Received: 26 October 2022 | Revised: 22 December 2022 | Accepted: 23 January 2023

DOI: 10.1111/jsr.13846

RESEARCH ARTICLE

Feasibility, efficacy, and functional relevance of automated auditory closed-loop suppression of slow-wave sleep in humans

Kristoffer D. Fehér[1,2] | Ximena Omlin[1,2] | Leila Tarokh[1,3] | Carlotta L. Schneider[1] | Yosuke Morishima[1] | Marc A. Züst[4] | Marina Wunderlin[4,5] | Thomas Koenig[1] | Elisabeth Hertenstein[1] | Benjamin Ellenberger[6] | Simon Ruch[7] | Flavio Schmidig[8] | Christian Mikutta[1,9] | Ersilia Trinca[1] | Walter Senn[6] | Bernd Feige[10] | Stefan Klöppel[4] | Christoph Nissen[1,2]

[1]University Hospital of Psychiatry and Psychotherapy, University of Bern, Bern, Switzerland

[2]Division of Psychiatric Specialties, Geneva University Hospitals (HUG), Geneva, Switzerland

[3]University Hospital of Child and Adolescent Psychiatry and Psychotherapy, University of Bern, Bern, Switzerland

[4]University Hospital of Old Age Psychiatry and Psychotherapy, University of Bern, Bern, Switzerland

[5]Department of Social Neuroscience and Social Psychology, Institute of Psychology, University of Bern, Bern, Switzerland

[6]Institute of Physiology, University of Bern, Bern, Switzerland

[7]Institute for Neuromodulation and Neurotechnology, Department of Neurosurgery and Neurotechnology, University Hospital and University of Tübingen, Tübingen, Germany

[8]Cognitive Neuroscience of Memory and Consciousness, Institute of Psychology, University of Bern, Bern, Switzerland

[9]Privatklinik Meiringen, Meiringen, Switzerland

[10]University of Freiburg Medical Center, Freiburg, Germany

Correspondence
Christoph Nissen, Division of Psychiatric Specialties, Geneva University Hospitals (HUG), Geneva, Switzerland.
Email: christoph.nissen@hcuge.ch

Funding information
Interfaculty Research Cooperation (IRC) Decoding Sleep, University of Bern, Switzerland

Summary

Slow-wave sleep (SWS) is a fundamental physiological process, and its modulation is of interest for basic science and clinical applications. However, automatised protocols for the suppression of SWS are lacking. We describe the development of a novel protocol for the automated detection (based on the whole head topography of frontal slow waves) and suppression of SWS (through closed-loop modulated randomised pulsed noise), and assessed the feasibility, efficacy and functional relevance compared to sham stimulation in 15 healthy young adults in a repeated-measure sleep laboratory study. Auditory compared to sham stimulation resulted in a highly significant reduction of SWS by 30% without affecting total sleep time. The reduction of SWS was associated with an increase in lighter non-rapid eye movement sleep and a shift of slow-wave activity towards the end of the night, indicative of a homeostatic response and functional relevance. Still, cumulative slow-wave activity across the night was significantly

reduced by 23%. Undisturbed sleep led to an evening to morning reduction of wake electroencephalographic theta activity, thought to reflect synaptic downscaling during SWS, while suppression of SWS inhibited this dissipation. We provide evidence for the feasibility, efficacy, and functional relevance of a novel fully automated protocol for SWS suppression based on auditory closed-loop stimulation. Future work is needed to further test for functional relevance and potential clinical applications.

KEYWORDS
auditory stimulation, closed-loop stimulation, sleep deprivation, slow-wave sleep

1 | INTRODUCTION

Slow-wave sleep (SWS), the deep stage of non-rapid eye movement (NREM) sleep, is a basic physiological process that is thought to serve important functions, such as the refinement of synaptic plasticity (Kuhn et al., 2016; Tononi & Cirelli, 2006). Modulating SWS is therefore of both basic science and clinical interest. Amidst progress in automatised boosting of SWS, there has been a lack of innovation in the development of protocols for automated SWS suppression.

Slow-wave sleep has been manipulated in humans for more than eight decades, ranging from simple awakenings during SWS to the selective modulation of sleep slow waves (SWs; for review Fehér et al., 2021). While more recently the focus has shifted to the enhancement of SWS (Ngo et al., 2013), suppressing SWS represents an important means to inform about the regulation and functions of SWS. SWS suppression might also have relevant clinical applications, such as antiepileptic (Bower et al., 2015) or antidepressant effects (Wolf et al., 2016). Indeed, suppressing sleep in patients with major depressive disorder (MDD) can lead to a rapid improvement of depressive symptoms (therapeutic sleep deprivation). Recent studies suggest that the suppression of SWS may actually drive this therapeutic effect (Goldschmied et al., 2015, 2019; Landsness et al., 2011), potentially through a modulation of synaptic plasticity (Wolf et al., 2016).

The development of stimulation protocols can be informed by prior work on the physiology of SWS. SWS is most prominently characterised by the presence of slow, high-amplitude rhythmic fluctuations (SWs) in electroencephalographic (EEG) recordings. Indeed, current online SWS state detection is based on the spectral signature of SWs (Fehér et al., 2021). Spectrally, synchronised SWs manifest as slow-wave activity (SWA; 0.5–4.5 Hz), which reflects the homeostatic component of sleep–wake regulation, showing an increase after wakefulness and a decline during sleep (Borbély, 1982). On a neural level, the SWs reflect a bistability of the resting membrane potential of cortical neurones, rhythmically transitioning between a depolarised up-state with high-frequency firing and a hyperpolarised down-state with a cessation of firing (Steriade et al., 1993). However, on an EEG topographic level SWS is also characterised by the alternating occurrence of distinctive topographic maps primarily reflecting these two brain states and their frontal dominance (Data S1: Figure S1).

To date, fully-automated SWS suppression protocols are lacking, potentially related to a number of challenges. First, reliable SWS detection is challenged by both substantive inter-individual differences and a strong homeostatic component of SWS. With regard to stimulation, automated protocols should efficiently suppress SWS, while remaining reactive to indices of arousal to prevent awakening. This is important in order to be able to selectively study or manipulate the specific functions of SWA within NREM sleep. Thus, prior studies on SWS disruption have relied on manual or semi-automated protocols requiring online monitoring and interventions by trained experimenters, which limits broader research and clinical applications (for review Fehér et al., 2021).

In this manuscript, we describe the development, implementation and evaluation of a fully-automated online detection and suppression of SWS in healthy humans and provide first evidence for feasibility and efficacy. The protocol includes a novel approach to detect and target SWS in real-time based on a topographic template of frontal SWs and a novel stimulation protocol, involving closed-loop modulated randomised bursts of pink noise. Acoustic stimulation has proven a reliable method for the modulation of SWS, which can be safely applied and combined with simultaneous EEG sleep monitoring (Fehér et al., 2021; Wunderlin et al., 2021). The primary aim of the study was to demonstrate a suppression of SWS in a stimulation compared to a sham night in a repeated-measures sleep laboratory study in humans. In addition, we assessed indices of functional relevance of SWS suppression as operationalised as the time course of SWA across the night and wake EEG theta activity. Evidence from microstructural, molecular, and electrophysiological studies suggests that SWA is a marker and modulator of the up- and downscaling of overall synaptic strength across the sleep–wake cycle (synaptic homeostasis hypothesis; Tononi & Cirelli, 2006). EEG theta activity represents a correlate of SWA during wakefulness (Finelli et al., 2000; Vyazovskiy & Tobler, 2005), with a sleep-related reduction, potentially reflecting the re-normalisation of overall synaptic strength.

2 | METHODS

2.1 | Participants

A total of 18 healthy university students participated in the present study, of which 15 participants were included in the final analysis

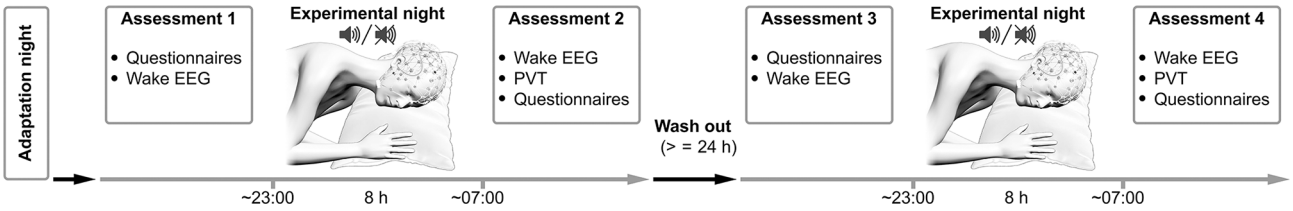

FIGURE 1 Study design. Participants underwent a repeated-measures design with an adaptation night followed by 2 experimental nights (auditory stimulation and sham) in a counterbalanced order. Participants were characterised at the electrophysiological (wake electroencephalography (EEG) and polysomnography) and behavioural level (psychomotor vigilance task [PVT] and questionnaires).

(eight females, mean [SD] age 23.5 [2.8] years; Data S1: Table S1). Two participants terminated their participation after the first night and one participant was excluded due to technical difficulties during 1 experimental night. The SWS detection algorithm was constructed prior to the main study, based on data from 2 sleep laboratory nights of a second cohort consisting of 12 healthy university students (nine females, mean [SD] age 23.3 [2.3] years). Written informed consent was obtained from all participants. The experimental procedures conformed to the Declaration of Helsinki and were approved by the Ethics Committee of the Canton Bern (Project-ID 2019-00984).

2.2 | Study protocol

Participants underwent a repeated-measures design consisting of 3 sleep laboratory nights; 1 adaptation night and 2 experimental nights (auditory stimulation and sham in counterbalanced order; Figure 1). EEG was recorded using a 128-channel EEG cap (MicroCEL, EGI Philips, USA). Questionnaires were administered in the evening and morning assessing sleep quality, sleepiness, mood, cognitive functioning, as well as potential side-effects after each experimental night (see Data S1). As disruption of SWS may affect vigilance (Van Der Werf et al., 2011), a psychomotor vigilance task (PVT) was used to assess vigilance in the morning. Participants were instructed to press a response button as fast as possible upon the presentation of a timer (inter-trial interval 2–10 s; total duration 5 min; Basner & Dinges, 2011). To assess the functional relevance of the stimulation protocol on processes of synaptic re-normalisation (Finelli et al., 2001; Kuhn et al., 2016; Vyazovskiy & Tobler, 2005), wake resting-state EEG theta activity was recorded in the evening and morning of the 2 experimental nights (Kuhn et al., 2016).

2.3 | The EEG recording and pre-processing

The EEG was recorded at a sampling rate of 500 Hz, referenced to channel Cz, and was pre-processed using MATLAB (R2019a, MathWorks Inc., Natick, MA, USA), the EEGLAB toolbox (Delorme & Makeig, 2004; http://sccn.ucsd.edu/eeglab/) and the FieldTrip analysis toolbox (Oostenveld et al., 2010; see Data S1 for details).

2.4 | Slow-wave sleep detection

Slow-wave sleep was detected online using a topographic template of frontal SWs, which was originally proposed for online phase prediction of local SWs (Ruch et al., 2022). The data used to create the topographic template was previously recorded in a sample of 39 healthy participants (Züst et al., 2019). The creation and adaptation of the topographic template for SWS detection is described in Figure 2a,b and in Data S1, and the performance is reported in Figure 3 and Table 1. Detection was highly selective as benchmarked against manual scoring, with 99.8% of the sham stimuli delivered during SWS or N2 during undisturbed sleep, while during real stimulation this was 94.7% (Figure 3). In fact, the SWS detection process in combination with a parallel fast arousal/artefact detection process performed rather conservatively, with a mean (SD) of 23.1% (12.0%) of polysomnographic SWS missed during the sham night and 39.4% (18.0%) during the stimulation night (Table 1).

2.5 | Auditory stimulation

The auditory stimulation protocol is described in Figure 2d,e, and detailed in Data S1. Auditory stimulation was applied via earphones (IP30 Insert Earphones; Radioear Corporation, USA). A hearing test was administered in the evening, as well as in the morning of the 2 experimental nights.

2.6 | Data processing and analyses

MATLAB was used for statistical analyses. To estimate effect sizes, Cohen's *d* was calculated for paired comparisons. The level of statistical significance was set at $p < 0.05$ (two-tailed) for all analyses. Sleep scoring was performed by an experienced rater blinded to the experimental condition.

2.6.1 | Sleep architecture

Our primary hypothesis was that the stimulation would shorten the time spent in SWS. Furthermore, the following variables of sleep continuity and architecture were evaluated: total sleep time (TST),

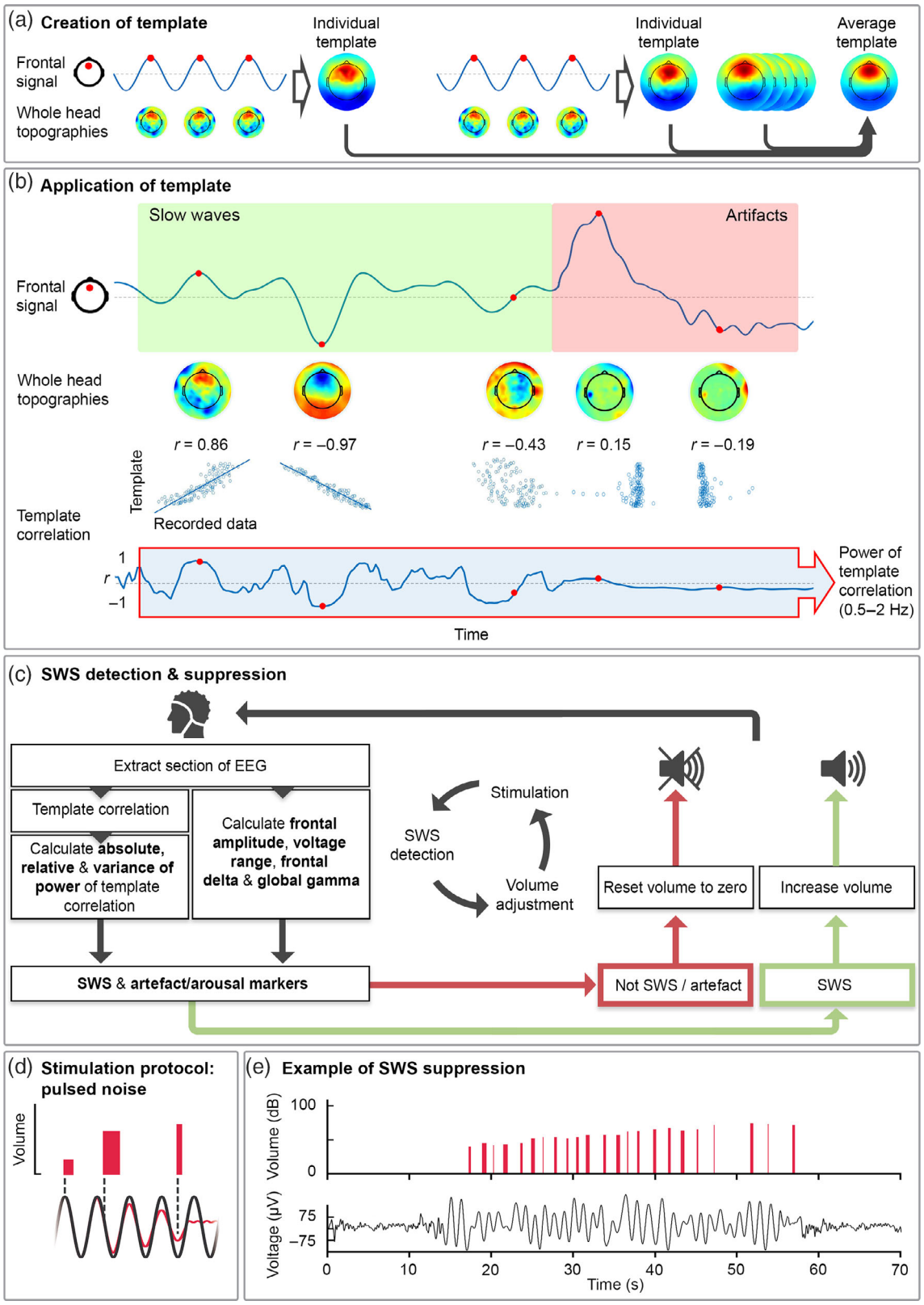

FIGURE 2 Legend on next page.

sleep efficiency (TST as a percentage of time in bed), sleep onset latency (period between lights off and first occurrence of sleep stage N2), wake after sleep onset (period of wake between sleep onset and lights on), the time spent in sleep stages N1, N2 and REM sleep, and the arousal index (number of arousals as a percentage of TST in hours). As sleep architecture data was not normally

distributed (Kolmogorov–Smirnov test), the Wilcoxon signed-rank test was used.

We also assessed the relative percentage of shifts and continuations per vigilance state, analysed through non-parametric paired tests using bootstrap statistics (5000 iterations). A *p* value was defined as the number of instances where the value obtained from random sampling was larger than that observed in the data divided by the number of iterations. In this way, we could calculate the probability of obtaining our results by chance, while controlling for familywise error rate (Maris & Oostenveld, 2007; Pernet et al., 2015).

2.6.2 | The EEG spectral analysis

Spectral power densities (10 overlapping 4-s sub-epochs per 30-s time bin, using a Hanning-window) were calculated for the following frequency bands: SWA: 0.75–4.5 Hz; theta: 4.5–9 Hz; alpha: 9–15 Hz; slow spindle activity: 9–12 Hz; fast spindle activity: 12–15; beta: 20–40 Hz. 30-s bins containing low-frequency (0.75–4.5 Hz) and high-frequency (20–40 Hz) artefacts were additionally excluded from the spectral analyses, being defined as power values >2× moving median of 15 × 30 s epochs, as well as >10 or >3000 μV^2/Hz respectively. Outlier channels, defined as >3 scaled mean absolute deviations from the median, were excluded before calculating averages across the scalp.

We first assessed the effect of our stimulation on SWA. As SWA is largest in SWS, we hypothesised that the SWS selective stimulation would lead to an overall reduction of SWA across NREM sleep. Given the selective stimulation during SWS, we hypothesised that SWA would be suppressed during SWS but not in N1 and N2 (hereon referred to as lighter NREM sleep). Furthermore, we assessed the possibility of a homeostatic response in terms of increased SWA in lighter NREM sleep. We used *t* tests for a paired comparison of the average log transformed SWA across the scalp during NREM sleep, SWS and lighter NREM sleep, across the night and participants.

To assess further local and global spectral changes across the scalp, the topographic distribution across derivations for spectral densities were analysed per power band using non-parametric paired tests performed on the power density values using bootstrap statistics.

To visualise the dynamics of the effect of our intervention across the night on the decay of process S (Borbély, 1982), we also calculated slow-wave energy (SWE); the cumulative sum of SWA during NREM sleep throughout the night from sleep onset. It has been

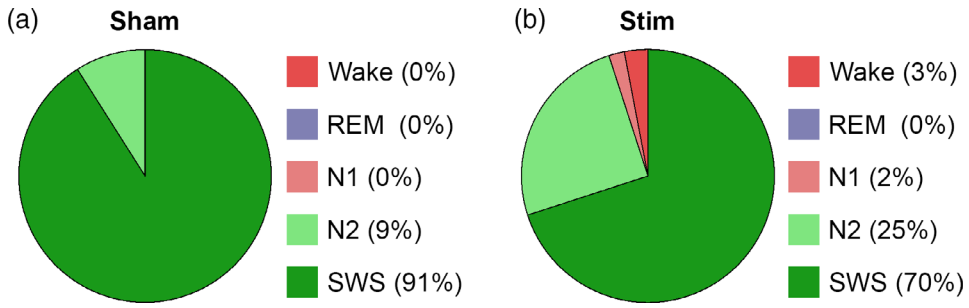

FIGURE 3 Percentage of delivered stimuli per sleep stage during sham and real stimulation. (a) Sham stimulation. As depicted, >90% of the (sham) stimuli were delivered during slow-wave sleep (SWS) and none during wake, rapid eye movement (REM) or N1 sleep, indicating successful performance of the protocol. (b) Real stimulation (Stim). As expected, more stimuli were delivered during N2 sleep and a few during wake and N1 sleep, related to the induced stage shifts through auditory stimulation.

FIGURE 2 Creation and application of a spatial template of frontal slow waves (SWs), for slow-wave sleep (SWS) detection and closed-loop suppression through auditory stimulation. (a) Creation of template. Fronto-central SWs are detected. The topographies at the time-point of a frontal SW peak are recorded, averaged across all instances, and normalised to create a spatial template of frontal SW peaks per individual. Finally, an average template is created across individuals. (b) Application of template to detect SWS. First, topographies are correlated with the topographic template. The correlation coefficient (Pearson's *r*) at a certain point in time is positive upon frontal SW peaks, negative upon troughs, while the correlation decreases between peaks and troughs or for artefacts. Second, the power over an extended period of the distinctive ~1 Hz rhythmic fluctuation of this correlation (red rectangle) is then used as a marker for SWS, with the advantages of being insensitive to amplitude differences and robust against artefacts. (c) SWS detection and closed-loop suppression through auditory stimulation. The template correlation is calculated over a moving window of the electroencephalographic (EEG) signal. The power, variance of power and percentage of power are used together with global gamma power (with lower gamma power indicating a deepening of sleep; Jones, 2020) to detect SWS. Frontal amplitude, voltage range and delta power together with global gamma power are used as artefact and arousal markers for quick suppression of stimulation. (d) Illustration of the pulsed noise stimulation protocol. Upon detection of SWS, bursts of pink noise are applied with a randomised duration (50–500 ms; 5 ms fade in/fade out) and inter-onset interval (1–4 s, with an exponentially decreasing probability density). A stochastic component (Ornstein–Uhlenbeck process; ±2.5 dB) is superposed on a linearly increasing drift (40–106 dB over 60 s) to add unpredictability in volume. (e) Illustration of SWS suppression through pulsed noise of increasing volume. Top: example stimulation with randomised inter-onset intervals, randomised burst durations, and randomised volume dynamics. Bottom: illustration of EEG trace.

Performance measures	N2 excluded, mean (SD)		N2 included, mean (SD)	
	Sham	Stimulation	Sham	Stimulation
F1	0.86 (0.07)	0.73 (0.13)	0.80 (0.08)	0.62 (0.08)
Cohen's kappa	0.81 (0.09)	0.67 (0.13)	0.76 (0.08)	0.56 (0.07)
Matthew's correlation coefficient	0.83 (0.08)	0.70 (0.11)	0.77 (0.08)	0.58 (0.07)
Sensitivity	0.77 (0.12)	0.61 (0.18)	0.77 (0.12)	0.61 (0.18)
Specificity	1.00 (0.01)	0.99 (0.01)	0.97 (0.04)	0.94 (0.07)
Accuracy	0.92 (0.04)	0.90 (0.04)	0.93 (0.02)	0.90 (0.04)

TABLE 1 Mean (standard deviation) for the slow-wave sleep detection performance measures, per experimental night, across participants, with N2 excluded or included in the performance evaluation.

observed that after partial SWS deprivation, there is a pressure to reach the equivalent cumulative sum of SWA as during undisturbed sleep (Dijk et al., 1987; Dijk & Beersma, 1989). In particular, as we specifically targeted SWS with the aim of pushing the brain state into lighter NREM sleep, we needed to assess whether an increased duration of lighter NREM sleep with a higher number of lower amplitude SWs might cancel out the effect of the SWS disruption on the cumulative sum of SWA. SWE was calculated in 5-min epochs, taking per epoch the average of clean 30-s SWA bins in NREM sleep multiplied by the number of 30-s NREM sleep epochs. Differences in the SWE, as well as SWA, during NREM were assessed by Wilcoxon signed-rank tests, corrected for multiple comparisons by false discovery rate (FDR; Benjamini & Hochberg, 1995). The topographic distribution of end-of-night SWE across derivations were analysed using non-parametric paired tests performed on the SWE values using bootstrap statistics.

To assess the overall effect of stimulation compared to sham on the evening to morning reduction of wake theta (3.5–8 Hz) power, we calculated a two-way repeated-measures analysis of variance (ANOVA) on the log transformed average theta power across the scalp, with time of day (evening/morning) and stimulation condition as independent variables. As post-hoc analyses, *t* tests were used for paired comparisons of the average log transformed theta power (FDR corrected). In order to further assess whether the effects were driven by our stimulation protocol, we assessed how the change between conditions in the evening to morning dissipation of theta power correlated with the changes between conditions in our significantly modulated sleep parameters.

2.6.3 | Slow-wave analysis

We used *t* tests for paired comparisons of the average count, peak amplitude, and density (count/min) of detected SWs (Mölle et al., 2009) across the scalp during NREM sleep, SWS, and lighter NREM sleep.

2.6.4 | Spindle event analysis

We used *t* tests for paired comparisons of the count and density (spindle events/5 min) of detected spindle events (Staresina et al., 2015) across the scalp, during NREM sleep, SWS, and lighter NREM sleep.

2.6.5 | Analysis of behavioural data

For the PVT, the mean response time (RT; for 100 ms ≤ RT), response speed (1/RT), number of valid stimuli, false starts, lapses (RT <500 ms), as well as lapses probability (number of lapses divided by number of valid stimuli) and performance score 1 minus the number of lapses and false starts divided by the number of valid stimuli (including false starts) were analysed using Wilcoxon signed-rank tests as the data was not normally distributed (one-sample Kolmogorov–Smirnov test). Subjective reports related to the subjective state before and after sleep, the side-effect questionnaire, and the visual analogue scale (VAS) were analysed using Wilcoxon signed-rank tests as the data was not normally distributed (one-sample Kolmogorov–Smirnov test).

3 | RESULTS

3.1 | Sleep continuity and architecture

In line with our primary hypothesis, we found a highly significant reduction of SWS compared to sham (−29.6%; $p = 0.0024$; $d = 0.90$). This effect was associated with an increase in sleep stage N2 (11.8%; $p < 0.001$; $d = 1.02$) and a reduction of REM sleep (−12.3; $p = 0.027$; $d = 0.66$; Figure 4).

In terms of vigilance state-transitions (Figure 5), we found that stimulation led to a significant decrease in continuity of SWS (−15.0%; $p < 0.0001$), as well as a decreased continuity of N2 sleep (−4.6%; $p = 0.0058$; Figure 5). We also found a decreased transition probability from wake to REM sleep (−67.0%; $p = 0.018$; Figure 5).

3.2 | The EEG spectral power

In line with our expectations, the stimulation protocol led to a significant reduction of SWA across the scalp during NREM sleep compared to the sham protocol (−23.1%; $p < 0.01$; $d = 0.98$; Figure 6a). This reduction was driven by a suppression of SWA during SWS in the stimulation condition (−21.6%; $p < 0.01$; $d = 0.77$; Figure 6f). In contrast, SWA was increased in lighter NREM sleep stages in the stimulation compared to the sham condition (+17.0%; $p < 0.01$; $d = 1.01$; Figure 6k). When exploring the spectral changes across frequency bands and sleep stages across channels, we found

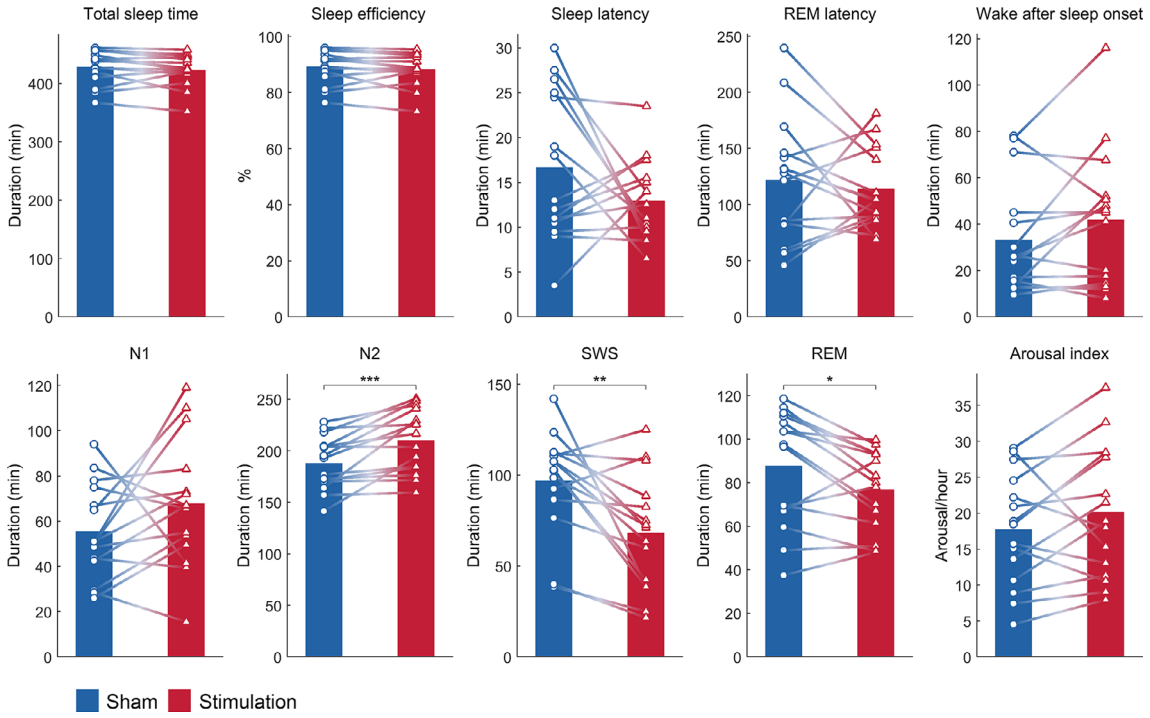

FIGURE 4 Parameters of sleep continuity and architecture. Horizontal lines with asterisks indicate significant differences between stimulation conditions. Wilcoxon signed rank test; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

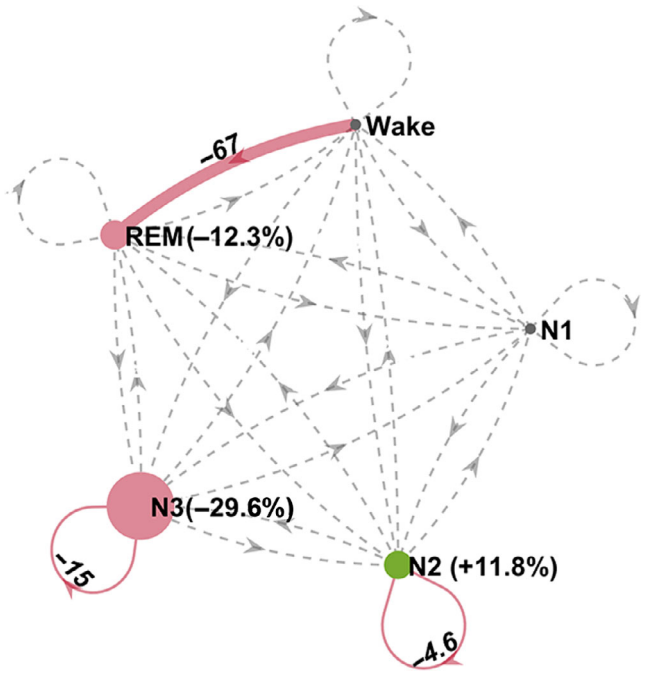

FIGURE 5 Changes in transitions between vigilance states and in state occurrence. Red indicates a significant decrease and green a significant increase during stimulation as compared to the sham night. Average percentage change to remain in or transition between vigilance states are shown above the edges. The size of the nodes reflects the absolute change in percentage. Nodes and edges with no significant change are shown in grey.

that spectral changes were specific to SWA in SWS, while the changes in average SWA across channels observed during lighter NREM did not survive bootstrapping statistics (Figure 6b,g,l).

End-of-night SWE across the scalp was significantly reduced in the stimulation compared to the sham condition (−22.6%; $p < 0.01$; $d = 0.92$; Figure 6p), corroborating that the increase of SWA during lighter NREM sleep did not cancel out the effect of SWA suppression during SWS. The topography of end-of-night SWE was similar to the average SWA across NREM sleep (Figure 6q).

There was a consistent response across participants to the stimulation in the SWE across the night (Figure 6r), from ∼20 min after sleep onset until lights on. While the accumulation of SWE during sham followed the expected dynamics of a steeper increase early in the night and an attenuated increase later in the night, SWE accumulation seemed to stay constant across the stimulation night (Figure 6r,s). Indeed, compared to the sham night, the SWE gradient (viz. SWA during NREM sleep) was steeper in the second half of the night (Figure 6s).

3.3 | Analyses of SWs

The stimulation protocol led to a significant reduction of SW count (−18.1%; $p = 0.045$; $d = 0.57$), amplitude (−11.7%; $p = 0.012$; $d = 0.74$) and density (−18.6%; $p = 0.029$; $d = 0.63$) across the scalp during NREM sleep compared to sham (Figure 6c–e). The suppression of SWs seemed driven by a selective suppression during SWS

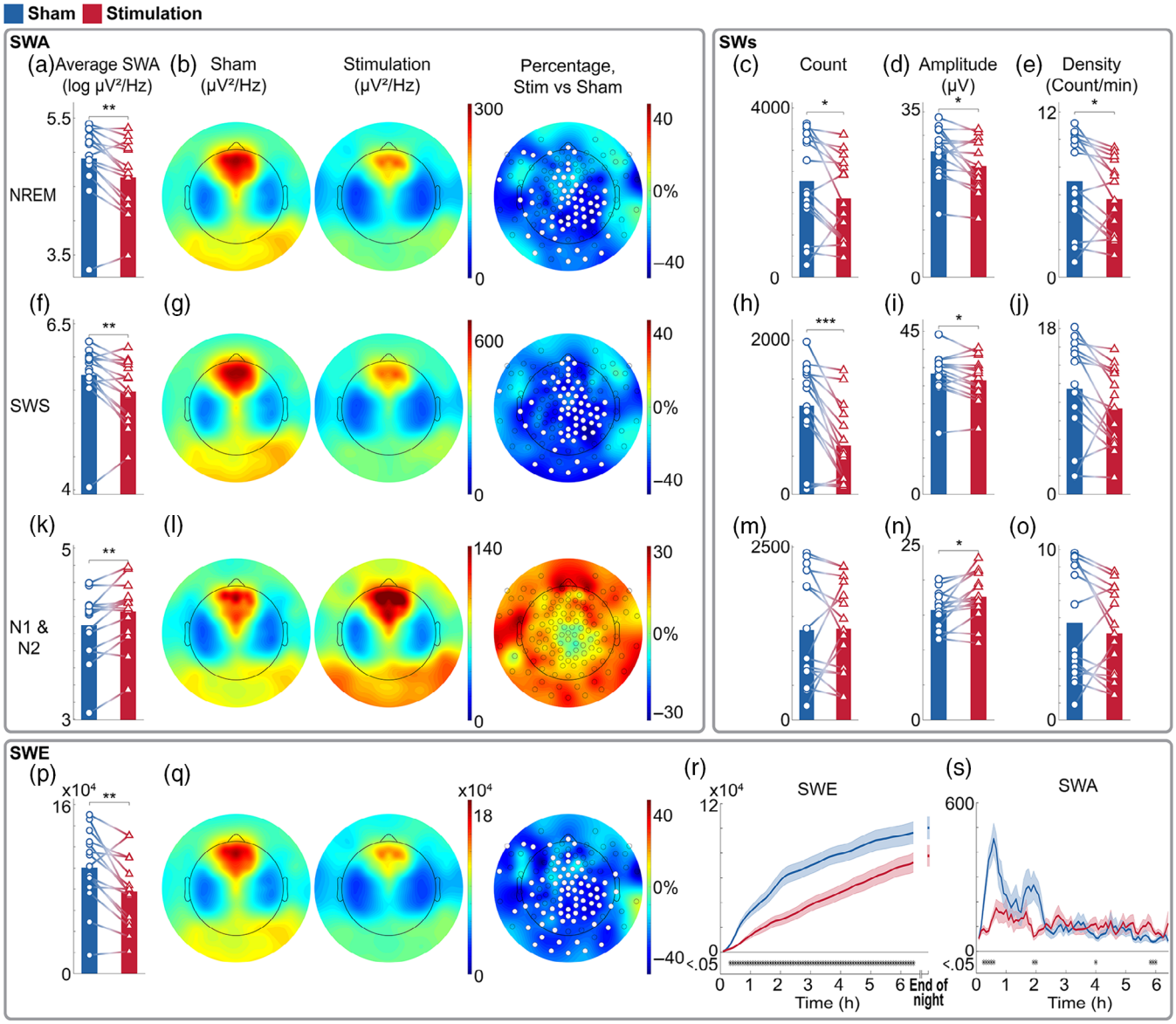

FIGURE 6 Changes in sleep microstructure. (a) Average log transformed slow-wave activity (SWA) across the scalp during non-rapid eye movement (NREM) sleep. (b) Topographic distribution across derivations for spectral density in the SWA band during NREM sleep. The first and the second panel depict the values averaged across the sham and stimulation nights respectively, while the third panel depicts the difference in percentage during the stimulation as compared to the sham night. (c) Average slow-wave (SW) count across the scalp during NREM sleep. (d) Average SW amplitude across the scalp during NREM sleep. (e) Average SW density (SW count/min) across the scalp during NREM sleep. (f) Average log transformed SWA across the scalp during slow-wave sleep (SWS). (g) Topographic distribution across derivations for spectral density in the SWA band during SWS. The first and the second panel depict the values averaged across the sham and stimulation nights respectively, while the third panel depicts the difference in percentage during the stimulation as compared to the sham night. (h) Average SW count across the scalp during SWS. (i) Average SW amplitude across the scalp during SWS. (j). Average SW density (SW count/min) across the scalp during SWS. (k) Average log transformed SWA across the scalp during lighter NREM sleep. (l). Topographic distribution across derivations for spectral density in the SWA band during lighter NREM sleep. The first and the second panel depict the values averaged across the sham and stimulation nights respectively, while the third panel depicts the difference in percentage during the stimulation as compared to the sham night. (m) Average SW count across the scalp during lighter NREM sleep. (n) Average SW amplitude across the scalp during lighter NREM sleep. (o) Average SW density (SW count/min) across the scalp during lighter NREM sleep. (p) Average slow-wave energy (SWE) across the scalp at the end of the night. (q) Topographic distribution across derivations for cumulative SWE at the end of the night. The first and the second panel depict the values averaged across the sham and stimulation nights respectively, while the third panel depicts the difference in percentage during the stimulation as compared to the sham night. (r) Average SWE from sleep onset across the night until lights on. Standard error shown as shaded area. As this interval differs across recordings, the shortest interval (6 h 25 min) across recordings is shown. (s) Average SWA during NREM sleep, from sleep onset across the night until lights on. This corresponds to the gradient of the SWE. Standard error is shown as shaded area. Topoplots with electrodes coloured white: $p < 0.05$. Bar plots with a vertical line with asterisks indicates a significant difference between stimulation conditions (paired-sample t test; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$). Differences between traces are indicated in the bottom plot for each 5 min time bin by an asterisk (Wilcoxon signed-rank test; FDR corrected; $^{*}p < 0.05$).

(Figure 6h–j), of SW count (−45.0%; $p < 0.001$; $d = 1.14$) and amplitude (−5.3%; $p = 0.037$; $d = 0.59$), while SW density was reduced on a trend level (−18.9%; $p = 0.056$; $d = 0.54$). In contrast, SW amplitude was increased during lighter NREM sleep (Figure 6m–o) during the stimulation as compared to the sham condition (+12.3%; $p = 0.011$; $d = 0.76$).

3.4 | Analyses of spindle events

The stimulation protocol did not lead to a significant change of spindle events or density (events/5 min) across NREM sleep. However, we found a reduced number of spindles (−25.8%; $p = 0.012$) and density (−26.1%; $p = 0.013$) in SWS. In contrast, both the number (+14.5%; $p < 0.01$) and density of spindle events (+13.4%; $p < 0.01$) were increased in lighter NREM sleep.

3.5 | Wake EEG theta power

One participant was excluded from the wake EEG analyses due to noisy data in the power spectrum. Analysing average EEG theta power across the scalp during wakefulness in the evening and morning (Figure 7), we found an interaction effect between stimulation condition and time of day ($p = 0.017$, $F = 7.4$). Post hoc paired comparisons (FDR corrected) revealed that these effects were driven by a decrease of theta power (−14.7%; $p < 0.01$) from the evening to the morning of the sham night only. Moreover, theta power in the morning was significantly higher after the stimulation compared to the sham night (+13.3%; $p < 0.01$). The full EEG spectrum is presented in Data S1: Figure S2. As shown, exploratory analyses revealed condition effects in other frequency ranges. However, we restricted the main analysis and interpretation to the EEG theta range.

In order to assess whether the changes in overnight dissipation of theta power were related to the suppression of SWS, we correlated the change between stimulation conditions in overnight dissipation of theta power and our significantly modulated sleep parameters. Firstly, we assessed the correlation with the changes in the duration of sleep stages (N2, SWS and REM sleep). We found a negative correlation with the between-condition change in SWS ($r = -0.65$; $p = 0.011$; Figure 7b), indicating that the more SWS was suppressed, the more the dissipation of theta was inhibited. We also assessed the correlation with SW features during SWS (SW count, amplitude, and density). We found a negative correlation with the between-condition change in SW count during SWS ($r = -0.70$; $p = 0.0050$; Figure 7c), indicating that the more the number of SWs during SWS were suppressed, the more the dissipation of theta power was inhibited. For the total number of SWs across NREM sleep, the significance of the correlation was at trend level ($r = -0.51$; $p = 0.065$). We found no further significant correlation with the change in outcome parameters.

3.6 | Behavioural data

There were no significant differences between the stimulation and sham night for measures of vigilance (PVT; Data S1: Table S4). However, due to data loss, data from only 10 of 15 participants could be analysed. There were no significant differences between the experimental nights on any of the items of the subjective reports (Data S1: Tables S5 and S6), VAS (Data S1: Table S7) or the side-effects questionnaire (Data S1: Table S8). This indicates that the stimulation was well tolerated. Participants reported hearing tones more often during the stimulation night compared to the sham night (scale from 1, 'certainly yes', to 5, 'not at all'; mean [SD] stimulation night score 3.3 [1.0]; mean [SD] sham night score 4.5 [0.6]; $p < 0.01$) but reported similar values prior to both nights when asked whether they expected to hear tones. There were no significant differences in hearing thresholds, neither between the time of day ($p = 0.90$) nor between the experimental nights ($p = 0.54$).

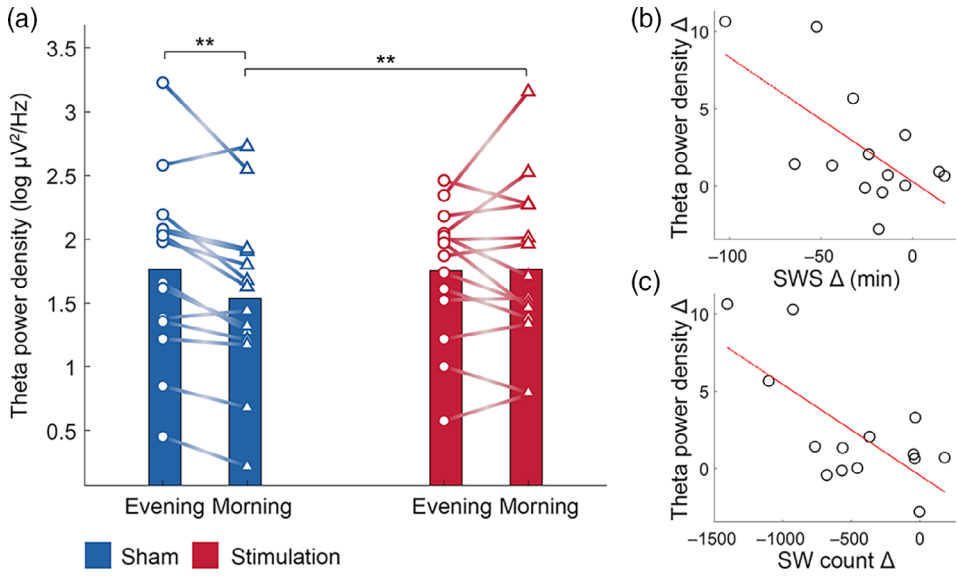

FIGURE 7 Average wake electroencephalographic (EEG) theta power across the scalp and its correlation with the outcome parameters. (a) Theta power in the evening and morning of the 2 experimental nights (Paired *t* test; $^{**}p < 0.01$). (b) Correlation of change in the stimulation compared to the sham condition between the duration of slow-wave sleep (SWS) and theta power from evening to morning. (c) Correlation of change in stimulation compared to sham between slow-wave (SW) count and theta power as a mean across the scalp from evening to morning.

4 | DISCUSSION

In the present study, we established and evaluated a fully automated auditory closed-loop protocol for selective suppression of SWS in healthy adults. The protocol includes a novel SWS detection approach based on a topographic template of frontal SWs and a new randomised pulsed-noise-stimulation protocol with a closed-loop modulation of volume to suppress SWS. The protocol shows good performance parameters; 95% of the stimuli were delivered during SWS or N2 sleep (Figure 3) and SWS was significantly reduced across NREM sleep by ~30% on the stimulation as compared to the sham night (large effect size). Further analyses demonstrated a shift from SWS into N2 sleep in the stimulation night, without a significant reduction of TST. Indicative of functional relevance, we observed an increase of SWA in lighter NREM sleep and indices of a SWA rebound at the end of the stimulation night (homeostatic response). While a reduction of wake EEG theta activity from the evening to the morning is characteristic for undisrupted sleep and potentially reflects synaptic downscaling (Tononi & Cirelli, 2006), stimulation diminished the decline of theta activity.

Our recent review and synthesis of the literature on SWS modulation identified 39 studies on selective disruption of SWS from the 1960s onwards (Fehér et al., 2021). Despite this long history, there is a lack of fully automatised protocols. More specifically, prior approaches required online supervision by trained experimenters to detect SWS or to supervise semi-automated protocols. While these studies have been successful in suppressing SWS and have corroborated the importance of SWS as well as its potential as a therapeutic target, their dependency on online supervision limits broader implementation and potential clinical applications.

Compared to previously published approaches for automatic sleep stage classification, online classification needs to be computationally light weight and cannot be informed by the context of the whole night to determine thresholds. Moreover, compared to SWS boosting (Cellini et al., 2019; Debellemaniere et al., 2018; Ferster et al., 2022; Garcia-Molina et al., 2018; Lustenberger et al., 2016; McConnell et al., 2019; Ong et al., 2018; Patanaik et al., 2018), SWS suppression faces additional challenges. SWS suppression entails a strong pressure for homeostatic rebounds throughout the night, requiring another specificity/sensitivity trade-off consideration to ensure good detection performance throughout the entire night. In contrast, good SWS detection performance at the end of the night is less important when SWS is kept intact, as SWS mostly occurs in the first 2 h after sleep onset. Disruptive, potentially arousal-inducing stimulation also requires a particularly reactive artefact/arousal detection throughout the night. This is for instance evident from a recently proposed automatised SWS suppression protocol (Ooms et al., 2017), where the course artefact/arousal detection process was associated with high percentage stimuli during wakefulness or arousal.

The present SWS detection approach builds on recent work on topography-based SW-phase detection (Ruch et al., 2022). Ruch et al. used the topographic approach to predict the upcoming phase of local SWs, while the present state detection capitalised on the slow oscillatory fluctuations of the correlation with the template to detect SWS. Typically, prior SW and SWS detection approaches have been based on amplitude and spectral power thresholds respectively (Arima et al., 2001; Drewes et al., 2000; Ju et al., 2017; Lentz et al., 1999; Ooms et al., 2017; Piantoni et al., 2013; Van Der Werf et al., 2009). Given the inter-individual variability and homeostatic component of SWs, these approaches are disadvantageous for whole night detection, as well as for implementation in populations with reduced SW amplitudes, such as older adults or patients with psychiatric disorders (Wunderlin et al., 2022). In contrast, the multidimensional topographical template-based approach offers robustness against changes in amplitude as well as artefactual EEG signals (Wunderlin et al., 2022). Our SWS detection process in combination with a parallel fast arousal/artefact detection process enabled a reliable detection of SWS with a low false positive rate of 1.0% ± 1.4% (range: 0.0%–5.0%) in the stimulation nights. This allowed for a selective suppression of SWS across participants and across the entire night while not affecting TST.

With regard to stimulation, our protocol is based on closed-loop modulated randomised bursts of pink noise. Previous SWS suppression studies have emphasised how acoustic stimulation of increasing volume can activate arousal promoting pathways. However, an observation from these studies is that predictive stimuli may not be sufficiently effective to suppress SWS within the safety limits for sound exposure, necessitating manual awakening by an experimenter by the means of, e.g., an intercom (Fehér et al., 2021). An interpretation of these observations is that predictive stimuli are suppressed along the hierarchy of the auditory processing, beyond the arousal pathways, while unpredictive stimuli propagate better. This is consistent with experimental and modelling work showing repetition suppression along the auditory pathways (Lesicko et al., 2022; Ulanovsky et al., 2003). The randomised duration and inter-stimulus intervals of our pink noise stimuli, together with a stochastic process superposed on the linear modulation of volume, were selected to add unpredictability in volume. Compared to pure tones, which have frequently been used in previous SWS suppression studies, pink noise elicits a response across a larger area of the cortex in humans with a lesser degree of habitation upon repeated and temporally predictable fixed-rhythm application of the same stimulus (Debellemanière et al., 2022).

In line with our primary aim, our main finding is a suppression of SWS in the stimulation compared to the sham night. Further analyses indicated an associated shift into lighter NREM sleep (N2), which is in line with the prior literature on SWS suppression (Fehér et al., 2021). Importantly, we did not observe a significant increase in arousal or wakefulness. With regard to vigilance state transitions, we observed a decreased continuity of SWS as well as N2 sleep in the stimulation condition. However, we did not observe a significant increase in the transitions from SWS into lighter NREM sleep. We also observed a decrease in the transitions from wake to REM, which we believe reflects the reduction in REM sleep.

According to the two process model of sleep regulation, SWA shows a strong homeostatic regulation with highest values at the beginning of the night followed by an exponential dissipation (Borbély et al., 1981). Our analysis of SWA demonstrates a disruption of this

time course in the stimulation night. More specifically, SWA was attenuated in the beginning of the night followed by a rebound at the end of the night. This observation is important as it points to a functional relevance and homeostatic response and is in line with previous observations on SWS suppression (Dijk et al., 1987). Of particular note, the rebound of SWA at the end of the night was not sufficient to prevent an overall reduction of SWS and SWA as indexed by significantly reduced SWE (that is, cumulative SWA across the night) in the stimulation night.

During wakefulness, SWA finds a correlate in EEG theta activity as a marker of homeostatic sleep propensity, increasing with time awake and being reduced after sleep (Finelli et al., 2000; Vyazovskiy & Tobler, 2005). Indicative of the functional relevance of the stimulation protocol, we observed an inhibited dissipation of theta power after the stimulation night. Moreover, the inhibition of dissipation of wake EEG theta power correlated with the reduction of SWS and total numbers of SWs in the stimulation compared to the sham night, while it did not correlate with changes in REM or N2 sleep. According to the synaptic homeostasis hypothesis, SWS promotes downscaling of synapses that have been potentiated towards saturation during wakefulness (Tononi & Cirelli, 2006). Sleep deprivation or selective suppression of SWS is expected to inhibit the processes underlying synaptic renormalisation (Wolf et al., 2016). While we did not measure potential indices of synaptic strength in the present study, our pattern of results is consistent with the notion that our stimulation protocol suppressed SWS to a functionally relevant extent, potentially related to attenuated synaptic downscaling. A translation of automated detection and suppression of SWS to animal models would bear the potential to further investigate neural mechanisms and consequences.

With regard to behaviour, we did not observe alterations in vigilance (PVT) and subjective reports of mood, sleepiness and cognitive functioning after the stimulation compared to the sham night. This might relate to a high capacity of healthy participants to compensate for the short-term effects of altered sleep. Future work is needed to test for longer-term effects after repetitive stimulation. To date, it is unclear how effects might accumulate or whether homeostatic rebounds might counteract longer-term effects. However, we also cannot rule out that a more extensive battery of cognitive tests would have brought to light impaired aspects of cognitive function after a night of SW suppression. Finally, it should be noted that due to data loss, the PVT performance data from 10 of the 15 participants were analysed.

The present line of research might have relevant basic science, as well as clinical implications. The protocol bears the potential to further investigate, beyond the level of correlation, potential functions of SWS, such as memory formation, synaptic reorganisation, or metabolic clearance. Selective suppression of SWS may also have clinical relevance. Selective suppression of SWS, potentially through modifications of synaptic plasticity, has been suggested to exert an antidepressant effect in patients with MDD (Wolf et al., 2016). Recent studies, which experimentally disrupted SWA (Goldschmied et al., 2019; Landsness et al., 2011) in individuals with MDD found an improvement in depressive symptoms that were correlated with the overnight reduction of SWA, suggesting a unique role of SWs in the therapeutic effect of sleep deprivation in MDD. We have previously proposed a model wherein therapeutic sleep deprivation compensates for attenuated synaptic strength in patients with major depression by preventing synaptic downscaling, thereby improving neural network functioning and the clinical symptomatology (Wolf et al., 2016). The present protocol provides a means to further test this model. While the impact of therapeutic sleep deprivation in patients with depression is remarkable and rapid, the effect is short-lived with the majority of patients relapsing following a period of subsequent sleep. The burden of staying awake for an entire night is also a significant limitation. Selective suppression of SWS might therefore constitute a less demanding and more sustainable alternative. In particular, effective treatment of neuropsychiatric disorders requires successful long-term application of stimulation, as short-term modification of SWs is unlikely to have long-lasting therapeutic or preventive effects. Finally, while the implementation of selective SWS deprivation in the clinical setting is challenging from several aspects, the present automatised selective SWS disruption protocol relies on an SWS detection approach that is applicable across different age groups and patient populations, and that works reliable across the night, eliminating the need for experimenters controlling the process.

In conclusion, we demonstrate the feasibility, efficacy and functional relevance of a newly developed SWS detection and suppression protocol based on auditory closed-loop stimulation. Further developments bear the potential for translation to broader and even ambulatory use of automated SWS detection and suppression, and potentially for new treatment developments, such as for MDD.

AUTHOR CONTRIBUTIONS

Kristoffer D. Fehér: conceptualisation, methodology, software, formal analysis, investigation, writing – original draft, revision of the manuscript, visualisation, supervision, project administration. Ximena Omlin: formal analysis, writing – original draft, revision of the manuscript. Leila Tarokh: formal analysis, writing – original draft, revision of the manuscript. Carlotta L. Schneider: investigation, supervision, revision of the manuscript. Yosuke Morishima: methodology, software, formal analysis, revision of the manuscript. Marc A. Züst: methodology, software, revision of the manuscript. Marina Wunderlin: investigation, revision of the manuscript. Thomas Koenig: methodology, revision of the manuscript. Elisabeth Hertenstein: investigation, supervision, revision of the manuscript. Benjamin Ellenberger: methodology, software, revision of the manuscript. Simon Ruch: methodology, software, revision of the manuscript. Flavio Schmidig: methodology, revision of the manuscript. Christian Mikutta: methodology, software, revision of the manuscript. Ersilia Trinca: investigation, revision of the manuscript. Walter Senn: methodology, software, revision of the manuscript. Bernd Feige: methodology, revision of the manuscript. Stefan Klöppel: funding acquisition, project administration, revision of the manuscript. Christoph Nissen: conceptualisation, writing – original draft, revision of the manuscript, supervision, project administration, funding acquisition.

ACKNOWLEDGEMENTS

This work has been supported by funding from the Interfaculty Research Cooperation "Decoding Sleep: From Neurons to Health & Mind", University of Bern. We thank Dr Lukas Krone from the University Hospital of Psychiatry and Psychotherapy, Bern, Switzerland, for

his comments on the manuscript. Open access funding provided by Universitat Bern.

CONFLICT OF INTEREST

None of the authors have any competing financial interests or personal relationships to disclose that could have appeared to influence the work reported in this paper.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions

ORCID

Kristoffer D. Fehér https://orcid.org/0000-0002-1205-7157
Ximena Omlin https://orcid.org/0000-0003-2508-9956
Leila Tarokh https://orcid.org/0000-0003-4014-428X
Carlotta L. Schneider https://orcid.org/0000-0003-0236-5946
Yosuke Morishima https://orcid.org/0000-0001-9363-697X
Marc A. Züst https://orcid.org/0000-0003-3043-2106
Marina Wunderlin https://orcid.org/0000-0001-8782-2821
Thomas Koenig https://orcid.org/0000-0002-1472-4638
Elisabeth Hertenstein https://orcid.org/0000-0001-6467-0933
Benjamin Ellenberger https://orcid.org/0000-0002-4787-0471
Simon Ruch https://orcid.org/0000-0002-5796-4543
Flavio Schmidig https://orcid.org/0000-0001-5257-0038
Christian Mikutta https://orcid.org/0000-0002-4096-3691
Ersilia Trinca https://orcid.org/0000-0002-5857-5996
Walter Senn https://orcid.org/0000-0003-3622-0497
Bernd Feige https://orcid.org/0000-0002-9436-1258
Stefan Klöppel https://orcid.org/0000-0001-6452-9964
Christoph Nissen https://orcid.org/0000-0001-9809-0275

REFERENCES

Arima, T., Svensson, P., Rasmussen, C., Nielsen, K. D., Drewes, A. M., & Arendt-Nielsen, L. (2001). The relationship between selective sleep deprivation, nocturnal jaw-muscle activity and pain in healthy men. *Journal of Oral Rehabilitation*, *28*(2), 140–148. https://doi.org/10.1046/j.1365-2842.2001.00687.x

Basner, M., & Dinges, D. F. (2011). Maximizing sensitivity of the psychomotor vigilance test (PVT) to sleep loss. *Sleep*, *34*(5), 581–591. https://doi.org/10.1093/sleep/34.5.581

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society. Series B (Methodological)*, *57*(1), 289–300.

Borbély, A. A. (1982). A two process model of sleep regulation. *Human Neurobiology*, *1*(3), 195–204.

Borbély, A. A., Baumann, F., Brandeis, D., Strauch, I., & Lehmann, D. (1981). Sleep deprivation: Effect on sleep stages and EEG power density in man. *Electroencephalography and Clinical Neurophysiology*, *51*(5), 483–495. https://doi.org/10.1016/0013-4694(81)90225-x

Bower, M. R., Stead, M., Bower, R. S., Kucewicz, M. T., Sulc, V., Cimbalnik, J., Brinkmann, B. H., Vasoli, V. M., St Louis, E. K., Meyer, F. B., Marsh, W. R., & Worrell, G. A. (2015). Evidence for consolidation of neuronal assemblies after seizures in humans. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *35*(3), 999–1010. https://doi.org/10.1523/JNEUROSCI.3019-14.2015

Cellini, N., Shimizu, R. E., Connolly, P. M., Armstrong, D. M., Hernandez, L. T., Polakiewicz, A. G., Estrada, R., Aguilar-Simon, M., Weisend, M. P., Mednick, S. C., & Simons, S. B. (2019). Short duration repetitive transcranial electrical stimulation during sleep enhances declarative memory of facts. *Frontiers in Human Neuroscience*, *13*, 123. https://doi.org/10.3389/fnhum.2019.00123

Debellemaniere, E., Chambon, S., Pinaud, C., Thorey, V., Dehaene, D., Léger, D., Chennaoui, M., Arnal, P. J., & Galtier, M. N. (2018). Performance of an ambulatory dry-EEG device for auditory closed-loop stimulation of sleep slow oscillations in the home environment. *Frontiers in Human Neuroscience*, *12*, 88. https://doi.org/10.3389/fnhum.2018.00088

Debellemanière, E., Pinaud, C., Schneider, J., Arnal, P. J., Casson, A. J., Chennaoui, M., Galtier, M., Navarrete, M., & Lewis, P. A. (2022). Optimising sounds for the driving of sleep oscillations by closed-loop auditory stimulation. *Journal of Sleep Research*, *31*(6), e13676. https://doi.org/10.1111/jsr.13676

Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*, *134*(1), 9–21. https://doi.org/10.1016/j.jneumeth.2003.10.009

Dijk, D. J., & Beersma, D. G. (1989). Effects of SWS deprivation on subsequent EEG power density and spontaneous sleep duration. *Electroencephalography and Clinical Neurophysiology*, *72*(4), 312–320.

Dijk, D. J., Beersma, D. G., Daan, S., Bloem, G. M., & Van den Hoofdakker, R. H. (1987). Quantitative analysis of the effects of slow wave sleep deprivation during the first 3 h of sleep on subsequent EEG power density. *European Archives of Psychiatry and Neurological Sciences*, *236*(6), 323–328.

Drewes, A. M., Nielsen, K. D., Rasmussen, C., Arima, T., Svensson, P., Rössel, P., & Arendt-Nielsen, L. (2000). The effects of controlled delta sleep deprivation on experimental pain in healthy subjects. *Journal of Musculoskeletal Pain*, *8*(3), 49–67. https://doi.org/10.1300/J094v08n03_05

Fehér, K. D., Wunderlin, M., Maier, J. G., Hertenstein, E., Schneider, C. L., Mikutta, C., Züst, M. A., Klöppel, S., & Nissen, C. (2021). Shaping the slow waves of sleep: A systematic and integrative review of sleep slow wave modulation in humans using non-invasive brain stimulation. *Sleep Medicine Reviews*, *58*, 101438. https://doi.org/10.1016/j.smrv.2021.101438

Ferster, M. L., Da Poian, G., Menachery, K., Schreiner, S., Lustenberger, C., Maric, A., Huber, R., Baumann, C., & Karlen, W. (2022). Benchmarking real-time algorithms for in-phase auditory stimulation of low amplitude slow waves with wearable EEG devices during sleep. *IEEE Transactions on Biomedical Engineering*, *1–1*, 2916–2925. https://doi.org/10.1109/TBME.2022.3157468

Finelli, L. A., Baumann, H., Borbély, A. A., & Achermann, P. (2000). Dual electroencephalogram markers of human sleep homeostasis: Correlation between theta activity in waking and slow-wave activity in sleep. *Neuroscience*, *101*(3), 523–529. https://doi.org/10.1016/S0306-4522(00)00409-7

Finelli, L. A., Borbély, A. A., & Achermann, P. (2001). Functional topography of the human nonREM sleep electroencephalogram. *The European Journal of Neuroscience*, *13*(12), 2282–2290.

Garcia-Molina, G., Tsoneva, T., Jasko, J., Steele, B., Aquino, A., Baher, K., Pastoor, S., Pfundtner, S., Ostrowski, L., Miller, B., Papas, N., Riedner, B., Tononi, G., & White, D. P. (2018). Closed-loop system to enhance slow-wave activity. *Journal of Neural Engineering*, *15*(6), 066018. https://doi.org/10.1088/1741-2552/aae18f

Goldschmied, J. R., Cheng, P., Armitage, R., & Deldin, P. J. (2019). A preliminary investigation of the role of slow-wave activity in modulating waking EEG theta as a marker of sleep propensity in major depressive disorder. *Journal of Affective Disorders*, *257*, 504–509. https://doi.org/10.1016/j.jad.2019.07.027

Goldschmied, J. R., Cheng, P., Kim, H. S., Casement, M., Armitage, R., & Deldin, P. J. (2015). Slow-wave disruption enhances the accessibility of positive memory traces. *Neurobiology of Learning and Memory*, *125*, 168–175. https://doi.org/10.1016/j.nlm.2015.09.006

Jones, B. E. (2020). Arousal and sleep circuits. *Neuropsychopharmacology*, *45*(1), 6–20. https://doi.org/10.1038/s41386-019-0444-2

Ju, Y.-E. S., Ooms, S. J., Sutphen, C., Macauley, S. L., Zangrilli, M. A., Jerome, G., Fagan, A. M., Mignot, E., Zempel, J. M., Claassen, J. A. H. R., & Holtzman, D. M. (2017). Slow wave sleep disruption increases cerebrospinal fluid amyloid-β levels. *Neurology*, *140*(8), 2104–2111. https://doi.org/10.1093/brain/awx148

Kuhn, M., Mainberger, F., Feige, B., Maier, J. G., Wirminghaus, M., Limbach, L., Mall, V., Jung, N. H., Reis, J., Klöppel, S., Normann, C., & Nissen, C. (2016). State-dependent partial occlusion of cortical LTP-like plasticity in major depression. *Neuropsychopharmacology*, *41*(6), 1521–1529. https://doi.org/10.1038/npp.2015.310

Landsness, E. C., Goldstein, M. R., Peterson, M. J., Tononi, G., & Benca, R. M. (2011). Antidepressant effects of selective slow wave sleep deprivation in major depression: A high-density EEG investigation. *Journal of Psychiatric Research*, *45*(8), 1019–1026. https://doi.org/10.1016/j.jpsychires.2011.02.003

Lentz, M. J., Landis, C. A., Rothermel, J., & Shaver, J. L. (1999). Effects of selective slow wave sleep disruption on musculoskeletal pain and fatigue in middle aged women. *The Journal of Rheumatology*, *26*(7), 1586–1592.

Lesicko, A. M., Angeloni, C. F., Blackwell, J. M., De Biasi, M., & Geffen, M. N. (2022). Corticofugal regulation of predictive coding. *ELife*, *11*, e73289. https://doi.org/10.7554/eLife.73289

Lustenberger, C., Boyle, M. R., Alagapan, S., Mellin, J. M., Vaughn, B. V., & Fröhlich, F. (2016). Feedback-controlled transcranial alternating current stimulation reveals a functional role of sleep spindles in motor memory consolidation. *Current Biology*, *26*(16), 2127–2136. https://doi.org/10.1016/j.cub.2016.06.044

Maris, E., & Oostenveld, R. (2007). Nonparametric statistical testing of EEG- and MEG-data. *Journal of Neuroscience Methods*, *164*(1), 177–190. https://doi.org/10.1016/j.jneumeth.2007.03.024

McConnell, B. V., Kaplan, R. I., Teale, P. D., Kronberg, E., Broussard, J. L., Guzetti, J. R., Sillau, S. H., Dhanasekaran, A. R., Kluger, B. M., & Berman, B. D. (2019). Feasibility of home-based automated transcranial electrical stimulation during slow wave sleep. *Brain Stimulation*, *12*(3), 813–815. https://doi.org/10.1016/j.brs.2019.02.014

Mölle, M., Eschenko, O., Gais, S., Sara, S. J., & Born, J. (2009). The influence of learning on sleep slow oscillations and associated spindles and ripples in humans and rats. *The European Journal of Neuroscience*, *29*(5), 1071–1081. https://doi.org/10.1111/j.1460-9568.2009.06654.x

Ngo, H.-V. V., Martinetz, T., Born, J., & Mölle, M. (2013). Auditory closed-loop stimulation of the sleep slow oscillation enhances memory. *Neuron*, *78*(3), 545–553. https://doi.org/10.1016/j.neuron.2013.03.006

Ong, J. L., Patanaik, A., Chee, N. I. Y. N., Lee, X. K., Poh, J.-H., & Chee, M. W. L. (2018). Auditory stimulation of sleep slow oscillations modulates subsequent memory encoding through altered hippocampal function. *Sleep*, *41*(5), zsy031. https://doi.org/10.1093/sleep/zsy031

Ooms, S. J., Zempel, J. M., Holtzman, D. M., & Ju, Y.-E. S. (2017). Automated selective disruption of slow wave sleep. *Journal of Neuroscience Methods*, *281*, 33–39. https://doi.org/10.1016/j.jneumeth.2017.02.008

Oostenveld, R., Fries, P., Maris, E., & Schoffelen, J.-M. (2010). FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Computational Intelligence and Neuroscience*, *2011*, 156869. https://doi.org/10.1155/2011/156869

Patanaik, A., Ong, J. L., Gooley, J. J., Ancoli-Israel, S., & Chee, M. W. L. (2018). An end-to-end framework for real-time automatic sleep stage classification. *Sleep*, *41*(5), zsy041. https://doi.org/10.1093/sleep/zsy041

Pernet, C. R., Latinus, M., Nichols, T. E., & Rousselet, G. A. (2015). Cluster-based computational methods for mass univariate analyses of event-related brain potentials/fields: A simulation study. *Journal of Neuroscience Methods*, *250*, 85–93. https://doi.org/10.1016/j.jneumeth.2014.08.003

Piantoni, G., Astill, R. G., Raymann, R. J. E. M., Vis, J. C., Coppens, J. E., & Van Someren, E. J. W. (2013). Modulation of γ and spindle-range power by slow oscillations in scalp sleep EEG of children. *International Journal of Psychophysiology*, *89*(2), 252–258. https://doi.org/10.1016/j.ijpsycho.2013.01.017

Ruch, S., Schmidig, F. J., Knüsel, L., & Henke, K. (2022). Closed-loop modulation of local slow oscillations in human NREM sleep. *NeuroImage*, *264*, 119682. https://doi.org/10.1016/j.neuroimage.2022.119682

Staresina, B. P., Bergmann, T. O., Bonnefond, M., van der Meij, R., Jensen, O., Deuker, L., Elger, C. E., Axmacher, N., & Fell, J. (2015). Hierarchical nesting of slow oscillations, spindles and ripples in the human hippocampus during sleep. *Nature Neuroscience*, *18*(11), 1679–1686. https://doi.org/10.1038/nn.4119

Steriade, M., Nuñez, A., & Amzica, F. (1993). A novel slow (<1 Hz) oscillation of neocortical neurons in vivo: Depolarizing and hyperpolarizing components. *The Journal of Neuroscience*, *13*(8), 3252–3265.

Tononi, G., & Cirelli, C. (2006). Sleep function and synaptic homeostasis. *Sleep Medicine Reviews*, *10*(1), 49–62. https://doi.org/10.1016/j.smrv.2005.05.002

Ulanovsky, N., Las, L., & Nelken, I. (2003). Processing of low-probability sounds by cortical neurons. *Nature Neuroscience*, *6*(4), Article 4–Article 398. https://doi.org/10.1038/nn1032

Van Der Werf, Y. D., Altena, E., Schoonheim, M. M., Sanz-Arigita, E. J., Vis, J. C., De Rijke, W., & Van Someren, E. J. W. (2009). Sleep benefits subsequent hippocampal functioning. *Nature Neuroscience*, *12*(2), 122–123. https://doi.org/10.1038/nn.2253

Van Der Werf, Y. D., Altena, E., Vis, J. C., Koene, T., & Van Someren, E. J. W. (2011). Reduction of nocturnal slow-wave activity affects daytime vigilance lapses and memory encoding but not reaction time or implicit learning. *Progress in Brain Research*, *193*, 245–255. https://doi.org/10.1016/B978-0-444-53839-0.00016-8

Vyazovskiy, V. V., & Tobler, I. (2005). Theta activity in the waking EEG is a marker of sleep propensity in the rat. *Brain Research*, *1050*(1), 64–71. https://doi.org/10.1016/j.brainres.2005.05.022

Wolf, E., Kuhn, M., Normann, C., Mainberger, F., Maier, J. G., Maywald, S., Bredl, A., Klöppel, S., Biber, K., van Calker, D., Riemann, D., Sterr, A., & Nissen, C. (2016). Synaptic plasticity model of therapeutic sleep deprivation in major depression. *Sleep Medicine Reviews*, *30*, 53–62. https://doi.org/10.1016/j.smrv.2015.11.003

Wunderlin, M., Koenig, T., Zeller, C., Nissen, C., & Züst, M. A. (2022). Automatized online prediction of slow-wave peaks during non-rapid eye movement sleep in young and old individuals: Why we should not always rely on amplitude thresholds. *Journal of Sleep Research*, *31*(6), e13584. https://doi.org/10.1111/jsr.13584

Wunderlin, M., Züst, M. A., Hertenstein, E., Fehér, K. D., Schneider, C. L., Klöppel, S., & Nissen, C. (2021). Modulating overnight memory consolidation by acoustic stimulation during slow-wave sleep: A systematic review and meta-analysis. *Sleep*, *44*(7), zsaa296. https://doi.org/10.1093/sleep/zsaa296

Züst, M. A., Ruch, S., Wiest, R., & Henke, K. (2019). Implicit vocabulary learning during sleep is bound to slow-wave peaks. *Current Biology*, *29*(4), 541–553.e7. https://doi.org/10.1016/j.cub.2018.12.038

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Fehér, K. D., Omlin, X., Tarokh, L., Schneider, C. L., Morishima, Y., Züst, M. A., Wunderlin, M., Koenig, T., Hertenstein, E., Ellenberger, B., Ruch, S., Schmidig, F., Mikutta, C., Trinca, E., Senn, W., Feige, B., Klöppel, S., & Nissen, C. (2023). Feasibility, efficacy, and functional relevance of automated auditory closed-loop suppression of slow-wave sleep in humans. *Journal of Sleep Research*, e13846. https://doi.org/10.1111/jsr.13846