Cover sheet

Study title	EEG gamma activity entrainment by periodic visual stimulation in sleep
Internal code	Gamma_Sleep
Date of protocol (yyyy-MM-dd)	2023-03-24
Version of protocol	v1.0

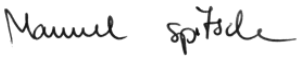
Principal Investigator	Prof. Dr. med. Josef Priller Klinikum rechts der Isar, Technical University of Munich Charité Berlin Prof. Dr. Manuel Spitschan Technical University of Munich Max Planck Institute for Biological Cybernetics
Team members	Dr. James Dowsett Ludwig-Maximilian University Munich Laura Hainke Technical University of Munich Ludwig-Maximilian University Munich

Contact details

Name	Prof. Dr. Josef Priller
Address	Klinik und Poliklinik für Psychiatrie und Psychotherapie Klinikum rechts der Isar Ismaninger Straße 22 81675 München
E-mail	josef.priller@tum.de
Phone	+49 (89) 4140 - 4201

Name	Prof. Dr. Manuel Spitschan
Address	Chronobiology & Health Georg-Brauchle-Ring 60 D-80992 Munich Germany
E-mail	manuel.spitschan@tum.de
Phone	+49 (89) 289 - 24544

Signatures

Munich, 24.03.2023		
Location, date		Prof. Dr. Manuel Spitschan
		Prof. Dr. Josef Priller

Synopsis

Basic information

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Research question

Gamma-band brain activity, especially at the frequency of 40 Hz, is fundamental for a range of cognitive functions including memory. It is already impaired at early stages of Alzheimer's Disease (Traikapi & Konstantinou, 2021) and recent research has been focusing on enhancing it by means of periodic sensory stimulation. First studies on mice (Iaccarino et al., 2016) and humans (He et al., 2021) point toward potential cognitive and circadian benefits, which may be related to improved clearance of pathological molecules such as amyloid-beta. Applying 40 Hz sensory stimulation during sleep could not only boost molecule clearance, which is posited to happen mainly during sleep, but also constitute a more convenient intervention for patients.

The present study will address questions of feasibility and effectiveness of visual 40 Hz stimulation during sleep in a young, healthy cohort. Results should inform on if and how such a procedure could be adapted for early-stage patients with dementia.

Study design

In this within-subjects study, participants will be invited to the sleep laboratory on three occasions, over a study period of one week. In an initial 1-hour session, visual stimulation will be applied during wakefulness. Then participants will come to the lab for two consecutive nights on a weekend, for 20 hours in total. Electroencephalography (EEG) and Polysomnography (PSG) will be recorded while they sleep. The first night will serve as a control and sleep baseline, with passive measurements only. Visual stimulation during sleep will be additionally applied in the second, experimental night. EEG power at 40 Hz will be compared between nights and sleep stages; self-reported sleep quality and PSG-derived sleep parameters will be assessed as well.

Study sample

Exclusion criteria

Domain	Criterion	Assessment method
Age	<18, >35 years of age	Self-report
Vision	Red-green colour blindness, any history of eye disease	Self-report, Ishihara test
Neurological disturbances	Any history of neurological symptoms, especially epilepsy, migraine, stroke, brain tumour, concussion	Self-report
Family history of epilepsy	Any first-degree relative diagnosed with epilepsy or seizures	Self-report
Sleep disturbances	Any symptoms in the past 6 months, especially	Self-report, Pittsburgh Sleep Quality Index (PSQI)

	insomnia, sleepwalking, bruxism, narcolepsy, restless legs syndrome, sleep apnoea; bad average sleep quality (PSQI > 5)	
Psychiatric disturbances	Any symptoms in the past 6 months, especially depressed mood, extreme mood swings, excessive worries, hallucinations or paranoia, substance abuse, suicidal thoughts	Self-report
Shift work	Any shift work in the past month	Self-report
Long-distance travel	Any travel across 2 or more time zones in the past month	Self-report
Substance use	Any use of illicit drugs, cannabis, nicotine, or psychopharmacological medication in the past month; current alcohol abuse (AUDIT > 15)	Self-report, Alcohol Use Disorders Identification Test (AUDIT), Nal Van Minden urine drug test
Chronotype	Chronotype measure MSFsc < 01:30 (“extremely early”) or > 06:00 (“extremely late”)	Micro Munich Chronotype Questionnaire

Sample size and sample size calculations

We will recruit a total of 30 participants.

Protocol in brief

Upon completion of an online screening questionnaire and inclusion in the study, participants will come to the sleep laboratory. In this first session, visual stimulation will be delivered during wakefulness with eyes closed, while effects are measured with EEG. After one week maintaining a regular sleep-wake schedule, on a weekend, participants will return to the sleep laboratory 1,5 hours before their usual bedtime on weekends. EEG will be recorded during wakefulness, then participants will be asked to go to sleep, while PSG and EEG continue to be recorded. On the second night, visual stimulation will be administered during sleep. The experimenter will control the stimulation depending on PSG sleep parameters and the effects will be measured with EEG. After each night, participants will also complete a sleep quality scale.

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List of abbreviations

EEG	Electroencephalography
PSG	Polysomnography
AD	Alzheimer's Disease
W	Wakefulness
N2	Deep sleep stage 2
N3	Deep sleep stage 3
REM	Rapid-eye movement sleep
LED	Light emitting diode

Background

State of the art

Gamma-band EEG activity, particularly at the frequency of 40 Hz, is fundamental for cognitive functions such as memory and already impaired in early stages of AD (Traikapi & Konstantinou, 2021). To counter this decline in gamma-band activity, periodic sensory stimulation has emerged as a new promising avenue: periodically presenting auditory or visual stimuli at 40 Hz can effectively entrain this form of neuronal activity in a non-invasive and non-pharmacological manner (McDermott et al., 2018). First studies reported multiple significant benefits of 40 Hz sensory stimulation in AD-model mice (Iaccarino et al., 2016; Martorell et al., 2019) as well as in human patients with mild AD (Chan et al., 2022; He et al., 2021).

In these studies, patients were exposed to the intervention for one hour a day, for several weeks or months. It led to improvements in AD biomarkers, cognition, and even circadian rhythms, a domain also affected by AD. One of the proposed mechanisms is the clearance of neurotoxic molecules, which 40 Hz sensory stimulation seems to support, at least in mice (Iaccarino et al., 2016). This clearance process is usually thought to be most active during sleep (Wang & Holtzman, 2020). Moreover, it has been shown that pulses of light can be used to shift circadian phase when applied during the night (Joyce et al., 2022). Considering the above, applying this intervention during sleep could add value in terms of convenience as well as effectiveness.

However, the feasibility of 40 Hz visual stimulation during sleep is unclear. So far, periodic visual stimulation during sleep has only been applied at frequencies lower than 10 Hz, to elicit circadian effects (Zeitzer et al., 2014) or to entrain brain activity in the corresponding frequencies, with effect magnitudes depending on sleep stage (Norton et al., 2017; Sharon & Nir, 2018). With subjects' eyes closed, visual stimulation at 40 Hz does seem to promote entrainment but so far, that has only been shown during wakefulness (Fitzgibbon et al., 2016; Jones et al., 2019; Murphy & Öngür, 2019). Therefore, determining whether 40 Hz visual stimulation can effectively enhance gamma-band EEG activity without disrupting young, healthy subjects' sleep is a crucial first step toward a more convenient and effective intervention for AD patients.

Summary of proposed study

In this within-subjects study, we will assess the effects of high-wavelength (red), low-illuminance (dim), temporally modulated (flickering) light delivered to subjects through closed eyes at a frequency of 40 Hz on EEG activity in different states. Over the course of one week, subjects will be asked to A) come to the laboratory for stimulation during wakefulness, B) maintain a constant sleep-wake schedule for 7 days, C) sleep at the laboratory for one night for a baseline assessment, and D) on the following night, return to the laboratory to receive the intervention during sleep. The experimental setup at the sleep laboratory will include PSG and EEG, as well as a stimulation device in form of a specialized sleep mask. Stimulation will be administered based on subjects' sleep stages as estimated through PSG to minimize arousals. EEG power at 40 Hz will be compared between nights and sleep stages; self-reported sleep quality and PSG-derived sleep parameters will be assessed as well.

Reasons for proposed study

Enhancing the brain's endogenous 40 Hz frequency seems to be beneficial for elderly people with mild AD. Sensory stimulation could be a non-invasive and low-cost intervention to boost 40 Hz activity, which is especially desirable given that current treatment options are expensive and of limited effectiveness. Receiving such stimulation during sleep would be more practical for patients than

having to allocate a portion of their day to the rather boring task of attending to a periodic sensory stimulus. Moreover, there could be positive effects on amyloid-beta clearance and circadian rhythms.

However, the feasibility of periodic visual stimulation during sleep to modulate EEG gamma activity is unclear. Therefore, the intervention should first be tested on a young and healthy sample to assess potential effects on EEG power and sleep quality. Results should inform on whether and how to adapt such a stimulation procedure for elderly people.

Objectives

The goal of this planned study is to determine the feasibility of periodic visual stimulation during sleep to modulate EEG gamma activity. Specifically, we will:

1. Test whether EEG activity at 40 Hz can effectively be entrained through closed eyes in wakefulness and different sleep stages.
2. Evaluate how feasible visual stimulation during sleep is in a young healthy cohort.
3. Explore potential impacts of this form of stimulation on sleep quality and architecture.

These specific aims will be approached through a well-controlled within-subjects laboratory study.

Study duration

Entire study

The entire study will take place over a total of 6 months.

For each participant

Each subject taking part in the study will be enrolling for 1 week, including a total of 3 in-laboratory visits.

Study sample

Description of study sample

In this study, we will recruit and enrol healthy participants aged 18-35 years who fulfil the following criteria: normal colour vision; no extreme chronotypes; no substance use; no recent shift work or long-distance travel; no neurological, psychiatric, or sleep disturbances.

Exclusion criteria

Domain	Criterion	Assessment method
Age	<18, >35 years of age	Self-report
Vision	Red-green colour blindness, any history of eye disease	Self-report, Ishihara test
Neurological disturbances	Any history of neurological symptoms, especially epilepsy, migraine, stroke, brain tumour, concussion	Self-report
Family history of epilepsy	Any first-degree relative diagnosed with epilepsy or seizures	Self-report

Sleep disturbances	Any symptoms in the past 6 months, especially insomnia, sleepwalking, bruxism, narcolepsy, restless legs syndrome, sleep apnoea; bad average sleep quality (PSQI > 5)	Self-report, Pittsburgh Sleep Quality Index (PSQI)
Psychiatric disturbances	Any symptoms in the past 6 months, especially depressed mood, extreme mood swings, excessive worries, hallucinations or paranoia, substance abuse, suicidal thoughts	Self-report
Shift work	Any shift work in the past month	Self-report
Long-distance travel	Any travel across 2 or more time zones in the past month	Self-report
Substance use	Any use of illicit drugs, cannabis, nicotine, or psychopharmacological medication in the past month; current alcohol abuse (AUDIT > 15)	Self-report, Alcohol Use Disorders Identification Test (AUDIT), Nal Van Minden urine drug test
Chronotype	Chronotype measure MSFsc < 01:30 (“extremely early”) or > 06:00 (“extremely late”)	Micro Munich Chronotype Questionnaire (µMCTQ)

Recruitment

We will recruit participants through a variety of means, including fliers, posters, and posts on social media. Additionally, participants will be recruited through mailing lists from General and Experimental Psychology, LMU, and Chronobiology & Health, TUM. On recruitment materials, a QR-code will be displayed that leads to study information and the screening questionnaire.

Sample size

In this study, we will be following a within-subjects design where each participant undergoes both conditions, serving as their own control. We expect to run this study in a total of 30 participants. An *a-priori* simulation-based power analysis indicates that this sample size is sufficient to detect effects of $d = 0.7$ at levels of $1\text{-}\beta = .8$ and $\alpha = .05$.

Protocol

Overview

The planned study follows a 4 X 2 within-subjects design. It is a laboratory study and an interventional clinical trial. The within-subject factors are condition (control night, experimental night) and stage [wakefulness (W), deep sleep stage 2 (N2), deep sleep stage 3 (N3), rapid-eye movement sleep (REM)]. All participants will undergo one stimulation session during wakefulness and one week later, one control night followed by one experimental night. The order of conditions will be the same for all

participants to help counter the "First Night Effect" (Agnew Jr. et al., 1966) and so any potential undiagnosed sleep disturbances can be spotted via PSG before subjects undergo the stimulation during sleep.

Screening

Demographic variables

At screening, we will ask participants for their age, sex, gender, and handedness.

Colour vision

At the first session, participants will be shown Ishihara plates to rule out red-green colour blindness (Clark, 1924).

Questionnaires

During screening, participants will complete a survey delivered via the online platform REDCap on a server set up and maintained by the Chronobiology & Health team at TUM. The server is set up as a virtual machine hosted by the Leibniz-Rechenzentrum der Bayerischen Akademie der Wissenschaften. The survey will cover all exclusion criteria and demographic variables as listed above. The following instruments will also be administered:

Alcohol Use Disorders Identification Test (AUDIT)

Participants will complete the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993), an instrument to examine substance and alcohol abuse, in the self-report version.

Pittsburgh Sleep Quality Index (PSQI)

Participants will complete the Pittsburgh Sleep Quality Index (PSQI; (Buysse et al., 1989), an instrument to determine sleep quality.

Munich Chronotype Questionnaire (MCTQ)

Participants will complete the Munich Chronotype Questionnaire Micro (μMCTQ; Ghotbi et al., 2020) to determine chronotype.

In-laboratory measurements

All study sessions will take place at the sleep laboratory of the Psychiatry department at Klinikum rechts der Isar. Each subject will have three appointments, one session during daytime on a day of choice and two overnight sessions, scheduled on weekends to avoid interference with clinical routine. At night, two subjects will be tested at a time.

Visual stimulation

The intervention to be applied in this study will be delivered through a customized sleep mask with in-built LEDs, electrically shielded and externally linked to a microcontroller. It was built by the technical workshop of the Max-Planck-Institute for Biological Cybernetics (Tübingen, Germany). The design of the stimulation device leans on commercially available masks (e.g., https://noctura.com/) as well as setups previously published by Norton et al. (2017) and Sharon & Nir (2018); a custom build was opted for in order to guarantee the required level of experimental control. This kind of procedure has been validated as safe and reliable (Figueiro et al., 2020; Sahni et al., 2017; Sivaprasad et al., 2018).

The device will feature LEDs of monochromatic red colour (610 nm wavelength) emitting light temporally modulated at 40 Hz. Illuminance values will never exceed 50 lux at eye level, a value which is much dimmer than, for example, an average office room (Nabil & Mardaljevic, 2005).

Physiological measurements

Polysomnography will be measured with the Neurofax system by Nikon Kohden. Additionally, the Mentalab Explore system by Mentalab will be used to record raw EEG data.

Urine drug test

Upon arrival at the lab for the first sleep measurement, a urine drug test (Nal van Minden multi-test drug screening) will be performed to rule out any drug use shortly before the experimental session. We will screen for traces of amphetamine, oxazepam, benzoylecgonine, morphine, and cannabis. Should any test be positive, participants will not be able to participate that evening.

Timeline

The experimental procedure for each participant will be as follows. On the first session, the exclusion criteria will be verified, the Ishihara colour vision test will be administered, and informed consent will be asked for. Then room lights will be dimmed for the setup of EEG and stimulation mask, which participants will be asked to wear with eyes closed during measurements. At the target illuminance level, two stimulation blocks of 10 min will be recorded, while subjects remain awake with eyes closed. A short break between blocks should help maintain subjects' alertness.

Two nights in a row will then be scheduled at the laboratory on a following weekend. Participants will be asked to keep a constant sleep-wake schedule for one week before the sleep sessions; on the three days before the first night, participants should refrain from unusual amounts of caffeine and any alcohol or drug intake. On the two days of the sleep sessions, only if it is usual for them to nap during the day, subjects should not nap for longer than usual. Subjects will be asked to arrive at the lab 1,5 hours before their habitual bedtime on free days, as indicated in the μMCTQ.

Upon arrival at the lab on the first night, subjects will be subjected to the urine drug test. If no test is positive, they will then be given enough time to complete their usual sleep routine before PSG, EEG, and stimulation mask are set up. The mask will not be energized on the baseline night. Subjects will remain in a semi-recumbent position for 10 min in order to record a wakefulness baseline, then they will lay down to sleep. Participants will be given 8 hours of sleep opportunity before they are awakened. After the setup is removed, the Gröningen Sleep Quality Scale (SQS) will be administered.

Subjects will return in the evening for the second study night. After nightly routines and experimental setup are complete, subjects will lay down to sleep right away. On this night, the intervention will be delivered as follows: the experimenter, trained to score sleep, will actively monitor PSG starting at subjects' bedtime. As soon as four consecutive PSG epochs (2 min total) are scored as deep sleep, the mask will be energized. To minimize arousals, the light will gradually fade in and then be kept constant overnight at the target illuminance level. If an awakening is registered by the experimenter, the stimulation will be interrupted and restarted as soon as four consecutive PSG epochs are scored as deep sleep. In the morning, after 8 hours of sleep opportunity and setup removal, the SQS will be administered.

Instruments

In this study, we will be using three measurement instruments. The following table states the devices, the manufacturer, their purpose, and any directive compliance status.

Device	Manufacturer	Purpose	Directive Compliance
Neurofax	Nihon Kohden	Polysomnography	CE, 3/42/EEC, EN-60601-1-2

Mentalab Explore	Mentalab	Electroencephalography	CE, 2014/30/EU, 2014/53/EU, 2015/863/EU
Drug-Screen®	Nal Von Minden	Drug screening	CE

Manufacturer declarations can be found in in Appendix A. All devices were purchased from internal funds of the investigators and were not sponsored by the manufacturers.

Participant remuneration

Participants will be remunerated for their time with 100 € upon completion of all study sessions. An individualized sleep report will also be offered.

Risks and benefits

Flickering light can cause seizures in a minority of people. However, a frequency of 40 Hz is barely perceptible as flicker and not harmful to people with no history or diagnosis of Epilepsy. Rigorous screening will ensure that only healthy subjects are recruited and exposed to the stimulation.

Participants' sleep quality may be affected by the intervention due to the unfamiliar setup and exposure to light at night. If that were the case, it would be restricted to the two study nights. Subjects with diagnosed or suspected sleep disturbances will not be enrolled. If a sleep disturbance is suspected based on PSG outputs of the control night, the experiment will be terminated before that person can be subjected to the visual stimulation during sleep.

In sum, we consider the detailed risks to be minor for young healthy participants given the biomedical knowledge that can be gained from the study.

Target criteria

The main purpose of this study is to quantify the effect of 40 Hz periodic visual stimulation on gamma-band EEG activity in various states. Therefore, the primary outcome will be EEG power at 40 Hz averaged across epochs within the same stage (W, N2, N3, REM). An induced Fast-Fourier-Transform (FFT) analysis will be run to determine levels of 40 Hz EEG activity in periods with and without stimulation. For further information regarding the feasibility of this approach, subjective and objective sleep quality will be assessed in form of the Gröningen Sleep Quality Scale score and PSG parameters (percentage of time per sleep stage, total sleep duration), respectively.

Data protection

Legal consent

Prior to any data collection, participants will be informed of how their data are processed and will have ample opportunities to ask questions. Participants will receive paper consent forms and detailed information about processing of their personal data, which will include their name and signature. These consent forms (see attached Legal *Declaration of Consent* including *Information Sheet* in accordance with the EU General Data Protection Regulation) will be retained in a locked cabinet at Klinikum rechts der Isar. Only selected people will have keys to this cabinet. Upon the start of their participation, in-lab subjects are assigned a subject ID number. This subject number will be used to

label data obtained on the task. At no point will the subjects' names be tied to their subject number. There will be no method to go from subject ID number to subject name or match subject data to subject identity.

Pseudonymization

At enrolment of the study, participants will be assigned a pseudonym participant ID which is necessary to ensure scheduling of appointments and planning of logistics of participation, will be stored in password-protected spreadsheet in a restricted location at Klinikum rechts der Isar. The linkage list between name and participant ID cannot be read, copied, modified or removed by unauthorized persons and its password will only be known to the experimenter and PI.

All data collected in this project will be only labelled using the pseudonyms and stored directly in a pseudonymised form. I.e., the data will be collected under a numerical ID without a reference to contact details and processed without any assignment to personal data of the participants.

The documentation of data and its archiving occurs in a pseudonymised form in a protected electronic database, to which only a limited number of authorised employees have access, including here doctoral students, who are obligated to professional and data secrecy. This data secrecy obligation will also continue to exist after termination of their employment.

Processing of personal data during the study

The processing of personal data will be carried out in such a way that the data can no longer be attributed to a data subject without the use of additional information. The additional information is kept separately and is subject to appropriate technical and organizational measures. Once data have been collected either in-lab or online, they are stored on secure, password-protected lab computers and server space accessible only to trained lab personnel.

Collected data may be used for the preparation of anonymised scientific research work and may also be published and used in an anonymised form in medical journals and scientific publications, so that a direct reference to participant person cannot be established.

Data analysis

The collected and saved data will be classified as health data under the "very high" protection level. The analysis of EEG data is performed in-house. All participating laboratory physicians and employees are subject to medical confidentiality as stipulated by German law.

Cooperation and data exchange with other research Institutes

Pseudonymised data will be shared with the Department of General and Experimental Psychology, Ludwig-Maximilians University, and the Department of Sports and Health Sciences, Technical University of Munich.

List of data types

Type of data	Location	Note
Participant name	Informed consent forms	Forms will be locked in a storage cabinet
Participant signature		
Name and participant ID linkage list	Password-protected spreadsheet on shared network drive accessible only to project personnel	Only the project team have access
Personal data (age, sex, gender, chronotype,	Data collected on password-protected storage server	

average sleep quality, handedness)		All digital data will be pseudonymised and labelled with participant ID
Electrophysiological data (PSG, EEG)		
Subjective sleep assessment (SQS)		

Insurance information

Does not apply.

Participant information sheet and informed consent form

The participant information sheet and informed consent form are attached to the application.

Study materials

All study materials are attached to the ethics application (Appendix B).

Appendix A

AppendixA_Mentalab-Explore.pdf

AppendixA_Nihon-Kohden-Neurofax.pdf

AppendixA_NalVonMinden_Drugscreen.pdf

Appendix B

AppendixB_SQS_de.pdf

AppendixB_SQS_eng.pdf

AppendixB_AUDIT_de.pdf

AppendixB_AUDIT_eng.pdf

AppendixB_PSQI_de.pdf

AppendixB_PSQI_eng.pdf

AppendixB_muMCTQ_de.pdf

AppendixB_muMCTQ_eng.pdf

AppendixB_PersonalData_de.pdf

AppendixB_PersonalData_eng.pdf

AppendixB_ExclusionCriteria_de.pdf

AppendixB_ExclusionCriteria_eng.pdf

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