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Timed acoustic stimulation of sleep in relapsing-remitting multiple sclerosis

Submission date 11/08/2021	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 12/08/2021	**Overall study status** Completed	
Last Edited 07/09/2021	**Condition category** Nervous System Diseases	

Plain English summary of protocol

Background and study aims

Multiple sclerosis (MS) affects about 110,000 people in the UK and almost 2.5 million worldwide. Immune system abnormalities cause damage to nerves in the brain and spinal cord and their protective covering or 'insulator' known as myelin. This leads to disability which can include visual disturbance, lack of coordination, bowel and bladder symptoms and paralysis. Fatigue, depression and cognitive impairment occur in up to 95% people with MS with a negative impact on quality of life and employment. Over 70% of people with MS report sleep problems and these have been associated with MS-related
symptoms and harmful effects on myelin in disease models. Currently, sleep abnormalities are poorly treated; available medications are of limited effectiveness and the side effects of treatment may make symptoms worse due to increased daytime sleepiness and confusion. In healthy people, improvements in sleep quality have been demonstrated with the delivery of soft sounds timed to occur during particular stages of sleep and coordinated with brain wave activity. This is known as 'timed acoustic stimulation of sleep' and has been shown to improve feelings of refreshment, well-being and memory, including in people with known impairment of thinking. Recently, Philips has developed a headband (SmartSleep®) that can be worn comfortably at night in the home but which also records brain wave activity and delivers sounds at the appropriate time during sleep. This study will examine whether SmartSleep® can improve sleep quality for people with MS with aim of reducing common MS symptoms including fatigue and memory problems and improving quality of life.

Who can participate?

People with relapsing-remitting multiple multiple sclerosis aged between 18 and 40 years who report sleep which is insufficiently refreshing.

What does the study involve?

Participants will be asked to wear a headband at night which plays soft tones during sleep as well as a wrist-worn monitor of activity. There will be a 1-week period of getting used to the headband, a 2-week 'sham' period, and a week between the active and placebo phases ('washout'), participants will be asked to wear the headband for 42 consecutive nights. All

assessments will occur within this time period. Participants will need to attend the clinical unit for assessments including examination and memory tests and will be asked to keep a sleep diary and complete regular questionnaires.

What are the possible benefits and risks of participating?
People who do not have multiple sclerosis have been shown to have an improvement in sleep quality and memory with acoustic stimulation of sleep. It is hoped that people with multiple sclerosis will also experience this. The devices are commercially available and are not expected to carry additional risk to participants.

Where is the study run from?
Bristol Brain Centre, Southmead Hospital, Bristol and University of Bristol (UK)

When is the study starting and how long is it expected to run for?
December 2018 to September 2022

Who is funding the study?
1. Above and Beyond Charity (UK)
2. Bristol and Avon MS Charitable Funds (UK)

Who is the main contact?
Dr Claire Rice
C.M.Rice@bristol.ac.uk

Contact information

Type(s)
Scientific

Contact name
Dr Claire Rice

ORCID ID
https://orcid.org/0000-0002-9851-4426

Contact details
Clinical Neurosciences, Level 1 Learning and Research Building,
Southmead Hospital
Bristol
United Kingdom
BS10 5NB
+44 (0)1174147802
c.m.rice@bristol.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)

286710

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
IRAS 286710, CPMS 50426

Study information

Scientific Title
Feasibility study of timed acoustic stimulation to improve efficiency and restorative quality of sleep in people with relapsing-remitting multiple sclerosis

Acronym
TAS in RRMS

Study objectives
Primary hypothesis:
1. Timed acoustic stimulation can enhance the efficiency of sleep in people with relapsing-remitting multiple sclerosis (RRMS) ≤40 years old

Secondary hypotheses:
1. A deficit in slow-wave activity (SWA, EEG power between 0.5-4 Hz) contributes to the pathophysiology of fatigue and cognitive dysfunction in RRMS
2. Improving efficiency of sleep in people with RRMS will improve symptoms of fatigue and cognitive dysfunction in people with RRMS leading to improved quality of life

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration

Study design
Double-blind placebo-controlled randomized crossover feasibility study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Relapsing-remitting multiple sclerosis (RRMS)

Interventions
Permuted block randomisation is conducted by the Bristol Trials Centre (https://bristoltrialscentre.blogs.bristol.ac.uk/).

Treatment arm: 2 weeks of consecutive nocturnal timed acoustic stimulation during sleep using SmartSleep®. Soft tones will be delivered through earphones during deep sleep (stage N3). The amplitude (stimulus intensity) and frequency (number of stimuli per unit time) of stimulation presentation will be systematically varied to identify optimal parameters for slow-wave induction during sleep. Individually, the software will determine the range of stimulus intensity from minimum level sufficient for perceptual response (e.g. lowest audible volume setting for an auditory stimulus) to a stimulus level that the subject deems comfortable to still allow sleep. This is important, as sleep maintenance requires stimulus intensity low enough to avoid awakening. While maintaining stimulation intensity within optimal range, the stimulus frequency will be at 1Hz. The software uses the ongoing electroencephalogram (brain wave) recording to determine the appropriate sleep stage and deliver the acoustic stimulation.

Together with a 1-week period of getting used to the headband, a 2-week 'sham' period when the soft tones are delivered but not phase-locked to sleep stage N3 and a week between the active and placebo phases ('washout'), participants will be asked to wear the headband for 42 consecutive nights. All assessments will occur within this time period.

Intervention Type
Device

Phase
Not Applicable

Primary outcome(s)
1. Feasibility of timed acoustic stimulation of sleep in multiple sclerosis, determined by:
1.1 Whether the pre-defined progression target is met; 50% of participants show a ≥10% increase in slow-wave activity (SWA, EEG power between 0.5-4Hz) induced by timed acoustic stimulation of non-rapid eye movement sleep. Measured at the end of 2 weeks timed acoustic stimulation (day 21 or day 42 depending on whether randomised to early or late stimulation)
1.2. Whether the target sample size of 12 is met within 6 months of the study opening to recruitment
1.3. Adverse events reported on Days 0-42

Key secondary outcome(s))
1. Neurophysiological parameters of sleep measured using electroencephalogram on days 0-42
2. Quality of sleep measured using a daily sleep evaluation questionnaire, sleep diary, Composite MotionWatch8 Sleep Quality Score and Pittsburgh Sleep Quality Index on days 0-42
3. Symptoms of multiple sclerosis measured using the MS Quality of Life-29 questionnaire, MS Impact Score (MSIS-29), Expanded Disability Status Scale (EDSS) and Brief International Cognitive Assessment for MS (BICAMS) on day 0, between days 21-28 and day 42
4. Quality of life measured using EQ-5D and Depression, Anxiety and Stress Scale – 21 items (DASS-21) on day 0, between days 21-28 and day 42

Completion date
30/09/2022

Eligibility

Key inclusion criteria
1. Able to provide written, informed consent prior to entry
2. Age ≥18 years and ≤40 years

3. Estimated Expanded Disability Status Scale (EDSS) ≤6 (able to walk but may use some assistance if required)
4. Diagnosis of relapsing-remitting multiple sclerosis (McDonald criteria)
5. Self-report non-restorative sleep, defined as sleep that is insufficiently refreshing

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Severe, chronic sleep disorder (e.g. insomnia, sleep apnoea, restless legs syndrome, narcolepsy based on review with study clinician)
2. Travel with time zone shift >3 hours in the last 3 weeks
3. Investigator anticipates poor compliance with the study protocol
4. Major neurological or psychiatric condition other than RRMS
5. Self-report of recurrent seizures/epilepsy or increased seizure risk (e.g. stroke, aneurysm, space-occupying lesion)
6. Must not be taking:
6.1. Noradrenergic, serotonergic, or anticholinergic medications, except if the participant has been on stable treatment (at least 3 months) for pain or mood disorders
6.2. Opioids or sympathomimetics (e.g. amphetamines, epinephrine/adrenaline)
6.3. Benzodiazepines
7. Intolerance of actigraph or SmartSleep® headband
8. Participating in a currently active interventional clinical study
9. Active infection
10. Positive COVID-19 test within last 28 days
11. High temperature, continuous cough, loss of taste or smell within last 28 days

Date of first enrolment
01/11/2021

Date of final enrolment
31/05/2022

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Bristol Brain Centre
Southmead Hospital
Bristol
United Kingdom
BS10 5NB

Sponsor information

Organisation
University of Bristol

ROR
https://ror.org/0524sp257

Funder(s)

Funder type
Charity

Funder Name
Above and Beyond Charity

Funder Name
Bristol and Avon MS Charitable Funds

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date