will be described, with the aim of exploring the rationale for addressing them together. To begin with, the simplest indication of the relationship is the observation that chronic pain and sleep problems commonly co-occur. In general chronic pain populations around 75% have sleep disturbance on patient reported measures (Sun et al., 2021), and 44% have a diagnosable sleep disorder based on polysomnography (Mathias et al., 2018), according to recent meta-analyses. Studies focussing specifically on painful musculoskeletal conditions find similar results, with prevalence of sleep problems over 70% (Abad et al., 2008; Parmelee et al., 2015). In the reverse direction it is reported that about 50% of people with chronic insomnia have chronic pain (Taylor et al., 2007). The studies in this thesis focus on individuals with fibromyalgia which, as well as chronic widespread pain, is characterised by related symptoms including low mood, fatigue and unrefreshing sleep. Indeed, unrefreshing sleep features in the diagnostic criteria for fibromyalgia (Wolfe et al., 2016) although is not essential to make the diagnosis. It is not surprising therefore, that the prevalence of sleep problems in fibromyalgia is particularly high, even compared to other painful conditions (Drewes, 1999). Among those diagnosed with fibromyalgia, 88% meet the ‘waking unrefreshed’ criterion (Vincent et al., 2013) and 96% have sleep problems of some kind (Bigatti et al., 2008). Beyond simply observing the high rate of co-occurrence, it is possible to infer more about the nature and directionality of this relationship from observational and experimental studies, which are reviewed in the following section.

1.1.3.1 A bidirectional but asymmetrical relationship

1.1.3.1.1 Evidence from micro-longitudinal studies

The relationship between chronic pain and sleep disturbance is often described as bidirectional, referring originally to the day-by-day variation in symptom severity an individual experiences, whereby worse pain results in poor sleep, and disturbed sleep exacerbates next day pain. This has been investigated in time-series designs sometimes referred to as micro-longitudinal studies, investigating a series of day-by-day interactions. In a classic early study of this kind in chronic pain, Affleck and colleagues (1996) tracked the self-reported symptoms of 50 individuals for 30 days, and found the relationship to be

bidirectionally reinforcing. They also found attention to pain to be important, having additional explanatory power regarding sleep quality beyond that of pain intensity alone.

In a more recent refinement of the micro-longitudinal method, Tang and colleagues (2012) designed a study specifically to shed light on the directionality of this day to day interaction among people with chronic pain and insomnia, incorporating actigraphy and more detail on the contribution of mood and cognitive arousal. Self-reported sleep quality assessed on a 0-10 rating scale was a consistent predictor of next day pain. Pre-sleep pain was less good at predicting sleep quality. An important insight from this study was greater significance of pre-sleep cognitive arousal in predicting sleep quality, which the authors relate to the hyperarousal model of insomnia (Riemann et al., 2010) and interpret on a cognitive-behavioural level as relating to rumination and worry about sleep. These findings were largely replicated in a subsequent daily diary and actigraphy study in individuals with chronic pain, which similarly found that reported sleep quality predicted morning pain, whilst evening pain did not predict sleep quality, although pre-sleep cognitive arousal did (Bean et al., 2021).

The same method has also been used outside of chronic pain. In acute pain (adults acutely hospitalised for burns) a study found that poor sleep worsened next day pain, but increased daytime pain did not predict poor sleep (Raymond et al., 2001). When applied at large scale to the general adult population in the United States the bidirectional relationship was evident (Edwards et al., 2008). The relationship was stronger for the prospective association of sleep on next day pain compared to that of pain on subsequent sleep, with standardised coefficient (Z value) for sleep on subsequent pain of -7.9 compared to -3.1 for pain on subsequent sleep. The strengths of this study include its size, using over 5,400 observations from 971 participants. It was limited by the scant measures used of both pain and sleep, restricted to a 5-point scale describing the frequency of pain symptoms over that day, and the amount of sleep obtained the previous night (i.e. self-reported total sleep time). Furthermore, given that this was a large, unselected sample and that both chronic pain and sleep problems are highly prevalent, it is unclear whether the correlations found reflect a dynamic seen in people with chronic pain and sleep problems specifically, or are a more ubiquitous feature in the general population.

These studies together add nuance and complexity to the well-established and intuitive bidirectionality in the short-term relationship between pain and sleep, which appears to be stronger in the direction of sleep disturbance impacting on pain and to involve psychological factors such as pre-sleep cognitive arousal.

1.1.3.1.2 Evidence from prospective cohort studies

The relationship has also been examined over longer time scales in cohort studies. Two large cohort studies from the UK shed light on predictive factors for the onset of chronic widespread pain. Motivated by the observation that psychosocial distress is common among people with fibromyalgia, and aiming to establish to what extent this precedes or predicts the onset of pain, Gupta and colleagues (2007) followed over 3000 adults from the general population, free from chronic widespread pain at baseline, for 15 months. Individuals with the highest sleep problem scores at baseline were at over 3 times the odds of developing chronic widespread pain compared to those with little to no sleep problems at baseline. It is surprising that as many as 10% (324 individuals) of the cohort had developed new onset widespread pain within this relatively short follow up period. This may reflect the higher response and successful follow up rate among older females. Although this incidence rate is probably inflated, the primary finding that sleep problems preceded and predicted chronic widespread pain remains stark. Similarly, in another prospective cohort study in the UK, over 4000 participants without widespread pain at baseline were followed up for 3 years. Over this period 18.5% of the cohort developed new onset widespread pain. Of the 11% of people who had non-restorative sleep 'most nights' at baseline 36% developed widespread pain, compared to just 16% of the remaining cohort. In a multivariate analysis, non-restorative sleep was the single strongest independent predictor, being found to double the odds of new onset widespread pain (McBeth et al., 2014).

Sleep also seems to have predictive power in those with already established chronic pain. In a one year follow up study of 600 individuals with fibromyalgia, severity of sleep problems predicted future level of pain, whilst the reverse relationship (of pain severity predicting sleep disturbance) was not seen (Bigatti et al., 2008).

There is also longitudinal evidence for the reverse direction, of pain influencing future sleep problems. In over 400 individuals who had previously had joint replacement for osteoarthritis, the presence of 'neuropathic pain features', as indicated the pain-DETECT questionnaire, predicted the development of sleep problems over the course of 2 years of follow up (Stocks et al., 2018). The association persisted after controlling for pain severity, and when neuropathic pain was excluded the relationship no longer held. The reverse direction was also found, in that those with poorer baseline sleep scores were also more likely to develop incident neuropathic pain features in particular, rather than worsened pain in general. Although the original construction of the pain-DETECT questionnaire was framed around neuropathic pain (Freynhagen et al., 2006),

this was in the sense of a binary dichotomy with nociceptive pain, without reference to the third category which is now considered, i.e. that of nociplastic pain. More recent validation studies of the pain-DETECT questionnaire show that it actually well identifies those with central sensitisation (Hochman et al., 2013). So, the implications of this study are that central mechanisms are likely to be important in the long-term association between sleep and pain.

Data from a large Norwegian cohort study in the general population with 11 years follow up has been analysed in separate studies examining each direction of the pain – sleep relationship. Firstly, it was found that those with widespread chronic musculoskeletal complains had two times the odds of developing insomnia, which was a greater effect than that of non-widespread musculoskeletal complaints or headache (Ødegård et al., 2013). Secondly, poor sleep was found to predict new onset of chronic widespread pain (Mundal et al., 2014). In this study, depression was not associated with new widespread pain, but elsewhere it has been suggested that low mood or diagnosed major depressive disorder does mediate the interaction (O'Brien et al., 2010; Emery et al., 2014). Data from an earlier phase of the same Norwegian cohort study was also analysed specifically regarding the impact of sleep problems on likelihood of incident fibromyalgia in women (Mork and Nilsen, 2012). A dose-dependent relationship between sleep problems and risk of fibromyalgia resulted in a relative risk of the diagnosis of more than 5 times for women over 45 years who had sleep problems 'often or always'.

The above longitudinal cohort designs rely usually on just two time points, which limits their ability to consider the variability or underlying trajectory of the risk factor. Recognising this, Afolalu and colleagues (2018) sought and reviewed literature where a *change* in sleep parameters over at least two baseline time points (therefore describing either deterioration, improvement or static) was correlated to a pain related outcome. Broadly in keeping with the above, a deterioration over time in sleep symptoms was associated with increased risk of developing a pain related condition, and with worsened pain related health status. Many observational studies have therefore examined the link between pain and sleep over short and long-time scales and overall the bidirectional association is widely substantiated, with indications that the direction of poor sleep leading to worse pain is more the powerful association, as reflected in a review of the issue (Finan et al., 2013).

1.1.3.1.3 Evidence from laboratory and experimental studies

Laboratory-based and therapeutic experimental studies also shed light on the pain and sleep relationship. As far back as the mid-1970s, experimental sleep

deprivation, specifically of deep NREM sleep, has been found to reproduce widespread muscle tenderness reminiscent of fibromyalgia (Moldofsky and Scarisbrick, 1976). In a well-controlled study involving healthy women, the effect of experimental sleep deprivation by forced awakening every hour was compared to simple sleep restriction to the same total sleep time by delayed bedtime. Interrupted sleep was found to impair pain inhibition and increase spontaneous pain, whereas simple sleep restriction did not show these effects (Smith et al., 2007). This raises the suggestion of a particular role for sleep continuity disturbance in the generation of associated pain. 'Pain inhibition' here was assessed via a test of Diffuse Noxious Inhibitory Controls (DNIC), whereby a phasic pain (here the pressure pain threshold test) should decrease compared to baseline when applied during the simultaneous presentation of a tonic pain elsewhere in the body (in this case a cold pressor test on the contralateral hand, i.e. held in ice water). For those whose sleep had been disturbed by forced awakening, the normal pain inhibitory effect disappeared. The concept is that the DNIC tests descending supraspinal pain inhibition, which experimental evidence suggests is deficient in fibromyalgia in particular (Julien et al., 2005). Thus, failure of descending inhibition may be implicated not just in the generation of pain in fibromyalgia but also specifically as a reason for poor sleep exacerbating and predicting that pain. It should be noted that this application of the DNIC concept is a step removed from its original description, which is of specific descending inhibitory effect directly recorded at the dorsal horns in anaesthetised animals (Le Bars et al., 1979). In contrast, the verbalised pain levels of conscious human individuals may be affected by additional factors such as attention, cognitive inputs and context. To avoid conflating these concepts the term Conditioned Pain Modulation is now advised for psychophysical paradigms such as in this case (Yarnitsky, 2010). Regardless of whether the inhibitory mechanism in question involves simple circuitry or more complex networks, its impairment by sleep continuity disturbance is a significant finding.

Further evidence comes from the effect of clinically treating sleep disturbance when it occurs alongside chronic pain. Sodium oxybate is a drug used in the treatment of narcolepsy and has been investigated in fibromyalgia. It is found to improve fibromyalgia-specific sleep parameters and sleep related symptoms (Moldofsky et al., 2010) and significantly, to improve pain (Russell et al., 2009). Sodium oxybate does act directly on sleep in people with narcolepsy, for example increasing slow wave sleep (Kothare and Kaleyias, 2010). However, as an agonist of the primary inhibitory neurotransmitter in the central nervous system, gamma amino butyric acid (GABA), its pharmacological actions are

broad and incompletely understood, so it is possible that it has some effect on pain mediated by mechanisms other than sleep.

A co-treatment effect is also seen with non-pharmacological therapies. A meta-analysis of non-pharmacological treatment for insomnia (largely this was cognitive behavioural therapy for insomnia) in those with chronic pain, showed improvements not only in insomnia but also in pain (N.K.Y. Tang et al., 2015). The effect size for improvement in pain was small, with standardised mean difference of 0.18 compared to 0.78 for sleep quality, but the findings do still support the notion that sleep is causally implicated in pain maintenance. It could also be argued that cognitive behavioural therapy is a non-specific intervention even when tailored to insomnia, so the positive effect on pain could be direct, rather than a consequence of the sleep improvement.

1.1.3.2 Specific sleep disturbances seen in fibromyalgia

The sleep disturbances in fibromyalgia have been investigated for several decades with disparate interpretations. Broadly, early enthusiasm for considering disturbances to sleep architecture as specific to and potentially pathogenic of the condition (Moldofsky, 2009) has moderated, with recognition that findings are variable and not unique to fibromyalgia. Polysomnography studies involving women with fibromyalgia and healthy controls have been recently systematically reviewed, with the most common findings being that women with fibromyalgia have lower sleep efficiency, lighter and more fragmented sleep (Diaz-Piedra, Di Stasi, et al., 2015). However, there were high levels of inconsistency between studies, with each of these findings being disputed by other studies finding no differences, and generally low average power of around 0.5 for most variables (indicating a substantial chance that a true difference could be missed). This was not a meta-analysis so no attempt to formally pool data was made. Despite the inconsistency, all studies found some difference between people with fibromyalgia and healthy controls in sleep assessed by polysomnography, the gold standard. This last point is pertinent as it is sometimes thought that sleep complaints in fibromyalgia represent solely sleep misperception, whereby feeling unrefreshed is wrongly attributed to insufficient sleep. Sleep misperception is one explanation for the discrepancies commonly found between sleep diary and device-measured sleep parameters, especially in those with chronic pain conditions (An et al., 2020). For example, a study highlighting sleep misperception in fibromyalgia collected actigraphy and partial sleep diary from 75 people with the condition and demonstrated an average discrepancy in total sleep time of over one hour between the methods (Okifuji and Hare, 2011). However, an alternative explanation is that actigraphy is inaccurate, and indeed it has been found in systematic review to

underestimate sleep onset latency and wake after sleep onset time, compared to polysomnography, in adults with chronic conditions (Conley et al., 2019). In summary then, it appears that the macrostructure of sleep is disturbed in fibromyalgia, with wide inter-individual variability, but generally showing light, fragmented sleep.

A microstructural sleep abnormality which has been of particular interest in fibromyalgia is an increase in alpha activity during NREM sleep, termed alpha intrusion or alpha-delta sleep. First associated with fibromyalgia (1975) and subsequently extensively studied by Moldofsky and colleagues, this idea gained traction being framed around the persuasive notion that the intrusion of alpha disrupts the restorative function of deep sleep, which causes the subsequent somatic symptoms (Roizenblatt et al., 2001). It has even been suggested as a potential biomarker for fibromyalgia (Rosenfeld et al., 2015). However, the underlying hypothesis of non-restorative sleep generating fibromyalgia symptoms has been comprehensively countered (Mahowald and Mahowald, 2000) and when systematically reviewed, the majority of polysomnography studies failed to find evidence of alpha intrusion (Diaz-Piedra, Di Stasi, et al., 2015). Since the studies in this thesis explore a neuromodulatory technique designed to increase alpha oscillations, it is important to highlight that the application of this technique is whilst the individual is still awake, the effect of sensory stimulation is short lived, and that the prevailing contemporary literature has moved away from considering alpha-delta sleep as something uniquely characteristic of fibromyalgia (Choy, 2015).

In summary, pain and sleep are linked over both short and long time periods, probably more strongly in the direction of sleep impacting on pain. Fibromyalgia in particular has been explored as a sleep problem and although findings have varied, light and fragmented sleep is most commonly found on instrumental measurement. Recognition of the relationship has stimulated enquiry into whether targeted treatment of sleep problems could be a key to unlock the perennial problem of effective chronic pain treatment (Smith and Haythornthwaite, 2004). Accordingly, sleep problems have been highlighted in recent research prioritisation exercises in fibromyalgia (James Lind Alliance, 2016; Fitzcharles et al., 2017). A recent research strategy developed by the European Pain Federation based on a prioritisation exercise involving over 600 pain researchers rated understanding the interaction between pain and comorbidities including sleep disorders, and developing novel treatments for these, as the top ranked most important research questions (Pickering et al., 2025).

1.1.4 The case for integrating treatments for chronic pain and sleep disturbance

Bringing together the evidence presented in the above section a compelling case emerges to consider pain and sleep together when devising new therapies. The separate threads and their implication for the therapeutic opportunity in doing so are presented in Table 1.1.

Table 1.1 A summary schema of the therapeutic opportunity presented by considering pain and sleep together

Evidence of	Suggests that
The frequent co-occurrence of chronic pain and sleep problems	Tackling the problems together would be efficient for health services and relevant to many patients, not just a niche subgroup
A day-to-day bidirectional interaction	A 'vicious cycle' of symptoms can exist
A strong and consistent influence of sleep quality on next day pain	Failing to address sleep quality in pain management will limit efficacy
The importance of psychological factors such as attention to pain and pre-sleep cognitive arousal	A user-controlled, relaxing/distracting pre-sleep intervention may have added benefits
A long-term association whereby each condition is a risk factor for deterioration of the other	There is an imperative to co-treat to avoid this counter influence opposing treatment efforts
Sleep continuity disturbance may be mechanistically involved in generation of centralised pain	There is an opportunity to treat an underlying causative pathway, increasing likelihood of long-term drug-free remission

In contrast to the positive opportunity outlined above, the current landscape of treatment is inadequate. Despite chronic pain featuring highly in the workload of primary care (Belsey, 2002) 40% of those living with chronic pain in Europe regard their pain as not well managed overall and 64% have inadequate pain control from medications (Breivik et al., 2006). Pain-relieving medications such as non-steroidal analgesics and opioids designed for acute pain have poor

efficacy in chronic pain and risk considerable harms from their poor side effect profile (Wehling, 2014; Chou et al., 2015). National guidelines recommend non-pharmacological modalities of treatment such as exercise programmes and psychological therapies (National Institute for Health and Care Excellence, 2021). Although some well conducted trials show moderate effectiveness (Lamb et al., 2010), these types of therapies need supervision from professionals, have a variable uptake and compliance, and a recent Cochrane review showed small benefits and low quality evidence (Williams et al., 2020).

Considering the prevalence and impact of chronic pain, treatments are required which are not only safe, well tolerated, effective and affordable, but can also be highly scalable, and ideally self-managed by individuals without repeated health care consultations.

1.2 Non-invasive neuromodulation as an approach to meet this need

The previous sections outlined the clinical problems of chronic pain and sleep disturbance, the potential opportunity of therapies that recognise the close integration of these symptoms, and some characteristics required of therapies to meet the scale and complexity of the problem. This section introduces neuromodulation as a potential avenue to address this need.

1.2.1 Neuromodulation strategies for chronic pain

Neuromodulatory treatments are one approach to meeting the need described above. Neuromodulation is defined by the International Neuromodulation Society as “the alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body” (International Neuromodulation Society, 2013). Although chemical agents are included in the definition, referring to direct application of agents to neurological sites such as intrathecal drug administration, most study in the field of neuromodulation refers to electrical stimulatory techniques. Whilst the International Neuromodulation Society does not focus on sensory stimulation modalities, sensory stimulation can justifiably be considered under the umbrella of neuromodulation since this too is targeted to neurological sites (albeit via sense organs), and regardless of the type of energy being applied the effect is a change in neuronal excitability. Therapeutically, neuromodulation offers the potential advantages of being personalisable, reversible, and (usually) non-pharmacological. Some methods are invasive, incurring the risk and expense of surgical implantation, battery replacement and greater consequences of hardware malfunctions. Invasive

modalities include deep brain stimulation and spinal cord stimulation, both delivering electrical impulses via directly implanted hardware. This work focuses on non-invasive stimulation, which offers the additional benefits of lower risk, lower cost, higher acceptability to users, increased scalability and, in some cases, the potential for home use.

The current landscape of non-invasive neuromodulation for chronic pain includes transcutaneous electrical nerve stimulation (TENS) which is widely used and available to buy off-the-shelf. Its action is at the level of the periphery and has a rapid onset and offset, active whilst the stimulation is being used, via a range of postulated mechanisms (Johnson, 2007). A recent meta-analysis designed to be inclusive of all pain diagnoses found moderate certainty evidence that TENS decreases pain intensity (Johnson et al., 2022), whilst a meta-analysis of TENS in fibromyalgia in particular showed a dose dependent relationship but overall no significant benefit (Amer-Cuenca et al., 2023).

Recent systematic reviews have addressed both transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) with both representing potential treatments in fibromyalgia but requiring higher quality evidence (Lloyd et al., 2020; Sun et al., 2022). TMS has also been recently applied to improve sleep quality in fibromyalgia, with positive findings in a small randomised controlled trial (Badr et al., 2024). A 2018 Cochrane review brought together the range of noninvasive brain stimulation techniques for chronic pain (O'Connell et al., 2018), demonstrating the high level of attention received by this area.

A further modality of non-invasive neuromodulation is via the phenomenon of entrainment, specifically of cortical activity in the alpha frequency band, which is the focus of this thesis. The rationale for targeting alpha is next explored, followed by a discussion of entrainment.

1.2.2 The alpha rhythm and its relevance to pain

Neural oscillations in the 8-12 Hz frequency band were the first identified rhythm in the human electroencephalogram (EEG) (Berger, 1929) and the distinctive pattern was termed alpha. Alpha oscillations are characterised not only by this frequency but by their monomorphic waveform, posterior distribution and reactivity pattern (being blocked by eye opening) (Fisch, 1999). The other cardinal frequency bands in the human EEG are delta (1-4 Hz), theta (4-8 Hz), beta (13-30 Hz) and gamma (>30 Hz). Alpha was long thought to represent an idling state, however, it has since been observed that alpha oscillations (or their desynchronisation) have active functions. Drawing on observations from both

sensory perception and task performance models, a hypothesis for the role of alpha in overall network functioning has been proposed as providing inhibitory gating between brain regions (Jensen and Mazaheri, 2010). By inhibiting task-irrelevant regions, resources are allocated and information routed to task-relevant regions. This inhibitory function of alpha, and correspondingly the selective release of inhibition with its desynchronisation, has been linked to attentional selection (Thut, Schyns, et al., 2011; Klimesch, 2012), expectation, regulation and prioritisation of sensory input (Van Diepen et al., 2019). These functions each have potential relevance for chronic pain and indeed pain-attention interactions are foundational to the concept of the dynamic pain connectome as discussed in section 1.1.1.1 (Kucyi and Davis, 2015). In support of the concept of alpha gating sensory information being functionally relevant for pain, it has been found that expectation of pain increases perceived pain intensity in line with the extent to which alpha decreases in the moment before an expected painful stimulus (the event-related desynchronization) (Babiloni et al., 2006). Further supporting observations are that attention to a painful stimulus is accompanied by a decrease in alpha activity (Hauck et al., 2015) whereas expectation of pain relief, from placebo analgesia, results in increased alpha activity (Huneke et al., 2013). A recent systematic review found the most frequently reported resting state quantitative EEG finding in people with fibromyalgia, compared to healthy controls, is low power across the lower frequency bands, particularly alpha (Silva-Passadouro et al., 2024). Baseline alpha power is also negatively correlated with pain in individuals with chronic back pain (Ahn et al., 2019). Further supporting evidence from the effect of modulating alpha is outlined below. There is reason to suspect therefore, that alpha is relevant in the neural communication which must necessarily integrate the spatially distinct components (sensorimotor, cognitive, motivational-affective) that generate the experience of pain, including in chronic pain where this system is maladapted.

1.2.3 Brain entrainment

This section introduces the concept of entrainment of neuronal oscillations, the role it serves physiologically and some features of entrainment pertinent to understanding its use as a neuromodulatory strategy.

Rhythms and periodicity are central features of many biological systems, including the human brain (Buzsáki, 2006; Thut et al., 2012). Populations of neurons depolarising in rhythmic synchrony gives rise to the oscillatory patterns of electrical activity detectable on EEG. Their distinct frequency bands are a

result of the physical architecture of neuronal networks, and are considered to service many brain functions by temporally linking distant brain regions (Buzsáki and Draguhn, 2004). The functional relevance of oscillations was not always recognised. Slow oscillations were formerly considered ‘noise’, or mere epiphenomena of the idling brain state, and it was not until the 1990s that oscillations were widely considered as active ingredients in cognitive processes (Karakaş and Barry, 2017). The influential ‘communication through coherence’ hypothesis states that phase locking of oscillations is essential for communication between neuronal groups, and this is the mechanism which enables cognitive flexibility over short time scales (Fries, 2005).

Entrainment refers to the feature of oscillating systems whereby they can become matched in phase to an external periodic force (Thut, Schyns, et al., 2011). That is, if an external input is applied repetitively at a frequency close to the natural oscillation, this causes a perturbation to the timing of the oscillator resulting in it becoming synchronised to the timing (phase) of the input. When applied to neural oscillations, the detectable result of entrainment on EEG is an increase in amplitude of oscillations around the frequency of the input, as more neuronal elements depolarise in synchrony at the population level. The net effect of this is best seen and quantified by analysing in the frequency domain, where the total signal strength (or ‘power’) is represented at each frequency of a given range of interest. The closer the frequency match between the driving stimulus and the endogenous oscillation, and the higher the intensity of the stimulation, the stronger the entrainment effect will be and the further it will propagate (Gallina et al., 2023), findings supported by a mathematical modelling approach (Otero et al., 2022).

Recognition of the significance of entrainment has dramatically increased in recent years. In 2008 an influential paper in Science represented a change in the thinking about the physiological role of entrainment of slow oscillations (Lakatos et al., 2008). It was demonstrated that slow waves in the sensory cortex become entrained to the rhythmic structure of inputs which are being attended to, with behavioural consequences such as decreased reaction time. This is part of the shift from considering slow oscillations as noise to appreciating their instrumental significance, as orchestrators of neuronal activity across distant brain areas. As interest in entrainment as a means to modify oscillations and thereby study their function grew, caution was raised that repetitive stimulation may produce a series of event-related potentials (ERPs) simply superimposed onto endogenous activity but not interacting with it, disputing the concept of steady state responses generated as a result of entrainment (Capilla et al., 2011). This perspective was countered by

demonstration that both stimulation intensity and proximity to the frequency of endogenous oscillations influence the production of steady state evoked potentials in a manner consistent only with entrainment as the underlying mechanism (Notbohm et al., 2016).

In 2019 Lakatos, Gross and Thut proposed a ‘unifying account of the roles of entrainment’ (Lakatos et al., 2019). A premise is that entrainment is ubiquitous in brain functioning. This role can be understood in the light of the observation that many of the inputs the brain receives are themselves rhythmic – whether because the sensory apparatus samples the environment periodically (visual, tactile) or the physical input is itself rhythmic (e.g. auditory). Furthermore, motor output is also often rhythmic, such as walking, and some behaviours require the coupling of sensory and motor rhythms, such as auditory sampling during speech production. The proposed role of entrainment in this context is summarised as “alignment of ongoing neuronal activity to the temporal structure of external rhythmic input streams” (Lakatos et al., 2019). As timing is often a predictable element of an ongoing stimulus, by entraining a closely matched neuronal oscillation the brain receives the stimulus at a consistent phase position, which effectively stabilises the ‘gain’ of the input since phase reflects neuronal excitability. The net effect of this is described as setting the ‘internal context’ for the interpretation of either sensory stimuli or internal content.

Importantly, entrainment is thought (by the same authors) to be supra-modal, in that inputs from one sensory modality can influence oscillations in brain areas outside of that modality. This has a functional rationale as it allows supporting inputs to enhance perception of one primary modality, such as visual cues aiding auditory perception (the movements of the lips of a speaker change what you ‘hear’). A colourful supporting example from the literature relates magicians’ use of visual attentional suppression by means of entrainment across sensory modalities, in this case using the ‘off-beat’ of an auditory count to hide the visual sleight of hand (Barnhart et al., 2018). The idea of supra-modality does not refer only to sensory modalities. Tapping along to the beat of music is an example of motor signals aligning to oscillations that have been entrained by auditory inputs. This supra-modality is important for the investigations presented in this thesis which utilise both audio and visual inputs. Although these may have different (greater or lesser) effects, the salient point is that entrainment is not mode-specific but inherently cross-regional. Further support that sensory entrainment propagates beyond the input area comes from a memory study using theta entrainment by simultaneous audio and visual stimulation presented either in or out of phase with each other, having

behavioural effects via hippocampal theta oscillations, which are distant from either input area (Clouter et al., 2017).

1.2.4 Entrainment as a mode of neuromodulation

Techniques of externally driving oscillatory activity via entrainment as a form of neuromodulation can be subdivided into transcranial and sensory stimulation modes. Transcranial stimulation can be achieved by electrical (alternating current stimulation alternating at the driving frequency) or magnetic stimulation (using rhythmic trains of pulses at the driving frequency). It has been shown that behaviourally relevant entrainment can be achieved by both transcranial magnetic stimulation (TMS) (Thut, Veniero, et al., 2011; Hanslmayr et al., 2014; Romei et al., 2016) and transcranial alternating current stimulation (tACS) (Helfrich et al., 2014). tACS encounters a limitation in the maximum intensity able to be applied before causing skin sensation or phosphenes, which is problematic both from an acceptability and methodological point of view, in that entrainment seen may have been via the sensory stimulation. It has been suggested that the current used in many protocols has been too low (Vöröslakos et al., 2018) and that this is responsible for the limited effect size seen from tACS (Lakatos et al., 2019). One negative study in tACS (Lafon et al., 2017) found that low frequency tACS did not entrain theta, whereas the positive control of auditory bursts did do so, indicating that sensory stimulation may offer advantages by avoiding this limitation.

Both visual and auditory rhythmic sensory stimuli can entrain neuronal oscillations. Visual stimulation at around 10 Hz has been shown in multiple studies to entrain in the alpha frequency band and have perceptual consequences, in terms of performance on visual detection tasks (Mathewson et al., 2012; De Graaf et al., 2013; Spaak et al., 2014; Kizuk and Mathewson, 2017; Wiesman and Wilson, 2019). Studies in auditory entrainment have established a similar baseline. Henry and Obleser (2012) used 3 Hz auditory stimuli and found listeners were better able to perceive brief gaps in the sound when their presentation was aligned to the phase of the entrained delta oscillations. Furthermore, by simultaneously modulating frequency and amplitude to two different frequencies (3 Hz and 5 Hz) the same research group found that neural oscillations were entrained at both frequencies and the strongest perceptual effect was when the phase of both coincided (Henry et al., 2014). Auditory 10 Hz stimulation has been shown to enhance alpha band oscillatory activity and improve performance on a visual detection task, demonstrating cross modality of perceptual effects (Ronconi et al., 2016).

Auditory entrainment has been found to be reliable over time within individuals on repeat testing (Cabral-Calderin and Henry, 2022). There are findings to suggest that auditory stimulation can entrain even at intensities which are below conscious perception or the threshold for production of auditory evoked responses (Ten Oever et al., 2017). Taken together, the foundational neurophysiological research strongly supports the efficacy of sensory entrainment and its functional relevance, and a recent authoritative review of this topic concluded:

"Overall, this accumulated evidence strongly points to the potential ameliorative and rehabilitative effects of the alpha-band sensory entrainment, making it a highly valuable tool that can be crosswise employed in various clinical populations and conditions." (Gallina et al., 2023)

1.2.4.1 Types of audio and visual rhythmic stimulation

Rhythmic visual stimulation is usually achieved with flicker, whereby a light source alternates on and off, or a presentation such as a shape on a screen appears and disappears at a chosen frequency. This is an on/off pulsed stimulation, or 'square wave', and is well established in the study of visual perception. It has the advantage that it can be very precisely timed, which is important in experimental paradigms where the stimulus must be phase aligned with ongoing endogenous activity. Whilst methods differ in how much of the visual field is exposed to the flicker stimulus, even small presentation areas are seen to entrain across the visual cortex due to connectivity patterns which have been suggested must involve subcortical routes, such as via the thalamus (Sokoliuk and VanRullen, 2016). Unsurprisingly, visual entrainment enhances oscillatory activity maximally in the occipital cortex (Spaak et al., 2014; Wiesman and Wilson, 2019), which is the site of the primary visual cortex and where alpha is usually maximal. This effect is seen to propagate forward to the parietal brain areas (Mathewson et al., 2012) and have large scale network effects on connectivity (Lithari et al., 2016), which may be strongest in parietal and prefrontal cortices (Petro et al., 2024).

Auditory stimulation presents several options for how to encode the driving stimulation frequency. Pulsed stimulation can again be used, such as the interval between clicks defining the driving frequency. An alternative is sinusoidal stimulation. A pure audio tone represents a sine wave whose wavelength defines the frequency of the tone. Sound is composed of pulses of air pressure changes, which are transmitted by the eardrum into vibrations in the inner ear apparatus. Transduction of these vibrations into nerve impulses by the cochlea preserves the original frequency through "phase-locking" (Purves,

2018) which presents the possibility of using the inherent oscillation of the sound itself to stimulate the brain at that chosen frequency. This is not an option with visual stimulation, the frequency of which is measured in terahertz and wavelength is not directly encoded by the retina into neural signals. This particularity of the auditory system can be harnessed when developing stimulation strategies to entrain chosen frequencies. The lower range of human hearing is 20 Hz. Methods to encode lower frequency signals in audible soundwaves can be by amplitude modulation or frequency modulation. In amplitude modulation a stable carrier frequency is altered in amplitude (volume) with interpeak interval representing the desired frequency. In frequency modulation the carrier tone is not static but oscillates at the desired frequency (producing a vibrato effect). Monoaural and binaural beats both utilise two separate pure tones with the difference between them being the entraining frequency. (For example, using simultaneous presentation of 400 Hz and 410 Hz pure tones to entrain 10 Hz.) When these are mixed externally, or digitally summed, such that both ears hear both tones, a monoaural beat is created which produces an audible vibrato effect. This is familiar to musicians as the quivering note heard when tuning a stringed instrument and two neighbouring strings are producing almost but not quite the same pitch. This is in fact amplitude modulation, since the effect of summing the two waves is to create a rhythmic oscillation in amplitude in the resultant wave. The binaural beat effect on the other hand is an auditory illusion produced when the two tones are not mixed externally, but instead presented separately to each ear, using headphones (Oster, 1973; Moore, 2013). The difference between the two tones is perceived as the binaural beat, but in this case the ‘mixing’ is happening neurologically, in subcortical locations in the auditory pathway. The key location for this is thought to be the medial nucleus of the superior olivary complex (Wernick and Starr, 1968), which is the first area to receive bilateral input in the ascending auditory pathway. Although pure tones rarely exist in nature, the neurological apparatus which creates the binaural beat percept is evolved to assist with localising sounds in space (Kuwada et al., 1979; Moore, 2013). Unsurprisingly, since they are quite different in origin, when directly compared binaural and monoaural beats have distinct effects, with different connectivity patterns (Orozco Perez et al., 2020) and only binaural beats enhanced interhemispheric coherence between auditory cortices (Solcà et al., 2016). On high density EEG, the topographic distribution of the power increase in auditory entrainment is not localised to the auditory cortex, but maximal centrally (Lustenberger et al., 2018).

In summary, whether audio or visual stimulation is used for entrainment, the effects are not confined to primary sensory cortices but propagate further. The

auditory modality presents a larger range of options for how to encode a driving frequency of stimulation. This could potentially correspond to more requirement for optimisation and more opportunity for personalisation for auditory stimulation.

1.2.5 Existing literature on entraining alpha to modify pain and sleep

Sensory alpha entrainment has been investigated in experimental pain, acute pain and chronic pain settings. In a small number of studies, entrainment has also been applied in protocols designed to impact on sleep as a means of treating sleep and pain problems together.

In a study involving 64 healthy participants, pain experimentally induced by laser reduced in intensity with both audio and visual alpha stimulation, maximally at 10 Hz (the centre of the alpha band), when compared to control stimulation at 1 Hz, where no effect on pain intensity was observed (Ecsy et al., 2017). Neurophysiological data from the same study showed that the reduction in self-reported pain intensity was accompanied by reduced amplitude of the laser evoked potential after 10 Hz stimulation (Ecsy et al., 2018).

In acute pain, one study from Turkey found that binaural beats at 10 Hz reduced pain severity and anxiety compared to classical music or no stimulation control in individuals having ureteric stents removed (Ölçücü et al., 2021). There was no EEG monitoring in this study to validate whether the pain improvement was associated with entrainment, but the inclusion of an attention control with classical music goes some way to mitigating this.

Regarding the evidence in chronic pain, in one feasibility study participants underwent 4 minutes of 10 Hz visual alpha stimulation, controlled against 7 and 1 Hz stimulation, finding that global alpha power increased with 10 Hz stimulation as expected. Although there was no overall reduction in pain intensity or unpleasantness, which it could be argued is unlikely to be achieved within 4 minutes in established chronic pain, 10 Hz stimulation did more frequently (in >50% of participants) result in clinically relevant decrease in numerical rating scales of pain compared to control stimulation (Arendsen et al., 2020). This study was extended, adding more participants in the same 4 minute, 10 Hz visual stimulation protocol, with the result that a significant decrease in pain intensity was detected, correlating with increased frontal alpha power (Lopez-Diaz et al., 2021). The magnitude of the decrease was on average modest (0.5 points on a 11-point numerical rating scale) and the effect size for the correlation between frontal alpha increase and pain reduction was medium ($r = 0.33$). Considering the small ‘dose’, this study nevertheless

provides support not only that sensory alpha entrainment is readily achievable in this clinical population, but there is a positive indication that it may have an impact on chronic symptoms, albeit only in the immediate term and in laboratory conditions. Similar findings in chronic pain patients are found when alpha entrainment is achieved with tACS. When bifrontal tACS was applied at 10 Hz for a single 40 minute session, although overall clinical improvement was borderline, a significant positive correlation was found between enhanced alpha oscillations in frontal and somatosensory regions and pain relief (Ahn et al., 2019).

Sensory entrainment has also been used in a series of studies with participants with chronic pain but in which the primary goal was to target their co-existent insomnia. In these studies Tang and colleagues used audio-visual stimulation decreasing in frequency from 8 to 2 Hz over 30 minutes, with the stated aim being to aid sleep onset by entraining low frequency oscillations. They conducted uncontrolled pilot studies of both younger (Tang et al., 2014) and older (H.-Y. Tang, M.V. Vitiello, et al., 2015) participants who had chronic pain and insomnia, demonstrating pre-post improvements in pain and insomnia. They subsequently included quantitative EEG analysis, showing enhancement of delta power with their stimulation compared to a non-active control (Tang et al., 2019). This was followed by a small randomised controlled trial of this intervention in thirty participants with osteoarthritis pain and insomnia, showing no between-group differences in sleep, pain or depression (Tang et al., 2021). There were pre-post improvements in both the stimulation and control group (placebo stimulation below 1 Hz), the intervention was acceptable and had high concordance. The authors identified that the range of sleep disturbances individuals experience (e.g., sleep onset problems versus sleep maintenance problems) alongside other sources of heterogeneity in this population present a challenge in study design, as it may be that certain subgroups may benefit differentially from this type of audiovisual stimulation.

In summary, neuromodulation by alpha entrainment for chronic pain and sleep via non-invasive sensory stimulation holds promise, in that there is:

- A plausible underlying programme theory based on the role of alpha
- Evidence that entrainment is functionally relevant and technically achievable through non-invasive sensory stimulation
- Indications from diverse settings to suggest it may impact positively on symptoms

Accordingly, alpha entrainment as a potential treatment modality has garnered recent attention, as evidenced by recent reviews on the topics (Ahmed et al., 2020; Maddison et al., 2023). However, gaps remain which need to be

addressed for this potential treatment to advance towards more definitive clinical testing. Specifically, clinical benefit has so far not been adequately replicated, particularly in naturalistic settings and over medium or long time periods. Furthermore, how stimulation should best be used in the daily lives of individuals with chronic problems and whether this is acceptable to them. Previous home-based entrainment studies have not directly measured EEG response and therefore rely on an assumption that clinical effect seen is via the mechanism of entrainment, but without contemporaneously showing this. In the one home based longitudinal night time entrainment study that does include EEG (Tang et al., 2019) the EEG measure was performed in a single lab visit during the study period, and therefore may not reflect what is occurring in naturalistic use of the intervention.

1.3 Home-based Brainwave Entrainment Technology (hBET)

The intervention under investigation, hBET, is a research tool developed for the study of chronic pain drawing on background work conducted by the Human Pain Research Group (a collaboration between researchers at the Universities of Manchester, Leeds and Liverpool, UK). Work contributing to the development of the application and its usability testing by people with chronic pain has previously been published (Jacob et al., 2020; Locke et al., 2020). hBET is a smartphone programme which delivers repetitive stimulation at 10 Hz by either visual or auditory modalities. It is therefore an ‘open loop’ stimulation, providing preset stimulation with no adjustment from feedback or real time modification. The visual mode uses the smartphone screen alternating between white and black at a frequency of 10 Hz. A virtual reality headset is used to hold the phone in front of participants’ eyes and exclude external light sources. Participants have their eyes closed during the stimulation. The auditory mode utilises binaural beats (described above) to create 10 Hz stimulation via tones at 400 Hz and 410 Hz independently to each ear, through stereo headphones. In the studies presented in this thesis hBET was applied for 30 minutes, after which the stimulation automatically ceased. This duration was chosen based on previous literature (Tang et al., 2019) and to target stimulation to the pre-sleep period without persisting through the whole sleep episode.

The intended immediate-term benefit of using hBET is to reduce the perception of pain by increasing alpha power via entrainment. The concept of applying this at night, pre-sleep is based on the schema that reducing pain at this point may also have benefits to sleep, and thereby augment the overall magnitude and longevity of the benefit to pain. What duration of intervention use might be

required to see this augmented long-term effect is unknown. The durations of use in the studies in this thesis (four weeks in Chapter 2; two weeks in each condition in Chapter 4) were chosen to meet the feasibility aims of the studies, balancing data volume against reasonable burden to participants in terms of daily monitoring and equipment use.

The studies in this thesis focus mainly on fibromyalgia. This was chosen as it represents a chronic pain group especially characterised by nociplastic pain (Clauw, 2015), where cortical mechanisms are particularly relevant therapeutic targets. It is also especially characterised by sleep disturbance, so the pre-sleep application of hBET in these studies is fitting. Fibromyalgia is a large subgroup of chronic pain and one currently lacking in effective management options. Therefore, evidence specific to this chronic pain condition is still externally valid and clinically relevant.

1.4 The purpose of feasibility studies

For a new treatment to become available to benefit patients its clinical and cost effectiveness must be demonstrated in randomised controlled trials, which require considerable resources. In order to justify this ethically and financially, the foundational evidence base must be sufficiently convincing of potential benefit, and enough must be known to design a successful and robust trial. A common way of addressing these needs is with feasibility studies. A feasibility study asks whether something can be done, should it be proceeded with, and if so, how (Eldridge et al., 2016). The UK's National Institute for Health and Care Research (NIHR) provides guidance on studies designed to be preparatory for full randomised trials. The principles it outlines is that these should establish the *promise* of the intervention, and that they should address the specific *uncertainties* pertinent to that intervention and the trial conduct it would require (National Institute for Health and Care Research, 2023). The relevant prerequisites for hBET to progress to a definite trial in this framework can be described in these terms as below.

Establishing the 'Promise' of the intervention

- Positive user experience and feedback able to further guide refinement of the intervention
- Data on usability showing the target population can easily use hBET as intended

- Preliminary data providing an estimate of effect on symptoms indicating this may be of a clinically meaningful magnitude

Uncertainties regarding the intervention

- Data demonstrating alpha entrainment is achieved in the conditions of intended use (pre-sleep, at home), giving confidence in the programme theory that clinical effect is via this mechanism

Uncertainties regarding trial design

- Preliminary data to inform sample size calculation
- Experience of recruitment, including speed, frequency of ineligibility, frequency of withdrawal
- Experience of how the target population uses the intervention in research conditions, including adherence to a protocol, to inform robust trial design
- Assurance that the research processes and outcome measures used are acceptable to participants and not overly burdensome
- Confidence that the home-based EEG monitoring tool and sham control condition function well and are feasible and acceptable to the target population

1.5 Project aim and objectives

Better management options for chronic pain and sleep disturbance are required. The background literature reviewed in Section 1.1 demonstrates that a strong case already exists for addressing chronic pain and sleep disturbance together, and that desirable qualities of an intervention to meet the population need would be highly scalable, home-based, and amenable to independent use. Section 1.2 draws together the existing knowledge on the potential of neuromodulation by alpha entrainment as a means of meeting this need, and that gaps in this knowledge remain. The intervention under study introduced in Section 1.3, hBET, needs further investigation to progress towards clinical use, which can be viewed through the framework of feasibility studies, as outlined in Section 1.4.

Therefore, the general aim is to study the feasibility and effect of home-based alpha brain entrainment delivered pre-sleep for people with chronic pain and sleep disturbance, in a way which helpfully informs future research. The objectives required to achieve this span the three studies that comprise this thesis.

The objectives of study 1 are:

- To give an indication of the effect of the intervention
- To establish feasibility of recruitment, frequency of withdrawal, adherence to the intervention to inform future efficacy trial design
- To assess whether individuals can use hBET independently at home pre-sleep

The objectives of study 2 are:

- To gather user experience to inform further development of the intervention and study design
- To assess acceptability of research processes and outcome measures

The objectives of study 3 are:

- To characterise the alpha entrainment effect of open-loop stimulation delivered in the home environment before sleep
- To assess the feasibility and acceptability of using a home-based EEG monitoring tool and a blinded, sham control condition
- To give an indication of the clinical impact of alpha stimulation on pain, sleep and related patient reported outcomes

The contribution of each study is illustrated in Figure 1.5.

STUDY 1 Feasibility study		STUDY 2 Qualitative study		STUDY 3 Home-based EEG study	
Providing	**Evidence gap addressed**	**Providing**	**Evidence gap addressed**	**Providing**	**Evidence gap addressed**
Indication of clinical effect	Effect size estimates for future sample size calculation. Whether further investigation is justified	User experience	User input on intervention refinement	EEG evidence on alpha entrainment effect	Mechanistic evidence of entrainment success. Feasibility and acceptability of home-based EEG method.
Evidence on success of home use of hBET in a clinical cohort	Usability in naturalistic setting	Participant perspectives on research processes	Acceptability	Data with sham stimulation	Assess placebo contribution and blinding success
Recruitment, dropout rates, adherence	Planning recruitment strategy and sample size estimation			Indication of alpha entrainment impact on clinical measures	How alpha relates to pain and sleep in these circumstances

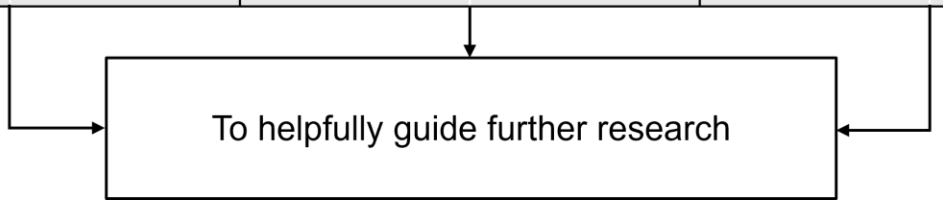

Figure 1.5 The component objectives of each study and overall aim

Chapter 2 A feasibility study of pre-sleep audio and visual alpha brain entrainment for people with chronic pain and sleep disturbance

This chapter presents the first published paper in this thesis. The focus of this paper at the initial stage of the programme of work is on establishing the fundamental feasibility of the approach, in terms of study processes and user acceptability, and providing an indication of the effect of the intervention to guide further development and study. It reports the results of an uncontrolled feasibility study of the use of hBET by individuals with chronic pain at home, pre-sleep, for one month. As an uncontrolled study, the focus is not on definitive quantification of effect, but the value lies in the real-life, longitudinal, domiciliary engagement with hBET by those experiencing chronic pain and sleep disturbance. An unforeseen opportunity of the COVID-19 pandemic was the impetus to move to wholly remote study procedures. This forced a change to traditional study conduct which holds potential benefits for participants and researchers. The experience of developing and using these new processes appropriately and effectively is part of the story and achievement of this study.

The paper is reproduced here having been reformatted for consistency with this thesis but with no changes to the content.

2.1 Metadata

Title:

A feasibility study of pre-sleep audio and visual alpha brain entrainment for people with chronic pain and sleep disturbance

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2.2 Abstract

Introduction: Chronic pain and sleep disturbance are bi-directionally related. Cortical electrical activity in the alpha frequency band can be enhanced with sensory stimulation via the phenomenon of entrainment, and may reduce pain perception. A smartphone based programme which delivers 10 Hz stimulation through flickering light or binaural beats was developed for use at night, pre-sleep, with the aim of improving night time pain and sleep and thereby subsequent pain and related daytime symptoms. The aim of this study was to assess the feasibility and give an indication of effect of this programme for individuals with chronic pain and sleep disturbance.

Materials and methods: In a non-controlled feasibility study participants used audio or visual alpha entrainment for 30 min pre-sleep each night for 4 weeks, following a 1 week baseline period. The study was pre-registered at ClinicalTrials.gov with the ID NCT04176861.

Results: 28 participants (79% female, mean age 45 years) completed the study with high levels of data completeness (86%) and intervention adherence (92%). Daily sleep diaries showed an increase compared to baseline in total sleep time of 29 min ($p = 0.0033$), reduction in sleep onset latency of 13 min ($p = 0.0043$), and increase in sleep efficiency of 4.7% ($p = 0.0009$). Daily 0–10 numerical rating scale of average pain at night improved by 0.5 points compared to baseline ($p = 0.027$). Standardised questionnaires showed significant within-participant improvements in sleep quality (change in median Global PSQI from 16 to 12.5), pain interference (change in median BPI Pain Interference from 7.5 to 6.8), fatigue (change in median MFI total score from 82.5 to 77), and depression and anxiety (change in median HADS depression score from 12 to 10.5 and anxiety from 13.5 to 11).

Discussion: Pre-sleep use of a smartphone programme for alpha entrainment by audio or visual stimulation was feasible for individuals with chronic pain and sleep disturbance. The effect on symptoms requires further exploration in controlled studies.

2.3 Introduction

Chronic pain represents a significant unmet global health need. It is highly prevalent, affecting one-fifth to one-third of adults (Fayaz et al., 2016; Dahlhamer et al., 2018) and represents one of the greatest contributors to disability globally (Global Burden of Disease Study Collaborators, 2017). Conventional analgesic medications have poor efficacy and unfavourable side effect profiles when used for chronic pain (Wehling, 2014; Chou et al., 2015) and many individuals regard their pain as inadequately controlled (Breivik et al., 2006). New paradigms of treatment are required, which is why the interplay between sleep and chronic pain has received increased attention in recent years as a priority area for research (James Lind Alliance, 2016; Fitzcharles et al., 2017).

Sleep problems are very common in people living with chronic painful conditions (Drewes, 1999; Abad et al., 2008), and almost universal in those with fibromyalgia (Bigatti et al., 2008). The relationship between pain and sleep is bidirectional (Affleck et al., 1996), and is seen to operate on both short (Tang et al., 2012) and long (Gupta et al., 2007; Stocks et al., 2018) time scales. Observationally, non-restorative sleep has been found to be a strong independent predictor of new onset widespread pain (McBeth et al., 2014), and experimental sleep deprivation and sleep fragmentation increases pain (Smith et al., 2007). There is a strong rationale for linking novel approaches to the intractable problem of chronic pain with sleep disturbance, given this close relationship.

Alpha entrainment is a neuromodulatory approach that has the potential to help people living with chronic pain. Entrainment is when an oscillating system becomes synchronised in phase to an external periodic force. Cortical electrical oscillations, or ‘brainwaves’, demonstrate this phenomenon in response to rhythmic stimuli, which can be sensory or direct electric or magnetic stimulation (Thut, Schyns, et al., 2011). Alpha entrainment refers to modulation of cortical activity in the alpha band (8–12 Hz). The overall role of the alpha rhythm has been proposed as providing inhibitory gating between brain regions (Jensen and Mazaheri, 2010), thereby re-routing resources and information to task-relevant areas. It is involved in pain expectation (Babiloni et al., 2006), attention to pain (Hauck et al., 2015) and expectation of pain relief (Huneke et al., 2013) and therefore provides a promising avenue for novel treatments, considering its entrainment is technologically achievable through non-invasive sensory stimulation. Alpha entrainment has been found to reduce experimental laser-induced pain in healthy participants (Ecsy et al., 2017) including with the electrophysiological correlate of reduced amplitude of the laser evoked potential

(Ecsy et al., 2018). In laboratory studies with individuals with chronic musculoskeletal pain, four minutes of 10 Hz sensory stimulation has been shown to successfully entrain alpha and decrease pain (Arendsen et al., 2020) and the degree of frontal alpha power increase is found to correlate with the reduction in pain (moderate strength correlation, Pearson *r* 0.33 for pain intensity, 0.40 for pain unpleasantness) (Lopez-Diaz et al., 2021). To our knowledge alpha entrainment has not previously been used pre-sleep in those with chronic pain, but other forms of non-invasive brainwave entrainment have been investigated for use at night in the home environment in this group. Audio-visual stimulation decreasing in frequency from 8 to 2 Hz was used by participants with chronic pain and insomnia aiming to aid sleep onset. It was shown that entrainment to the stimuli (in this case delta power) was successful (Tang et al., 2019), and in both younger (Tang et al., 2014) and older (H.-Y. Tang, M. V. Vitiello, et al., 2015) participants who had chronic pain and insomnia improvements were seen in both symptoms. In a pilot randomised controlled trial, adherence to the intervention was 99% and participants found it easy to use (Tang et al., 2021), indicating that the concept of audio-visual stimulation at night may be acceptable in this population. Outside of chronic pain, alpha entrainment has been used by healthy participants as one part of a stimulation programme aiming to optimise sleep quality (Abeln et al., 2014). In this pilot trial, the first quarter of a 90 minute sensory stimulation programme used 8 Hz (lower range of the alpha frequency) stimulation, and subsequently lower frequencies, and found improvements in participant reported sleep quality. Alpha entrainment therefore holds promise for the treatment of the closely linked problems of chronic pain and sleep disturbance. We designed a smartphone application called home-based Brainwave Entrainment Technology (hBET) to deliver 10 Hz alpha stimulation. This is the first time this modality has been used pre-sleep by those with chronic pain.

The aim of this study is to explore the feasibility of pre-sleep use of hBET with individuals with chronic pain and sleep disturbance and give an indication of the effect of the treatment.

2.4 Materials and methods

This was an uncontrolled feasibility study, comparing pre- and post-intervention measures. There was no randomisation and participants were not blinded to the intervention received. Participants were 28 individuals living with chronic pain and sleep disturbance, recruited from NHS clinics dealing with chronic pain in two regions in the north of England (Leeds and Manchester) and via online

publicity materials. Inclusion criteria were: age 18-80, non-cancer pain of over 3 months' duration including nocturnal pain of at least 4/10 (on 0-10 NRS), and self-reported sleep difficulties (defined as trouble falling asleep, difficulty staying asleep, waking up too early, or waking up unrefreshed on 3 or more nights per week during the past month). Individuals were excluded from participating if they had: any seizure disorder, photosensitivity, planned pain intervention during the study period, hearing and vision problems causing inability to use the stimulation, or inability to consent.

2.4.1 Intervention

The hBET programme is a smartphone application specifically developed by the Human Pain Research Group (a collaboration between researchers at the Universities of Manchester, Leeds and Liverpool, UK) to provide repetitive stimulation at 10 Hz by either visual or auditory modalities for investigation of the treatment of chronic pain. Development of the application (Jacob et al., 2020) and user co-design (Locke et al., 2020) have been reported. The 10 Hz frequency was chosen as it is at the centre of the alpha band, and was found to more effectively reduce experimental pain than high (12 Hz) or low (8 Hz) alpha (Ecsy et al., 2017). This is an example of open-loop stimulation, as the programme feeds in 10 Hz stimulation with no reference to participants' online brainwave state or individualised peak alpha (Janssens et al., 2021). The visual programme uses the smartphone screen to create 10 Hz visual flicker by alternating between white and black screen at this frequency. A virtual reality headset is used to hold the phone in front of participants' eyes and exclude external light sources. Participants have their eyes closed during the stimulation. The screen brightness is pre-set at mid-range, but is under participants' control. The auditory programme utilises binaural beats to create 10 Hz stimulation since a 10 Hz tone is below the range of human hearing. A binaural beat is produced when different tones are presented to each ear, with the binaural beat frequency being the difference between the two tones (Schwarz and Taylor, 2005). Tones at 400 Hz and 410 Hz are used in hBET as this range has been shown to produce the binaural beat effect most strongly (Oster, 1973). It is therefore necessary that headphones are used rather than an external speaker. For increased comfort in a lying position, participants are provided with a sleep headband with integrated headphones [model PT28, Perytong, Shenzhen, China]. The volume of auditory stimulation is under participants' control. The equipment participants used in the study is shown in Figure 2.1.

Figure 2.1 Equipment used; Sleep headband with integrated wireless headphones, headset to hold phone for visual stimulation mode, smartphone with hBET app loaded, Motionwatch 8 actigraph watch.

2.4.2 Procedures

Remote processes were used due to the Covid-19 pandemic. Participants were familiarised with the study equipment, sleep and pain diary and questionnaire schedule via an online videoconference meeting. There was a one-week baseline period followed by a four-week intervention period, during which time participants were asked to use hBET each evening. It was advised to be used immediately pre-sleep, when the participant was settled in bed and ready to try to get to sleep. The stimulation ceases after 30 minutes but could be restarted if desired. Participants had the choice to use the audio or visual option on any night, which allowed for the range of user preferences found on previous studies (Locke et al., 2020).

2.4.3 Measures

Demographic information and past medical history including pain diagnosis and medication use was collected from participants' own reports using a paper questionnaire at baseline. Diagnoses were not extracted from medical records or reconfirmed by the study team.

A pain and sleep diary was completed each morning. This incorporated 0-10 numerical rating scale (NRS) for average pain over the last 24 hours and average pain last night, and sleep timing used wording conforming to the consensus sleep diary (Carney et al., 2012). Sleep parameters calculated as follows: total sleep time is the time between trying to fall asleep to final awakening, minus the sleep latency and the total time awake after sleep onset; sleep efficiency is total sleep time divided by duration of the sleep episode, which is the time from starting to try to sleep to getting out of bed, (presented as a percentage). Sleep onset latency and Wake after sleep onset do not require calculations and are addressed directly on the sleep diary. In addition, in the diary participants rated the quality of their sleep and how refreshed they felt in the morning on a 0-5 NRS. Nightly actigraphy was also used to monitor sleep using Motionwatch 8 [CamNtech Ltd, Cambridge, UK]. Standardised questionnaires were the Brief Pain Inventory (Cleeland and Ryan, 1994) completed weekly, the Pittsburgh Sleep Quality Index (Buysse et al., 1989), Multidimensional Fatigue Inventory (Smets et al., 1995), Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983), and five level EQ-5D (Herdman et al., 2011), all completed at baseline and study completion. Qualitative data on acceptability and user experience were also gathered through semi-structured interviews with each participant at the completion of the study. Analysis of these interviews is presented in Chapter 3 of this thesis. A summary of the study flow and outcome measures schedule is provided in Figure 2.2.

	Initial appointment →	Baseline period 1 week →	hBET use period 4 weeks →	At completion/ final appointment
Daily pain and sleep diary		✓	✓	
Nightly actigraphy		✓	✓	
Weekly BPI	✓	✓	✓	✓
PSQI	✓			✓
HADS	✓			✓
MFI	✓			✓
EQ5D	✓			✓
Semi-structured Interviews				✓

Figure 2.2 Study flow and assessment schedule

2.4.4 Analysis

Data from questionnaires were scored using standardised methods for each measure. Sleep and pain diaries were converted to digital format (Microsoft Excel 2016) for the calculation of sleep parameters as described above.

Data from Motionwatches were downloaded and processed using the bespoke software Motionware (version 1.2.28, CamNtech, Cambridge, UK). Sleep periods for each night of data were marked up according to the watch marker button presses, which participants were instructed to press at the beginning and end of each sleep episode. Where these were absent the period was marked up manually based on triangulation of the actigraphy data and the sleep diary. In most cases the participant had omitted to press the marker button upon waking, and the end of the sleep episode could be reliably judged from the watch being taken off and this corresponding to the diary report of final rise time. When the sleep period could not confidently be marked up the data for that night were not included.

To explore the impact of the intervention, pre- and post- measures were compared on a within-participant basis, using the baseline week compared to periods when hBET was used. Following the baseline week, participants had the choice each night whether to use Audio or Visual hBET. Since each option is a strategy to achieve the same effect of alpha entrainment, the primary analysis considers hBET as one intervention irrespective of modality. This allows an element of personalisation in the intervention to account for individual preference and improve the likelihood of engagement. Disaggregated results for Audio and Visual are presented as supplementary material (Appendix B). Data from each condition (visual and audio) were included in the analysis if the participant used the condition for at least 5 nights, to account for periods where participants trialled a modality but had a strong user preference for the other modality.

Statistical analyses were conducted using paired t-tests or Wilcoxon sign rank tests for data which were non-normally distributed. Effect sizes were calculated with Cohen's d or, in the case of non-normally distributed data, the effect size r was calculated by dividing the Z-statistic from the Wilcoxon sign rank test by the square root of the sample size. Cohen's d was considered small if 0.2 - 0.5, medium if 0.5 – 0.8, and large if > 0.8. Effect size r was considered small if 0.1 - 0.3, moderate if 0.3 – 0.5, large if > 0.5 (Cohen, 2013).

Ethical and regulatory approval for the study was granted by the Health Research Authority and NHS Research Ethics Committee reference 19/YH/0313 and procedures followed were in accordance with the Helsinki

Declaration. The study was pre-registered at ClinicalTrials.gov with the ID NCT04176861.

2.5 Results

Twenty-eight individuals (22 female, 6 male) participated and their demographic and background data are shown in table 2.1.

Table 2.1 Participant background and demographics (n=28)

Female	22 (79%)
Age in years (mean, SD)	45 (12)
Employment status	
Unemployed	15 (54%)
Full time work	6 (21%)
Part time work	3 (11%)
Retired	4 (14%)
Duration of pain in years (median, range)	9 (1.2 – 40)
Duration of sleep problems in years (median, range)	8 (1.2 – 30)
Age in years at pain onset (median, range)	33 (13 – 69)
Diagnosis (reported by participant)	
Fibromyalgia / chronic widespread pain syndrome	26 (93%)
Osteoarthritis	8 (29%)
Chronic low back pain	4 (14%)
Chronic fatigue syndrome	4 (14%)
Migraine/cluster headaches	2 (7%)
Trigeminal neuralgia	1 (4%)
Complex regional pain syndrome	1 (4%)
Medication use	
Number of pain medications (median, range)	2 (0 - 5)
Opioid	16 (57%)
Gabapentinoid	14 (50%)
Paracetamol	14 (50%)
Non-steroidal anti-inflammatory	7 (25%)
Tricyclic antidepressant	6 (21%)
Serotonin and noradrenaline reuptake inhibitor	4 (14%)
Benzodiazepine	3 (11%)
Triptan	2 (7%)
Other	2 (7%)

To inform the feasibility assessment, data completeness and attrition are displayed in Figure 2.3.

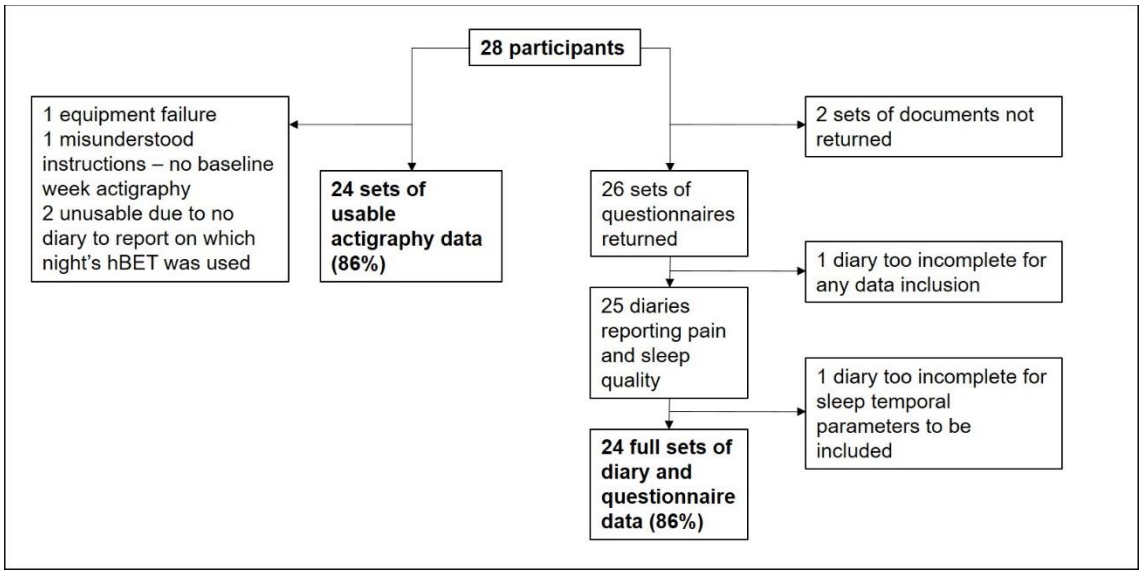

Figure 2.3 Data completeness and sources of attrition

Overall, participants chose to use Audio hBET on 458 nights and Visual hBET on 187 nights. This gives an adherence rate of 92% in participants for whom diary records were available (hBET used on 645 of 700 available nights). Five participants tried Visual hBET for fewer than 5 nights before choosing to discontinue it and return to Audio. These quickly aborted periods of Visual use are not included in the analysis, leaving 175 nights of Visual hBET use.

2.5.1 Sleep and pain diaries

Sleep and pain diary data for hBET use periods compared to baseline periods are shown in Table 2.2. There was a small improvement in average pain scores both at night and over 24 hours, as reported on the 0-10 numerical rating scale (NRS), and this difference was statistically significant but small in magnitude when averaged over all participants (effect size small; 0.47 and 0.41 respectively). Larger effect sizes were seen in the improvements in total sleep time and sleep efficiency (medium effect size; 0.67 and 0.78 respectively). Ratings given each morning on the quality of sleep did not improve but ratings of how refreshed participants felt did improve from a median of 2 to 2.75 on a 0-5 NRS.

Table 2.2 Sleep and pain diary results

	n	Mean (SD) at Baseline (175 nights)	Mean (SD) in hBET condition (633 nights)	Change (hBET compared to baseline)	P value for paired difference* between hBET and baseline	Effect size
Average pain over 24 hours (0-10 NRS)	25	6.4 (1.9)	6.1 (1.8)	-0.3 (0.7)	**0.0499**	0.41**
Average pain at night (0-10 NRS)	25	5.9 (2.0)	5.4 (2.1)	-0.5 (1.1)	**0.0265**	0.47**
		Mean (SD) at Baseline (168 nights)	Mean (SD) in hBET condition (610 nights)	Change (mean (SD))		
Sleep Onset Latency (mins)	24	51.0 (38.8)	38.4 (26.3)	-12.6 (23.7)	**0.0043**	0.58***
Wake After Sleep Onset (mins)	24	36.8 (32.6)	27.4 (26.7)	-9.0 (19.3)	**0.0333**	0.43***
Total Sleep Time (mins)	24	389.7 (80.4)	419.1 (78.8)	29.4 (43.9)	**0.0033**	0.67**
Sleep efficiency (%)	24	74.6 (11.1)	79.3 (11.1)	4.7 (6.1)	**0.0009**	0.78**
		Median (IQR) at Baseline	Median (IQR) in hBET condition	Change (median (IQR))		
Median number of awakenings	24	3 (2)	2 (1)	-1 (1)	**0.0074**	0.55***
Median quality rating (0-5 scale)	24	3 (1)	3 (1)	0 (0.125)	0.4063	
Median refreshed rating (0-5 scale)	24	2 (1)	2.75 (1)	1 (1)	**0.0004**	0.72***

*Paired t-test for continuous and normally distributed variables, Wilcoxon sign rank test for non-continuous or non-normally distributed variables. **Cohen's d for t-tests. ***r for Wilcoxon sign rank tests.

2.5.2 Actigraphy

No significant difference in sleep was seen with hBET compared to baseline when measured with actigraphy, as shown in Table 2.3. Actigraphy results diverged from sleep diary results, particularly in Sleep Onset Latency, which was on average reported to be 28 minutes higher in diaries than estimated by actigraphy, and in Wake After Sleep Onset, which was reported to be 35 minutes lower in diaries than estimated by actigraphy.

Table 2.3 Actigraphy results (n=24)

	Mean (SD) at Baseline (165 nights)	Mean (SD) in hBET condition (538 nights)	Change (hBET compared to baseline)	P value for paired difference* between hBET and baseline
Sleep Onset Latency (mins)	20.2 (27.8)	18.9 (25.6)	-1.3 (12.9)	0.9317
Wake After Sleep Onset (mins)	67.8 (44.0)	63.7 (32.4)	-4.0 (18.0)	0.2831
Total Sleep Time (mins)	398.8 (85.6)	402.0 (83.5)	3.1 (38.3)	0.6926
Sleep efficiency (%)	81.2 (10.6)	82.2 (10.5)	1.0 (3.5)	0.3914

*Paired t-test for continuous and normally distributed variables, Wilcoxon sign rank test for non-continuous or non-normally distributed variables

2.5.3 Questionnaires

Standardised questionnaires conducted at baseline and completion demonstrate improvements in sleep quality, fatigue, mood and pain interference, as shown in Table 2.4. In addition, the Brief Pain Inventory has a specific question on the extent to which pain is felt to interfere with sleep, scored from 0 (does not interfere) to 10 (completely interferes). The median response fell from 7.8 at baseline to 6.8 at the end of the study (p=0.004) and is of particular interest given the hypothesised mechanism of action of the intervention. (Note that this is distinct from the overall Pain Interference score, reported in Table 2.4).

Table 2.4 Questionnaire data (n=26)

	Baseline median (IQR)	Completion* median (IQR)	P-value**	Effect size (r)
Global PSQI	16 (4.5)	12.5 (8.25)	**0.0016**	0.62
MFI Total	82.5 (19.75)	77 (15.75)	**0.0089**	0.51
HADS Depression	12 (5.25)	10.5 (6.25)	**0.0095**	0.51
HADS Anxiety	13.5 (7.5)	11 (6.5)	**0.0107**	0.50
BPI Pain Severity	6.3 (2.6)	6.0 (2.8)	0.2711	
BPI Pain Interference	7.5 (3.3)	6.8 (3.1)	**0.004**	0.56
EQ-5D-5L index value	0.27 (0.41)	0.32 (0.48)	0.1711	

* In the case of BPI, this includes measures taken during hBET use, as well as on completion

** Wilcoxon sign rank test

PSQI, Pittsburgh Sleep Quality Index; MFI, Multidimensional Fatigue Inventory; HADS, Hospital Anxiety and Depression Scale, BPI, Brief Pain Inventory; EQ-5D-5L, the 5 level EuroQol score.

2.5.4 Responder analysis

An exploratory post-hoc responder analysis was conducted based on whether participants reported an improvement in the Brief Pain Inventory pain interference score by at least 1 point, which has been suggested as the minimal clinically important change (Dworkin et al., 2008). Partial response was defined as an improvement less than 1 point, and non-response being no change or worsening. This measure was selected on the basis of the hypothesis that hBET exerts is effect by improving pain and sleep, and consequently the overall impact and intrusiveness of this cluster of related symptoms, better captured in this compound metric than in a single item NRS such as pain severity. This is supported by users' descriptions of how sleep and pain interact, which involves mood and activity levels (expanded on in qualitative findings from this study, published elsewhere), which grounds this choice in the experience of users. The aim of this analysis was to explore the utility of this approach, rather than to

make conclusions on treatment effect. ‘Responders’, as defined in this way, tended to have better improvements across the range of self-reported symptom areas and actigraphy, as summarised in Table 2.5.

Table 2.5 Responder analysis

	All hBET	Responders n=9	Partial responders n=9	Non-responders n=7
Pain diary – mean (SD)				
Change in average pain over 24 hours (0-10 NRS)	-0.3 (0.7)	**-0.5 (0.8)**	**-0.2 (0.7)**	**-0.1 (0.6)**
Change in average pain at night (0-10 NRS)	-0.5 (1.1)	**-0.9 (1.2)**	**-0.4 (1.2)**	**-0.1 (0.5)**
Sleep Diary – mean (SD)				
Change SOL (mins)	-12.6 (23.7)	-8.9 (12.3)	-14.6 (33.4)	-14.3 (21.7)
Change in mean WASO (mins)	-9.0 (19.3)	**-18.6 (23.1)**	-2.3 (18.3)	-6.7 (12.7)
Change in mean TST (mins)	29.4 (43.9)	21.5 (21.7)	34.0 (59.3)	32.5 (44.9)
Change in sleep efficiency (%)	4.7 (6.1)	**5.3 (6.6)**	**5.0 (7.4)**	**3.8 (4.1)**
median quality rating (0-5 scale)	0 (0.125)	0.3 (0.4)	0.4 (0.5)	-0.4 (0.8)
median refreshed rating (0-5 scale)	1 (1)	**1.1 (0.2)**	**0.8 (0.7)**	**0.4 (0.9)**
Number of awakenings	-1 (1)	**-1.3 (1.0)**	**-0.8 (1.7)**	**-0.3 (1.0)**
Change in % nights with quality rated 3+	8.7 (31.5)	**17.3 (22.6)**	**10.5 (25.5)**	**-9.6 (28.9)**
Change in % mornings with refreshed rated 3+	19.6 (26.2)	**34.0* (18.8)**	**14.7 (18.0)**	**9.5 (15.8)**

Actigraphy - mean (SD)				
Change in mean SOL (mins)	-1.3 (12.9)	**-5.0 (17.1)**	**-2.2 (10.6)**	**2.0 (10.4)**
Change in mean WASO (mins)	-4.0 (18.0)	**-10.1 (25.2)**	-0.1 (9.7)	-5.2 (14.7)
Change in mean TST (mins)	3.1 (38.3)	-3.2 (35.9)	9.7 (32.8)	-7.0 (43.0)
Change in sleep efficiency (%)	1.0 (3.5)	**2.2 (3.1)**	**1.2 (3.5)**	**-0.5 (4.2)**
Questionnaire data - median (IQR)				
Change in Global PSQI score	-1.5 (4.25)	**-3.0** (6.0)**	0.0 (4.0)	-1.0 (2.0)
Change in MFI Total score	-3.5 (9.0)	**-7.0 (3.0)**	**-2.0 (13.0)**	**2.0 (3.0)**
Change in HADS Depression score	-1 (4)	-1 (2.5)	0 (5)	-1 (4)
Change in HADS Anxiety score	-1 (3.25)	-1 (4)	-1 (3.5)	-2 (4)
Change in BPI Pain Interference with sleep	-0.8 (2.3)	**-2.5** (1.9)**	**-0.3 (1.3)**	**0.0 (1.8)**
Change in BPI Pain Severity	-0.1 (1.5)	**-1.3** (1.6)**	**0.0 (0.5)**	**0.5 (0.3)**
Change in EQ-5D-5L index value	0.0 (0.3)	**0.25** (0.35)**	**0.0 (0.22)**	**-0.01 (0.11)**
*Change in BPI Pain Interference****	*-0.5 (1.5)*	*-1.9 (0.6)*	*-0.3 (0.5)*	*0.4 (0.7)*

Responders are participants who reported an improvement in the Brief Pain Inventory pain interference score by at least 1 point, partial responders by less than 1 point, non-responders showed no change or worsening. The shading highlights other outcomes which improve most in responders, and where the gradient of effect is in agreement with the responder categories.

* Responder group significantly different to other groups combined (independent samples T test, $p<0.05$)

** Responder group significantly different to other groups combined (Mann-Whitney U-test, $p<0.05$)

***This is the variable by which the responder categories were defined

Expanding on four selected variables of interest from Table 2.5, Figure 2.4 shows the response categories trending with other outcomes, as boxplots to visualise the spread of data. Panels A and B show change in daily diary measures of pain, at night and over 24 hours respectively, during hBET use compared to baseline. Panel C shows greater improvements in sleep quality (measured with PSQI) in Responders (this group also being statistically significantly different to the other two groups) and boxplot D shows a trend for greater improvements in fatigue (measured with MFI) in Responders than in the other groups, although this was not statistically significant.

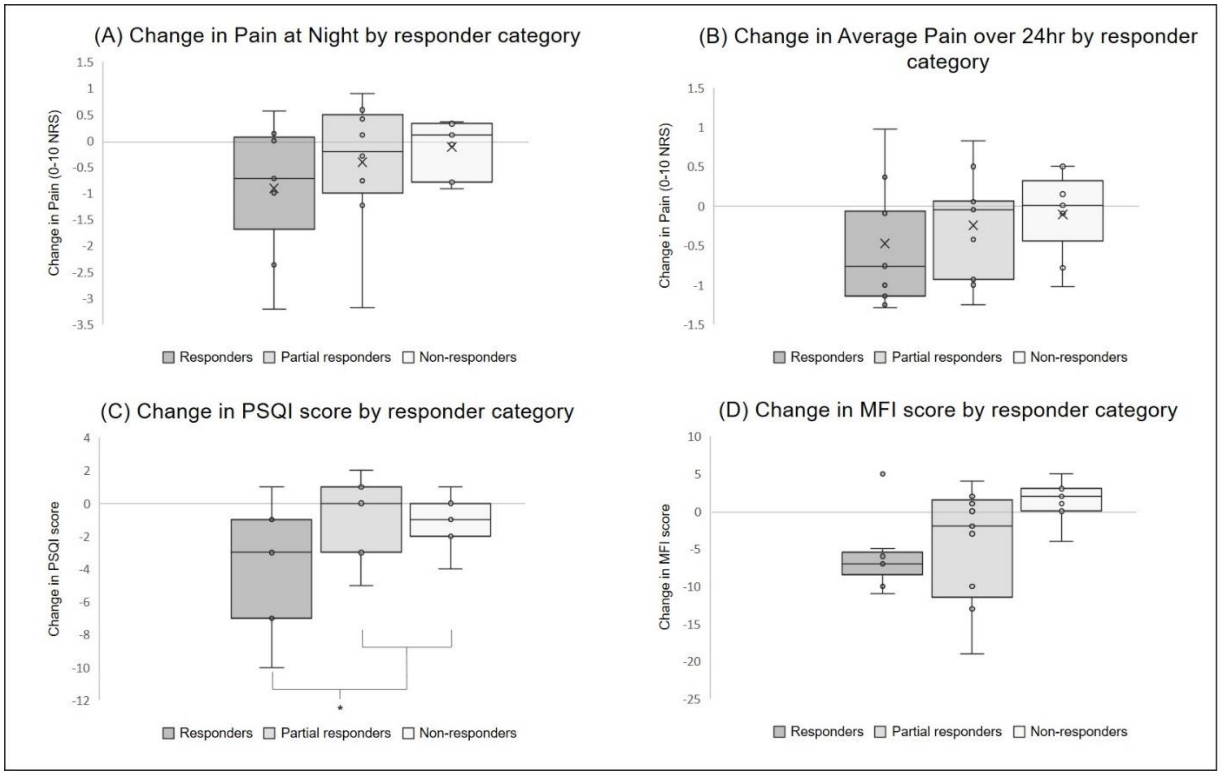

Figure 2.4 Boxplots showing selected outcomes by responder category

Responders are participants who reported an improvement in the Brief Pain Inventory pain interference score by at least 1 point, partial responders by less than 1 point, non-responders showed no change or worsening. Arithmetic means represented by 'X' in panels A and B, not included in the non-continuous variables.

* statistically significant difference between responders and other categories in PSQI change (p=0.026).

2.6 Discussion

Home-based, pre-sleep use of a smartphone programme for alpha entrainment by audio or visual stimulation was feasible for individuals with chronic pain and sleep disturbance. The findings are drawn from domiciliary use of hBET over 4 weeks, in a relatively unselected sample, which gives a level of ecological validity. This study represents the first application of alpha entrainment pre-sleep in those living with chronic pain and sleep disturbance, and the findings will inform the development of further trials in this area.

The hypothesised mechanism of action of hBET is a positive effect on both night time pain and improved sleep, subsequently leading to improved day time pain and related symptoms. Whilst it is well established that pain and sleep interact with each other, the purported inhibitory gating role of alpha could reasonably be expected to modulate both pain perception and sleep onset discretely, but the independent relevance of each in this population requires further study. Caution is needed in the interpretation of the changes in symptoms reported in this uncontrolled study, and conclusions about efficacy cannot be drawn. However, the experiences of users and pattern of response can usefully inform hypothesis generation and the design of future research. There is an indication that the improvements in patient-reported measures of sleep may be of larger magnitude or more readily observed than those of pain. Whilst the BPI pain severity score, which is derived entirely from 0-10 NRS pain ratings, did not improve across the whole group, the BPI pain interference score, which takes into account the impact of pain on various activities and functions, did improve. This may reflect different responsiveness of these measures over relatively short time periods in established chronic pain, or reflect the mechanism of action of this neuromodulatory intervention, and is not fully explained by this study. It is also notable that even the improved scores across many domains still remain above clinical thresholds, such as sleep efficiency (remains below 80%), sleep onset latency (remains over 30 minutes), anxiety and depression scores (remain over the ‘case’ threshold of 8 (Bjelland et al., 2002)) and PSQI scores (remain markedly over the threshold of 6 indicating ‘poor sleepers’ (Buysse et al., 1989)). The responder analysis is exploratory, and does not offer conclusions on effect, but adds weight to the notion that sleep and pain symptomology are acting together, and is consistent with the hypothesised mechanism that targeting both may lead to positively reinforcing benefits to daytime symptoms. It provides a possible approach to pre-specified response definition in future studies.

In this study, diary-reported measures of sleep onset, time and continuity improved whereas actigraphy assessed sleep measures were unchanged. Discrepancy between actigraphy and sleep diary, particularly in chronic pain, has been reported many times and given different interpretations. Systematic review and meta-analysis comparing methods of sleep assessment in chronic pain patients finds the most consistent discrepancy is that actigraphy gives lower estimates of Sleep Onset Latency than diary report, (by 23 minutes in meta-analysis) (An et al., 2020). This was the case in the current study, with overall 28 minute difference found. This has often been referred to as sleep misperception, with the inference that actigraphy provides a superior 'objective' measure. Noting that daytime experience plays a large part in how people with chronic pain judge their sleep (Ramlee et al., 2018) one interpretation is that sleep diary and actigraphy are measuring different constructs. However, it is also possible that actigraphy may be less accurate in this group. Studies using polysomnography have contested the idea that sleep complaints in fibromyalgia are due to sleep misperception (Diaz-Piedra, Catena, et al., 2015) and when systematically reviewed, actigraphy is found to overestimate total sleep time and underestimates sleep onset latency and wake after sleep onset time, compared to polysomnography, in adults with chronic conditions (Conley et al., 2019). Future studies incorporating electroencephalographic (EEG) monitoring would provide the multiple benefits of more accurate and detailed sleep determination and staging, insight to the validity of actigraphy in this population and direct evaluation of the alpha entrainment effect of this intervention. It is also possible that EEG monitoring could optimise the intervention, either through personalisation to the individual peak alpha, or by using closed-loop stimulation.

Limitations of this study mean it is not possible to conclude that the observed improvements result only from the intervention, as this is an uncontrolled, open-label feasibility study, not designed to determine efficacy. The limitations include the possibility of bias resulting from participant or researcher enthusiasm for the open-label intervention, placebo and secular (time) effects. Participants were aware of the aim of the study and that they were trialling a novel approach to chronic pain which may have appealed and promoted a placebo effect, which is not controlled for. This was mitigated against with transparency from the researchers and study documentation that the effectiveness of the intervention is as yet unknown. A passive effect due to time, such as regression to the mean, is unlikely as the participants had very longstanding symptoms of median 9 years and were not recruited in a way which would enrich the sample with those experiencing acute 'flares' of symptoms. Bias in participant reported

outcomes was mitigated against by encouraging honest responses. Diary entries may be less susceptible to this bias, being completed iteratively day after day, and it is notable that the findings from diary entries agree with those from baseline and completion questionnaires, although they are generally of smaller effect size. Gender and age were not controlled for at this feasibility stage, but are likely to be relevant covariates in the effect on symptoms, which should be accounted for in future study design. Finally, the study only considers a relatively short time period of four weeks of intervention use, with no longer term follow up. This leaves open the possibility of either a novelty effect exaggerating the benefits, or a more incremental effect being missed due to the short duration of this study. Anecdotal clinical observations tend to suggest that sleep improvements precede improvements in pain, which would require longer a study duration to capture.

In conclusion, hBET appears to be a feasible intervention for the home setting and evaluation under controlled conditions of its clinical effect is warranted.

Chapter 3 User experiences of pre-sleep sensory alpha brainwave entrainment for people with chronic pain and sleep disturbance

This chapter presents the second published paper comprising this thesis. It reports a qualitative assessment of the experiences of users of hBET gained through extensive interviews. It complements the quantitative information on usage patterns, and the structured participant-reported questionnaire measures reported in Chapter 2 by adding a fundamentally different type of data. Incorporating this into the overall evaluation of how the clinical population in question interact with hBET adds a valuable dimension to the contribution of this project. By following an established method, this chapter provides a transparent and rigorous presentation of personal, granular experiences with a richness and texture which cannot be gained from quantitative metrics and structured questionnaires. The analysis was conducted with objectives aligning to those of the overall project and thereby provides insights which directly inform the progress of this research field.

The paper is reproduced here having been reformatted for consistency with this thesis but with no changes to the content.

3.1 Metadata

Title:

User experiences of pre-sleep sensory alpha brainwave entrainment for people with chronic pain and sleep disturbance

Authors:

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3.2 Abstract

Aims: To explore the user experiences of pre-sleep alpha entrainment via a smartphone-enabled audio or visual stimulation programme for people with chronic pain and sleep disturbance.

Methods: Semi-structured interviews were held with 27 participants completing a feasibility study of pre-sleep entrainment use for 4 weeks. Transcriptions were subject to template analysis.

Results: Five top-level themes generated from this analysis are presented. These report on the participants' impressions of the pain-sleep relationship, their previous experiences of strategies for these symptoms, their expectations, and their experience of use and perceived impact on symptoms of both audio and visual alpha entrainment.

Conclusions: Pre-sleep audio and visual alpha entrainment were acceptable to individuals with chronic pain and sleep disturbance and perceived to have symptomatic benefits.

Plain Language Summary

In this study, people who had used an experimental treatment for chronic pain called alpha entrainment, which was delivered by audio (tones through headphones) or visual (flickering light) stimulation just before sleep each night for four weeks, were interviewed about their experiences. Analysis of the interview transcripts generated findings in five large areas; the participants' impressions of the relationship between pain and sleep, previous strategies they had tried, expectations of using this intervention, and their experiences of using it and how it affected their symptoms. Overall, they found using this type of sensory stimulation last thing at night to be acceptable in a real-life setting, coherent with prior understanding and many felt it to have benefits for sleep and pain symptoms, with few side effects. Comfort of the equipment and having the choice of different types of stimulation were important. Further development should be guided by these user experiences.

3.3 Introduction

Chronic pain conditions are among the greatest contributors to disability globally (Global Burden of Disease Study Collaborators, 2017). Prevalence rates of one-fifth of adults in the United States (Dahlhamer et al., 2018) and between one-third and half of those in the United Kingdom (Fayaz et al., 2016) demonstrate that the current treatment approach is ineffective. Forty percent of those living with chronic pain in Europe regard their pain as not adequately controlled (Breivik et al., 2006), and the poor efficacy and considerable side effect profile of conventional analgesic medications when used for chronic pain is well known (Wehling, 2014; Chou et al., 2015). In the search for treatments for chronic pain which are safe, well tolerated, effective and affordable, and can also be personalised and self-managed by individuals without repeated health care consultations, sleep may represent an important avenue for innovation.

Sleep problems are experienced by over 70% of those with chronic painful conditions (Drewes, 1999; Abad et al., 2008), rising to 96% of those with fibromyalgia, where the severity of sleep problems predicts the level of pain (Bigatti et al., 2008). The relationship between chronic pain and sleep disturbance is bidirectional (Affleck et al., 1996), and operates in terms of day to day symptom fluctuation (Tang et al., 2012) and likelihood of new symptomatology developing over a period of years (Gupta et al., 2007; Stocks et al., 2018), with non-restorative sleep found to be a strong independent predictor of new onset widespread pain (McBeth et al., 2014). Experimental sleep deprivation and fragmentation increases pain (Smith et al., 2007), whilst non-pharmacological treatment for insomnia in those with chronic pain improves not only insomnia but also pain, at least temporarily (N.K.Y. Tang et al., 2015; Selvanathan et al., 2021). In recognition of this close relationship, sleep problems have been highlighted in recent research prioritisation exercises (James Lind Alliance, 2016; Fitzcharles et al., 2017).

Brain entrainment has received interest in recent years as a potential neuromodulatory approach to chronic pain. Entrainment refers to an oscillatory system becoming phase synchronised (falling in step) with an external input, which could be anything from a repeated direct physical force to, as in this case, rhythmic sensory stimulation. Alpha entrainment refers to modulation of cortical electrical oscillations (‘brainwaves’) in the alpha band (8–12 Hz) and can be achieved with rhythmic stimulation which can be sensory or direct electric or magnetic stimulation (Thut, Schyns, et al., 2011). Since alpha rhythm is involved in pain expectation (Babiloni et al., 2006), attention to pain (Hauck et

al., 2015) and expectation of pain relief (Huneke et al., 2013) its modulation has been explored as a potential treatment for pain. Both healthy volunteers and individuals with chronic pain have used alpha entrainment in laboratory settings (Ecsy et al., 2017; Ecsy et al., 2018; Arendsen et al., 2020; Lopez-Diaz et al., 2021) and in more realistic home-based settings (Locke et al., 2020). Alpha entrainment has not previously been used pre-sleep in those with chronic pain, but other forms of non-invasive brainwave entrainment have been investigated for this use. Audio-visual stimulation decreasing in frequency from 8 to 2 Hz was applied to participants with chronic pain and insomnia aiming to aid sleep onset. In a pilot randomised controlled trial, adherence to the intervention was 99% and participants reported high ease of use on a Likert scale (Tang et al., 2021), but no more detailed qualitative exploration of user experience of this type of neuromodulation is available in the current literature.

This sparsity of user experience must be addressed for this field to move forward. Health systems including in the UK are responding to the immense challenge presented by long term conditions such as chronic pain by prioritising community and home-based management and digitally enabled care (National Health Service, 2019). Simultaneously the medical technology sector is seeing rapid growth (UK Government Official Statistics, 2022). However, medical devices for use in the home environment require particular attention to usability (Tase et al., 2022), without which safety can be compromised and the benefits of the technology will fail to be realised. Although research into neuromodulation for chronic pain has increased dramatically in recent years (Knotkova et al., 2021), the detailed experience of users is often neglected. Since chronic pain is a condition best understood through a biopsychosocial perspective (Gatchel et al., 2007), these experiences are likely to be crucial to our understanding of how interventions operate and why response differs between individuals. Furthermore, the Evidence Standards Framework for Digital Health Technologies required by the UK's National Institute for Health and Care Excellence states that user acceptability must be incorporated in the design of digital health technologies (National Institute for Health and Care Excellence, 2022). Our feasibility study of pre-sleep alpha entrainment for those with chronic pain and sleep disturbance found pre-post improvements in participant-reported measures of pain and sleep parameters, which should stimulate the controlled studies needed for further investigation (Halpin, Casson, et al., 2023). This paper builds on those results by providing the rare detail on the experience of individuals interacting with this home-based technology, offering insights of relevance both within and beyond this specific intervention.

The intervention used in this study, known as Home-based Brainwave Entrainment Technology (hBET), uses visual or auditory stimulation at 10 Hz to increase the power of alpha brainwave activity. The stimulation is delivered via a smartphone application, using either flickering light displayed in front of the user's closed eyes, or binaural beats (Jacob et al., 2020). In the visual stimulation case the phone is placed over the eyes in a virtual reality phone-holding headset. The user sees a flickering light effect through their closed eyelids. In the audio stimulation case headphones are used and slightly different pure tones played into each ear, creating a humming effect. Screen brightness and volume are under the user's control. A 10 Hz repetitive stimulus is created in both cases. Applying alpha entrainment at bedtime aims to improve night pain and interrupt the dysfunctional relationship between pain and sleep, is a potential treatment for chronic pain and coexistent sleep disturbance. To be developed further following best co-design practice it requires in-depth investigation of acceptability and usability by the target population.

The aim of the present study is to explore the user experiences of hBET, to inform the future development of the technology and its evaluation. Specifically, we aimed to explore the participants' existing attitudes, behaviours and expectations pertaining to sleep and pain, identify research feasibility and process issues, and elicit experiences of using hBET in terms of acceptability, effect on symptoms, and adverse effects.

3.4 Methods

Since pain is not a simple sensory experience, but a dynamic interaction between sensory and contextual (affective, motivation, cognitive) factors (Melzack and Casey, 1968), it is crucial that the exploration of novel treatments encompass the perceptions and experiences of users. For this reason, qualitative methods were prioritised within the design of this feasibility study of hBET and considered to be the primary outcome measure. This paper reports on these qualitative findings, whilst the results of before-and-after quantitative measures are published elsewhere (Halpin, Casson, et al., 2023).

3.4.1 Study Design

Semi-structured interviews were conducted with individuals with chronic pain and sleep disturbance who had used hBET alpha brainwave entrainment for 4 weeks in the context of a feasibility study. Paradigmatically, the design was informed by a 'subtle realist' approach (Brooks et al., 2015), in that the researcher's influence is acknowledged, whilst still assuming the existence of a

shared and accessible external reality. Specifically, the primary researcher's role as a rehabilitation physician (SH) situates them in a particular way socially to the participants, which is acknowledged as relevant to the findings and interpretation. However, the researcher had no role in the clinical care of participants. Ethical and regulatory approval for the study was granted by the Health Research Authority and NHS Research Ethics Committee reference 19/YH/0313 and procedures followed were in accordance with the Helsinki Declaration. The parent study was pre-registered at ClinicalTrials.gov with the ID NCT04176861.

3.4.2 Participants

A convenience sample of individuals with chronic pain and sleep disturbance were recruited from across the north of England. They primarily heard about the study through NHS musculoskeletal and rehabilitation clinics. Details of the study were also available in online publicity such as the National Institute for Health Research website, which was the route for a minority of participants, but in both cases they were people who had long term contact with health services due to chronic pain. Study processes were entirely separate to their usual clinical care, which continued in parallel. No stipulation was made on recency of medication changes prior to the start of the study, but timing of involvement in the study was planned to avoid any periods where significant interventions or medication regime changes were planned.

Inclusion criteria were: age 18–80 years, having chronic non-cancer pain (recurring pain ≥ 3 months duration), having nocturnal pain (NRS 0–10 worst pain ≥ 4), and self-reported sleep difficulties (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 a planned pain intervention during the 4-week hBET use period, seizure disorder, photosensitivity, hearing or sight problems causing inability to use hBET, or cognitive problems or dementia or a mental health condition causing inability to consent or participate in the study.

Initial contact with the research team was by either email or telephone. Eligibility screening against the inclusion and exclusion criteria above was done by telephone. Participants were given the study information sheet and had opportunity to ask questions before providing written informed consent. The protocol for the feasibility study involved participants being familiarised with the hBET app on a supplied smartphone during a one-to-one session with the researcher, followed by a one-week baseline period during which their sleep and pain levels were monitored. They then used hBET each evening just before

sleep for 20–30 minutes, and could choose whether to use the audio or visual programmes on any given night. The equipment used by participants is shown in Figure 3.1.

Figure 3.1 Equipment used by participants. Headband with integrated Bluetooth speakers for audio stimulation mode, headset to hold phone for visual stimulation mode, smartphone displaying home-based Brainwave Entrainment Technology application menu and MotionWatch.

Sleep and pain levels and hBET usage were monitored with daily diary and actigraphy, and standardised questionnaires assessing pain, fatigue, mood, sleep quality and health related quality of life were completed pre- and post- the hBET use period. The results of these quantitative measures are published separately (Halpin, Casson, et al., 2023). Electroencephalogram was not measured in this study. Therefore, although the mechanism of action supported by previous studies is alpha entrainment, we did not directly measure spectral power in the alpha band in this experiment.

3.4.3 Interviews

Within 5 days of completion of the hBET use period a final meeting with the researcher was held, usually remotely over a video link in light of the Covid-19 pandemic, at which a semi-structured interview was conducted. Some

participants had a family member present in the room but only the participant contributed to the interview. Interviews were conducted by one male researcher (SH) with experience and training in qualitative interviewing and a professional background in rehabilitation medicine. The interviewer had no prior clinical relationship with any of the participants and was not known to them outside of the context of the study. Participants' knowledge of the interviewer was therefore primarily as a researcher, motivated to investigate potential novel treatments for pain and desiring to understand the real-life experience of users. The interview schedule was designed to facilitate exploration of how participants approached hBET in the context of their experience of chronic pain and sleep disturbance and previous treatments, their experience of using hBET, its effect on their symptoms and usability. Interviews lasted between 30 and 60 minutes and were audio recorded and transcribed verbatim.

3.4.4 Data analysis

Transcripts were analysed using template analysis, which is an approach to thematic analysis which emphasises the hierarchical arrangement of themes in a template (King, 2017). Template analysis is compatible with a range of epistemological stances and has been successfully used in combination with a subtle realist approach in the exploration of chronic pain previously (McCluskey et al., 2011). Template analysis allows the identification of *a priori* themes, which suited this study in that it helped structure the template to meet its several key aims. However, these *a priori* themes were tentative and subject to reconsideration as the analysis progressed. Following reading and re-reading of the data, a subset of 10 interviews were coded to the initial template which was then modified in discussion with the whole research team. The remaining interviews were then coded by one researcher (SH) with resultant codes scrutinised and modified by a senior co-author (RJOC), with divergences discussed to revise the template. The template was then further refined to best represent the most relevant findings, with critical input from all authors. The target sample size was set in advance to meet the aims of all aspects of the feasibility study, rather than by assessment of data saturation. However, it is judged that analysis of this relatively large sample of 27 interviews has adequately generated the themes of importance to the research question. Analysis was conducted using NVIVO software (QSR International Pty Ltd, 2018 Version 12 Plus).

The final template contained six top level themes; impressions of the pain and sleep relationship, previous experiences of therapies and strategies tried,

expectations of hBET, experience of use and impact of symptoms of Audio hBET, experience of use and impact of symptoms of Visual hBET, and research processes. The final template is presented in supplementary material (Appendix C). Here we report findings from the first five themes which have the greatest relevance to readers on the user experience of hBET.

3.5 Results

3.5.1 Participants

Of the 28 participants who completed the hBET feasibility study (Halpin, Casson, et al., 2023) 27 took part in an interview, with one choosing not to due to their personal time commitments. Participants had a mean age of 45 years (SD 12.4) and 21 (78%) were female. Fourteen were unemployed and a further 4 retired, with 3 of these being under 60. The remaining 9 were in full or part time work. These individuals had experienced chronic pain for between 1.2 and 40 years, with a median of 8 years. In the majority, the onset of pain and sleep problems was simultaneous, with reported sleep disturbance also having a median duration of 8 years. Diagnoses as reported by the participants included fibromyalgia in 24 cases, chronic widespread pain in a further two, and trigeminal neuralgia in one. This last case represents a different category of chronic pain but was not excluded from the analysis as retaining a range of participants was felt to be beneficial to meet the aims of the current study, regarding user experiences. Three participants were currently taking no pain medications, with others taking between one and five (median of two). Classes of medications being taken for pain were: opioids (16), gabapentinoids (14), paracetamol (14), non-steroidal anti-inflammatories (7), tricyclic antidepressants (6), serotonin and norepinephrine reuptake inhibitors (4), benzodiazepines (3), triptans (2), others (2).

3.5.2 Impressions of the pain and sleep relationship

The close and complex interrelation of sleep and pain was endorsed and expanded on in many responses. The concept of a bi-directional relationship was identified by many, often described as ‘cyclical’, ‘intertwined’, ‘hand-in-hand’, and was embellished with personal examples.

The most straightforward facet of the relationship, and often the first identified, was the impact of pain on sleep, which was experienced as the dominant

direction by some responders. One responder related this to the greater tendency to attend to pain at night time:

> *“I think, obviously I've got pain throughout the day, but at night, because there's nothing else to focus on, I feel it more. So when I'm actually trying to fall asleep I just feel it a lot more than throughout the day, when I'm actually busy with something else” (P23).*

Another described this dominance of pain as making other solutions less relevant:

> *“I think because the pain was disturbing my sleep so much that the sleep hygiene routine would never break through that.” (P16).*

Mood and activity levels were implicated by participants as factors in the sleep-pain relationship. Anxiety, including anxiety about sleep itself, was a reason for poor sleep and, equally, low mood and motivation were also experienced as consequences of poor sleep. Activity was implicated with a rich complexity of interactions proposed by interviewees. This web of relationships is described with example quotes in Figure 3.2

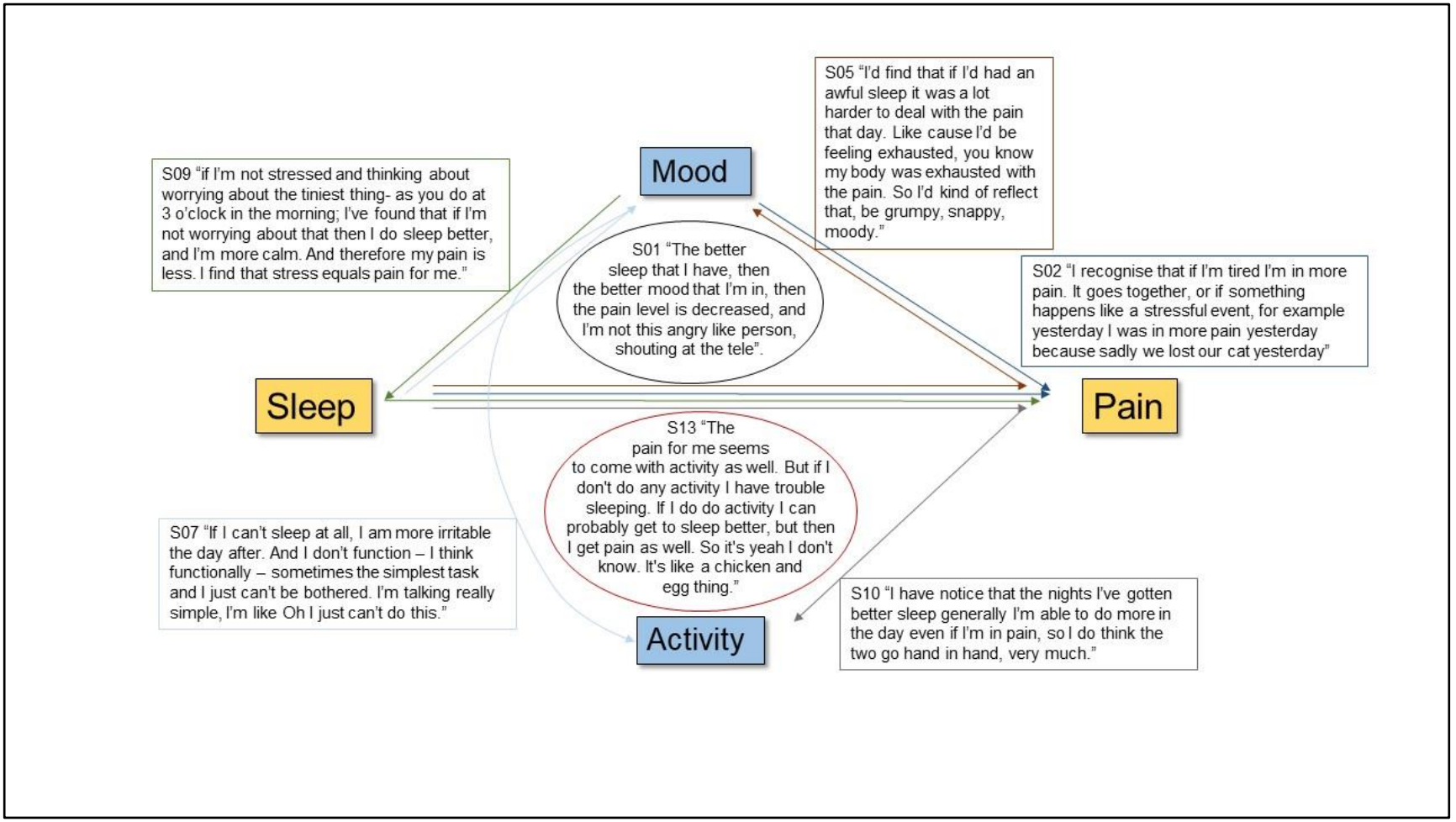

Figure 3.2 Reported web of relationships between sleep, pain, mood and activity with illustrative quotes

Arrow colours correspond to the quotation supporting that aspect of the web of interactions.

Participants drew a distinction between pain ‘level’ and their ability to ‘cope’ or ‘deal’ with the pain. The benefits of good sleep are not considered only in terms of reducing the pain level, but in making the same level more tolerable. This relates to insightful comments about the difficulties of judging pain, in the context of a study which included a daily pain diary using a simple numerical rating scale (0–10). Describing a day with particularly upsetting and stressful circumstances:

> *“I think if I were to just solely judge the pain, it probably would have been similar to a different day. But if I were to judge everything else I would give it a higher score.” (P23).*

Similarly,

> *“the [pain] is just there anyway, but sometimes it's amazing how it's there but you can cope with it. It's kind of you can push it to the background sometimes.” (P27).*

For multiple participants sleep difficulties were related to a sense of their bodily state being out of step with their mental state, with body being tired but mind racing.

> *“I can feel dog tired, body is aching, but I get in bed and my mind is just racing, going” (P08).*
>
> *“As much as you are desperate for sleep you can’t do it. Your body’s sort of said no! Because you’re in so much pain, or just not tired enough, or you’re restless, or your mind’s working at a million miles an hour” (P09).*

3.5.3 Previous experiences of therapies and strategies

All participants had tried medications for their symptoms and all but three were currently taking pain medications. The relationship with medications ranged from appreciative of the benefit that some felt they had gained from medications, to serious concern; about tolerance, harm and side effects and a common desire was expressed to reduce medications. Several responses indicated a change over time in their relationship and reliance on medications, captured in the sub-theme of ‘journey of realisation that medications alone won’t work’. Held alongside this was the common reality that medications are in fact the mainstay of management offered.

3.5.4 Expectations of hBET

The dominant sentiment around expectations was positive, with many respondents understandably hopeful that their symptoms would improve. This

was often framed in terms of experience of comparable interventions or belief that the rationale was credible or coherent with their prior understanding of their pain experience.

> *"I was like, 'well It makes sense!' … All sorts of sensory stimuli affect the brain in certain ways, like you can have migraines triggered by sounds. So if a migraine could be triggered by a sound, surely sounds that you purposefully input can do things as well" (P16).*

Despite this positivity, participants were also cautious about having overly high expectations, and referred to trying to keep an open mind.

> *"I had an open mind because I didn't want to have that in the back of my head that this was going to work, you know?" (P09).*

> *"I wasn't expecting a cure or expecting it to be placebo either, just expecting to see what happens" (P22).*

Others were more sceptical, having tried many things in the past unsuccessfully. Several respondents expressed being 'willing to try anything', but this was in the context of referring only to non-pharmacological options and offered more optimistically than with a sense of desperation.

> *"I'll try anything as long as it's like not drug related. You know, if it's something that involves not taking drugs that's better for you. So I'll go in to anything open minded and try it" (P18).*

This narrative is in keeping with participants having been through many years of chronic pain, refractory to previous treatment attempts, who have learnt from experience that pain may be something they have to manage long term rather than expecting a 'cure'.

3.5.5 Audio hBET; experience of use and impact on symptoms

The dominant sentiment expressed on the impact of audio hBET was that it had a positive effect on sleep difficulties. This was most often described as helping with sleep onset, being quicker, easier, and giving confidence that the participant would be able to get to sleep, thereby reducing anxiety about sleep. Sleep onset improvement was closely followed by comments about improvement in consolidation of sleep, waking fewer times and perceiving the sleep to have been deeper.

> *"I found the audio really, really helpful! I found that I was going to sleep a lot faster. I was waking up less during the night. And I just felt generally better rested" (P15).*

> *"There's more nights when I've slept through than I would have normally. It's a long time since I've not had broken sleep … so for me that that's a positive, a big positive" (P29).*

> *"It was nice! My partner commented as well and said I've not tossed around anywhere near as much as usual. And I've been a lot more settled and, like, I've been in a lot deeper sleep than usual" (P18).*
>
> *"All the anxiety around going to sleep seems to have been taken away because for some reason I do manage to get to sleep quite easily" (P27).*

Four participants gave potentially convergent opinions on *how* they felt the audio stimulation achieved this perceived positive effect, which relate to the theme within *Impressions of the pain and sleep relationship* of the body being tired but mind racing. They described it blocking out other thoughts:

> *"For me, it blocks everything going on in my head. It blocks me thinking 'oh God, what are we going to have for tea tomorrow?', and things like that. So it concentrated my mind, and stopped me thinking about other things" (P02).*
>
> *"If you relax and listen, it does kind of clear your mind, 'cause you can't think about anything else. You can't think 'oh we need bread' or 'oh that bill needs paying'; you can't do any of that. Which is reminiscent to me of riding my motorbike – you can't be thinking about other things because you've got to concentrate on the mechanics of riding" (P08).*

Other benefits were described as being more refreshed in the morning, increased total sleep time and requiring less of other treatments to aid sleep, which included alcohol and strong opiates. There were no negative effects on sleep reported, whilst two participants felt it had no discernible benefit to their sleep.

Improvement to pain was also a common theme, though not affirmed by as many participants as reported a benefit to sleep. As well as generally reduced pain, this was put in terms of reduced pain compared to what would have been expected in stressful circumstances, or around a symptom flare, reflecting the day-to-day fluctuation of fibromyalgia type pain.

> *"There's days where, if my little boy's played up all day, I'll think I'm going to suffer for it tomorrow. [But] I've had a really good sleep and then been fine" (P18).*
>
> *"The thing that I noticed most that's different is that even if I have a pain flare during the day, my night time pain was a lot less than it would have been previously" (P16).*

Some insights from users also distinguished the effect to be particularly on the widespread 'fibro' pain specifically.

> *"Most of the time you get like the all-over pain … But then, over the weeks [of using hBET], although I've still had pain, it's almost been isolated, so you can kind of deal with it" (P21).*

> *"The fibro pain, after a couple of weeks, had lessened – like the shoulder pain and the upper back pain – those sort of went, pretty much. I mean, my shoulder was still giving a sort of niggle, but for the most part after a couple of weeks they sort of disappeared" (P02).*

Other wider effects were being able to be more active in the day, (hitting the 'fibro wall' later in the day or not at all), and a positive psychological impact, with hBET frequently being described as relaxing, specifically despite stressful circumstances.

Audio hBET was described as easy to use and incorporate into the pre-sleep routine, with no major usability issues identified. Eight participants found the audio tones unpleasant or distracting.

> *"I only used it a few nights because I found it irritating! I just didn't like it." (P07).*

> *"It's just this annoying buzz, and I just wanted it gone, the sooner the better!" (P22).*

When asked about side-effects only four reported any and these were all occasional or transient, being: occasional increase in pre-existing tinnitus, transient dizziness, transient restlessness, transient feeling sick.

3.5.6 Visual hBET; experience of use and impact on symptoms

During the study participants could choose whether to use audio or visual stimulation on any given night. Across all participants fewer chose to use the visual option, and there were two and a half times as many nights recorded in total using audio hBET compared to visual hBET. The prevailing reason for this was clearly expressed by participants as relating to usability issues. Those who struggled with the visual option chiefly found wearing the headset uncomfortable and cumbersome. The headset itself is not integral to visual hBET use, but simply holds the smartphone in the required position to display visual flicker stimulation through closed eyelids. Thus several participants suggested alternative delivery methods, such as a screen or light suspended above their head to avoid the need for a headset. Although this was the dominant reason for visual stimulation being less popular, visual stimulation was also less commonly preferred in itself, with some users finding it unpleasant or not relaxing.

> *"How can I describe it? Like strobe lights, just there pulsing away… I didn't like it at all" (P06).*

In contrast, others liked the 'trance-like' feeling of using visual stimulation, as one vividly described:

> *"It was relaxing to use it, it was like being a passenger in a car, and driving through a woodland or something like that where you get the light coming through the trees, and the shadow is flashing over the car the whole time and you end up nodding off in the back of the car. It reminded me of being a kid and, you know, sleeping on long journeys, that's what it reminded me of" (P26).*

Thus there is an element of personal preference to the choice of stimulation modality. More side-effects were described with visual stimulation, which were headaches, reported by five participants which in two cases were a severe migrainous type of headache. These did not require medical intervention but did result in those participants reverting to using the audio option in preference.

Participants who used the visual hBET option reported improvement to sleep more readily than improvement to pain. As for audio hBET, improvement to sleep onset was most often commented on, as well as fewer awakenings during the night.

> *"My sleep pattern is still all over the place but at least I was getting some sleep with it! A couple of times I woke up and I still had the equipment on me head after 4 or 5 hours sleep … that's really unusual. I'm normally waking up, tossing and turning or shaking to try to get rid of the pain or I just give up on it altogether. ... But a few nights of using the visual stuff it was just great. And even my partner noticed. In fact they said this morning it's a shame that equipment's going back, cause you've had better sleep with that equipment than you have for years!" (P26).*

Less predominant but still important was the report of some participants noting no marked effect on sleep, despite tolerating the equipment. The overall sentiment of the visual experience varied quite widely between users, from very positive to immediately rejecting, as one participant put it "*it's trial and error, I think*" (P08).

Reports on effect on pain were more balanced, with participants finding it more difficult to discern whether changes were attributable to visual hBET or other circumstantial factors, even when they had experienced improved sleep.

> *"I didn't seem to wake up half as much compared to normal. Pain-wise, they were still quite high" (P19).*

> *"It has been a little bit different, but part of me wonders whether that was, cause with my husband being home, I don't do as much" (P07).*

Wider effects described were of improvement in mood, including a sense of hope that their chronic symptoms can be modulated, and desire to keep using the equipment.

3.6 Discussion

Individuals with chronic pain and sleep disturbance who had used non-invasive alpha entrainment by audio or visual stimulation for four weeks took part in semi-structured interviews to elicit their experiences, which were transcribed and subjected to template analysis. This found that audio and visual stimulation at bedtime was acceptable to this cohort and its rationale was coherent with prior understanding of their pain experience. The comfort and practicality of equipment was a key consideration. Positive impacts on chronic sleep and pain symptoms were described, and there were few side effects. The audio modality was more popular both in terms of usability and in the impact on symptoms, but the range of preferences among the group benefitted from having a choice of options available.

Pain and sleep were interrelated in a web of interactions which included mood and activity, endorsing the premise that sleep is important in the experience of chronic pain. The concept of a bidirectional link between chronic pain and sleep disturbance is core to the rationale of the feasibility study, and therefore was a known idea introduced in discussions about participating in the study. Nevertheless, it was marked that the concept was easily recognised and endorsed by participants, with colourful personal examples. The fact that the influence of pain on sleep was the strongest identified relationship by this group supports the rationale for an intervention on pain at night to intervene in this web of symptoms. Although neither mood nor activity levels featured in the interview schedule, respondents frequently detailed the role of these factors in the sleep-pain relationship and they were incorporated into the model. An implication of this is that measuring sleep, pain, mood and activity should be considered when hoping to intervene on these related symptoms. Relatedly, participants engaged with the complexity of assessing pain, which is an inherently subjective experience (Turk and Melzack, 2011). By highlighting the relevance of fluctuant disease-related factors (such as fibromyalgia flares), activity levels and contextual factors, this analysis points to the value of measuring outcomes across the dimensions of impairment, activity, participation and context, as modelled by the International Classification of Functioning, Disability and Health (World Health Organization, 2001).

The analysis brought out intriguing descriptions of a feeling of dyssynchrony between body and mind states, with a breakdown of the easy, natural sequence of sleep onset, and correspondingly a suggestion that the benefit of hBET on

sleep onset was via calming the mind to align with the body's tiredness. This could be conceived to support the notion that thoughts were calmer in line with alpha entrainment, corresponding to the proposed inhibitory function the alpha rhythm on attention and other cognitive processes (Jensen and Mazaheri, 2010; Klimesch, 2012), and increased occipital and parietal alpha power has been found in response to meditation (Stapleton et al., 2020), although this is speculative as EEG was not measured in this study. It also opens an avenue of enquiry regarding the role of interoception and metacognition in the generation of symptoms which could respond to alpha entrainment, and in selection of individuals most likely to benefit. This requires further careful research.

In terms of impact of hBET on the symptoms of pain and sleep disturbance, key findings were that although both improved, the positive sentiment around sleep improvement surpassed that of pain, which is interesting in the light of the hypothesis that alpha entrainment improves pain, and thereby sleep. Possible explanations are that pain improvement was sufficient to benefit sleep but not to impact the restrospective assessment of pain, which is known to be affected by recency, salience and assimilation effects (Mason et al., 2011), further complicated by impaired memory of the period immediately pre-sleep. Another possibility is that hBET benefits sleep by an independent mechanism, such as inhibiting attention to stimuli or cognitions other than pain. Future research should seek to understand the immediate and accumulating impacts of this intervention from the user's perspective to refine how it might best be incorporated in real life use.

A limitation to this study is the possibility of reporting bias resulting from the interviewer being the researcher who guided the participants into the study, potentially leading to participants feeling a preference to report positively on the experience. This was mitigated against by encouragement to be honest and framing the value of their experience whether positive or negative. The finding that many negative impressions were reported, for example about the comfort of particular equipment, indicates that the participants did feel able to share these experiences. This aligns with participants' descriptions of their own expectations, which were open-minded and informed by previous experiences of diverse treatment modalities, many of which had been ineffective (potentially even to the point of inducing a nocebo effect). The cohort in this study had a mean age of 45 and were majority female, which mirrors population level studies of chronic pain prevalence (Fayaz et al., 2016). The cohort consisted of

a majority with fibromyalgia and chronic widespread pain, and one outlying participant with neuropathic pain (trigeminal neuralgia). This reflects the broad eligibility criteria chosen for this early stage of exploration of the treatment modality, but future studies with more mechanistic focus will benefit from a less heterogeneous population.

This study has found that use of a non-invasive sensory stimulation technology pre-sleep was acceptable to users with chronic pain and sleep disturbance, with encouraging reports of benefit to symptoms for many and few side effects. This should stimulate further rigorous investigation into this treatment modality, incorporating user insights particularly regarding comfort and ease of equipment use and further modification, particularly of the visual stimulation headset design.

3.7 Conclusion

Pre-sleep alpha entrainment by audio or visual stimulation was an acceptable intervention to people with chronic pain and sleep disturbance, and was perceived to be associated with improvements to sleep and pain symptoms.

3.8 Summary Points

- Alpha entrainment is a promising neuromodulatory treatment for chronic pain, and the perspectives of users are crucial to its development
- This study reports on the experiences of 27 individuals with chronic pain who used alpha entrainment by audio or visual stimulation pre-sleep for four weeks
- Using alpha entrainment pre-sleep at home was found to be acceptable and relevant from the perspective of users. Comfort was a key factor and having a choice of sensory modalities helped account for individual preferences
- Participants vividly described a close relationship between sleep problems and pain experience, and the interaction also involved mood and activity levels
- Overall, a positive impact on pain and sleep symptoms was described, with variation between participants and a preference for audio stimulation
- These user perspectives should guide and stimulate development of non-invasive neuromodulatory approaches for chronic pain and sleep disturbance

Chapter 4 Pre-sleep alpha brain entrainment by audio or visual stimulation for chronic widespread pain and sleep disturbance: A randomised crossover feasibility trial

The final paper in this series significantly advances our knowledge on the effect and utility of sensory alpha entrainment, from both mechanistic and feasibility perspectives. It adds to the previous findings by introducing a control condition and direct physiological monitoring of brain activity during stimulation, whilst retaining the benefits of implementing this in ecologically realistic conditions of the user's own home, over many nights of use. The findings shed new light on the how alpha entrainment operates under these real life conditions, and provide early indications of clinical effect which inform and stimulate further work. The experience gained of home-based, pre-sleep EEG monitoring is directly relevant to the future development of the intervention. In the context of a rapidly changing technological landscape where out-of-laboratory advanced monitoring is increasingly possible, this study is situated at the vanguard in exploiting this potential at the intersection of the fields of neuromodulation, pain and sleep.

The paper is reproduced here having been reformatted for consistency with this thesis but with no changes to the content.

4.1 Metadata

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4.2 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.

4.3 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) (Queiroz, 2013; Heidari et al., 2017). 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 (Lloyd et al., 2020; Sun et al., 2022). 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) (Thut, Schyns, et al., 2011). 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 (Hassaan et al., 2020). 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 (Ecsy et al., 2017; Ecsy et al., 2018) and reduction in intensity of clinical chronic pain, which is correlated with the degree of entrainment (Arendsen et al., 2020; Lopez-Diaz et al., 2021).

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 (Bigatti et al., 2008) and the relationship between the symptoms has long been observed to be mutually reinforcing (Affleck et al., 1996). Perhaps unexpectedly, the relationship is stronger in the direction of sleep acting on pain (Tang et al., 2012; Bean et al., 2021). Sleep may even be mechanistically implicated in symptom generation in fibromyalgia. The sleep disturbance seen in fibromyalgia is characterised by fragmentation (Diaz-Piedra, Di Stasi, et al., 2015),

experimentally shown to impair descending pain inhibition (Smith et al., 2007), which is known to be deficient in fibromyalgia in particular (Julien et al., 2005). This correlates with the experience of individuals, who describe sleep and pain problems interacting in a cycle (Halpin, Tang, et al., 2023). 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 (Jacob et al., 2020; Xing et al., 2023). '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 (Halpin, Casson, et al., 2023; Halpin, Tang, et al., 2023). 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.

4.4 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.

4.4.1 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.

4.4.2 Procedures

Largely remote procedures were used as these had been found to be effective in previous work during the Covid-19 pandemic (Halpin, Casson, et al., 2023) 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 (Gallina et al., 2023). 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 (Halpin, Casson, et al., 2023). 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.

4.4.3 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 (Halpin, Casson, et al., 2023), user co-design (Locke et al., 2020) and qualitative user feedback (Halpin, Tang, et al., 2023) 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 (Bazanova and Vernon, 2014) and was previously found to be the optimal alpha frequency for analgesia (Ecsy et al., 2017). 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 (West et al., 2011). The auditory mode uses binaural beats (different frequencies presented to each ear, with the binaural beat frequency being the difference between them) (Schwarz and Taylor, 2005) 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 (Xing et al., 2023). 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.

4.4.4 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 (Arnal et al., 2020). 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 (Carney et al., 2012). 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.

4.4.5 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 (8–13 Hz), for the reason that endogenous alpha at surrounding frequencies may also be entrained, as has been suggested based on the underlying neural mechanisms (Gallina et al., 2023) and mathematical modelling (Otero et al., 2022). 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 (De Gennaro et al., 2001). 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 artefact removal technique for low channel counts (Arpaia et al., 2022). Parameters of the ASR method were set as follows: the automatic artefact identification threshold was set to 10, based on previous work optimising ASR parameters for low channel counts (Cataldo et al., 2022); 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 (Donoghue et al., 2020) (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.

4.4.6 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 and the effect of the intervention on alpha power were 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.

4.5 Results

Nineteen participants were enrolled between September 2022 and June 2023. Patient flow through the study is shown in Figure 4.1.

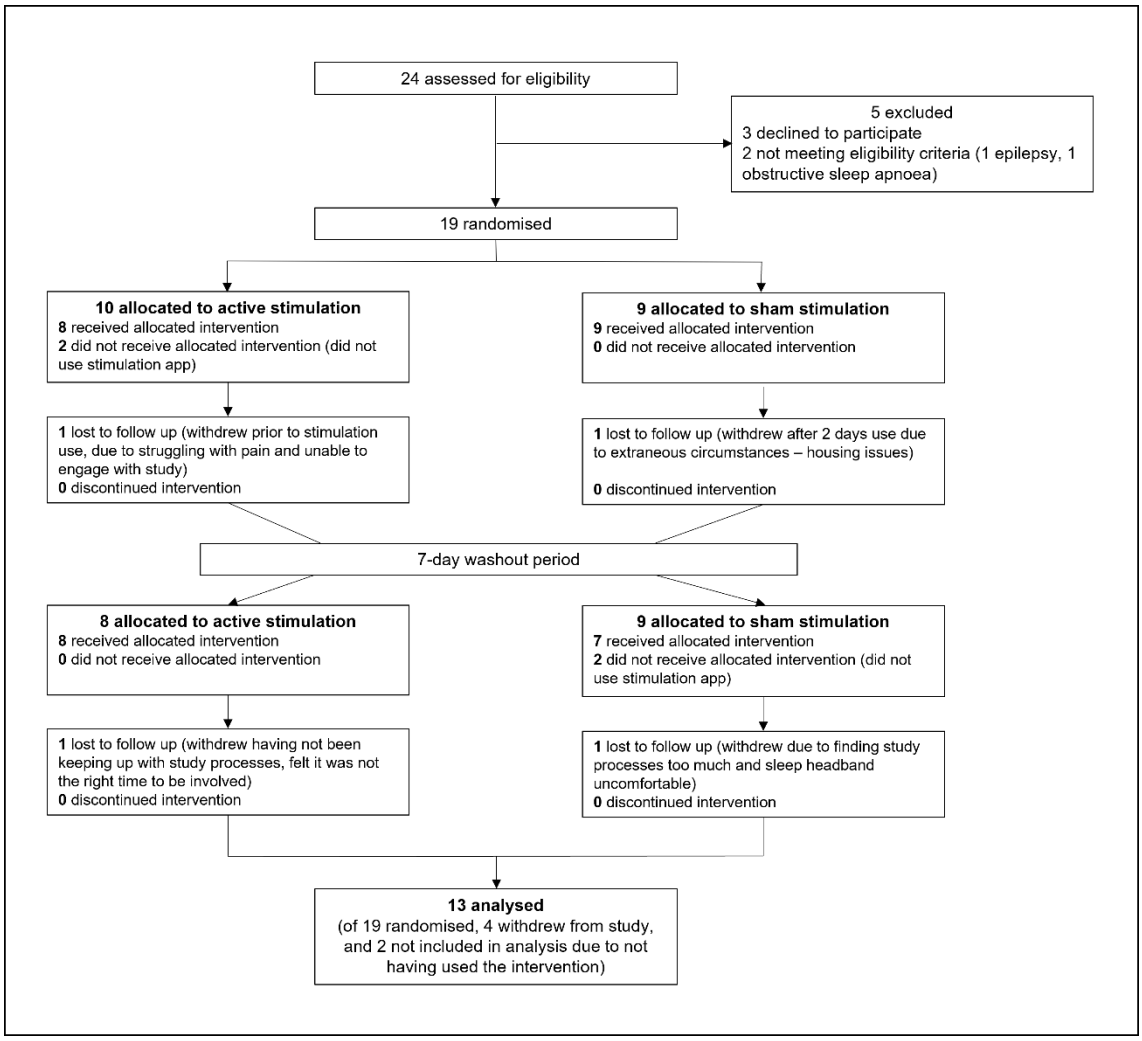

Figure 4.1 Participant flow through the study

The clinical and demographic profile of participants is shown in Table 4.1. This compares the participants randomised to each sequence of active and sham stimulation, and all participants receive both in this crossover design.

Table 4.1 Clinical profile of participants, by allocation.

	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

ACR, American College of Rheumatology. FM, fibromyalgia. SNRI, serotonin and noradrenaline reuptake inhibitor. TCA, tricyclic antidepressant. Medical history obtained from patient report.

4.5.1 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 4.1. 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 (Appendix D1).

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.

4.5.2 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.

4.5.3 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 material (Appendix D2). 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 4.2.

Table 4.2 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)

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

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 material (Appendix D3).

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.

4.5.4 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 quality in each condition with randomised direct comparison of active and sham stimulation are shown in Figure 4.3 (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). The daily measures of sleep are shown in Table 4.3.

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 material, Appendix D4).

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 material, Appendix D5. 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.

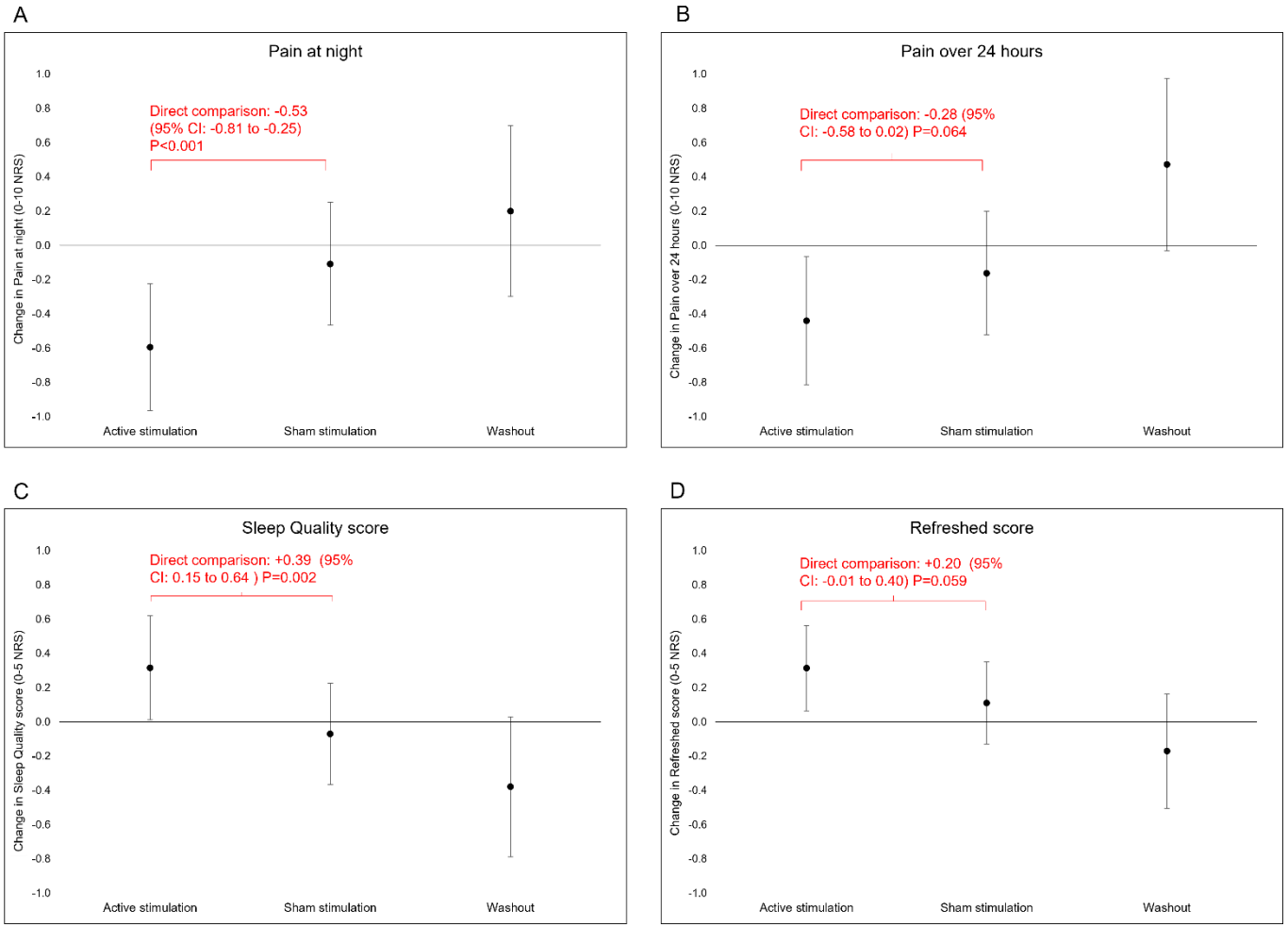

Figure 4.2 Difference (and 95% confidence interval) in active stimulation, sham stimulation and washout periods compared to baseline for daily diary report of A) Pain at night B) Pain over 24 hours C) Sleep quality score and D) Refreshed score. Also displaying result of the direct active – sham comparison. NRS, numerical rating scale.

Table 4.3 Daily sleep measures

	Baseline Mean (SD)		**Sham stimulation** Mean (SD)		**Active stimulation** Mean (SD)		**Comparison of Active - Sham simulation** (95% CI)		P value
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 4.4 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.

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

4.5.5 Questionnaire measures

The results of questionnaire-based measures at baseline and after active and sham stimulation periods are shown in Table 4.4. 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 (2011). 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.

4.6 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% (Farrar et al., 2001). 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 (Tzellos et al., 2010). 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 (Vancampfort et al., 2024). 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 (Halpin, Casson, et al., 2023) 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 (Tang et al., 2012; Bean et al., 2021), but with the finding that therapeutic effect on sleep also improves pain (N.K.Y. Tang et al., 2015). 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 (Riemann et al., 2010). 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 (Huneke et al., 2013), or the effect of attending to a sensory stimulus, which is also associated with modulation of alpha activity in complex ways (Van Diepen et al., 2019). 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 (Wolfe et al., 1995) but given that the gender ratio is closer to 2:1 when using recent diagnostic criteria (which omit tender point examination) (Vincent et al., 2013) 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.

Chapter 5 Discussion

5.1 Summary of the aim and contribution of this project

The general aim of this project was to study the feasibility and effect of a home-based pre-sleep alpha entrainment programme for use by individuals with chronic pain and sleep disturbance, and to do this in a way which could usefully guide further research. Three studies were completed to achieve this aim, as presented in the preceding chapters.

In the first study, participants with chronic pain and poor sleep used the hBET programme for four weeks, in an uncontrolled, open label design. Individuals with well-established chronic pain and severely disturbed sleep were able and willing to use hBET at home before sleep. It was used on 92% of the 700 nights for which diary reports were available, representing a high adherence rate for a behavioural intervention which involves longitudinal engagement including modification of usual bedtime routine. This clearly demonstrates that the technique is fundamentally feasible for the study population. The improvements in participant reported measures of pain, sleep, mood and fatigue point to users' impressions of benefit to symptoms, including support for the concept of pain and sleep acting in concert.

In the second study, detailed qualitative data gathered systematically from users of hBET in the first study were analysed to shed light on their experiences of engaging with the intervention and provided new insights into how pain and sleep interact. The reciprocal interaction between pain and sleep was validated and its complexity elaborated upon. There was universal endorsement of the existence of the relationship, *and* heterogeneity in the lived experience of individuals. Individuals' preferences about hBET and the range of experiences of its effect on symptoms were highlighted. The level of detailed attention to the voice and experiences of users represents a rare contribution in the field. The insights gained will direct future development of the research programme, with ongoing patient and public involvement and engagement activities. This is an essential part of health intervention development, optimising the effectiveness, acceptability and equity of the end result, as well as being a requirement of funders.

The third study added rigour of design and mechanistic detail by including a sham control and home-based EEG monitoring, in a crossover randomised design. For the first time, this demonstrated feasibility of an audio or visual pre-sleep intervention in conjunction with home EEG for this population, which is an

important finding for progression in the direction of an individualised system. It also for the first time demonstrated that even in home-based conditions over several weeks, hBET does enhance alpha power, including when compared against a carefully designed sham, controlling for the non-rhythmic aspects of sensory stimulation, attention, and expectation. A final crucial contribution of this study is the indication of benefit to symptoms, specifically pain at night and sleep quality, which are the variables most directly targeted by the intervention.

In section 1.4 the purpose of feasibility studies was detailed, in terms of establishing the *promise* of an intervention and addressing relevant *uncertainties.* These can now be reviewed to summarise the contribution made by the body of work in this thesis, which will lead into a discussion of the emergent uncertainties which set the direction for future research.

Table 5.1. A review of the purposes set out in section 1.4 with summary of contribution

Purpose identified at the outset of these studies	Reflection on contribution, outcome and outstanding requirements
Establishing the 'Promise' of the intervention	
Positive user experience and feedback able to further guide refinement of the intervention.	Achieved. Ongoing PPIE remains necessary.
Data on usability showing the target population can easily use hBET as intended.	Acquired. Delivery for visual stimulation requires improvement.
Preliminary data providing an estimate of effect on symptoms indicating this may be of a clinically meaningful magnitude.	Convergent evidence of benefit to symptoms from each study is of an inconclusive magnitude but justifies further exploration of this mode of intervention.
Uncertainties regarding the intervention	
Data demonstrating alpha entrainment is achieved in the conditions of intended use (pre-sleep, at home), giving confidence in the	Evidence gained substantiating alpha entrainment from hBET compared to sham control, in at-home use. A novel finding which motivates further work.

programme theory that clinical effect is via this mechanism.	
Uncertainties regarding trial design	
Preliminary data to inform sample size calculation.	Achieved. Justifiable sample size calculations can now be made.
Experience of recruitment, including speed, frequency of ineligibility, frequency of withdrawal.	Achieved. This learning informs realistic planning of future recruitment strategies.
Experience of how the target population uses the intervention in research conditions, including adherence to a protocol, to inform robust trial design.	Achieved.
Assurance that the research processes and outcome measures used are acceptable to participants and not overly burdensome.	Achieved.
Confidence that the home-based EEG monitoring tool and sham control condition function well and are feasible and acceptable to the target population.	Valuable insights gained: Home based EEG involves trade-offs in data quality and involves procedures which some participants require support with.

Taken together, this body of work has examined this potential management option from both physiological and feasibility perspectives. In the following sections some of the key findings will be explored in more detail specifically with reference to their implications for further research.

5.2 Implications and future recommendations

5.2.1 Pre-sleep sensory stimulation is acceptable but ongoing co-design is needed

The actual usage of hBET reported in chapters 2 and 4, and the user feedback reported in chapter 3, both attest to the acceptability of the intervention for use in the pre-sleep period. This was not a foregone conclusion prior to these

studies, especially considering that an individual's bedtime routine is very personal, the participants were selected on the basis that they already had sleep problems, and that equipment was required to be set up and worn for each use. A consideration with relevance for future studies is to what extent this acceptability relied on the availability of a choice of sensory modalities (visual or audio) and whether this should be retained.

The benefit of having choice of modalities in the first, open-label study was made apparent by some users finding one mode relaxing or pleasant and the other intolerable, whilst other users had the opposite preference. Had only one option been available it is likely there would have been a greater dropout rate and conclusion of overall lower acceptability. Most users preferred the audio mode, but this was not an overwhelming majority; when participants had free choice to use audio or visual modes on any given night, audio was more popular by a factor of 2.5 (458 vs 187 nights of use). However, in the crossover study when users had to choose at the outset whether to use audio or visual modes throughout, only 1 of 13 chose visual. The largest reason for people disliking the visual stimulation was the delivery device (virtual reality headset) rather than the stimulation itself, which could be improved in further developments.

The potential disadvantage of having a choice of modalities is that it complicates study interpretation. Although both are intended to be acting via alpha entrainment, scientific peers and medical device regulators may reasonably want to know about the disaggregated results of each modality, effectively treating them as two different interventions. Being sufficiently powered to independently assess each mode would inflate the size and cost of effectiveness studies. Also, the exclusion of people with epilepsy may not have been judged necessary if the intervention was audio stimulation alone.

The tension between flexibility and rigidity in intervention design could be seen as one example of the necessary decision between prioritising internal or external validity. Internal validity reflects how well a study's design and conduct establish the causal effect of the intervention, whilst external validity reflects the extent to which the findings can be generalised. This tension is common to all interventional health research and in general is managed by making design choices which align to how early or advanced is the phase of study for that particular intervention. Internal validity could be maximised by having narrow inclusion criteria, tightly prescribed usage of the intervention and a comparison which controls as rigorously as possible for biases. This is suitable for accurately answering early mechanistic questions on the study's own terms, but the artificiality of the groups and the interventions may limit the ability to

generalise the findings to other situations or provide clinically relevant information. In later phase effectiveness studies the external validity can be maximised by broader participant inclusion, to better reflect who may actually be offered the intervention in a health service; accepting more variability in the exact usage pattern of the intervention, as would happen in real life use; and comparing against a clinically relevant situation such as treatment as usual, even if this is somewhat heterogenous. Relating this to the development of hBET, the reality is not a simple linear process along the traditional clinical study phases. Instead, the situation is a cycle of design, testing and redesign, which complicates the distinction between mechanistic phase and clinical phase of study. When multiple questions are being asked simultaneously, (as in Chapter 4), design choices must be made thoughtfully and may involve compromises to balance the demands of internal and external validity.

The current findings demonstrate the basic acceptability of the concept and feasibility of the research processes, but it is important that participant and public involvement and engagement (PPIE) is not a one-off event, and the need for ongoing co-design of both the intervention and future research protocols remains. The findings from these studies provide a starting place, and they do highlight the importance of personal preference in the stimulation experience. For highest impact, future design must achieve high acceptability alongside a transparent and rigorously testable mechanistic theory.

5.2.2 Alpha is entrained but could be optimised

Viewing the findings of these studies in the light of the broader literature gives rise to considerations about how the sensory stimulation may be optimised for future work. The most substantial of these relates to the possible significance of individual alpha frequency (IAF) and the concepts and options around personalising the stimulation.

5.2.2.1 Individual alpha frequency

The specific frequency within the alpha band displaying the maximum spectral power is called the individual alpha frequency (IAF), or peak alpha frequency, and it varies between individuals. It can be calculated simply as the frequency where the highest peak occurs or by methods to represent the centre of gravity of the alpha peak, by calculating a weighted average across the whole alpha band. IAF is considered to represent a stable trait, rather than state-like

property (Grandy et al., 2013) but does tend to decline over the adult age range, after peaking in the twenties (Turner et al., 2023).

5.2.2.2 Open-loop entrainment; is 10 Hz optimal?

In the studies of open loop entrainment presented in this thesis, stimulation at 10 Hz was chosen because this lies at the centre of the distribution of individual alpha peak frequency across individuals (Bazanova and Vernon, 2014), and is a standard option often used in rhythmic stimulation research (for example, (Helfrich et al., 2014; Hopfinger et al., 2017; de Graaf et al., 2020)). The findings presented in Chapter 4 show this strategy did result in increased alpha power, with the superiority to non-rhythmic sham providing evidence that this was at least partly via the mechanism of entrainment. However, it did not work for all participants, and the effect size of the increase over sham was small across the whole group. Therefore, an outstanding question is whether this was the optimal choice for the population and application under study, and moreover whether a strategy to individualise the stimulation frequency would be more effective.

Initially, whilst 10 Hz is a good estimate for a general population, this might not hold true for the chronic pain population. As mentioned above, IAF slows with advancing age, which may limit the efficacy of entrainment in older user groups if this is not taken into account. Slow IAF and chronic pain itself have also been linked in laboratory-based and clinical pain studies. A study using capsaicin heat pain as an experimental model of chronic pain found that lower IAF predicted higher pain, and also that the degree to which peak alpha frequency decreased with pain onset was associated with pain severity (Furman et al., 2018). Regarding clinical populations, when 18 women with fibromyalgia were compared with 18 female age-matched healthy controls, a significant slowing of IAF of 9.6 Hz vs 10.3 Hz was found (Lim et al., 2016). The same pattern was found in people with neuropathic pain compared to healthy controls (Sarnthein et al., 2006) and in chronic pancreatitis (de Vries et al., 2013), where the difference was 9.5 Hz compared to 9.9 Hz. Complicating these findings, McLain and colleagues (2024) showed no difference in PAF between people with chronic widespread pain and healthy controls, but that the PAF of those with chronic widespread pain exceeded that of people with chronic back pain. It is unsurprising that findings disagree across small case control studies, with different selection criteria, EEG protocols, and methods of analysis. However, if a future experimental protocol required a blanket rule is to be applied, then opting for 9.5 Hz stimulation could be justified based on the current evidence as a closer match for the chronic pain population.

5.2.2.3 Individualised stimulation frequency

The alternative to applying a blanket rule is some form of individualisation. There is evidence supporting this approach from entrainment studies in both fundamental neuroscience and in clinical application. Baseline EEG was used to individualise tACS stimulation frequency in a study assessing the effect of different durations of stimulation on alpha entrainment (Stecher and Herrmann, 2018). When the individualised stimulation frequency as chosen in this way was compared to the actual IAF measured towards the end of the stimulation period, in over half of participants there was a mismatch of at least 1 Hz, and an exploratory analysis showed this mismatch had explanatory power in the variance of entrainment success. This indicates that tACS may be most effective when delivered at individualised frequencies, and also that the individualisation strategy used in this case produced inaccurate and potentially suboptimal results. In the field of alpha entrainment to study visual perception, Janssens and colleagues (2021) demonstrated a more technically refined approach to individualised assessment of IAF at baseline which resulted in a better match with the task-specific IAF than selecting 10 Hz for all participants. They also confirmed that IAF was a stable trait when recorded over multiple occasions. However, they did not assess whether the individualised strategy actually resulted in better entrainment (or enhanced resultant perceptual effect), but rather stated it was an assumption that optimal stimulation frequency would be the peak frequency during the task. Another study into the effect of tACS on visual perception showed stimulation at IAF, but not stimulation at IAF +/- 2 Hz, resulted in entrainment and effect on task performance (Kemmerer et al., 2022). This supports the notion that, in this paradigm at least, matching IAF should be the goal and mismatches of the size which would occur without an individualised strategy (i.e. +/-2 Hz) have relevant consequences.

There are also findings from clinical studies of entrainment as a therapy which point to the significance of IAF. A report of 68 people receiving 10 Hz rTMS as a treatment for major depressive disorder found a significant correlation between the degree of IAF-stimulation mismatch and the clinical outcome after the 30 session treatment course, as measured by change from baseline on the self-reported 30-item Inventory of Depressive Symptomatology (Corlier et al., 2019). The study does not report on any differential effect of TMS on EEG parameters such as alpha power, and the association is an observational finding so potentially prone to confounding. For example, it could be that those with the lowest IAF compared to the healthy population benchmark of 10 Hz (who are also those with a higher mismatch) also had more treatment resistant depression, and therefore fared worse clinically. The finding has since been replicated (Roelofs et al., 2021) with added detail that the relationship between IAF and clinical outcome was best described by a quadratic curve with a peak

at 10 Hz, supportive of the hypothesis that it is specifically the IAF proximity to stimulation rather than the absolute value of IAF that was important.

5.2.2.4 Closed-loop systems and entrainment

Another method of individualisation would be a closed-loop system, whereby stimulation parameters (here, frequency) vary in real time in response to an on-line physiological signal (here, EEG derived IAF). Whilst there are no examples of this specifically in entrainment, there are adjacent stimulation modalities which are useful to examine. Closed loop stimulation has been used to increase the amplitude of specific oscillations by delivering precisely phase-locked stimuli. The stimulus arrives as a specific point in the waveform of the ongoing oscillation, thereby modifying its characteristics. The area of enhancement of slow oscillations in sleep is within this field, as recently reviewed by Fehér et al (2021). The work most closely related to the present studies is from Hebron and colleagues (2024) which demonstrates a method of closed loop alpha modulation by auditory clicks phase aligned to different points of the alpha waveform. Termed “alpha Closed Loop Auditory Stimulation”, it shows that clicks delivered in different phase positions result in differential effects on alpha power and frequency, and moreover that these differences have behavioural consequences. The stimulation in this case is not rhythmic, and not operating via entrainment. Entrainment involves an external driving rhythm to which the ongoing oscillations of a system phase align, rather than the externally applied force itself being phase aligned. Current closed loop methods are therefore distinct from entrainment, but they do expand the landscape of potential neuromodulatory techniques to influence brain oscillations. What a closed loop system may look like in entrainment would be periodically sampling IAF during a stimulation session and modulating the stimulation frequency accordingly, therefore would not be as ‘tightly’ closed-loop as the phased locked systems, and technically more easily achieved.

5.2.2.5 Frequency matching; how close is close enough?

The question of how closely the frequency of the driving stimulation and IAF need to match is key to understanding the relevance of individualisation. There is no universal answer to this since it depends on multiple variables. Modelling (Otero et al., 2022) and experimental (Notbohm et al., 2016) studies show that the likelihood of achieving entrainment is a function of both the proximity of the stimulation frequency match with endogenous oscillations, and level of stimulation intensity. So, a stimulation of strong intensity can be further from the IAF and still entrain (or to put it another way, can entrain a wide range of frequencies), whereas precisely tuned stimulation does not have to be so

intense. The theoretical underpinning of this relationship is the Arnold tongue phenomenon, which can be visualised as the triangular area of high entrainment likelihood when the two parameters of frequency match and stimulation intensity are graphed (Notbohm et al., 2016). One practical implication is that individualisation may hope to optimise entrainment by varying frequency or intensity (within individual's comfort) or both. Frequency can be tailored to IAF at the outset, based on its stability as a trait, or modulated in real time with closed loop feedback. Intensity could theoretically be varied by changing brightness, volume, or potentially the use of simultaneous audio and visual stimulation, rather than one or the other, all of which require testing.

5.2.2.6 The costs of individualisation

There are arguments in favour of individualised stimulation and practical ways to go about it, but there are also potential downsides to proceeding in this way. In the above example of rTMS for major depressive disorder, proximity of IAF to 10 Hz explained just 6.3% of the variance in treatment outcome. This may not reflect the potential size of the available gains of personalisation in sensory stimulation for chronic pain, a different modality and different clinical area, but it raises the issue that personalisation may provide only a marginal gain in effectiveness. This comes at the cost of significantly increasing the complexity of the intervention itself and associated healthcare or professional time required. Individualisation by measuring baseline IAF incurs the cost and burden of performing some form of baseline EEG. Closed-loop stimulation would require the device itself to incorporate EEG, which increases its cost and impedes scalability, and possibly increases setup time and difficulty for the user, although we have demonstrated that fundamentally the stimulation and EEG combination can be acceptable. The astonishingly high prevalence of chronic pain outlined in Chapter 1 means that greatest overall health impact may result from a simpler intervention which can be widely scaled.

In summary, there are compelling reasons to individualise stimulation, with potential enhanced neurophysiological effect, but the increased complexity of the intervention would need to be justified in terms of scalability. To rigorously address this will require further studies to quantify the added benefit and costs of increasing complexity, meaning potentially multiple intervention arms, and including assessment of their differential health economic impact.

5.2.3 Clinical effect is present but appears small in magnitude

The intention of hBET is to be a useful tool to help people with chronic pain, primarily by the action of reducing pain itself, with the hypothesised successive benefit to sleep intended to augment this effect. However, reductions in pain

seen in both the open label study reported in Chapter 2 and the crossover study reported in Chapter 4, whilst statistically significant, were of an absolute magnitude of about 0.5 points on a 0–10 numerical rating scale. This is not a large change. Furthermore, participant reported measures of sleep structure and quality improved, but the instrumented measures largely did not. How should this be interpreted and what does it mean for whether the work should be taken forward? Firstly, these are feasibility studies, not primarily designed to assess clinical efficacy. Nevertheless, research funding is a limited resource, so preliminary work is naturally scrutinised to assess the degree of promise of the intervention. It could be said that seeing a difference at all, especially when compared to a sham which thoroughly controlled placebo, over an intervention period of just 2 weeks with respect to a mean history of pain of approximately 10 years, is surprising and encouraging. To comprehensively study clinical effect would require both longer intervention period (e.g. 6 months) and follow up period (e.g. 12 months). The concept that the sleep improvement yielded by reducing night pain should itself subsequently unlock further relief of pain and other symptoms remains a hypothesis at this point, albeit one supported by a wide literature, and will require these longer study durations to substantiate. The finding that sleep quality improved cumulatively over the intervention use period in the crossover study is a small hint in favour of the notion that larger benefits may be available from longer term use. However, an alternative interpretation is that the intervention simply has a small benefit at group level and little effect on sleep. Whilst longer studies may provide time for the interventions action to accrue larger effects, another large scale pattern in health research is that small studies often yield larger treatment effects than larger studies (Dechartres et al., 2013). For consistency with the aims and methodologies used, these studies should not be overinterpreted; they have not proven clinical efficacy; but neither should they be dismissed. The arguments presented above, regarding the likelihood that the physiological action of the intervention itself can be optimised by individualisation, suggest it would be prudent to withhold judgement on the ultimate magnitude of the clinical effect available. The triangulated evidence so far acquired from different methods provides strong assurance that alpha entrainment is acceptable, not detrimental to symptoms, with a promising indication of improvement to symptoms; this can be viewed as satisfactory for this stage of development.

Further analyses of the data reported in these studies could also be revealing regarding the full potential magnitude of effect available from sensory alpha entrainment. Exploring the effect of age as a covariate in entrainment success and clinical effect is justified based on knowledge of changes in IAF and connectivity in aging (Scally et al., 2018). If age is an important factor this would

be a further argument for personalisation of stimulation. The spectral power analyses in Chapter 4 report only on alpha band changes, in line with alpha entrainment being the mechanism under study. However, analysis of other frequency bands may reveal more about the cross-frequency response to stimulation. Other low frequency bands (delta, theta) have previously been found to be of low power in people with fibromyalgia compared to healthy controls, whilst beta power is sometimes found to be high (Silva-Passadouro et al., 2024). Furthermore, it has been observed that alpha/theta and alpha/beta power ratios behave differently in people with chronic pain undergoing evoked pain, compared to healthy controls (Ding et al., 2024). Future advancements in the neurophysiology of pain may reveal more nuanced neuromodulatory targets than alpha power alone. However, based on the aims of these studies it was appropriate to focus primarily on alpha spectral power changes.

The broader context for assessing the adequacy of a pain intervention's clinical benefit must be the nature of the condition, and the comparative performance of other available treatments. The limitations of pharmacological options are well established and are a motivation for this investigation. For example, in the use of gabapentinoids in fibromyalgia, the number needed to treat for one partial response (30% improvement) has been estimated at 7 to 8.5 (Häuser et al., 2009; Tzellos et al., 2010). Chronic pain is a complex condition with individual perpetuating factors which span the bio-, psycho- and social domains. If hBET ultimately has a place in clinical care it will not be as a panacea but part of an ecosystem with other interventions including lifestyle changes, talking therapies, other technological interventions and pharmacological treatments. It may be that hBET works best alongside something else, for example CBT-I, or only when something else has been tried, such as a pain management programme. If this technology does in future progress to effectiveness trials, the questions should include 'for whom is this treatment likely to be beneficial?', and 'alongside what?'. Effectiveness-implementation hybrid trial design (Curran et al., 2012) is an approach to simultaneously assess effect on clinical outcomes and address how it might be operationalised a health system, for optimal clinical and cost effectiveness.

5.3 Limitations

The studies presented in this thesis are subject to several limitations. The limitations intrinsic to the study designs are discussed in the individual chapters. Other limitations were the result of choices investigators made, and will be scrutinised here. One is the short intervention duration in each study, and the

lack of long-term follow up. A recent systematic review and meta-analysis of tDCS for pain relief in fibromyalgia found on meta-regression that the protocol duration was the only factor positively associated with effect size; specifically, protocols lasting four weeks or longer were superior to shorter ones (Teixeira et al., 2023). This could correspond a limitation to these studies from an effectiveness perspective, but as feasibility studies they fulfilled their aims. Nevertheless, longer durations would be needed to be confident the full clinical effect was reached, and longitudinal follow up to characterise whether response is sustained. These data would be essential to make any conclusions as to the effectiveness and cost-effectiveness of the intervention.

Several patient-reported outcome measures in the form of questionnaires and daily diaries were used in these studies. This is appropriate and unavoidable as the measurement of pain (and other symptoms) necessarily involves the individual's expressed report, but all instruments carry inherent limitations. These studies used a daily diary rating of pain at night and pain over 24-hours, both reported in the morning on an eleven-point numerical rating scale. This had the strength of being quick and easy for the participant to complete, allowing daily repeated measures, but incurs a limitation regarding recall, especially regarding the effect of sleep on the recall of night pain. The numerical rating scale has been found to be more sensitive to detecting change than two common alternatives, the visual analogue scale and verbal rating scale (Williamson and Hoggart, 2005). The Brief Pain Inventory was also used to measure pain, administered weekly. This has been used many times in studies of fibromyalgia (Williams and Arnold, 2011). Here, in both studies the Pain Interference score improved to larger degree than the Pain Severity score, where the change was not statistically significant. This is in keeping with psychometric validation findings that these are measuring separate domains (Tan et al., 2004). The Pain Interference score is derived from questions about the impact of pain on various activities and functions, whilst the Pain Severity score is an average of four 0-10 NRS pain ratings. This differential responsivity may reflect higher sensitivity to change of the impact on specific daily functions compared to an overall score, in people who have had pain for many years. This could also be related to qualitative report in Chapter 3 that people may make compensatory behaviour changes in response to effective analgesia, resulting in doing more functionally (improved pain interference), consequently maintaining their 'level' of pain (unchanged pain severity). Regarding sleep quality, this was assessed with the PSQI questionnaire, which has been validated in Spanish cohort with fibromyalgia (Hita-Contreras et al., 2014) and found to be suitable for use in this condition (Climent-Sanz et al., 2020). It is widely used, offering comparisons across many studies, and takes only 5-10

minutes to complete. The wording of the PSQI refers to ‘the past month’, which aligned well with the duration of the first study but not with the crossover study, in which respondents were instructed to consider the previous 2 weeks (the duration of each condition) instead. This change in reference duration is a potential weakness, however similar magnitude of improvement was seen in both studies (16.0 to 12.5 vs 15.2 to 11.8).

Related symptoms were also measured: fatigue with the MFI; and anxiety and depression with the HADS. These have both been found suitable for use in fibromyalgia (Ericsson and Mannerkorpi, 2007; Vallejo et al., 2012). However, this range of measures does not capture all of the domains in the core set for fibromyalgia proposed by an expert working group (Mease et al., 2009), lacking assessment of physical functioning, tender points and cognition, which is a limitation to these studies.

A further limitation is the change in inclusion criteria from any non-cancer chronic pain in the first study to fibromyalgia specifically in the crossover study. This introduces a caveat when synthesising the results across the studies, but not a critical weakness. Firstly, 93% of those included in the first study did have fibromyalgia or chronic widespread pain, and secondly assessments of acceptability, user feedback and feasibility of research processes are less likely to be sensitive to pain diagnosis. In contrast, the assessment in future studies of neurophysiological and clinical efficacy may be more dependent on the underlying pain mechanisms, and hence selection by specific diagnosis would be more important. Fibromyalgia was chosen to represent a chronic pain cohort especially characterised by nociplastic pain. Future studies may continue the focus on fibromyalgia or may include other pain cohorts (such as focal musculoskeletal pain) depending on the hypotheses, but these should remain distinct groups. The logic of focussing on a single diagnosis to reduce heterogeneity in underlying pain mechanism could be extended by selecting participants based on certain theory-driven characteristics. For example, a trial of a neuromodulatory strategy to increase IAF might select patients with slow IAF, to enrich the sample with individuals most likely to respond. Possible strategies to personalise neurostimulation by rTMS for pain have been recently reviewed (Ciampi de Andrade and García-Larrea, 2023) and include targeting TMS frequency and phase to endogenous target oscillations (analogous to the suggestion in 5.2.2.4) and selection based on pain phenotyping using questionnaires. These concepts could be applied to trial selection criteria or defining subgroups. The costs of narrowing selection criteria are reduction in generalisability and increased difficulty translating the results into clinical services. However, increased personalisation may be an inevitable trend in all

pain therapeutics, if the only way to overcome frequent non-response and poor group-level effects of pain therapies is to tailor treatments to the patient-specific mechanisms at play. This would be an argument in favour of more tightly defining selection criteria or *a priori* subgroups in trials.

The design choice to offer participants the option of using either audio or visual stimulation was a decision made to increase acceptability, which had demonstrable benefits, but can also be seen as a limitation in terms of interpretation, as discussed in section 5.2.

A challenge to the interpretation of the study in Chapter 4 is how confidently the neurophysiological and clinical changes seen can be attributed to the intervention, rather than residual placebo effect. The main methodological strength in favour of the positive interpretation is the use of a sham control as the main comparison. The sham was designed to provide a very similar sensory experience but not be capable of entrainment. It is argued to have been effective based on the feedback of users that they could not distinguish it from active stimulation and that they engaged with both as potential treatments, not with the expectation of an 'inactive' period. These impressions were provided in brief, structured, verbal feedback, and not quantified, and also relied on participants' recall, which can be seen as a limitation. Since intervention order was balanced and randomised the issue of recall introduces no systematic bias. If, however, some feature of the sham stimulation lowered user expectations compared to the active stimulation, then this would leave room for placebo effect. However, this interpretation goes against the stated experience of users and attributes a lot of significance to what, at most, are subtle differences in the experience of using sham stimulation compared to active. The alternative explanation asserted in Chapter 4 is that the small clinical effect was indeed the result of alpha entrainment, which is in keeping with the background literature outlined in Chapter 1. It can also be seen in the light of the interesting finding that the sham stimulation did result in an increase in alpha power above baseline, although smaller than that of active stimulation. Placebo analgesia (the expectation of pain relief) has been found to increase alpha power (Huneke et al., 2013). This indicates that alpha is involved in endogenous pain modulation (which supports it as a neuromodulatory target). Crucially, the alpha power increase in the active stimulation condition significantly exceeded that in sham. The most straightforward explanation is that both conditions benefitted from some expectation of pain relief, and entrainment produced an effect above and beyond this. That is to say, the sham condition fulfilled its function as intended. Contemporaneous quantification of participants' belief about each condition could have further clarified the sham's performance.

5.4 Summary and conclusion

To summarise how the present findings direct future research as explored in the above sections, there are two main areas to address; first intervention optimisation and then moving to assessment of efficacy and effectiveness. Specific emergent uncertainties have been identified for the intervention optimisation phase to address, under the broad question of whether individualisation of stimulation significantly improves performance. Within this are the specific issues of whether either baseline IAF assessment or closed loop monitoring improve entrainment over open loop; whether individualisation of stimulation intensity can be harnessed to improve entrainment; and how these design developments can simultaneously improve user experience and acceptability. Following this, the question of what clinical benefit the improved intervention offers for people with chronic pain can be addressed, informed by the learning from these studies, in a longitudinal, home-based, randomised, controlled study. Therefore, there is now a logical and achievable path to providing definitive direction to the research and clinical community on whether sensory alpha entrainment is a viable treatment for individuals with chronic pain and sleep disturbance.

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Appendix A. HRA approval

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

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06 November 2019

Dear Professor Jones

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Home-based Brainwave Entrainment Technology (hBET) for management of chronic pain and sleep disturbance. A feasibility study.**
IRAS project ID:	**261462**
Protocol number:	**NHS001542**
REC reference:	**19/YH/0313**
Sponsor	**University of Manchester**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report

(including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **261462**. Please quote this on all correspondence.

Yours sincerely,
Christie Ord

Approvals Specialist

Email: hra.approval@nhs.net

Appendix B. Supplementary material to Chapter 2

B.1 Audio and Visual hBET modalities disaggregated

Table B-1 Sleep and pain diary results for Audio hBET (n=23)

	Mean (SD) at Baseline (161 nights)	Mean (SD) in Audio hBET condition (458 nights)	Change (Audio compared to baseline)	P value for paired difference* between audio and baseline	Effect size
Average pain over 24 hours (0-10 NRS)	6.5 (1.9)	6.3 (1.8)	-0.2	0.0949	
Average pain at night (0-10 NRS)	6.0 (1.9)	5.5 (2.1)	-0.5	**0.0441**	0.45**
Sleep Onset Latency (mins)	51.1 (39.7)	38.7 (27.0)	-12.3	**0.0056**	0.58***
Wake After Sleep Onset (mins)	38.0 (32.9)	28.7 (26.6)	-9.3	**0.0459**	0.42***
Total Sleep Time (mins)	390.3 (82.1)	414.5 (87.3)	24.2	**0.0234**	0.51**
Sleep efficiency (%)	74.4 (11.3)	78.8 (11.2)	4.4	**0.0007**	0.82**
Median quality rating (0-5 scale)	2.4 (1.0)	2.4 (1.0)	0.0	1	
Median refreshed rating (0-5 scale)	1.5 (0.9)	2.2 (1.1)	0.6	**0.0018**	0.7***

Median number of awakenings	3.1 (2.3)	2.3 (2.1)	-0.8	**0.0108**	0.5***
% nights with quality rated 3+	52.2 (30.6)	55.4 (32.2)	3.2	0.6115	
% mornings with refreshed rated 3+	26.6 (23.0)	43.7 (32.3)	17.1	0.2173	

*Paired t-test for continuous and normally distributed variables, Wilcoxon sign rank test for non-continuous or non-normally distributed variables

**Cohen's d for t-tests

***r for Wilcoxon sign rank tests

Table B-2 Sleep and pain diary results for Visual hBET (n=13)

	Mean (SD) at Baseline (91 nights)	Mean (SD) in Visual hBET condition (175 nights)	Change (Visual compared to baseline)	P value for paired difference* between Visual and baseline	Effect size
Average pain over 24 hours (0-10 NRS)	6.1 (2.1)	5.5 (1.7)	-0.6	0.0884	
Average pain at night (0-10 NRS)	5.6 (2.1)	5.3 (2.0)	-0.3	0.2909	
Sleep Onset Latency (mins)	56.6 (51.0)	37.2 (33.7)	-19.4	0.0418	0.64**
Wake After Sleep Onset (mins)	23.3 (27.1)	17.4 (27.5)	-5.9	0.2783	
Total Sleep Time (mins)	366.1 (81.3)	408.1 (97.9)	42.0	0.0303	0.69**
Sleep efficiency (%)	76.9 (12.0)	81.8 (11.4)	4.8	0.0581	
Median quality rating (0-5 scale)	2.9 (0.6)	3.0 (0.4)	0.1	0.7127	
Median refreshed rating (0-5 scale)	1.5 (0.8)	2.7 (0.6)	1.1	0.0022	0.85***
Median number of awakenings	2.9 (2.8)	2.3 (2.9)	-0.6	0.0473	0.55***

% nights with quality rated 3+	62.6 (27.7)	72.2 (16.2)	9.5	0.2983	
% mornings with refreshed rated 3+	27.5 (17.0)	55.3 (23.3)	27.8	0.0042	0.79***

*Paired t-test for continuous and normally distributed variables, Wilcoxon sign rank test for non-continuous or non-normally distributed variables

**Cohen's d for t-tests

***r for Wilcoxon sign rank tests

Appendix C. Supplementary material to Chapter 3

C.1 hBET User experiences thematic template

Numbers mean the number of individual participants contributing to this code/total number of excerpts contributing to this code.

C.1.1 Prior beliefs, experiences and expectations

- **Impressions of pain-sleep relationship**
  - Attention to pain, lack of distractions (worse at night) 1/4
  - Pain and sleep are closely interrelated 13/20
  - Pain impacting sleep is the main effect 8/8
  - Activity interacts with the sleep pain relationship 4/4
  - Mood interacts with the sleep pain relationship 10/13
  - Stress and restlessness prevent sleep 3/3
  - Unrefreshing sleep has mental, emotional impact 3/3
  - Bed as a refuge from pain 1/1
  - Dread of bed time 3/3
  - Body -mind dyssynchrony; brain 'wakes up' when wants to go to sleep 2/2
  - Body tired but mind racing 3/4

- **Previous experiences of therapies and strategies tried**
  - Medications 15/32
    - Achieved some benefit from medications 6/7
    - Medications, with some good effect 6/7
    - Concern about medications 12/23
      - Bad side effects with meds given for sleep 1/1
      - Bad side effects with pain medications 3/5
      - Doctors reluctant to provide sleeping meds 2/2
      - Mindset - journey of realisation that meds alone wont work 5/5
      - Reluctant to take sleeping tablets 1/1
      - Trying to reduce pain medications 2/5
      - Worried about tolerance or harm from medications 3/4
    - Medications have been the mainstay of treatment 7/9
  - Non-medications 26/68
    - Sleep hygiene; some awareness but generally poor application 18/23

- aware of sleep hygiene but poor application 4/4
- existing good sleep hygiene behaviours 5/6
- existing poor sleep hygiene behaviours 11/13

- Experience with other audio or visual interventions 15/20
- Experience with other non-drug interventions 19/33
- Tendency for short term use and novelty effect 4/4
- Stigma around using or seeking alternative treatments 2/2
- Tried everything they can find (but nothing helps) 5/6

❖ **Expectations of hBET**

- Positive, hopeful, excited 10/14
  - Excited- to get off pain meds 2/2
  - Hopeful it would improve mood, stress 3/3
  - Positive expectations based on prior knowledge and beliefs 6/9
- Open minded, tried to avoid high expectations 4/5
- Degree of scepticism 5/6
- Will try anything 7/8
  - Any improvement would be good so willing to try anything 3/3
  - Will try anything non-drug related 4/5
- Higher expectations of audio than visual 7/10
  - Expected to feel dizzy with Visual 2/2
  - Negative expectations of visual 5/6
  - Positive expectations of audio due to previous helpful audio stim 2/2
- Reflective on own expectations 3/4
  - Awareness that taking action can induce placebo 1/1
  - Doing something proactive is helpful (placebo) 1/1
  - Effect mediated by understanding of mechanism 1/1
  - Overly high hopes are a problem 1/1
- low expectations doesn't believe pain will ever change 1/4

C.1.2 Experience of using hBET

❖ **Audio - experience of use and impact on symptoms**

- **Effect on pain**
  - No benefit to pain despite tolerating well 4/5
  - Positive effects on pain 7/21
    - Felt it was a cumulative effect 1/2
    - Helps around flares or periods of stress 1/1
    - Mitigates effect of flares, quicker recovery 2/2
    - More refreshed, delayed pain build up 1/1

- Pain improved even though sleep no longer 1/1
- Pain less widespread and more manageable 1/2
- Reduced pain 7/12

➢ **Effect on sleep**

- Noticed no benefit to sleep 2/2
- Positive effect on sleep 15/56
  - better sleep consolidation 8/11
  - better total sleep time 4/4
  - blocks out other thoughts 4/6
  - Deeper sleep 3/4
  - helped getting to sleep 10/15
  - More refreshed 6/7
  - reduced the anxiety of going to sleep 1/3
  - used less of other treatments (alcohol, meds) 2/4
  - Went to sleep whilst wearing it 2/2

➢ **Usability**

- App bug; can't lock the phone 2/2
- didn't disturb sleeping partner 1/1
- didn't follow protocol - used when not ready for sleep 3/4
- displaced another existing strategy (listening to music) 1/1
- Found it unpleasant, irritating, distracting 8/11
- headband problems - moves position, uncomfortable 9/10
- Liked the headband 8/9
- pitch considerations 6/7
- **Side effects 4/5**
  - Occasionally amplified tinnitus 1/1
  - Transient dizziness 1/2
  - Transient feeling sick 1/1
  - Transient restlessness 1/1
- straightforward to use 11/17
- timed programme thoughts 7/7
- timescale of effect; accumulative vs rapid etc 4/5
- used alongside guided meditation, breathing ex – helpful 2/3
- volume considerations 5/5
- worked better when stopped paying attention to it 2/2

➢ **Wider effects** 14/30

- Able to be more active in the day 4/5

- Improved mood, positivity 1/1
- positive effect despite stressful circumstances 3/3
- Relaxing 8/12
- wants to continue using it 7/9

❖ **Visual- experience of use and impact on symptoms**

➢ **Effect on pain**

- able to deal with pain better 1/1
- less stiff and painful in the morning 1/2
- No or minimal effect on pain 10/11
- worsened pain 3/5

➢ **Effect on sleep**

- No or minimal effect on sleep 5/6
- Positive effects 9/27
  - better consolidated sleep 6/9
  - blocks out other thoughts 1/1
  - helped get into a deep sleep 1/2
  - helped get to sleep 8/14
  - More refreshed 1/1

➢ **Usability**

- App bugs; accidentally pressing screen 3/3
- Basically relevant and practical, apart from headset issue 1/1
- Effect on sleeping partner was manageable4/5
- Headset issues
  - comfort is deciding factor in preferences 1/1
  - didn't like having something over eyes 2/4
  - Faffy 1/2
  - headset comfortable 5/5
  - headset uncomfortable, heavy, clunky, cumbersome 15/20
  - suggestion for alternative to headset 7/11
  - tolerated headset but couldn't fall asleep wearing it 1/1
- more engaging than meditation 1/1
- not relaxing, not pleasant, didn't like it 5/7
- Pleasant, relaxing, like a trance 3/4
- **Side effects 6/10**
  - Bad mood in morning with visual 1/2
  - Headaches with visual 5/8
- Straightforward to use 3/3
- Timescale - effect tended to improve or build up 4/7

- Timescale - effect tended to wear off 1/2
- wanted more instruction in how to interact with it 1/1

➢ **Wider effects 4/5**

- helped mood, given hope 2/2
- wanted to continue using it 3/3

C.1.3 Research processes

❖ Training was helpful and appropriate 13/13
❖ Remote processes generally successful and convenient 5/5
❖ Reflections on completing sleep diary 25/30
❖ Questionnaires generally relevant and non-burdensome 15/19
❖ Considerations on app-based data reporting 7/7
❖ Using the actigraphy watch 15/16
❖ Research timescale issues; flares and fluctuations 5/6
  ➢ Flares or fluctuations as possible confounding factor 3/4
  ➢ menstrual cycle influences pain 1/1

Appendix D. Supplementary material to Chapter 4

D.1 Sensitivity analysis of auditory stimulation only

A sensitivity analysis was performed to examine whether the one participant who used the visual modality affected the overall result. Excluding this participant made no difference to the key clinical outcomes, as shown in Table 4.5. In keeping with the main analysis, average pain at night, sleep quality score, total sleep time measured with Dreem and sleep onset latency on sleep diary were all significantly improved in active stimulation compared to sham, by similar magnitudes of effect. The confidence interval around the estimate for the effect on Refreshed Score narrowed slightly, just taking this result over an alpha threshold of 0.05 for statistical significance, but the magnitude of the effect of active stimulation was almost unchanged (improvement of 0.22 compared to improvement of 0.20 on a 0–5 scale). Also, total sleep time as measured on actigraphy slipped just under the 0.05 threshold, but the effect estimate is not meaningfully different, and total sleep time measured in all three ways (diary, Dreem headband and actigraphy) is essentially unchanged on this sensitivity analysis.

Table D-1 Results of sensitivity analysis including only participants who used the audio mode.

Sensitivity analysis removing the one participant using Visual mode	Comparison of Active - Sham simulation (95% confidence interval)		P value
Daily measures of pain and sleep quality (n=12)			
Pain at night (0-10 NRS)	-0.50	(-0.77 to -0.23)	**<0.001**
Pain over 24 hours (0-10 NRS)	-0.22	(-0.52 to 0.09)	0.160
Sleep quality score (0-5 NRS)	0.41	(0.15 to 0.66)	**0.002**
Refreshed score (0-5 NRS)	0.22	(0.01 to 0.43)	**0.041**
Sleep diary (n=12)			
Total sleep time (minutes)	-5.3	(-29.9 to 19.3)	0.673
Sleep onset latency (minutes)	-8.2	(-14.0 to -2.3)	**0.006**
Sleep efficiency (%)	0.73	(-2.5 to 4.0)	0.656
Wake after sleep onset (minutes)	-4.1	(-9.8 to 1.5)	0.149
Dreem headband sleep measures (n=8)			
Total sleep time (minutes)	23.0	(0.4 to 45.6)	**0.047**
Sleep onset latency (minutes)	-2.3	(-8.2 to 3.5)	0.432
Sleep efficiency (%)	1.7	(-0.3 to 3.7)	0.102
Wake after Sleep onset (minutes)	-2.8	(-10.4 to 4.8)	0.463
Actigraphy sleep measures (n=12)			
Total sleep time (minutes)	22.8	(0.7 to 46.2)	0.057
Sleep onset latency (minutes)	-0.9	(-5.5 to 3.7)	0.698
Sleep efficiency (%)	1.2	(-0.3 to 2.6)	0.117
Wake after sleep onset (minutes)	3.4	(-0.9 to 7.8)	0.123

D.2 EEG channel correlation and disaggregated results

The five bipolar channels generated by the Dreem headband are: F7-O1 (Channel 1), F8-O2 (Channel 2), F8-F7 (Channel 3), F8-O1 (Channel 4) and F7-O2 (Channel 5). The alpha results obtained from the four fronto-occipital channels were well correlated with one another. The channels sharing an occipital electrode (1 and 4, 2 and 5) were most strongly correlated (correlation coefficient of 0.87 and 0.88 respectively), followed by the channels sharing a frontal electrode (1 and 5, 2 and 4; correlation coefficients 0.77 and 0.78) and less well correlated were the channel pairs sharing neither electrode (1 and 2, correlation coefficient 0.71; 4 and 5, correlation coefficient 0.68). This is consistent with a predominantly occipital origin of alpha, as would be expected. The frontal channel, F8-F7 (Channel 3), correlated poorly with the other four (0.27-0.32), and behaved markedly differently, showing much lower and more dispersed values for alpha power (negative overall result in the log base 10 scale) as shown in Table 4.6. Since the hypothesis motivating this study is about increasing global alpha power, this is judged to be better reflected in the fronto-occipital channels, and the main analysis focussed on these, modelled as a joint multivariate outcome.

Tables 4.7 and 4.8 show the results of the analysis of alpha power compared to baseline, and the direct randomised comparison of active and sham stimulation, each by channel.

Table D-2 Comparison of overall alpha power and standard deviation in each of 5 bipolar channels

Channel	Overall average alpha power (dB)	SD
1	4.94	2.87
2	4.81	3.19
3	-3.65	7.06
4	5.04	2.82
5	4.61	3.32

Table D-3 Alpha power in each condition compared to baseline period, by channel.

Effect of stimulation on alpha power compared to baseline											
	Active stimulation				Sham stimulation				Washout			
Channel	Estimate	95% CI		P	Estimate	95% CI		P	Estimate	95% CI		P
1	1.94	1.27	2.60	<0.001	1.40	0.72	2.08	<0.001	0.63	-0.28	1.55	0.174
2	1.55	0.79	2.31	<0.001	0.90	0.14	1.66	0.02	0.63	-0.42	1.68	0.24
3	3.13	0.82	5.44	0.008	2.90	0.59	5.21	0.014	2.49	-0.67	5.66	0.122
4	1.49	0.84	2.13	<0.001	1.20	0.55	1.85	<0.001	0.40	-0.49	1.30	0.372
5	1.92	1.14	2.70	<0.001	1.36	0.59	2.14	0.001	0.85	-0.22	1.92	0.118

Table D-4 Randomised comparison of alpha power with active vs sham stimulation, by channel

	Direct comparison of active and sham stimulation			
Channel	Estimate	95% CI	P	Cohen's d
1	0.48	0.01 to 0.96	0.044	0.19
2	0.61	0.05 to 1.17	0.034	0.20
3	0.22	-1.54 to 1.99	0.803	0.08
4	0.27	-0.18 to 0.71	0.245	0.11
5	0.51	-0.02 to 1.05	0.06	0.17

D.3 Alpha power by participant

Inspection of fronto-occipital alpha power characteristics by participant is shown in Figure 4.4. This demonstrates two participants with markedly different overall profiles, motivating the exploration of whether baseline alpha characteristics should inform intervention, as explored in the analysis leaving these two participants out.

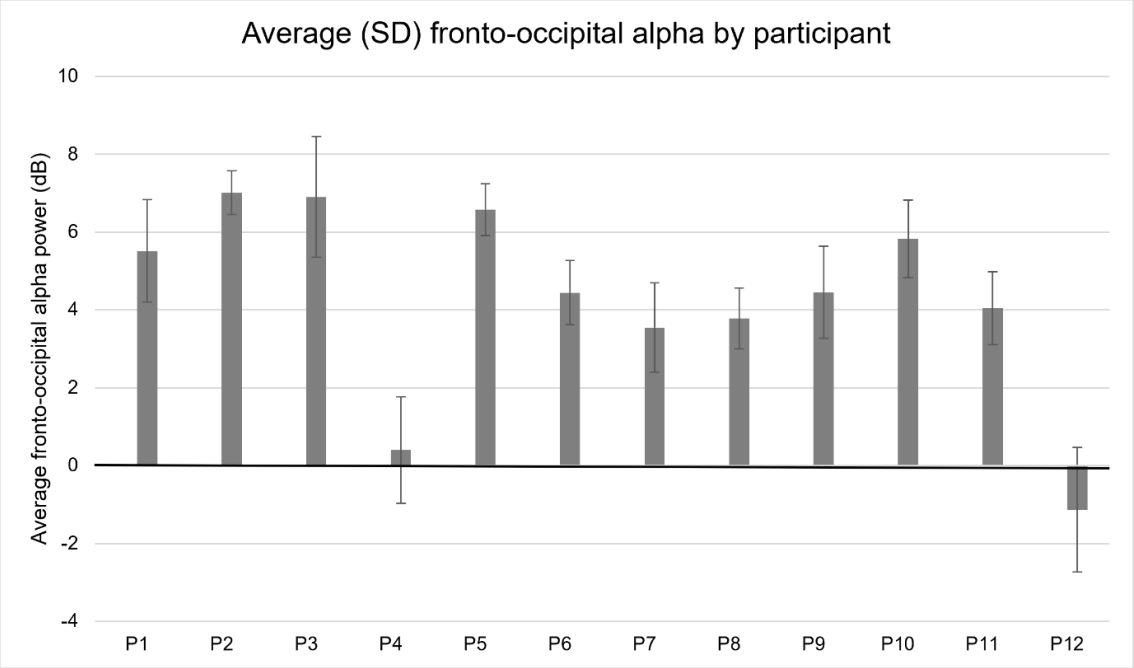

Figure D-1 Participant by participant inspection of overall detected fronto-occipital alpha power. P#, Participant number. SD, standard deviation.

D.4 Sleep architecture results from Dreem headband

The duration and proportions in each sleep stage in each condition, and the comparison of active and sham stimulation are shown in Table 4.9.

Table D-5 Full sleep architecture results

Dreem sleep staging (n=13)	Baseline		Sham stimulation		Active stimulation		Comparison of Active - Sham simulation			
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Estimate	95% confidence interval		P value
N1 duration	33.3	(12.2)	29.6	(12.2)	33.6	(13.7)	2.98	-0.05	6.02	0.054
N2 duration	231.6	(69.7)	208.2	(80.2)	221.9	(80.2)	18.65	3.04	34.25	0.019
N3 duration	61.0	(34.5)	58.8	(34.6)	58.5	(36.3)	3.22	-3.71	10.14	0.36
REM duration	103.6	(46.5)	103.2	(41.8)	105.8	(50.9)	-0.69	-11.21	9.83	0.897
NREM duration	325.9	(68.6)	296.6	(80.5)	313.9	(77.8)	24.69	6.85	42.53	0.007
N1 %	8.2	(3.8)	7.8	(3.8)	8.2	(3.5)	0.10	-0.69	0.88	0.805
N2 %	53.4	(11.5)	50.8	(12.4)	52.0	(13.0)	1.81	-0.62	4.24	0.143
N3 %	14.5	(8.7)	15.2	(9.4)	14.5	(9.5)	0.18	-1.47	1.83	0.83
REM %	23.9	(10.3)	26.2	(10.6)	25.3	(12.2)	-2.08	-4.28	0.12	0.064
NREM %	76.1	(10.3)	73.8	(10.6)	74.7	(12.2)	2.08	-0.12	4.28	0.064

D.5 Day by day change in pain at night

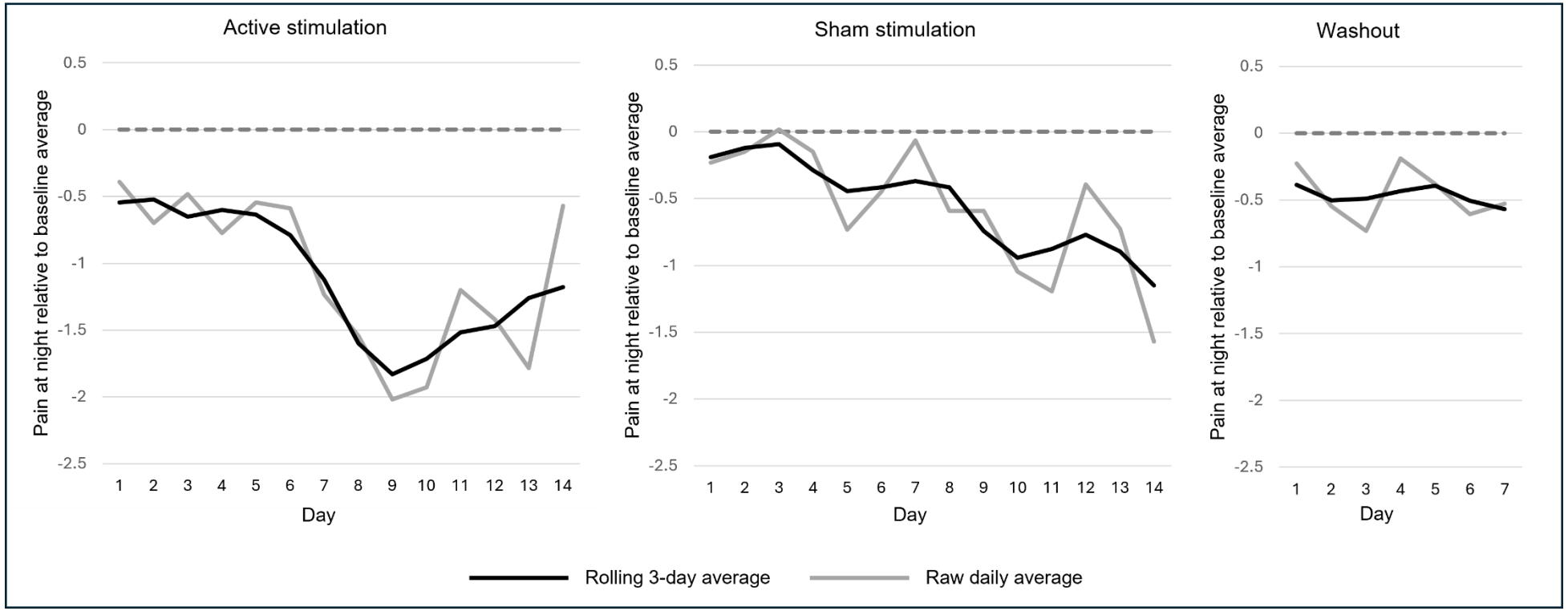

Figure D-2 Pain at night score (0–10 numerical rating scale), referenced to individual baseline and averaged across participants, shown for each sequential day in each experimental condition. Dotted line indicates no change from individual baseline average, negative scores below this line indicate an improvement in pain at night.